The space-time continuum: examining the cortical contributions to spatial and temporal processing

Philip A. Blankenship

Follow this and additional works at: https://huskiecommons.lib.niu.edu/allgraduate-thesesdissertations

Recommended Citation

This Dissertation/Thesis is brought to you for free and open access by the Graduate Research & Artistry at Huskie Commons. It has been accepted for inclusion in Graduate Research Theses & Dissertations by an authorized administrator of Huskie Commons. For more information, please contact jschumacher@niu.edu.
Spatial and temporal processing are critical for an animal’s survival. Many neurological disorders are associated with disruptions of these processes. Converging lines of evidence have suggested that these processes are mediated by a cortico-striatal network of structures. Limited research has investigated the role of the medial agranular cortex (AGm) and posterior parietal cortex (PPC) in relation to their overlap in spatial and temporal processing. The current study evaluated the roles of the AGm and PPC in spatial processing and interval timing. Long-Evans rats received unilateral devascularization of either the left hemisphere AGm or PPC followed by testing in the Morris water task (MWT), dark exploration, and food protection. Unilateral damage to these structures was observed to spare performance in all three tasks with a few exceptions. AGm lesion rats were observed to travel longer distances during the first two days of acquisition and demonstrated higher degrees of changes in heading during dark exploration. The selective behavioral disruptions observed in AGm lesion rats may reflect impairments in egocentric spatial or attentional processing.
NORTHERN ILLINOIS UNIVERSITY

DEKALB, ILLINOIS

AUGUST 2018

THE SPACE-TIME CONTINUUM: EXAMINING THE CORTICAL CONTRIBUTIONS TO SPATIAL AND TEMPORAL PROCESSING

BY

PHILIP A BLANKENSHIP

©2018 Philip Anthony Blankenship II

A DISSERTATION SUBMITTED TO THE GRADUATE SCHOOL IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE DOCTOR OF PHILOSOPHY

DEPARTMENT OF PSYCHOLOGY

Dissertation Director:

Douglas G. Wallace
ACKNOWLEDGEMENTS

I would like to thank my dissertation director and advisor, Dr. Doug Wallace, for his help and guidance throughout this project. I am also grateful for the input and time that my committee members have provided. Furthermore, I wish to thank Marco Kopecky, Rebecca Weil, Rachel Jollie, Victoria Kwaben, Brenda Vance, and Amy French for their immense help with behavioral testing and data analysis associated with this project. Lastly, I am greatly appreciative for the Psychology Department and the Graduate School for funding and my fellow neuroscience and behavior members for their advice, perspectives, and willing ears.
DEDICATION

To Staci Rose, my love and biggest supporter, for all your patience, persistence, and understanding. I could not have done this without you. This accomplishment is as much mine as it is yours.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIST OF TABLES</td>
<td>vii</td>
</tr>
<tr>
<td>LIST OF FIGURES</td>
<td>viiI</td>
</tr>
<tr>
<td>LIST OF STRUCTURAL ABBREVIATIONS</td>
<td>x</td>
</tr>
<tr>
<td>CHAPTER 1. INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>Spatial Orientation</td>
<td>3</td>
</tr>
<tr>
<td>Spatial Deficits and Neglect Syndrome</td>
<td>13</td>
</tr>
<tr>
<td>A Neural Network for Spatial Processing and Directed Attention</td>
<td>15</td>
</tr>
<tr>
<td>Temporal Processing</td>
<td>31</td>
</tr>
<tr>
<td>Temporal Deficits and Neglect Syndrome</td>
<td>36</td>
</tr>
<tr>
<td>A Neural Network for Temporal Processing</td>
<td>39</td>
</tr>
<tr>
<td>A Proposed Integrated Neural Network for Processing Space and Time</td>
<td>44</td>
</tr>
<tr>
<td>Research Question and Hypotheses</td>
<td>45</td>
</tr>
<tr>
<td>CHAPTER 2. EXPERIMENT 1</td>
<td>48</td>
</tr>
<tr>
<td>Methods</td>
<td>48</td>
</tr>
<tr>
<td>Subjects</td>
<td>48</td>
</tr>
<tr>
<td>Surgery</td>
<td>48</td>
</tr>
<tr>
<td>Apparatus</td>
<td>50</td>
</tr>
<tr>
<td>Procedure</td>
<td>51</td>
</tr>
<tr>
<td>Data Analysis</td>
<td>52</td>
</tr>
<tr>
<td>Chapter</td>
<td>Page</td>
</tr>
<tr>
<td>------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>Histology</td>
<td>54</td>
</tr>
<tr>
<td>Results</td>
<td>55</td>
</tr>
<tr>
<td>Histology</td>
<td>55</td>
</tr>
<tr>
<td>AGm lesions</td>
<td>55</td>
</tr>
<tr>
<td>PPC lesions</td>
<td>58</td>
</tr>
<tr>
<td>Place learning measures</td>
<td>58</td>
</tr>
<tr>
<td>General performance characteristics</td>
<td>58</td>
</tr>
<tr>
<td>Sequential analysis</td>
<td>63</td>
</tr>
<tr>
<td>Probe day measures</td>
<td>64</td>
</tr>
<tr>
<td>General performance characteristics</td>
<td>64</td>
</tr>
<tr>
<td>Sequential analysis</td>
<td>67</td>
</tr>
<tr>
<td>Matching-to-place measures</td>
<td>69</td>
</tr>
<tr>
<td>Discussion of experiment 1 results</td>
<td>71</td>
</tr>
<tr>
<td>3. EXPERIMENT 2</td>
<td>76</td>
</tr>
<tr>
<td>Methods</td>
<td>76</td>
</tr>
<tr>
<td>Subjects</td>
<td>76</td>
</tr>
<tr>
<td>Apparatus</td>
<td>76</td>
</tr>
<tr>
<td>Procedure</td>
<td>76</td>
</tr>
<tr>
<td>Data Analysis</td>
<td>77</td>
</tr>
<tr>
<td>Results</td>
<td>78</td>
</tr>
<tr>
<td>Chapter</td>
<td>Page</td>
</tr>
<tr>
<td>---------</td>
<td>------</td>
</tr>
<tr>
<td>General Measures of Locomotor Function</td>
<td>78</td>
</tr>
<tr>
<td>Sequential Analysis</td>
<td>79</td>
</tr>
<tr>
<td>Discussion of Experiment 2 Results</td>
<td>85</td>
</tr>
<tr>
<td>4. EXPERIMENT 3</td>
<td>90</td>
</tr>
<tr>
<td>Methods – Food Protection</td>
<td>90</td>
</tr>
<tr>
<td>Subjects</td>
<td>90</td>
</tr>
<tr>
<td>Apparatus</td>
<td>90</td>
</tr>
<tr>
<td>Procedure</td>
<td>91</td>
</tr>
<tr>
<td>Data Analysis</td>
<td>91</td>
</tr>
<tr>
<td>Results</td>
<td>92</td>
</tr>
<tr>
<td>Motoric and Motivational Factors</td>
<td>92</td>
</tr>
<tr>
<td>Spatial Characteristics of Food Protection</td>
<td>95</td>
</tr>
<tr>
<td>Temporal Characteristics of Food Protection</td>
<td>98</td>
</tr>
<tr>
<td>Discussion of Experiment 3 Results</td>
<td>98</td>
</tr>
<tr>
<td>5. GENERAL DISCUSSION</td>
<td>105</td>
</tr>
<tr>
<td>BIBLIOGRAPHY</td>
<td>120</td>
</tr>
<tr>
<td>Figure</td>
<td>Page</td>
</tr>
<tr>
<td>--------</td>
<td>------</td>
</tr>
<tr>
<td>1. Percent cortical tissue affected for AGm lesions</td>
<td>57</td>
</tr>
<tr>
<td>2. Percent cortical tissue affected for PPC lesions</td>
<td>60</td>
</tr>
</tbody>
</table>
## LIST OF FIGURES

<table>
<thead>
<tr>
<th>Figure</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Diagram of groups for Blodgett et al., 1949</td>
<td>10</td>
</tr>
<tr>
<td>2. Proposed cortico-striatal network mediating spatial and temporal processing</td>
<td>16</td>
</tr>
<tr>
<td>3. Food protection behaviors</td>
<td>23</td>
</tr>
<tr>
<td>4. Organization of food protection behaviors</td>
<td>33</td>
</tr>
<tr>
<td>5. Diagram of task used by Danckert et al., 2007</td>
<td>37</td>
</tr>
<tr>
<td>6. Lesion extent of AGm lesions</td>
<td>56</td>
</tr>
<tr>
<td>7. Lesion extent of PPC lesions</td>
<td>59</td>
</tr>
<tr>
<td>8. General performance measures for place learning in the MWT</td>
<td>62</td>
</tr>
<tr>
<td>9. Sequential analysis of swimming behavior for the first two days of place learning</td>
<td>65</td>
</tr>
<tr>
<td>10. Probe trial performance measures</td>
<td>66</td>
</tr>
<tr>
<td>11. Sequential analysis of probe trial swimming behavior</td>
<td>68</td>
</tr>
<tr>
<td>12. Matching-to-place general performance measures</td>
<td>70</td>
</tr>
<tr>
<td>13. Measures of locomotor functioning</td>
<td>80</td>
</tr>
<tr>
<td>14. Sequential analysis of progressions</td>
<td>82</td>
</tr>
<tr>
<td>15. Sequential analysis of stopping behavior</td>
<td>84</td>
</tr>
<tr>
<td>Figure</td>
<td>Page</td>
</tr>
<tr>
<td>--------</td>
<td>------</td>
</tr>
<tr>
<td>16. Concentric circles used to measure the distance between noses of the dodger and robber.</td>
<td>93</td>
</tr>
<tr>
<td>17. Motoric and motivational factors of food protection</td>
<td>94</td>
</tr>
<tr>
<td>18. Spatial characteristics of food protection</td>
<td>96</td>
</tr>
<tr>
<td>19. Temporal characteristics of food protection</td>
<td>99</td>
</tr>
<tr>
<td>Structure</td>
<td>Abbreviations</td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Medial Agranular Cortex</td>
<td>AGm</td>
</tr>
<tr>
<td>Posterior Parietal Cortex</td>
<td>PPC</td>
</tr>
<tr>
<td>Dorsocentral Striatum</td>
<td>DCS</td>
</tr>
<tr>
<td>Medial Prefrontal Cortex</td>
<td>mPFC</td>
</tr>
<tr>
<td>Nucleus Basalis</td>
<td>NB</td>
</tr>
<tr>
<td>Globus Pallidus</td>
<td>GP</td>
</tr>
<tr>
<td>Substantia Nigra pars Compacta</td>
<td>SNc</td>
</tr>
<tr>
<td>Substantia Nigra pars Reticulata</td>
<td>SNr</td>
</tr>
<tr>
<td>Dorsal Tegmental Nucleus</td>
<td>DTN</td>
</tr>
<tr>
<td>Lateral Mammillary Nucleus</td>
<td>LMN</td>
</tr>
</tbody>
</table>
CHAPTER 1
INTRODUCTION

Space and time are fundamental dimensions of our existence. Processing this information is a critical component for survival; from getting to an important meeting on time to learning when a renewable food source is available and where it is located, both humans and animals use spatial and temporal information to organize their behaviors (Gallistel, 1990). A variety of neurological disorders have been shown to disrupt these processes. For example, patients that have experienced stroke often exhibit disruptions in spatial and temporal processing (Meerwaldt & Van Harskamp, 1982). In their latest update, the American Heart Association (2016) has reported that stroke is the second-leading global cause of death, accounting for 11.8% of total deaths worldwide in 2013. Stroke is currently the fifth-leading cause of death in the United States, associated with the deaths of approximately 129,000 people annually (AHA, 2016).

While the incidence of stroke remains high, research has shown that over the last decade, stroke-related deaths have dropped 18 percent (Centers for Disease Control and Prevention, 2012). Although stroke-related deaths are on the decline, stroke remains the leading cause of serious, long-term neurological disability in the United States (CDC, 2012; AHA, 2016). Of patients that survive stroke, approximately 15-30% are left permanently disabled while 20% require institutional care months after stroke onset (CDC, 2012).

The estimated direct and indirect costs associated with stroke averaged $73.7 billion in 2010, stemming from health expenditures and lost productivity (CDC, 2012). Costs are projected to triple by 2030, increasing to $184.1 billion annually (AHA, 2016), largely due, in part, to
inadequate therapies or behavioral interventions. Although several therapies (i.e. administration of dopaminergic agonists, CIMT, mirror therapy, or brain stimulation) exist, they often produce modest functional improvements (often focusing on compensatory responding) or rarely generalize across therapeutic contexts (Reep, Corwin, Cheatwood, Van Vleet, Heilman, & Watson, 2004; see Faralli, Bigoni, Mauro, Rossi, & Carulli, 2013). The lack of effective available therapies and the rising costs associated with stroke recovery demonstrate a critical need for research investigating the neural mechanisms that contribute to these widespread cognitive deficits.

Often following stroke, patients display multimodal (visual, tactile, auditory, etc.) impairments in attending, responding, or orienting to stimuli presented to the side of the body that is contralateral, or opposite, to the side of the brain the stroke occurred on, known as neglect syndrome (Kerkhoff, 2001; Heilman, Watson, & Valenstein, 2003). This disorder is associated with impairments in several cognitive domains including spatial and temporal processing. For example, patients with neglect syndrome often display deficits in responding to stimuli within an egocentric reference frame or fail to access a cognitive representation of their contralesional hemispace (Bisiach and Luzzatti, 1978). Further, neglect patients have been shown to struggle in tasks assessing the temporal aspects of attention (Husain, Shapiro, Martin, & Kennard, 1997; Rorden, Mattingley, Karnath, & Driver, 1997; Hillstrom, Husain, Shapiro, & Rorden, 2004) and time perception (Harrington, Haaland, & Knight, 1998; Danckert et al., 2007; Merrifield, Hurwitz, & Danckert, 2010). Neglect syndrome is observed in some capacity in approximately 40% of all patients with cortical strokes (Heilman, Watson, & Valenstein, 1993; Reep, Corwin, Cheatwood, Van Vleet, Heilman, & Watson, 2004). Symptoms are most
frequently observed following damage or destruction of the dorsolateral posterior parietal cortex, dorsolateral premotor-prefrontal cortex, or cingulate cortex (Mesulam, 1990).

As discussed, stroke is the leading cause of serious, long-term disability in the United States. A common consequence of stroke is the development of neglect syndrome, a neurological disorder characterized by a variety of impairments to cognitive domains including spatial and temporal processing. Current behavioral or pharmacological-based therapies have been shown to promote minimal recovery or rarely generalize across therapeutic contexts. As a consequence, direct and indirect stroke-related costs are projected to triple by 2030. The development of more effective therapies, therefore, depends on establishing a more robust model of cortical stroke that is sensitive to the deficits previously described. The current series of experiments have been designed to assess the deficits characterized in spatial and temporal domains of cognitive functioning associated with cortical stroke. In addition, a review of the neural networks that support these processes and an understanding of this neurobiology is essential for modeling neglect syndrome and the subsequent assessment of more efficacious therapies following cortical stroke. The following sections consider the neuropsychology and neurobiology of neglect syndrome as it pertains to spatial orientation and temporal processing.

**Spatial Orientation**

To navigate through their respective environments, animals rely on two sources of spatial information (Gallistel, 1990). One source of navigational information involves using environmental cues. These spatial cues consist of any visual, auditory, or olfactory-generated stimuli. When these cues are limited or unavailable, animals will prioritize the use of self-movement cues which include vestibular, proprioception, optic flow, and motor efferent copies.
that are generated during movement (Gallistel, 1990). Accurate navigation through space is dependent on an organism using these sources of spatial information to establish and maintain a trajectory from their current spatial location to the intended goal location or end point. To maintain orientation, animals can make use of several navigational strategies. These strategies are hierarchically prioritized depending on access to environmental cues and their familiarity with the surrounding environment (Maaswinkel & Whishaw, 1999).

Under conditions in which an animal is familiar with its environment and/or has access to environmental cues, it has access to several navigational strategies. If navigation requires traveling to a salient landmark that serves as the animal’s trajectory end point (i.e. a renewable food source or refuge), they can rely on a beacon homing strategy (Gallistel, 1990). Beacon homing involves the use of a specific external cue (or landmark), that also serves as the goal location for the present trajectory, to guide movement. For example, rats are much quicker to locate a rewarded arm (and made significantly fewer arm entries to find it) in an eight-arm radial maze when the rewarded arm possessed a visually distinctive intramaze pattern (Hogarth, Roberts, Roberts, & Abrom, 2000). In addition to dry mazes, beacon homing has been observed in water tasks (Redhead, Roberts, Good, & Pearce, 1997). Explicitly, manipulating spatial strategies, by way of positioning a salient beacon, has been shown to influence water task performance. Rats that were exposed to a salient beacon atop a hidden escape platform (beacon group) had significantly lower escape latencies when compared to rats that experienced an ambiguously placed beacon, not associated with the platform (pilot group). Interestingly, the use of this strategy is not limited to the visual modality. Rats have been shown to use odor cues to navigate to a goal location in dry and water tasks. Rats were able to follow a scented string on a
table top to a food reward location (Wallace, Gorny, & Whishaw, 2002). Odor tracking has also been observed to facilitate navigation to a submerged escape platform in the Morris water task (Means, Alexander, & O’Neal, 1992). While this strategy is effective with the presence of a salient landmark and requires a low cognitive demand, environmental changes (like the removal of the landmark) significantly disrupt navigation. Such changes promote the use of a more flexible (and potentially more cognitively demanding) navigational strategy.

Piloting involves navigating toward a goal location by computing the relative distance and direction of that location from multiple environmental landmarks (Gallistel, 1990). For example, when the platform and beacon were removed in a probe trial, rats in the beacon group (group that experienced a salient beacon placed atop the hidden escape platform) spent significantly less time swimming in the quadrant where the platform had previously been located when compared to the pilot group (group that experienced an ambiguously placed beacon). This dissociation in Morris water task performance is suggestive of beacon group rats relying on beacon homing to locate the platform (and ignoring environmental cues) while pilot group rats engaged in piloting, or using the relationship between the ambiguously placed beacon and other environmental cues to navigate toward the platform location. This later strategy is more robust to environmental changes, when compared to beacon homing, due to the remaining environmental relationships established. Other work has provided support for this conclusion. When landmarks in the environment (extramaze or distal cues) or within a testing arena (intramaze or proximal cues) are held consistent, rats were able to accurately navigate to a submerged escape platform that was moved between trials (Morris, 1981; Redhead, Roberts, Good, & Pearce, 1997; Pearce, Roberts, & Good, 1998). However, if environmental cues are not held consistent or
environmental changes have occurred, errors in navigation may arise and the stimuli become unreliable sources of spatial information and eventually become uninformative to the animal (Sutherland & Dyck, 1984; Maaswinkel & Whishaw, 1999). In the event that relational cues are no longer reliable sources of spatial information, the use of more dynamic strategies is required.

Similar to piloting, cognitive mapping is a more flexible and dynamic navigational strategy that involves utilizing several distal and directional relationships between environmental stimuli to determine the trajectory toward a perceived goal location. This strategy is dependent on the navigator possessing a cognitive map, or a mental symbolic representation of an individual’s surroundings that allows the individual to utilize various landmark relationships to navigate differentially from place to place (Tolman, 1948; O’Keefe & Nadel, 1978; Poucet, 1993). This complex representation facilitates the use of multiple trajectories toward a goal location and allows for the use of short cuts through their environment. The seminal piece of evidence to suggest that rats are capable of making detours or short cuts through their environment can be seen in the sun-burst maze (Tolman, Ritchie, & Kalish, 1946). During the training phase of the task, rats were run through an elevated maze consisting of a starting alley that opened into a circular arena. After having entered the circular arena, rats were to travel down another winding alley (consisting of one left and two right turns) to reach a food box. Following training, the elevated maze was transformed into the sun-burst maze (see Tolman, Ritchie, & Kalish, 1946 Fig. 2 for a detailed illustration of the apparatus). With the sun-burst design, rats experienced the same starting alley that opened up to the same circular arena; however, the original alleyway to the food box was now blocked. Instead, rats were now exposed to 18 different alleys that shot off in varying degrees. Surprisingly, instead of choosing the alley with
the orientation closest to that of the original, rats tended to choose the alley that served as the most direct trajectory to the food box. This pattern of results suggests that the rats did not merely encode the original route of the elevated maze; rather, it suggests that the rats encoded the specific spatial location of the food box, providing evidence for the ability to encode their environment and adapt their path to changes within the environment accordingly. An important characteristic to mention associated with the aforementioned spatial strategies (beacon homing, piloting, and cognitive mapping) is that all of them are dependent on access to environmental cues or familiarity with the environment. When either of these requirements is not met (i.e. when environmental cues are restricted, not informative, or are not accessible), animals can rely on self-movement cues to guide navigation.

In situations where access to environmental cues is restricted or an animal is in a novel or unfamiliar environment, they can rely on internally-generated self-movement cues to guide navigation. One navigational strategy that explicitly relies on the use of self-movement cues is dead reckoning (or path integration). Dead reckoning involves the online process of integrating changes in heading and position within a specific temporal duration to compute the necessary trajectory to a former location or where movement was originally initiated (Darwin, 1873; Mittelstaedt and Mittelstaedt, 1980; Etienne, 1980; Gallistel, 1990; Maaswinkel & Whishaw, 1999; Etienne and Jeffery, 2004). For example, the establishment of a refuge is critical to a rat’s survival. As a consequence, survival depends on the rat’s ability to accurately return to its refuge. When foraging for food in a novel environment or under nightfall (conditions where environmental cues may be uninformative or restricted), rats will estimate direction and distance to their refuge by way of dead reckoning (Maaswinkel, Jarrard, & Whishaw, 1999). To obtain
this information, the rat will have had to have kept a “log” of changes in angular heading and linear movements (Wallace, Martin, & Winter, 2008). Rats are believed to use this strategy when foraging for food under dark conditions (Whishaw, Hines, & Wallace, 2001) or when visual information is restricted (Maaswinkel, Jarrard, & Whishaw, 1999). Specifically, blindfolded rats were able to reliably return to their refuge after foraging for a food item. Even when the foraging arena was rotated after a rat had left their established refuge, to displace odor cues, it was still able to reliably return to its refuge (Maaswinkel, Jarrard, & Whishaw, 1999). It is suggested that the accurate return trips were associated with the rat using self-movement cues to guide movement. As previously discussed, rats prioritize the use of environmental and self-movement cues to navigate through their environment. These sources of spatial information can be processed in several frames of reference.

As navigation generally occurs within a stimulus-rich environment, it is necessary to discuss the representation of objects within space and the processing of spatial information within various frames of reference. Spatial locations can be specified relative to either allocentric or egocentric reference frames (O’Keefe & Nadel, 1978; Paillard, 1991; Kesner, Farnsworth, & DiMattia, 1989). An allocentric (or object-centered) spatial reference frame involves processing orientation relative to specific external stimuli representing locations or the relationships between them within the environment that are independent of one’s body orientation in space (Kesner et al., 1989; Paillard, 1991; Iachini, Ruggiero, Conson, Trojano, 2008). A classic allocentric-based spatial assessment is the Morris water task (Morris, 1981; Morris, Garrud, Rawlins, & O’Keefe, 1982). Typically, the Morris water task involves a rat being trained to swim to a submerged escape platform in a circular swimming pool. In the task, rats were released
from the periphery of the pool (facing the wall) and then allowed to swim around the pool until they encountered a hidden platform, which allowed the rat to escape the water. Rats were believed to assess the location of the platform using an allocentric-based strategy (i.e. piloting). For example, rats could have assessed their location and the location of the platform relative to stationary landmarks or extra-maze room cues (Morris et al., 1982). Dry-maze variants of the water task have also been developed. Specifically, the cheeseboard task involves a rat searching for a hidden food item within a circular tabletop arena (Kesner et al., 1989; King & Corwin, 1992). Similar to the Morris water task, rats were placed at the periphery of the arena and allowed to explore the board until they found the food item. For the first 20 trials, the food item’s location was not changed. As with the Morris water task, rats’ latency to find the food item decreased across trials. It was suggested that this change in performance was attributed to the rats engaging in an allocentric searching strategy in which they assessed the food item’s location relative to the stimuli located around the room. In addition to processing spatial information from an allocentric perspective, spatial cues can also be processed via an egocentric (or body-centered) frame of reference, which can occur independently from allocentric processing.

An egocentric reference frame involves processing orientation relative to the self (O’Keefe & Nadel, 1978; Kesner et al., 1989; Paillard, 1991). Within an egocentric frame of reference, spatial representations are taken from the perspective with which they are experienced (Iachini et al., 2008). For example, consider giving an individual directions to the nearest gas station from your current location. Perhaps from where you are now, the gas station requires the individual to drive straight for two blocks and make a right turn and then it will be on their left-hand side four blocks down. In this example, yours and the individual’s assessment of where the gas station is,
in reference to their (your) current position in space, reflects the perspective with which the traveling will have occurred. Similarly, rats have been shown to adopt egocentric-based strategies to solve variants of the radial arm maze. For example, rats were shown to commit fewer choice-point errors in an elevated T-maze when employing an egocentric response-based learning strategy (Blodgett, McCutchan, & Mathews, 1949). In the task, rats experienced an elevated T-maze that was interchangeable at spatial positions (see Figure 1). To attempt to dissociate the use of different spatial learning strategies, rats experienced various manipulations of the food box location, direction from choice point to food box, or the turn at the choice point. One group (the Place Group) experienced the food box held in a consistent spatial location across trials. This constituted a place-learning strategy where the rat solved the maze by returning to the same spatial location for food. Rats in this group may have been expected to employ a piloting strategy (previously discussed; allocentric reference frame) in which they assessed the direction to travel at choice points based on relationships between extra-maze stimuli and the general food box location. In addition, a second group (the Direction Group) experienced a common direction from the choice point to food location across spatial locations. This constituted a direction-based learning strategy where the rat was expected to adopt a strategy in which they always turned to a specific direction to reach the food (i.e. the food box will always be in the west). Lastly, a third group (the Response Group) had to learn to make a common turn at the T-maze choice point. This constituted a response-based learning strategy in which the rat was expected to adopt a strategy of turning in a specific direction to reach the food (i.e. always turn left or turn right to reach the food bin).
Figure 1: Diagram of groups for Blodgett et al. (1949). (A) A Place Group of rats experienced the food box held in common across spatial location changes (S2/F2 & S4/F2). (B) A Direction Group of rats experienced a common direction from the choice point to food location across spatial locations (S1/F1 & S4/F2). (C) A Response Group of rats experienced having to make a common turn at the choice point between the two locations (S1/F1 & S2/F2).
These last two strategies (direction and response-based) involved the rats assessing the location of the food box relative to where they were in space (or within an egocentric frame of reference). When compared, the results of the experiment indicated that those rats that engaged in an egocentric strategy (i.e. direction or response learning strategies) performed significantly better (made significantly less choice errors) than those rats that were tasked with an allocentric, place learning task (Blodgett et al., 1949).

Similar spatial learning strategies have been observed to solve a variant of the eight-arm radial maze (Kesner et al., 1989; King & Corwin, 1992). In this variant of the task, rats were trained to solve a “turn right” or “turn left” task. When placed at the end of a randomly selected arm, rats were to learn that the only rewarded arms were those that were immediately adjacent to the rats’ starting arm. In other words, rats were rewarded for entering and exploring adjacent arms to the either the immediate left or right of the arm they started in. Successful performance in the task is suggested to depend on the rats’ development of an egocentric searching strategy (either “turn left” or “turn right” when leaving the starting arm). The above behavioral assessments provide support for a rodent’s ability to process spatial information in multiple ways including an allocentric or egocentric frames of reference.

As discussed, rats have access to two primary sources of spatial information (environmental and self-movement cues). Each of these sources is associated with several spatial navigation strategies. With access to environmental cues, rats are capable of engaging in beacon homing, piloting, and cognitive mapping. When these cues are restricted or environmental stimuli are not meaningful, rats can utilize dead reckoning (a self-movement cue-based strategy). Assuming an animal is intact or healthy, it can use these strategies to find resources and return
safely to their refuge while avoiding predation; however, in cases of pathology, like neglect syndrome, the ability to reliably engage in these spatial processes is compromised. While a great deal of work has examined the role of subcortical structures like the hippocampus in spatial processing, the specific contributions of cortical structures to spatial processing have received far less attention. Therefore, the following section will discuss the contributions of cortical structures to spatial orientation.

**Spatial Deficits and Neglect Syndrome**

As previously mentioned, neglect syndrome is observed in some capacity in approximately 40% of all patients with right hemisphere cortical strokes (Heilman et al., 1993; Reep et al., 2004). Neglect symptomology is especially likely to manifest following damage or destruction of the dorsolateral posterior parietal cortex, dorsolateral premotor-prefrontal cortex, or cingulate cortex (Mesulam, 1990). While neglect syndrome is associated with a variety of cognitive deficits, a hallmark of the disorder is sensory inattention. Also referred to as sensory neglect, this neurological deficit is characterized by failures in attending, responding, or orienting toward novel or meaningful stimuli of various modalities that are presented to the side contralateral to the brain insult (Heilman, 1979; Meerwaldt & Van Harskamp, 1982; Reep et al., 2004). For example, a neglect patient may fail to eat food on the contralesional side of their plate or may fail to groom the contralesional side of their face or body (Halligan & Marshall, 1993; Halligan, Fink Marshall, & Vallar, 2003). In addition to this attentional impairment, neglect is also associated with severe spatial and cognitive deficits (Heilman et al., 1993).

Patients with sensory neglect may also display lateralized spatial deficits in accessing a cognitive representation of their contralesional hemispace (the mental representation of one’s
environment associated with the left or right side of the body), referred to as hemispatial neglect (Denes, Semenza, Stoppa, & Lis, 1982; Heilman et al., 1993). For example, when asked to draw or copy a picture, patients with prefrontal cortex damage displaying hemispatial neglect will fail to draw portions of the picture that are located in the hemispace contralateral to the brain insult or contralesional hemispace. This pattern of results has been reported on several occasions (Paterson & Zangwill, 1944; McFie, Piercy, & Zangwill, 1950; Denny-Brown & Banker, 1954). Further, when patients with hemispatial neglect are asked to bisect a line (draw a perpendicular line going through the midpoint of a presented line), they may instead, quarter the line, bisecting the half of the line presented in ipsilesional hemispace (Heilman & Valenstein, 1979). Moreover, when these patients are presented with multiple lines on a sheet of paper and asked to cancel them out or cross them out (draw a perpendicular line through them, similar to the line bisection task), they demonstrated failures in crossing out lines on the contralesional side of the page (Mark & Heilman, 1998). The lateralized impairments previously described also have implications for navigating within an egocentric reference frame.

Recall that egocentric processing or assessing location within an egocentric frame of reference is relative to the self (or a self-reference frame). Patients with hemispatial neglect exhibit impairments in accessing contralesional hemispace. For example, when two patients with left unilateral neglect were asked to picture themselves in an Italian square and report their surroundings within an egocentric perspective, they were unable to report details associated with the left (contralesional) side (Bisiach & Luzzatti, 1978). In other words, when asked to picture themselves in the southern-most part of the square and report what they were observing, these patients were able to accurately describe (with great detail) the details of the square (i.e. where
buildings and landmarks were located) within their right hemispace or information that would have been located to the right of the individual within that particular perspective; however, details from their left hemispace were largely omitted. Interestingly, when asked to picture themselves on the opposite side of the square (i.e. the northern-most part of the square) details of the square that were originally omitted (due to being represented in the impaired contralesional hemispace) were now represented in their intact right hemispace and accurately reported. This pattern of results suggests that hemispatial neglect is associated with a lateralized disruption of egocentric space; however, the ability of the patients to accurately report their surroundings when represented in ipsilesional hemispace suggests that the disorder spares allocentric spatial processing. As these deficits to egocentric spatial processing are associated with damage to cortical structures including the medial prefrontal cortex (mPFC) and posterior parietal cortex (PPC), the role of these structures in spatial processing must be considered.

### A Neural Network for Spatial Processing and Directed Attention

Neuroanatomical and behavioral approaches as well as the use of rodent models have greatly advanced understanding of the network of structures involved in directed attention (Milner, 1987; Brown, 2002). Work with these models has provided several lines of evidence to suggest that a network of cortical and striatal structures mediates spatial processing of egocentric and allocentric information (Kesner et al., 1989; King & Corwin, 1992; Corwin & Reep, 1998; Wolbers, Weiner, Mallot, Buchel, 2007). Specifically, connections between the medial agranular cortex (AGm; a subcomponent of the medial prefrontal cortex or mPFC), posterior parietal cortex (PPC) and their subcortical projection zone, the dorsocentral striatum (DCS) are believed to form a circuit of structures mediating the processing of environmental cues related to
egocentric and allocentric navigation (see Figure 2; Bucci, Holland, & Gallagher, 1998; Cheatwood, Reep, & Corwin, 2003; Reep & Corwin, 2009; Reep, Corwin, Cheatwood, Van Vleet, Heilman, & Watson, 2004; Wu, Corwin, & Reep, 2009). Several approaches have been used to investigate this network of brain structures.

Early research investigating the contributions of cortical structures to spatial processing focused on the mPFC, a large, heterogeneous group of cortical subcomponents. Specifically, this work employed large aspiration lesions of this area to examine egocentric and allocentric processing in rats (Kesner et al., 1989). Rats were trained on a series of behavioral tasks, including the adjacent arm (a variant of the radial arm maze) and cheeseboard tasks (a dry analogue of the Morris water task; for details, see above). Rats that received bilateral mPFC lesions displayed impairments in learning the adjacent arm task (an egocentric-based task), taking significantly longer to acquire the task and only performing slightly better than chance. Conversely, bilateral mPFC lesions facilitated learning during the cheese board task (an allocentric-based task). This pattern of performance suggests a role for the mPFC in the mediation of egocentric processing (Kesner et al., 1989; however, see Kolb, Sutherland, & Whishaw, 1983). While this behavioral work provides a foundation for examining the contributions of frontal cortical areas to spatial processing, the course nature and large extent of mPFC lesions used in the study limit its specificity and reduce the ability to determine which specific subcomponents were the cause of the above impairments. As such, subsequent work utilized more selective means to examine the role of mPFC subcomponents and develop a more
Figure 2: Proposed cortico-striatal network mediating spatial and temporal processing. The medial agranular cortex (AGm), a subcomponent of the medial prefrontal cortex (mPFC), and the posterior parietal cortex (PPC) receive glutamatergic projections from thalamic nuclei (Thal) and cholinergic projections from the nucleus basalis (NB). The striatum receives glutamatergic projections from the AGm and PPC and sends GABAergic projections to the globus pallidus (GP) and substantia nigra pars reticulate (SNr). The substantia nigra pars compacta (SNc) sends dopaminergic feedback to the striatum and the GP sends GABAergic projections back to the thalamic nuclei.
specific interpretation of function. Evidence has implicated the AGm as a likely mPFC subcomponent responsible for egocentric processing.

Neuroanatomical techniques have been important in dissociating areas within the mPFC. In the rat, the AGm is considered to be a multimodal frontal eye field involved in producing head orientation responses. Track tracing studies have provided evidence implicating the AGm in the processing of egocentric spatial information (Reep, Godwin, & Corwin, 1990). Several studies have used fluorescent axonal tracers to examine the organization of the AGm's rostrocaudal and mediolateral afferent (Reep, Corwin, Hashimoto, & Watson, 1984) and efferent (Reep, Corwin, Hashimoto, & Watson, 1987) connections. In these studies, rats were injected with retrograde (or anterograde, respectively) axonal tracers into the AGm and surrounding areas. Following a survival period, rats were perfused and their brains extracted. This work has revealed that rostral AGm has several corticocortical connections including the lateral agranular cortex (AGl), posterior parietal cortex (PPC), various sensory association regions and input from various thalamic nuclei including the ventral lateral, mediodorsal and ventromedial. Additionally, rostral AGm has several projections from limbic/paralimbic structures including the orbital, perirhinal, retrosplenial, and entorhinal cortices (Reep et al., 1984; 1987), structures that have also been implicated in processing spatial information (Boulougouris, Dalley, & Robbins, 2007; Winters & Busey, 2005; Barker, Bird, Alexander, & Warburton, 2007; Sargolini et al., 2006; Winter, Köppen, Ebert, & Wallace, 2013). The widespread, multimodal connections of the AGm suggest that it may be a likely structure mediating the various sensory impairments associated with neglect.
Damage to the AGm, or its various connections, is associated with manifestations of neglect symptomology that are consistent with those observed in human patients. Specifically, unilateral damage to the AGm is associated with multimodal deficits in attending, orienting, or responding to stimuli that have been presented to contralesional hemispace (Corwin, Kanter, Watson, Heilman, Valenstein, & Hashimoto, 1986; King & Corwin, 1990). In these studies, rats are observed in neglect testing, an assessment of egocentric responding. Neglect testing involves gently restraining a rat and presenting it with a series of visual, auditory, and tactile stimuli to both hemispheres (ipsilesional and contralesional). Rats’ degree of head orientation was used as a measure of egocentric responding. Unilateral destruction of the AGm resulted in severe lateralized impairments in responding to each mode of stimuli on the contralesional side, characterized as multimodal or hemispatial neglect (Corwin et al., 1986; Crowne & Pathria, 1982; King & Corwin, 1990; Van Vleet, Heldt, Pyter, Corwin, & Reep, 2003). Damage to this structure has also been associated with performance deficits in egocentric spatial tasks (King & Corwin, 1992). The adjacent arm and the cheeseboard tasks (see above) were used to examine the role of the AGm in egocentric and allocentric spatial processing. Bilateral AGm lesions produced severe performance impairments on the egocentric-based adjacent arm task while sparing performance on the allocentric-based cheeseboard task. Unilateral AGm lesions produced intermediate deficits on the arm-maze task relative to bilateral lesions. These behavioral deficits parallel those observed following bilateral mPFC lesions (Kesner et al., 1989) and are consistent with the AGm mediating responding to egocentric spatial information. As mentioned, tracing work has shown that the AGm has extensive corticocortical connections. As the AGm has been implicated in egocentric-based spatial processing, it may be the case that the cortical structures that it shares connections with may share a role in similar processes.
In addition to its many cortical connections, the AGm is highly interconnected with the PPC (Reep et al., 1984; 1987; Reep, Godwin, & Corwin, 1990; Chandler, King, Corwin, & Reep, 1992; Reep, Chandler, King, & Corwin, 1994; Reep, Corwin, & King, 1996). This interconnectivity suggests that the PPC may play a similar role in egocentric- spatial processing and directed attention. As with unilateral lesions of the AGm, unilateral lesions of the PPC produce severe lateralized impairments in responding to multimodal stimuli on the contralesional side (King & Corwin, 1993). Further, severing the fiber connections between the two structures via transverse knife-cuts, while maintaining the integrity of structures themselves, produced severe multimodal neglect that is qualitatively similar to that observed following unilateral AGm or PPC lesions (Burcham, Corwin, Stoll, & Reep, 1997). The above lines of evidence provide support for the PPC in mediating egocentric responding; however, damage to this structure is associated with deficits in allocentric processing. For example, bilateral PPC lesions have been shown to disrupt performance on allocentric-based spatial tasks while sparing performance on egocentric-based spatial tasks (Kesner et al., 1989; King & Corwin, 1992). Specifically, rats that received bilateral lesions of the PPC demonstrated spared performance in the adjacent arm maze while displaying disruptions in the cheeseboard task. Lateralized differences were observed for unilateral PPC lesions. Right PPC (RPPC) lesions were associated with more significant impairments in the task during early trials when compared to left PPC (LPPC) lesions; however, all unilateral lesion animals performed at control levels by the end of testing (King & Corwin, 1992). Further, allocentric disruptions have also been observed in an allocentric version of the radial arm maze and in the Morris water task (Kolb & Walkey, 1987; Save & Moghaddam, 1996). In both tasks, bilateral PPC lesions resulted in slower acquisition of the task when it required the use of extra-personal spatial information. These results provide support for a role of
the PPC in egocentric responding but also allocentric processing. Together, the above lines of evidence indicate dissociative roles for the AGm and PPC in the processing of environmental cues such that the AGm mediates egocentric processing and the PPC mediates allocentric processing. Anatomical findings have shown that despite their dissociable roles in spatial processing, both structures send strong projections to the DCS.

Track tracing has provided evidence to suggest that the primary projection zone of the AGm and PPC is the DCS. Retrograde axonal tracing was used to examine the cortical the subcortical projections to the DCS (Cheatwood, Reep, & Corwin, 2003). Rats were injected with Fast Blue or Diamidino Yellow, two reliable retrograde axonal tracers, into the DCS. Following a survival period of 3 to 5 days, animals were perfused and their brains extracted. Results demonstrated strong, dense axonal projections from the AGm and the PPC that converged in the DCS. This work was supported later by anterograde tracing (Reep, Cheatwood, & Corwin, 2003; Cheatwood, Corwin, & Reep, 2005). Rats were injected with biotinylated dextran amine (BDA), a frequently used anterograde tracer, into the AGm or PPC. Following a survival period of 7 to 10 days, rats were perfused and brains extracted. Again, the results revealed dense connections between the two cortical structures but also dense projections to the DCS. As the AGm and PPC have been implicated in spatial processing and directed attention, work began to focus on the DCS as a subcortical component of this network.

Several lines of evidence have supported for a role of the DCS in mediating spatial processing and directed attention. Early lesion work has shown that damage to this area impairs egocentric spatial processing (Potegal, 1969). For example, bilateral lesions of the DCS disrupted performance in an egocentric-based radial arm maze task (similar to the methodology
of Kesner et al., 1989). This task involved rats learning an egocentric rule (such as always investigate the arm immediately left or right of the starting arm’s location). Rats that received bilateral DCS lesions never exhibited levels of performance above chance, suggesting that the DCS mediates egocentric responding. This work has been further supported by neglect testing work. Unilateral lesions of the DCS produce neglect-like impairments that are qualitatively similar to deficits observed following unilateral AGm or PPC lesions. Specifically, rats that have received unilateral DCS lesions exhibited significantly higher contralateral neglect of visual, auditory, and tactile modalities when compared to rats with lateral striatum or control rats (VanVleet, Burcham, Corwin, & Reep, 2000; VanVleet, Heldt, Guerrettaz, Corwin, & Reep, 2002). Other egocentric deficits have been reported using the operant-based 5-choice serial reaction-time task (5CSRTT). The 5CSRTT is composed of a multi-choice operant chamber designed to assess lateralized sensory performance, similar to the presentation of visual stimuli during neglect testing. Following training, rats received unilateral quinolinic acid injections into the DCS and were reassessed in the task. Lesion rats were found to exhibit impaired performance on the side contralateral to the lesion. This manifested as lower choice accuracy on the contralateral side, increased latency to respond to a visual target on the contralateral side, and perseveration of responses to a particular aperture (Brasted, Humby, Dunnett, and Robbins, 1997). Most recently, the role of the DCS in egocentric processing has been examined using the food protection task (Blankenship, Cheatwood, & Wallace, 2017). Food protection involves a rat (the dodger) consuming and protecting a food item from hungry conspecific (or robber; Whishaw & Tomie, 1987; 1988). To protect the food item from theft, a dodger will engage in one of two food protection behaviors: dodging or bracing. Dodging behavior is defined as any attempt to escape the conspecific that involves transferring the food pellet to the rat’s mouth and
using its forelimbs to make a full body movement away from the approaching conspecific (see Figure 3A). Bracing behavior is defined as any behavior that involves attempting to escape from an approaching conspecific where the forelimbs are not removed from the food item during the length of the behavior (see Figure 3B; Whishaw & Tomie, 1987). Among other factors, the ability to protect the food item is dependent on the animal detecting and responding to the incoming conspecific which may be mediated by egocentric processing. Unilateral excitotoxic lesions of the DCS produced lateralized impairments in protecting the food item from theft. Specifically, lesioned dodgers were significantly more likely to be stolen from when the robber approached the lesioned dodger from the contralesional side (Blankenship, Cheatwood, & Wallace, 2017). These above data suggest that the neural circuitry for processing egocentric information should be expanded to include the DCS and that this subcortical structure may play a critical role in integrating cortical information.

Impairments in egocentric processing may have consequences for other spatial processes, such as self-movement cue processing or the ability to use dead reckoning to estimate direction and distance. Recall that dead reckoning is a navigational strategy that is utilized when access to environmental cues is limited. This strategy is dependent on self-movement cues (vestibular
Figure 3: Food protection behaviors. Dodging behavior (A) refers to any attempt to escape the conspecific involving the transfer of the food pellet to the rat’s mouth and using its forelimbs to make a full body movement away. Bracing behavior (B) is characterized as any behavior that involves escaping an approaching conspecific that does not involve the use of the forelimbs. Figure adapted from Blankenship, Cheatwood, & Wallace, 2017.
information, proprioception, optic flow, and motor efferent copies) to estimate distance and direction back to the location that movement originated from (Gallistel, 1990). While a plethora of work has suggested that these cues are processed by a network of limbic system structures including the hippocampal formation and its projections (Maaswinkel, Jarrard, & Whishaw, 1999; Wallace & Whishaw, 2003), more recent work has suggested that this network should be expanded to include cortical structures. For example, human imaging work has shown that the mPFC is activated during dead reckoning tasks (Wolbers, Weiner, Mallot, & Büchel, 2007). In the task, participants took part in a virtual dead reckoning task under fMRI. The task consisted of participants traveling through a featureless space along two lengths of a triangle before stopping and point wiring toward the starting location. Increased hippocampal and mPFC activation was shown to be a significant predictor of performance in the task, suggesting that the mPFC may mediate performance in dead reckoning tasks. Other work in rats using spontaneous exploration has provided conflicting results.

Examination of exploration under dark conditions is one way to assess self-movement cue processing and dead reckoning. Spontaneous exploration in rats is organized into two levels: macro and micro. At the macro level, rats introduced into a new environment will establish a home base. Determination of a home base is based on the presence of prolonged amounts of time in the general area, stopping behavior, and several instances of grooming behavior (Eilam & Golani, 1989; Clark, Hines, Hamilton, & Whishaw, 2005). At the micro level, rats will organize their exploratory trips around the established home bases (Eilam & Golani, 1989; Drai, Benjamini, & Golani, 2000). Exploratory trips away from the home base consist of several stops and progressions. They are typically characterized as being slower and more circuitous
(complex) than those directed towards the home base location. Conversely, return trips are much faster and more direct. Return trips are typically scaled to the distance between the rat’s current location and their home base location (Wallace, Hamilton, & Whishaw, 2006; Wallace, Choudhry, & Martin, 2006). The organization of exploratory behaviors has been shown to be independent of environmental cue access. Specifically, under dark conditions or when environmental cues are restricted self-movement cue processing or dead reckoning is expected to be guiding navigation (Gallistel, 1990; Etienne & Jeffery, 2004; Wallace, Martin, & Winter, 2008). Lesions of the mPFC were shown to disrupt outward segment movement coordination and homeward segment direction estimation independent of lighting conditions (light or dark). When compared to controls, mPFC lesion rats traveled longer distances on their homeward segments, had significantly more circuitous homeward segments and accrued significantly larger homeward segment heading errors (Blankenship, Stuebing, Winter, Cheatwood, Benson, Whishaw, & Wallace, 2016). This pattern of results is consistent with mPFC lesions impairing motor coordination, response inhibition, and egocentric processing. These impairments are associated with disrupting characteristics of spatial orientation; however, the lack of specificity in the disruptions (i.e. impairments observed across all lighting conditions) indicates that this structure does not directly contribute to self-movement cue processing or dead reckoning. Instead, it may be the case that the mPFC provides these resources to support self-movement cue processing and may play an indirect role in dead reckoning. Despite the ambiguous role of the mPFC in dead reckoning, several lines of evidence have implicated the involvement of the PPC in self-movement cue processing.
A number of behavioral studies have also suggested that the PPC contributes to self-movement cue processing and dead reckoning. One commonly used task to examine dead reckoning is the food hoarding task. In the task, food items are randomly placed on a circular searching arena and a rat is tasked with searching on the arena for the food and subsequently returning to its established home base for consumption (for a review, see Winter, Blankenship, & Mehlman, 2017). Hoarding trips are organized into outward or searching segments and homeward segments (similar to what has been described with spontaneous exploration). Searching segments consist of all movement associated with leaving the refuge to finding a food item. These segments are typically circuitous, consisting of various stops and progressions. The homeward segment consists of all movement following the collection of the food item to entering the home base for consumption. Observations of intact rats have shown that return trips are often ballistic, accurately directed at the refuge. This task mimics behaviors that are naturally occurring in wild rats and has the capacity to dissociate multiple sources of spatial information (Mittelstaedt & Mittelstaedt, 1980; Maaswinkel & Whishaw, 1999; see Winter, Blankenship, & Mehlman, 2017). Explicitly, manipulating the availability of environmental cues (through manipulating the visibility of the home base; hidden probe) allows for assessment of local or distal environmental cue use to guide navigation while restricting the use of environmental cues (through changing lighting conditions; dark probe) predisposes the use of self-movement cues to guide movement. Lesions of the PPC have been shown to disrupt performance in the food hoarding task, particularly affecting the accuracy of homeward progressions. For example, rats with bilateral parietal lesions were shown to make significantly more complex and less accurate homing paths back to their home base in a food hoarding task when tested under dark conditions compared to controls (Save, Guazzelli, & Poucet, 2001). Together, these behavioral results
provide evidence of differential contributions of the mPFC and PPC to self-movement cue processing. Specifically, the mPFC has been shown to play an indirect role (providing resources to support dead reckoning) while the PPC has been shown to be critical for this type of processing. This differential contribution to self-movement cue processing is another line of evidence to support dissociable cortical contributions to spatial processing. As of yet, no work has examined the role of the DCS in self-movement cue processing; however, other work has provided support for this structure, the mPFC, and PPC as being structures associated with a larger neural network mediating directed attention and preferential responding to different angular directions.

Research has demonstrated the existence of a head direction cell circuit that has been implicated in supplying egocentric spatial information. Head direction (HD) cells exhibit firing characteristics that are tuned to a specific angular heading (0°-359°). These neurons fire at a steady rate, but firing rates decrease back to their baseline rates as the animal's head turns away from the preferred direction. Different HD cells have their own unique preferential directions for firing, resulting in cell activation and firing for any direction the rat is oriented within an environment. For example, a particular HD cell (or set of cells) may preferentially fire when a rat’s head is oriented toward the northern cardinal direction, independent of its actual location. Head direction cells were first identified in the postsubiculum, a structure that is adjacent to the hippocampus (Ranck, 1984). Head direction cells have also been found in other subcortical structures such as the mammillary nuclei (Blair, Cho & Sharp, 1998; Stackman & Taube, 1998), retrosplenial cortex (Cho & Sharp, 2001), thalamus (Taube, 1995), and the entorhinal cortex (Quirk, Muller, Kubie, & Ranck, 1992). Theories as to the circuit’s connections suggest that the organization is believed to originate in the reciprocal connections between two subcortical nuclei: the dorsal tegmental
nucleus (DTN) and the lateral mammillary nuclei (LMN). The DTN contains cells sensitive to angular head velocity (which receives vestibular input from the nucleus prepositus hypoglossis and medial vestibular nucleus). The LMN contains cells sensitive to both angular velocity and direction. Signals are then projected to limbic (from retrosplenial cortex to entorhinal cortex and then to the hippocampus) and striatal regions (from laterodorsal thalamic nucleus to the dorsal striatum). Here the directional information sent from the DTN and mammillary nuclei can be integrated with place/location information in the hippocampus and entorhinal cortex. From there, this integrated place and direction information is sent to sensory cortical structures, including the mPFC and parietal cortex, to provide a sense of one’s spatial orientation in the environment (Weiner, & Taube, 2005).

Work with the head direction cell network has suggested that the mPFC, PPC, and DCS play indirect roles in processing head direction information; however, other work has demonstrated the presence of HD cells in these structures. While recordings of the mPFC have not revealed the presence of HD cells (Jung, Qin, McNaughton, & Barnes, 1998), other work has documented them in PPC of rats performing in a radial-arm maze (Chen, Lin, Green, Barnes, & McNaughton, 1994). In the study, electrodes were lowered into the PPC and neurons recorded. Of the 257 cells recorded, seven exhibited characteristics associated with head direction. Interestingly, these cells exhibited the greatest preferential firing when the rat was making turns rather than demonstrating preferential firing to a specific direction, suggesting that these HD cells are sensitive to angular velocity changes. This is consistent with the PPC mediating egocentric responding in other tasks. Other work has shown that the DCS possesses HD cells. In a similar approach to the study just described, electrophysiological recordings of neurons in the
DCS were taken while the rat performed in a radial-arm maze (Mizumori, Ragozzino, & Cooper, 2000; Ragozzino, Leutgeb & Mizumori, 2001). Unlike the HD cells observed in the PPC, HD cells recorded in the DCS exhibited preferential firing that corresponded with a specific direction (specific to a salient distal landmark) under light conditions. Specifically, directional preferences in firing rotated when a salient distal visual cue was moved. Testing under dark conditions was associated with a disruption in directional firing; however, similar head direction preferences were observed regardless of condition. This pattern of activation seems to suggest that the DCS may serve to facilitate the ability to switch between navigational strategies. This seems to support the neuroanatomical work showing that the DCS receives strong projections from the AGm, believed to mediate egocentric processing, and the PPC, which is believed to mediate allocentric processing.

Together, this body of research has suggested that the processing of environmental cues, relative to egocentric and allocentric processing, is mediated by a corticostriatal network of structures including the mPFC (specifically the AGm), PPC, and DCS. The AGm and PPC have been shown to mediate egocentric responding (or directed attention); however, these structures differentially contribute to spatial processing in that the AGm mediates egocentric processing and the PPC supports allocentric processing. These structures are highly interconnected with one another and both send projections to the DCS, which has also been implicated in egocentric and allocentric processing. Damage or disruptions of these structures has also been shown to influence performance in dead reckoning tasks. While the mPFC has been shown to indirectly influence self-movement-cue processing (Blankenship et al., 2016), lesions of the PPC have been shown to disrupt performance in dead reckoning tasks (Save, Guazzelli, & Poucet, 2001).
Further, the PPC and DCS indirectly influence the head direction (HD) cell network as they have been shown to contain HD cells that are sensitive to angular velocity and head orientation respectively. Spatial deficits observed following damage to these structures may stem from disruptions in egocentric responding or proprioceptive information. These indirect influences on self-movement cue processing may also stem from the fact that these same structures have been implicated in temporal processing related to interval timing (the seconds-to-minutes range). The following sections will review temporal processing and consider the contributions of the AGm, PPC, and DCS to this domain.

**Temporal Processing**

Another major cognitive domain that is impacted with neglect syndrome is time. Time is a fundamental dimension of life. From determining when to go to sleep or wake up to the temporal pacing associated with being able to walk, talk, play instruments or sports, time is a critical element of most everyday activities (Buhusi & Meck, 2005). Time is also intimately linked with spatial processing. For example, global positioning systems (GPS) establish current position by triangulating temporal information related to changes in signal relays from satellites. Similarly, bats, owls, and frogs utilize coincidence detection whereby they generate an accurate topographic representation of their environments by comparing minute latency differences in the arrival time of sound at each ear, also referred to as the inter-aural time difference (ITD; Grothe, 2003). Specifically, bats are capable of navigating through their environment through localizing low frequency sounds. The rebounding echoes from their emissions inform the bat about its environment. If the echo rebounds off an object directly in front of the bat, the ITD should be zero as it reaches each ear at approximately the same time. Conversely, if an echo rebounds from
terrain that is uneven or exists on one side of the bat’s body, it should reach each ear at different latencies, creating an ITD. For bats and other species that rely on coincidence detection, spatial processing is dependent on the perception of time. In turn then, timing and time perception are critical for survival.

Interval timing refers to processing temporal information that occurs between the seconds-to-minutes range (Meck, 1983; Church, 1984; Gibbon, Church, & Meck, 1984; Meck, 1996; Meck & Benson, 2002; Meck, 2003; see Buhusi & Meck, 2005). Interval timing is crucial for several behaviors, such as foraging (Kacelnik & Brunner, 2002) but is especially critical for decision making and conscious time estimation (Richelle, et al., 1980; Gallistel, 1990). Interval timing has been observed across a variety of species including birds (Buhusi, Sasaki, & Meck, 2002), fish (Drew, Zupan, Cooke, Couvillon, & Balsam, 2005), rodents (Roberts & Church, 1978; Roberts, 1981; Gibbon, Church, & Meck, 1984) and humans (Ratikin et al., 1998). Three types of behavioral tasks have been used to examine interval timing: estimation, production, and reproduction (for a review, see Paule et al., 1999). Time estimation tasks require subjects or participants to discriminate between durations of stimuli. For example, a light or tone may be presented to a participant and they are instructed to press a button when they estimated a length of time had passed that corresponds with that specific stimulus (Holroyd and Krigolson, 2007; Becker, Nitsch, Miltner, & Straube, 2014). Time production tasks require a subject to produce specific durations of time. For example, having a participant hold down a key on a computer for a specific duration of time that corresponds with an inter-stimulus presentation interval (Ivry & Hazeltine, 1995). While these tasks provide sensitive measures of temporal control, they are prone to confounds such as response inhibition. More reliable tasks employ temporal
reproduction procedures which require subjects to reproduce a temporal interval of a specific duration that has been previously observed.

Two types of reproduction task that have been used extensively across a variety of species are the peak-interval (PI) procedure (also known as the peak procedure) and temporal bisection task. The peak procedure consists of a combination of fixed-interval (FI) trials (the subject is rewarded for their first response after a criterion time has elapsed following the onset of a stimulus) and PI trials (the stimulus remains presented for a much longer duration than the criterion time and no reward is given; Roberts, 1981; Meck, 1996; Hinton and Meck, 1997; Rakitin et al., 1998). Mean responding on PI trials typically follows a normal distribution around the criterion duration (despite the stimulus being presented for a much longer duration). Specifically, animals show a gradual increase in responding with maximum responding (peak responding) observed at the animal’s expected time of reinforcement. In addition, the distribution of responding is directly proportional to the criterion duration (Meck, 1996; Matell & Meck, 2000). In the temporal bisection task, subjects are trained to discriminate between short (2s tone) and long (10s tone) duration stimuli by responding on different levers (Church & Deluty, 1977). Following training, subjects are then presented with additional stimuli of intermediate durations. Performance is measured as the probability of responding on the long lever as a function of stimulus duration. Other work has shifted away from operant-based tasks toward examining timing in naturalistic behaviors like food protection.

In contrast to traditional, operant-based reproduction tasks, recent work has used the food protection task as a measure of a rat’s sensitivity to time. The organization of food protection behaviors has been shown to be dependent on the animal’s subjective time to consume
their food item (Whishaw & Gorny, 1994). Specifically, longer estimates are associated with an increased likelihood of eliciting dodging behaviors; whereas shorter estimates are associated with more bracing behaviors (see Figure 4). These observations suggest that examining the organization of food protection behaviors may provide a novel paradigm for evaluating interval timing. Through the use of these tasks as well as the observations of humans and animals performing them, several conceptual models of interval timing have been developed.

The dominant model of interval timing is an information-processing model, also known as the pacemaker-accumulator model (Treisman, 1963). This model suggests that interval timing is mediated by an “internal clock” and consists of three distinct stages: a clock stage, memory stage, and decision stage (Meck, 1983; Church, 1984; Gibbon, Church, & Meck, 1984; Meck, 1996; Meck & Benson, 2002; Meck, 2003; Buhusi & Meck, 2005). The first stage of the model (the clock stage) effectively transforms the passage of physical time into subjective psychological time (Meck & Benson, 2002). To do this, the clock consists of a pacemaker, a switch, and an accumulator. The pacemaker emits a series of pulses at regular intervals (similar to a metronome ticking at a regular, constant rate). These pulses are then gated via an attentional switch (comprised of various attentional processes). When the switch is closed (completing the circuit), it allows the flow of pacemaker-emitted pulses to pass into an accumulator, but when the switch is open (disconnecting the circuit), it blocks pulses from being accumulated. The switch closes in response to the detection of temporally significant information (i.e. a rewarded stimulus presentation; Meck & Church, 1983). When the temporally significant information becomes no longer significant (the rewarded stimulus is removed), the switch then opens to stop the flow of pulses into the accumulator. The number of pulses are then integrated in the accumulator and
Figure 4: Organization of food protection behaviors. The organization of food protection behaviors is dependent on the animal’s subjective time to consume their food item. Longer estimates are associated with an increased likelihood of eliciting dodging behaviors; whereas shorter estimates are associated with more bracing behaviors. This results in a pattern consistent with higher probabilities of engaging in dodging behavior during early samples of a food protection trial. This probability then decreases during later samples where the estimate to eat what remains of the food item are significantly smaller. The smaller estimate during later samples is associated with increased probability of engaging in bracing behavior.
stored in working memory.

During the memory stage, the currently stored accumulator value is then compared to previously stored pulse values that correspond with the expected time of the temporally significant event. If the values stored in working memory for the current temporal interval are similar enough to previously stored values based on a comparator, a decision is made (respond accordingly based on previous iterations to the temporally relevant event) during the decision stage. The current pulse value is then stored in reference memory with the other distribution samples for this temporal duration and can subsequently affect future behavior (associated with that temporally significant event). This information processing model has been critical in the examination of the neural structures mediating interval timing processes. Behavioral studies examining individuals with neglect syndrome have shown that in addition to spatial impairments, temporal processing (related to the interval timescale) is also impaired.

**Temporal Deficits and Neglect Syndrome**

In addition to affecting spatial and attentional processes, patients with neglect have also been observed to exhibit deficits in temporal processing. For example, stroke patients displaying neglect symptoms have been reported to display deficits in assessments of time perception (Harrington, Haaland, & Knight 1998). During the task, patients were presented with a standard tone pair consisting of two tones (75dB and 50ms in duration) separated between either a 300ms or 600ms temporal interval. Subsequently, patients were presented with a comparison tone pair that was separated by a randomized temporal interval that could have been longer or shorter than the standard pair interval. Following the presentation of the comparison tones, patients were instructed to indicate whether the interval between the comparison tone pair was longer or
shorter than the interval between the standard tone pair. After controlling for frequency perception deficits (like auditory neglect), patients with right hemisphere damage of either the prefrontal cortex damage of posterior inferior parietal cortex were shown to overestimate the temporal intervals they experienced under both standard pair intervals (300ms and 600ms) significantly more often than control counterparts. This deficit was most profoundly observed when the standard pair temporal interval was longest (600ms). Further work has shown that hemispatial neglect (via prefrontal or parietal cortex damage) impairs temporal estimation of a visual, illusory-motion stimulus (Danckert et al., 2007). During each trial of the task, participants observed an illusory motion stimulus, consisting of a darkened sphere traveling around a series of hollow spheres (see Figure 5) for a set temporal interval of either 5, 15, 30, or 60 seconds. Unlike the previously described temporal estimation task, counting of durations was prevented by having participants audibly recite a number that was briefly flashed in the center of the illusory motion stimulus. After the darkened sphere had traveled completely around, participants were asked to report the duration of the illusory motion stimulus presentation. Individuals with right hemisphere damage of the prefrontal or posterior parietal cortical areas not exhibiting neglect (RBD group) and right hemisphere damaged individuals exhibiting neglect (Neglect group) significantly underestimated objective temporal durations (5, 15, 30, or 60 seconds) of the illusory events when compared to a healthy control (HC) group. This temporal deficit was more pronounced in the neglect group than the RBD group. A critical consideration, however, is whether these temporal deficits are an artifact of spatial perception deficits in these neglect patients. As discussed, temporal deficits were reported for both the RBD and neglect groups. Both of these groups experienced damage of the prefrontal and/or parietal cortex. That individuals without neglect demonstrated similar (but to lesser degree) deficits in temporal
Figure 5: Diagram of the task used by Danckert et al., 2007. During each trial of the task, participants observed an illusory motion stimulus, consisting of a darkened sphere traveling around a series of hollow spheres for a set temporal interval of either 5, 15, 30, or 60 seconds. Counting of durations was prevented by having participants audibly recite a number that was briefly flashed in the center of the illusory motion stimulus. After the darkened sphere had traveled completely around, participants were asked to report the duration of the illusory motion stimulus presentation.
processing suggests that these deficits can be viewed as being independent of spatial deficits or attentional deficits associated with neglect. The exaggerated deficits observed in neglect patients may be due to the widespread nature of cognitive impairments associated with neglect syndrome. Taken together, these two studies and their behavioral results provide evidence to support a role for prefrontal and parietal cortical areas in mediation of time perception. Rodent work has provided further support for this role and has suggested that temporal processing of seconds-to-minutes information is dependent on a neural network of cortical and subcortical structures including the AGm, PPC, and DCS.

**A Neural Network for Temporal Processing**

Earliest work investigating the behavioral mechanisms underlying interval timing has focused on the prefrontal cortex (PFC). Damage to the PFC has been shown to produce various disruptions in temporal reproduction tasks. For example, rats were shown to demonstrate a rightward shift in peak responding on a 40s PI procedure, despite responding appropriately prior to surgery (Meck, Church, Wenk, & Olton, 1987). Responding was shown to shift from approximately 40s after stimulus onset prior to surgery to approximately 50s following surgery. The rightward shift in responding is suggestive of a decrease in the passage of subjective time. This is akin to having two metronomes, each generating a different amount of ticks or pulses (i.e. 45 and 70) within an objective temporal duration (i.e. 60 sec). These differences in pulse generation are associated with different subjective senses of the passage of time. An individual with a metronome generating the 45 pulses within 60 seconds may perceive that less time has passed when compared to an individual that has experienced the metronome that has generated
70 pulses within the same objective temporal duration. Other work examining the PFC noted that
damage was associated with increases in subjective time rather than decreases in a PI procedure
(similar to the individual exposed to the 70 pulse metronome). Rats that received bilateral PFC
lesions exhibited significant leftward shifts in PI responding (Dietrich, Frederick & Allen, 1997).
Peak responding was shown to shift from 40s preoperatively to 30s postoperatively suggesting
an increase in rats’ subjective passage of time. These conflicting shifts in responding may have
been due to the course nature of PFC lesions. Specifically, several lesions in the Deitrich et al.,
1997 study were shown to have damaged the corpus callosum. This damage could differentially
influence the ability of the intact hemisphere to provide compensation for the damage caused,
potentially resulting in the conflicting results. Interestingly, more focused damage to the PFC has
also produced conflicting results related to interval timing, although these inconsistencies may be
task-specific. For example, peak responding remained unaffected following aspiration lesions of
the mPFC (Dietrich, Frederick & Allen, 1997) while several other studies have reported that
mPFC lesions produce significant impairments in responding during a reaction time (RT) task.
Performance in this task is dependent on rats’ ability to withhold lever pressing/responding until
a trigger stimulus is presented after variable durations of time. After presentation of the trigger
stimulus, rats must respond as fast as possible. Excitotoxic lesions of the mPFC resulted in
significant increases in premature responding (Broersen & Uylings, 1999). These results were
also observed following reversible inactivations (muscimol) of this structure (Risterucci et al.,
2003; Narayanan, Horst, & Laubach, 2006). Premature responding in this task was thought to
reflect an inability to estimate the duration of time (foreperiod) until the trigger stimulus was
presented. These inconsistencies in the literature may be task dependent in that PI tasks require
the reproduction of temporal durations while RT task require the subject to estimate a given
temporal duration. While this may be the case, conflicting results may also reflect the coarse nature of the lesions produced. Examination of the specific subcomponents of the mPFC has implicated the AGm and other cortical regions in interval timing processes.

Research examining the specific subcomponents of the mPFC has implicated the AGm, in the processing of interval timing information. Reversible inactivation of the rostral forelimb area (RFA; encompassing the AGm) has produced shifts in responding to a trigger stimulus during a RT task. This task is similar to the previously described peak procedure; however, instead of lever pressing, rats were required to press and hold a lever for a specific duration of time (1s). Immediately following the hold duration, rats’ reaction time to release the lever was assessed. After extensive training, rats would exhibit release reaction times of less than 600ms after the hold duration. After receiving bilateral muscimol inactivation, rats exhibited a rightward shift in reacting to the trigger stimulus, reacting significantly slower than rats that received saline (Smith, Horst, Liu, Caetano, & Laubach, 2010). This rightward shift in responding following inactivation suggests that the AGm may mediate clock stage pacemaker-pulse accumulations. Additional work has suggested that the accumulation of pacemaker-pulses and their storage may depend on other cortical structures like the PPC.

The AGm and PPC have been shown to be highly interconnected and this connectivity has suggested that the PPC may also be involved in interval timing. While no rodent work has been conducted regarding the PPC and interval timing, work in humans has suggested that this cortical structure may also play a role in temporal processing. Inactivation of the PPC via transcranial direct current stimulation (tDCS) was shown to disrupt performance in a time reproduction task. Participants then experienced tDCS inactivations of either the left or right PPC.
and were run through a time reproduction task (Vicario, Martino, & Koch, 2013). Repeated tDCS over the right PPC produced deficits in temporal accuracy, resulting in participants overestimating temporal intervals; however, when tDCS of left PPC occurred, it decreased the variability in responding to different temporal intervals. These results suggest that the PPC may serve as a comparator of clock stage values. The AGm and PPC have also been shown to have connections with subcortical structures including the nucleus basalis (NB) and DCS.

In addition to having reciprocal connections with each other, the AGm and PPCs also have strong connections with other subcortical structures. Tract-tracing work has provided evidence that the AGm and PPC share strong connections with the NB (Mesulam, 1981; Mesulam, Mufson, Levey, & Wainer, 1983; Haring & Wang, 1986; Woolf, 1991). Interestingly, case studies have revealed that in addition to corticostriatal and nigrostriatal connections, the NB also deteriorates during the progression of PD (Nakano & Hirano, 1984; Zarrow et al., 2003). Lesions of the NB (or AGm) produce impairments in rats’ ability to time two stimuli simultaneously, but not sequentially (Olton, Wenk, Church, & Meck, 1988). In addition, NB damage has also been shown to augment peak responding during PI tasks (Meck, Church, Wenk, & Olton, 1987; Olton, 1989). In these studies, NB lesions produced a gradual rightward shift in peak responding, suggesting that lesions increased rats’ remembered time of reinforcement. If this is the case, it provides evidence to suggest that the NB may mediate the retrieval of previously stored values or play a role in the storage of new accumulated values. This behavioral evidence provides support for the AGm and PPC receiving subcortical afferents from the NB, other work has shown that these cortical structures share extensive connections with the dorsal striatum.
Other track tracing work has shown that both structures have axonal projections that terminate in the DCS (Kemp & Powell, 1971; Reep, Godwin, & Corwin, 1990; Sakai, Grofova, & Bruce, 1998; Reep & Corwin, 1999; Reep, Cheatwood, & Corwin, 2003; Cheatwood, Reep, & Corwin, 2003; 2005). This convergence zone of cortical structures, which have been implicated in interval timing, suggests that the DCS may be an important integrator of temporal information related to the clock stage of interval timing. Lesions of the dorsal striatum have been shown to disrupt performance in the temporal bisection task (Clarke & Ivry, 1997). Further, dorsal striatum lesions impaired responding to two distinct temporal intervals in the peak procedure (Dallal & Meck, 1993; Meck, 2006). Additionally, a recent study has shown that unilateral excitotoxic lesions of the DCS disrupt temporal characteristics of food protection (Blankenship, Cheatwood, & Wallace, 2017). Specifically, lesions of the DCS produced a rightward shift in the transitioning between dodging and bracing behaviors (behavioral transitions; the point at which the percentage of bracing behavior is greater than the percentage of dodging behavior, which typically occurs around the third sample of a given food protection session). This rightward shift in transitioning was characterized by more dodging behavior and was thought to reflect an increase in lesion rats’ subjective time to consume the food item (recall that a longer time to consume the food item is associated with an increase likelihood of dodging and short times are associated with more bracing). The combination of lesion work and neuroanatomical tracing studies have provided evidence to suggest that interval timing processes are mediated by a network of cortical, striatal, and subcortical structures (Matell, Meck, & Nicolelis, 2003; Matell & Meck, 2004). Damage to these structures produces significant deficits in performing temporal reproduction tasks. Specifically, damage to the AGm, PPC, or DCS produce pronounced shifts in responding associated with modification of the internal clock while lesions of the NB produce
gradual horizontal shifts in responding that are consistent with modification of the memory stage of interval timing. Together, this body of research provides the framework for a neural network mediating temporal processing within the seconds-to-minutes range. In conjunction, separate research has suggested that these structures may also mediate spatial processes associated with egocentric and allocentric processing. The overlap in function of this neural network provides a foundation for establishing an integrated model for examining spatial and temporal processing.

**A Proposed Integrated Neural Network for Processing Space and Time**

Until recently, egocentric processing and interval timing have been treated as separate literatures. This parallel investigative approach fails to acknowledge the considerable evidence suggesting that a cortical-striatal network of structures may serve to mediate both processes. The lack of a converging literature suggests that taking an integrative approach may be the next step in attempting to elucidate the mechanisms underlying the complex syndrome of impairments observed in neglect patients. Specifically, research from separate bodies of research has implicated a cortical (the AGm and PPC) – striatal (DCS) network of structures in egocentric processing, egocentric responding, and temporal processing. Each of these bodies of literature has examined the contributions of these structures in isolation and only recently has work been done examining the integrative roles of these structures (Blankenship, Cheatwood, & Wallace, 2017). This lack of integrative research may stem from the behavioral tasks that have been employed to examine these structural contributions. For example, interval timing research employs the temporal bisection and peak interval procedures, which are sensitive to interval timing but are unable to provide an assessment of spatial processing. Conversely, behavioral tasks employed to examine egocentric and allocentric processing, like the adjacent-arm maze and
cheeseboard task, are sensitive to spatial processing deficits but are unable to assess deficits in temporal processing. As discussed, neglect syndrome is a debilitating, complex neurological consequence of stroke that affects several domains of cognitive functioning including spatial and temporal processing. Rodent models of the disorder have been crucial in determining the mechanisms that underlie the dysfunctions observed in the disorder. In order to elucidate the mechanisms behind these multimodal impairments observed following cortical stroke, behavioral assessments developed to examine the contributions of these cortical structures need to possess the capacity to dissociate between spatial and temporal processing deficits.

Successful food protection has been shown to be dependent on egocentric spatial processing (see above). The organization of food protection behaviors is believed to be dependent on temporal processing and the rat’s subjective time to consume a food item (Whishaw & Gorny, 1994; Blankenship et al., 2017B). Specifically, longer estimates of time are associated with an increased likelihood of engaging in dodging behaviors, whereas shorter estimates are associated with an increase in bracing behaviors. As such, rats will exhibit behavioral transitions between dodging and bracing throughout a food protection trial. These characteristics of the food protection task provide the capacity to dissociate between spatial and temporal processing and the deficits that may arise from damage to the AGm or PPC. Therefore, the current proposal intends to use the food protection task (and other behavioral assessments) to investigate the contributions of the AGm and PPC in spatial and temporal processing.

**Research Question and Hypotheses**

As discussed, further elucidation of the mechanisms underlying neglect syndrome requires an integrative approach. The current series of studies used a variety of behavioral assessments to
investigate the integrative contributions of cortical structures, the AGm and PPC, in spatial and temporal processing. All rats were run through each behavior task in the same order as previous work has failed to find testing order effects on spatial performance (distance or direction estimation) after counterbalancing task order of the Morris water task and a food hoarding task (Köppen et al., 2015). As such, the order of testing for all rats was as follows. First, allocentric-spatial contributions of these structures was evaluated through the Morris water task. After completing the Morris water task, rats were run through two spontaneous exploration sessions under dark conditions to assess the contributions of the AGm and PPC to self-movement cue processing. Lastly, rats were run through the food protection task to provide an assessment of egocentric spatial and interval timing processes. The ordering of these behavioral tasks is intended to first ascertain a coarse measure of spatial ability with the Morris water task and proceed to finer analyses of self-movement cue, egocentric and interval timing processes. Previous work has shown that rats with lesions to the hippocampal formation (Whishaw, Cassel, & Jarrard, 1995; Whishaw & Jarrard, 1996; Whishaw & Tomie, 1997), which has been implicated in spatial processing, are capable of solving the Morris water task after extended training. These rats may have utilized compensatory strategies to solve the task, making it difficult to dissociate the specific contributions of neural structures (like the AGm and PPC) to spatial processing within the task (as other intact structures may allow for compensatory strategy use). As such, this task will serve as a coarse assessment of allocentric spatial processing. The spontaneous exploration and food hoarding tasks are designed to be able to dissociate various spatial processes, like self-movement cue and egocentric processing, respectively and therefore, were used for more fine analysis of spatial and temporal processing.
The aim of the current series of studies was to determine the roles of the AGm and PPC in spatial and temporal processing. It was expected that rats that received unilateral lesions of the AGm will exhibit in a differential pattern of behavioral deficits when compared to rats that received unilateral lesions of the PPC. It was expected that unilateral AGm lesions would spare performance in the Morris water task and spontaneous exploration under dark conditions while disrupting both spatial (ability to protect the food item) and temporal (organization of food protection behaviors) characteristics of food protection. Specifically, it was hypothesized that AGm lesions will produce lateralized (contralesional) impairments in the ability to protect a food item from theft while also disrupting the organization of food protection behaviors. Conversely, unilateral lesions of the PPC were expected to impair acquisition and retention of the Morris water task, disrupt the organization of exploratory behavior under dark conditions, and disrupt the spatial and temporal characteristics of food protection. Similar to unilateral AGm lesions, unilateral PPC lesions were predicted to produce lateralized impairments in the ability to protect the food item from theft while disrupting the organization of food protection behaviors. Together, the examination of these cortical structures served to provide a foundation for novel approaches to therapies associated with stroke-related damage to the frontal or parietal cortex.
CHAPTER 2
EXPERIMENT 1

Methods – Morris Water Task

Subjects

Thirty-seven female (90 days old) Long-Evans rats obtained from the Northern Illinois University rodent colony served as subjects for the first experiment. Rats were pair housed in plastic cages with the colony room temperature being maintained at 21 +/− 2 degrees Celsius. Rats were held on a 12 h light/dark cycle. All studies and behavioral testing was approved by NIU’s IACUC.

Surgery

Pilot Work

To determine the procedures for creating lesions of the AGm and PPC, several pilot lesions were produced. Each pilot lesion involved augmenting the stereotaxic coordinates associated with the location of each skull window. Specifically, pilot lesions were conducted reducing the size of the skull window by 10 or 15 percent to determine which reduction resulted in the lowest medial-lateral (ML) range of damage to ensure that damage to surrounding structures was minimized. As the ML extent of AGm skull windows is approximately 2.0mm, a 10% reduction resulted in an ML range of 1.8mm, while a 15% reduction resulted in an ML
range of 1.7mm. Regarding PPC lesions, the ML extent is approximately 3.0mm. As such, a 10% reduction resulted in an ML range of 2.7 mm, while a 15% reduction resulted in an ML range of 2.5mm. Based on pilot work, it was decided that a 10% reduction produced the most complete damage while minimizing damage to surround structures and white matter.

*Surgical Procedure*

Under aseptic conditions, all rats were anesthetized with a mixture of isoflurane and oxygen.

All AGm lesions (n = 10) were made on the left hemisphere. This decision was predicated on previous work showing that unilateral lesions of the left AGm produce more consistent neglect impairments whereas unilateral lesions of the right AGm produce less consistent impairments and are even associated with shifts in the laterality of neglect symptoms and the display of allesthesia and allokinesia (Vargo, Corwin, King, & Reep, 1988; King & Corwin, 1992). To create the lesion, four holes were drilled into the skull using a fine dental burr. These holes were then connected to form a skull ‘window’, extending from 5.0 mm anterior to -2.0 mm posterior to bregma and 1.85 mm lateral to .15 mm medial to bregma. Following removal of the skull window overlying the appropriate brain region, the underlying dura was removed, exposing the vasculature below. Subsequently, the vasculature was wiped away using a saline moistened cotton swab. Following the cessation of bleeding, the skin was sutured and the area was treated topically with Neosporin.

For PPC lesion rats (n = 10), four holes were drilled into the skull using a fine dental burr. These holes were connected to form a skull ‘window’, extending from -3.0 mm anterior to -4.2 mm posterior and from 4.0 mm lateral to 1.6 mm medial to bregma. Following removal of
the skull window overlying the appropriate brain region, the underlying dura was removed exposing the vasculature below. Subsequently, the vasculature was wiped away using a saline moistened cotton swab. Following the cessation of bleeding, the skin was sutured and the area treated topically with Neosporin.

Sham rats (n = 10) were anesthetized with a mixture of isoflurane and oxygen. Using a scalpel, an incision was made to the scalp exposing the skull. After making an incision, the skin was sutured and the area treated topically with Neosporin. Following surgery, all rats received access to rat chow mash (a mixture of ground rodent pellets, water, and sucrose). Rats were given a 14-day recovery period prior to beginning behavioral testing. Following a two-week recovery, all rats began testing in the first experiment.

The remaining seven rats did not undergo surgery. These rats were used expressly for the use of food protection interactions as hungry conspecifics (robbers). Their purpose was to elicit food protection behaviors from the surgery rats by attempting to wrest the food item away from them.

**Apparatus**

The water task apparatus was a large circular pool (1.73 m diameter × 0.60 m in height) filled with water (19-21°C). The water was made opaque by adding white non-toxic paint (Sargent Art). The hidden escape platform (15 cm diameter and 28 cm in height) was submerged 2 cm below the surface of the water. The apparatus was located in a rectangular room (2.77 m × 4.42 m) containing many extra-maze visual cues (not including the experimenters). For example, a poster was placed on one wall while a sink with overtop metal cabinet was positioned on an opposite wall, adjacent to the testing room door. The two remaining walls had unique duct-tape
designs and cues. In addition to the aforementioned cues, the experimenters served as consistent extra-maze cues. One experimenter stood next to the metal cabinet adjacent to the sink while the other stood next to the door during testing. To record trials, a bullet camera, attached to a DVD recorder, was mounted to the ceiling directly above the pool.

**Procedure**

Consistent with other work employing the Morris water task (Morris, 1981), rats were trained under light conditions to swim to a hidden escape platform, submerged 2 cm below the water. Each trial consisted of a rat being transported from their holding cage (located just outside of the testing area) and placed in the water facing the pool wall at one of the four-cardinal (N,S,E,W) compass directions. After being released, the rat was allowed to swim freely until either they located the hidden escape platform or 60 s had elapsed. If the rat failed to locate the escape platform after 60 s had elapsed, the rat was guided to the platform by the experimenter. After locating or being led to the escape platform, the rat remained on the platform for an additional 30 s before being removed from the pool and dried off before being returned to their holding cage. After each trial was completed the water in the pool was strained and stirred to displace any potential odor cues (Means, Alexander, & O’Neal, 1992).

The procedure of the Morris water task involved three phases: place training, a probe trial, and matching-to-place. Rats received five days of place training with four trials per day. During place training, rats were trained to locate a stationary hidden platform located in the northeast quadrant of the pool. On the sixth day of testing, all rats experienced one probe trial in which the hidden platform was removed from the pool. Similar to place training, rats were allowed to swim for 60 s; however, during the probe trial, the amount of time spent in each
quadrant was analyzed. Following the probe trial, rats experienced three days of matching-to-place (MTP). During MTP, the location of the hidden escape platform changed every other trial. Each MTP day consisted of two trials, one in which the location of the platform moved to a new quadrant (different from the previous day of testing) and another trial in which the platform remained in the same new location. For example, if the platform was located in the northeast quadrant on the last day of place training, it was moved to the southeast quadrant on the first trial of MTP day 1. Following this trial, the platform remained in that location (southeast quadrant) and the latency to locate the platform was assessed. This pattern of paired trials continued for three days such that the platform was moved from the northeast to southeast on MTP day one, moved from southeast to southwest on MTP day two, and from southwest to northwest on MTP day three (the final day of testing).

**Data Analysis**

The Ethovision (NOLDUS, Leesburg, VA, USA) motion tracking system was used to quantify movement and performance characteristics of rats in the Morris water task. Performance in the task was analyzed for each trial across all days of testing. Water task trials were defined as all movement from the release of the rat into the pool until it reached the escape platform or 60 s had elapsed.

Several measures were used to examine general characteristics of performance during the task. First, latency to reach the platform was recorded for each trial. As previously discussed, the maximum amount of time for a given trial was 60 s; after which the researcher guided the rat to the escape platform. Latency was averaged across the four trials for each day of place learning and across two trials for each day of MTP. In addition, the peak speed for each trial was
recorded. The peak speed for a trial is the point in which the highest velocity was achieved during a given swim path. Next, the total distance traveled was calculated for each trial and averaged across days. Lastly, the path circuitry (or the complexity) of swim paths was measured by taking the outward shortest distance (the Euclidean distance between the release location and the escape platform location) and dividing it by the total distance traveled during that trial. This results in a range from zero (most complex) to one (most direct). Path circuitry was averaged across the four trials for each day of place learning and across each day of MTP.

Two measures were used to assess spatial performance in the task. First, heading error was assessed as a measure of direction estimation. Heading error was obtained by calculating the angle subtended by: (1) the point associated with center of the escape platform, (2) the starting point of a given swim path (N, S, E, or W location), and (3) the point in which the peak in speed occurs during the swim path. In addition, the Brown’s score (Brown and Whishaw, 2000) was used as an assessment of the rats’ preference for the target quadrant of the pool (the quadrant that the hidden platform was in), during the probe day. The Brown’s score reflects the percentage of time spent in the target quadrant (Q_{target}) relative to the amount of time spent in the other three quadrants (Q_1, Q_2, & Q_3). It is calculated using the following formula:

\[ Brown’s = \left[ (Q_{target} - Q_1) + (Q_{target} - Q_2) + (Q_{target} - Q_3) \right] / 3 \]

Brown’s score values range from -33 (indicating an avoidance of the target quadrant all together) to 100 (not spending any time outside of the target quadrant).

Following a macro analysis of water maze performance, a sequential analysis of the first two days of place learning and the probe trial were conducted. Sequential analysis of swimming behavior involved deconstructing the swim path into its respective progressions and pauses.
From there, it is possible to gather a micro analysis of swimming behavior. Specifically, progression path circuitry was calculated for all progressions and averaged. In addition, changes in path heading (which typically occur during pauses between two progressions) were quantified for each pause in swimming and averaged. Changes in heading involved calculating the angle subtended by the: 1) preceding progression peak speed location, 2) average location of the pause, and 3) subsequent progression peak speed location. Lastly, the ability to scale peak speeds to distances traveled, or movement scaling, was calculated from each individual progression.

Repeated-measures ANOVAs were used to evaluate main effects of group, day, and the group by day interactions for all intended measures. All analyses will be run with alpha set at 0.05.

**Histology**

*Cresyl Violet*

Following completion of all behavioral testing, all rats were euthanized and perfused intracardially with phosphate-buffered saline and then a 4.0 % paraformaldehyde solution. Following perfusion, all rats’ brains were extracted from the skull and placed in 4.0 % paraformaldehyde for 24 hours. Brains were then transferred into a 30% sucrose solution for an additional 24 hours, which served to cryo-protect them. Brains were cut into 40 μm coronal sections and mounted on chromalum-subbed slides. Subsets of sections were stained for Cresyl violet and analyzed using an Olympus BH-2 microscope and photographs of the sections were taken with an Olympus DP72 camera.

Photos of the slices were used to verify that lesions were confined to the AGm and PPC respectively. AGm lesions were considered to have been successful if they were confined within
an anterior-to-posterior (AP) range of 5 mm to -2.0 mm (relative to bregma) and up to 1.85 mm lateral to the sagittal sinus. Successful lesions caused only minimal damage to the adjacent lateral agranular cortex (AGl), dorsal cingulate cortex, and cingulum bundle while sparing white matter. Similarly, successful PPC lesions were those that were confined within a -3.0mm to -4.2 mm AP range and a 1.6 mm to 4.0 mm medial-lateral (ML) range to bregma, while ensuring minimal damage to the forelimb representation area.

Results

Histology

AGm Lesions

Lesions were considered successful if they were within the previous described stereotaxic dimensions (e.g. +5.0mm to -2.0mm AP and 1.85mm to 0.15mm ML) and were focused on the Fr2 (M2) region of the cortex. Unsuccessful lesions were those that were not confined within these dimensions or those that affected the corpus callosum or subcortical structures including the cingulate cortex. Subsets of sections stained with Cresyl violet are provided of a minimum and maximum lesion extent (see Figure 6A & 6B). Examination of the histology associated with AGm lesions revealed that all lesions were focused on the Fr2 region of the cortex, with two cases showing damage extending minimally into the Fr1 region. Specifically, all lesions were observed to extend from approximately +4.00 AP to -2.16 AP and lesions were observed to affect approximately 69% of the Fr2 cortical area when compared to controls (see Table 1).
Figure 6: Lesion extent of AGm lesions. Cresyl violet stained sections of a maximum (A) and minimum (B) extent are presented for AGm lesions.
Table 1: Percent cortical tissue affected for AGm lesions.

<table>
<thead>
<tr>
<th>Case</th>
<th>+4.20 AP</th>
<th>+2.16 AP</th>
<th>-2.04 AP</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>69.56522</td>
<td>75.36232</td>
<td>111.1111</td>
<td>85.34622</td>
</tr>
<tr>
<td>4</td>
<td>47.82609</td>
<td>88.11594</td>
<td>88.88889</td>
<td>74.94364</td>
</tr>
<tr>
<td>6</td>
<td>84.78261</td>
<td>86.95652</td>
<td>59.25926</td>
<td>76.99946</td>
</tr>
<tr>
<td>7</td>
<td>65.21739</td>
<td>118.2609</td>
<td>66.66667</td>
<td>83.38164</td>
</tr>
<tr>
<td>14</td>
<td>32.6087</td>
<td>82.6087</td>
<td>88.88889</td>
<td>68.03543</td>
</tr>
<tr>
<td>17</td>
<td>41.30435</td>
<td>69.56522</td>
<td>88.88889</td>
<td>66.58615</td>
</tr>
<tr>
<td>18</td>
<td>8.695652</td>
<td>102.029</td>
<td>88.88889</td>
<td>66.53784</td>
</tr>
<tr>
<td>22</td>
<td>21.73913</td>
<td>52.17391</td>
<td>44.44444</td>
<td>39.4525</td>
</tr>
<tr>
<td>26</td>
<td>41.30435</td>
<td>82.6087</td>
<td>83.33333</td>
<td>69.08213</td>
</tr>
<tr>
<td>28</td>
<td>47.82609</td>
<td>52.17391</td>
<td>88.88889</td>
<td>62.96296</td>
</tr>
</tbody>
</table>

Total Group Percent Affected | 69.3328

Note. All lesions were focused on the Fr2 region of the cortex, with two cases showing damage extending minimally into the Fr1 region. Specifically, all lesions were observed to extend from approximately +4.0 AP to -2.16 AP and lesions were observed to affect approximately 69% of the Fr2 cortical area when compared to controls.
Lesions were considered successful if they were within the previous described stereotaxic dimensions (e.g. -3.0mm to -4.2mm AP and 4.0mm to 1.6mm ML) and were focused on the MPtA region of the cortex. Unsuccessful lesions were those that were not confined within these dimensions or those that affected the forelimb representation areas. Subsets of sections stained with Cresyl violet are provided of a minimum and maximum lesion extent (see figure 7A & 7B). Two PPC rats were dropped from the study as Cresyl violet staining failed to reveal a visible lesion. Examination of the histology associated with PPC lesions revealed that all lesions were focused on the MPtA region of the cortex, with three cases showing damage extending minimally into the LPtA region. Specifically, all lesions were observed to extend from approximately -2.80 AP to -4.20 AP and lesions were observed to affect approximately 69% of the Fr2 cortical area when compared to controls (see Table 2).

**Place Learning Measures**

*General Performance Characteristics*

Several measures were used to quantify general performance characteristics associated with place learning or acquisition of the water task. First, latency, or the time that it took rats to reach the hidden escape platform, was calculated for each trial across the five days of place learning. A repeated-measures ANOVA was conducted on latency with group (AGm vs. PPC vs. sham) as a between subjects measure and day (1, 2, 3, 4, and 5) as a within subjects measure. The ANOVA revealed a significant main effect of day \([F(4, 100) = 35.472, p < 0.001, \eta^2_{\text{partial}} = 0.587]\); however, the main effect of group \([F(2, 25) = 0.409, p = 0.668, \eta^2_{\text{partial}} = 0.032]\) and the group x day interaction \([F(8,100) = 1.397, p = 0.207, \eta^2_{\text{partial}} = 0.101]\) were not significant. Linear
Figure 7: Lesion extent of PPC lesions. Cresyl violet stained sections of a maximum (A) and minimum (B) extent are presented for PPC lesions. Two PPC lesion rats were dropped from the study due to lack of a visible lesion after Cresyl violet staining.
Table 2: Percent cortical tissue affected for PPC lesions.

<table>
<thead>
<tr>
<th>Case</th>
<th>-3.24 AP</th>
<th>-3.6 AP</th>
<th>-4.08 AP</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>56.25</td>
<td>97.05882</td>
<td>77.55102</td>
<td>76.95328</td>
</tr>
<tr>
<td>12</td>
<td>62.1364</td>
<td>66.17647</td>
<td>24.4898</td>
<td>50.93422</td>
</tr>
<tr>
<td>15</td>
<td>118.75</td>
<td>55.88235</td>
<td>61.22449</td>
<td>78.61895</td>
</tr>
<tr>
<td>16</td>
<td>59.375</td>
<td>67.64706</td>
<td>46.93878</td>
<td>57.98694</td>
</tr>
<tr>
<td>19</td>
<td>93.75</td>
<td>44.11765</td>
<td>61.22449</td>
<td>66.36405</td>
</tr>
<tr>
<td>21</td>
<td>29.6875</td>
<td>67.64706</td>
<td>52.1564</td>
<td>49.83032</td>
</tr>
<tr>
<td>24</td>
<td>131.25</td>
<td>67.64706</td>
<td>77.55102</td>
<td>92.14936</td>
</tr>
<tr>
<td>30</td>
<td>118.75</td>
<td>101.4706</td>
<td>30.61224</td>
<td>83.61094</td>
</tr>
</tbody>
</table>

**Total Group Percent Affected**  \[69.55601\]

Note. All lesions were focused on the MPtA region of the cortex, with two cases showing damage extending minimally into the LPtA region. Specifically, all lesions were observed to extend from approximately +4.0 AP to -2.16 AP and lesions were observed to affect approximately 69% of the Fr2 cortical area when compared to controls.
trend analysis of groups’ latencies was significant \[ F(1, 25) = 120.317, p < 0.001, \eta^2_{\text{partial}} = 0.828 \], showing that latencies to find the platform decreased across days of acquisition (see Figure 8A). Also, peak speeds, or the maximum speed achieved during a given trial, were recorded for all trials and averaged for each day of place learning. The repeated-measures ANOVA revealed a significant main effect of day \[ F(4, 100) = 20.057, p < 0.001, \eta^2_{\text{partial}} = 0.445 \]; however the main effect of group \[ F(2, 25) = 1.138, p = 0.337, \eta^2_{\text{partial}} = 0.083 \] and the group x day interaction \[ F(8, 100) = 1.330, p = 0.237, \eta^2_{\text{partial}} = 0.096 \] were not significant. Linear trend analysis of groups’ peak speeds was significant \[ F(1, 25) = 59.606, p < 0.001, \eta^2_{\text{partial}} = 0.705 \], showing that peak speeds were observed to decrease across days of acquisition (see Figure 8B). In addition, total distance traveled was calculated across days of place learning. The repeated-measures ANOVA revealed a significant main effect of day \[ F(4, 100) = 35.159, p < 0.001, \eta^2_{\text{partial}} = 0.584 \] and a significant group x day interaction \[ F(8, 100) = 2.069, p = 0.046, \eta^2_{\text{partial}} = 0.142 \]; however, the main effect of group \[ F(2, 25) = 1.117, p = 0.343, \eta^2_{\text{partial}} = 0.082 \] was not significant. AGm lesion rats were observed to travel greater distances across the first and second days of place learning when compared to PPC and sham rats (HSD p < .05). Linear trend analysis of groups’ distance traveled was significant \[ F(1, 25) = 123.803, p < 0.001, \eta^2_{\text{partial}} = 0.832 \], showing that distances traveled decreased across days for all groups (see Figure 8C). Further, path circuity, or the measure of a swim path’s complexity, was calculated for each trial
Figure 8: General performance measures for the place learning component of the Morris water task. Latency (A), peak speed (B), distance traveled (C), path complexity (D), and heading error (E) were observed to decrease across days of place learning, consistent with learning the location of the hidden platform. AGm lesion rats were observed to travel greater distances across the first and second days of place learning when compared to PPC and sham rats.
and averaged for each day of place learning. The repeated measures ANOVA revealed a significant main effect of day \( [F(4, 100) = 16.924, p < 0.001, \eta^2_{\text{partial}} = 0.404] \); however, the main effect of group \( [F(2, 25) = 0.659, p = 0.526, \eta^2_{\text{partial}} = 0.050] \) and the group x day interaction \( [F(8, 100) = 0.848, p = 0.563, \eta^2_{\text{partial}} = 0.064] \) were not significant. Linear trend analysis of groups’ path circuity was significant \( [F(1, 25) = 64.903, p < 0.001, \eta^2_{\text{partial}} = 0.722] \), showing that swim path complexity decreased across days of acquisition (see Figure 8D). Lastly, heading error, or the angle subtended by the location of the escape platform, the animal’s release location, and the location of the animal’s peak speed within that trial, was calculated for each trial across place learning. The repeated measures ANOVA revealed a significant main effect of day \( [F(4, 100) = 4.581, p = 0.002, \eta^2_{\text{partial}} = 0.155] \); however, the main effect of group \( [F(2, 25) = 0.215, p = 0.808, \eta^2_{\text{partial}} = 0.017] \) and the group x day interaction \( [F(8, 100) = 0.608, p = 0.769, \eta^2_{\text{partial}} = 0.046] \) were not significant. Linear trend analysis of groups’ heading error was significant \( [F(1, 25) = 17.047, p < 0.001, \eta^2_{\text{partial}} = 0.405] \), showing heading error decreased across days of acquisition (see Figure 8E).

**Sequential Analysis**

In addition to examining the general characteristics of movement within the water task, a fine-grain analysis of early acquisition swimming behaviors was conducted. Specifically, swim paths from the first two days of acquisition were decomposed into pauses and progressions. Average change in heading between progressions, progression path circuity, and movement scaling were calculated from at least two trials from the first two days of acquisition with 8 or more progressions. First, the one-way ANOVA conducted for progression path circuity failed to reveal a significant main effect of group \( [F(2, 25) = 0.824, p = 0.450, \eta^2_{\text{partial}} = 0.062] \). No
significant differences were observed in average progression path circuity during the first two
days of acquisition between the three groups (see Figure 9A). Next, the one-way ANOVA
carried out for change in heading failed to reveal a significant main effect of group \[F(2, 25) =
1.052, p = 0.364, \eta^2_{\text{partial}} = 0.078\]. No significant differences were observed between groups for
the degree of change in heading between progressions during the probe trial (see figure 9B).
Lastly, the one-way ANOVA conducted for movement scaling failed to reveal a significant main
effect of group \[F(2, 25) = 0.345, p = 0.711, \eta^2_{\text{partial}} = 0.027\]. No significant differences were
observed in each group’s capacity to scale their movement speeds to the distance they traveled
(see figure 9C).

**Probe Day Measures**

*General Performance Characteristics*

Following seven days of place learning, all animals experienced a probe day in which the
hidden escape platform was removed as an assessment of location retention. Brown’s score, and
sequential analysis (change in heading, progression path circuity, and movement scaling) were
calculated from a 60 second probe trial. First, the one-way ANOVA conducted for Brown’s
score failed to reveal a significant main effect of group \[F(2, 25) = 0.119, p = 0.733, \eta^2_{\text{partial}} =
0.005\]. No significant group differences were observed in preference for quadrant containing the
hidden platform (see Figure 10A). Next, the one-way ANOVA conducted for peak speed failed
to reveal a significant main effect of group \[F(2, 25) = 0.403, p = 0.672, \eta^2_{\text{partial}} = 0.031\]. No
significant differences were observed in peak speed during the probe trial between the three
groups (see Figure 10B). Further, the one-way ANOVA conducted for distance traveled failed to
reveal a significant main effect of group \[F(2, 25) = 0.516, p = 0.603, \eta^2_{\text{partial}} = 0.040\]. No
Figure 9: Sequential analysis of swimming behavior for the first two days of place learning. No significant differences were observed between groups for average progression path circuity (A), changes in heading between progressions (B), and movement scaling (C).
Figure 10: General performance measures for the probe trial of the Morris water task. No significant differences were observed for Brown’s score, a measure of preference for the hidden platform’s quadrant location (A). In addition, no significant group differences were observed for general performance measures including peak speed (B), total distance traveled, (C), swim path complexity (D), and degrees of heading error, relative to the former hidden platform location (E).
significant differences were observed between groups for total distance traveled during the probe trial (see Figure 10C).

Also, the one-way ANOVA conducted for path circuity failed to reveal a significant main effect of group \(F(2, 25) = 0.026, p = 0.974, \eta^2_{\text{partial}} = 0.002\]. No significant differences were observed between groups for swim path complexity during the probe trial (see figure 10D). Finally, the one-way ANOVA conducted for heading error failed to reveal a significant main effect of group \(F(2, 25) = 0.033, p = 0.968, \eta^2_{\text{partial}} = 0.003\]. No significant differences were observed between groups for degrees of heading error during the probe trial (see figure 10E).

**Sequential Analysis**

As with the trials from the first two days of place learning, a sequential analysis of probe trial swimming behavior was conducted. First, the one-way ANOVA conducted for progression path circuity failed to reveal a significant main effect of group \(F(2, 25) = 0.824, p = 0.450, \eta^2_{\text{partial}} = 0.062\]. No significant differences were observed in peak speed during the probe trial between the three groups (see Figure 11A). Next, the one-way ANOVA conducted for change in heading failed to reveal a significant main effect of group \(F(2, 25) = 1.052, p = 0.364, \eta^2_{\text{partial}} = 0.078\]. No significant differences were observed between groups for the degree of change in heading between progressions during the probe trial between the three groups (see figure 11B). Lastly, the one-way ANOVA conducted for movement scaling failed to reveal a significant main
Figure 11: Sequential analysis of probe trial swimming behavior. No significant differences were observed between groups for average progression path circuity (A), changes in heading between progressions (B), and movement scaling (C).
effect of group \([F(2, 25) = 0.345, p = 0.711, \eta^2_{\text{partial}} = 0.027]\). No significant differences were observed in each group’s capacity to scale their movement speeds to the distance they traveled (see Figure 11C).

**Matching-to-Place Measures**

Following the probe day, rats experienced three days of matching-to-place in which the location of the hidden escape platform was moved to novel quadrants of the pool. Several repeated-measures ANOVAs were conducted with group (AGm vs. PPC vs. sham) as a between subjects measure and trial (T1, T2) as a within subjects measure. The repeated-measures ANOVA conducted for latency revealed a significant main effect of trial \([F(1, 25) = 45.287, p < 0.001, \eta^2_{\text{partial}} = 0.644]\); however, the main effect of group \([F(2, 25) = 1.181, p = 0.323, \eta^2_{\text{partial}} = 0.086]\), and the group x trial interaction \([F(2, 25) = 1.347, p = 0.278, \eta^2_{\text{partial}} = 0.097]\) were not significant. Latency was observed to decrease from MTP1 to MTP2 trials for all groups (see Figure 12A). Next, the repeated-measures ANOVA for peak speed revealed a significant main effect of trial \([F(1, 25) = 15.818, p = 0.001, \eta^2_{\text{partial}} = 0.388]\); however, the main effect of group \([F(2, 25) = 2.379, p = 0.145, \eta^2_{\text{partial}} = 0.145]\) and the group x trial interaction \([F(2, 25) = 1.041, p = 0.368, \eta^2_{\text{partial}} = 0.077]\) were not significant. Peak speeds were observed to decrease from MTP1 to MTP2 trials for all groups (see Figure 12B). Additionally, the repeated-measures ANOVA conducted for distance traveled revealed a significant main effect of trial \([F(1, 25) = 24.226, p < 0.001, \eta^2_{\text{partial}} = 0.492]\); however, the main effect of group \([F(2,25) = 2.106, p = 0.143, \eta^2_{\text{partial}} = 0.144]\) and the group x trial interaction \([F(2, 25) = 2.023, p = 0.153, \eta^2_{\text{partial}} = 0.139]\) were not significant. Distance traveled was observed to decrease from MTP1 to MTP2 trials for all groups of rats (see Figure 12C). Further, the repeated-measures ANOVA for path
Figure 12: General performance measures for the matching-to-place component of the Morris water task. Latency (A), peak speed (B), distance traveled (C), path complexity (D), and heading error (E) were observed to decrease across matching-to-place trials, consistent with rats learning to update the location of the hidden platform.
circuity revealed a significant main effect of trial \(F(1, 25) = 24.61, p < 0.001, \eta^2_{\text{partial}} = 0.496\); however, the main effect of group \(F(2, 25) = 2.115, p = 0.142, \eta^2_{\text{partial}} = 0.145\), and group x trial interaction \(F(2, 25) = 1.420, p = 0.261, \eta^2_{\text{partial}} = 0.102\) were not significant. Swim paths were observed to become more direct between MTP1 and MTP2 trials across all groups (see Figure 12D). Finally, the repeated-measure ANOVA conducted for heading error revealed a significant main effect of trial \(F(1, 25) = 5.822, p = 0.023, \eta^2_{\text{partial}} = 0.189\); however, the main effect of group \(F(2, 25) = 0.120, p = 0.867, \eta^2_{\text{partial}} = 0.010\) and the group x trial interaction \(F(2, 25) = 1.455, p = 0.253, \eta^2_{\text{partial}} = 0.104\) were not significant. Heading error was observed to decrease between MTP1 and MTP2 trials across all groups (see Figure 12E).

**Discussion of Experiment 1 Results**

Examination of performance in the MWT evaluated the contributions of the AGm and PPC to allocentric spatial processing. Performance in the MWT is dependent on a rat learning where the goal location (or hidden platform) is relative to relationships with extra-maze stimuli present in the room. When performance in the task was examined for rats that received unilateral pial stripping of the left hemisphere AGm or PPC, no disruptions were observed in key performance measures. Specifically, during place learning, all groups of rats displayed decreased latencies to reach the platform across days of place learning, demonstrated increases in swim path directness to the platform, and demonstrated decreases in heading error. The only performance difference observed was a significant interaction for distance traveled. AGm lesion rats were observed to travel significantly longer distances than PPC and sham rats across the first two days of testing; however, this difference was no longer significant following day two. This group difference is consistent with previous work showing that damage to the AGm produces deficits in acquisition,
but not retention for some spatial tasks (Sutherland, 1985). Together, this pattern of performance suggests that all groups were able to learn the location of the hidden platform during place training. Further, all groups were observed to have similar Brown’s scores for quadrant preference during a probe trial. Lastly, all groups exhibited decreases in latency, increases in path directness, and decreases in heading error between MTP1 to MTP2 trials during the matching-to-place portion of the task. Moreover, when swimming behaviors were analyzed via sequential analysis, all groups exhibited similar levels of progression path circuitry and changes in heading between pauses in swimming. Lastly, all groups demonstrated strong correlations in scaling their movement speeds to swim distances. Taken together, these results suggest that unilateral damage of the left hemisphere AGm or PPC was not sufficient to disrupt allocentric processing.

While sparing of task performance following unilateral lesions of the AGm is consistent with previous work showing that unilateral damage spares performance in an allocentric-based cheeseboard task, sparing of performance following unilateral PPC lesions is contrary to the current research hypothesis and is inconsistent with previous work showing that damage to the PPC disrupts performance in allocentric-based spatial tasks. For example, damage to this structure has been shown to produce poorer performance in locating a hidden food item in a cheeseboard task (Kesner, Farnsworth, & DiMattia, 1989; King & Corwin, 1992). Several important considerations will be discussed that address the discrepancy between the current study’s results and those of previous work.

One difference between the current study and previous work is the level of damage observed in the PPC. A majority of the work reporting deficits in allocentric-based spatial tasks
has utilized techniques, like aspiration, that produce coarse, non-specific levels of damage. This approach often produces a lesion that is unselective, damaging other cortical structures, like the visual cortex, or results in damage to white matter, like the fimbria, and even subcortical structures, like the hippocampus (Kesner, Farnsworth, & DiMattia, 1989; King & Corwin, 1992). Disruption of such structures, specifically the fimbria or hippocampus, could have exacerbated the impairments observed in those tasks. Conversely, the pial stripping approach minimizes damage to white matter and subcortical structures. This approach produces a focal lesion that minimizes damage to other surrounding structures. As discussed above, pial stripping of the PPC produced relatively focused damage to areas of the MPtA while minimizing damage to the LPtA. The differences in lesion approach and extent may have contributed to the differences in performance observed in the current study.

Another important difference between the methodology of the current study and that of previous work is the use of unilateral vs. bilateral lesions. Work that has shown impairments in allocentric-based spatial tasks, like the Morris water task or its dry analogue, the cheeseboard task, has observed the most robust effects following bilateral PPC lesions (Kolb & Walkey, 1987; Kesner, Farnsworth, & DiMattia, 1989; King & Corwin, 1992). Despite this trend, performance deficits following bilateral damage to the PPC have produced conflicting results. For example, large bilateral lesions of the associative parietal cortex (encompassing the PPC) were observed to spare performance in a traditional MWT setup; however, parietal damage was observed to impact performance in a version of the task dependent on processing proximal spatial cues (Save & Poucet, 2000). Further, these lesions were not observed to affect preference for the hidden platform quadrant on a probe trial or the ability to locate the hidden platform in novel locations during matching-to-place. Similarly, other work has only found mild
impairments in acquiring the location of the hidden platform (Save & Moghaddam, 1996). In particular, lesion rats demonstrated higher latencies to locate the hidden platform only for the first day of place learning and were observed to exhibit control-level latencies thereafter. Moreover, lateralized disruptions in allocentric task performance were observed for unilateral lesions of the PPC (King & Corwin, 1992). Specifically, performance was observed to be disrupted in rats that received unilateral lesions of the right hemisphere PPC; however, rats that received unilateral PPC lesions of the left hemisphere were observed to demonstrate spared performance. Similar lateralized impairments have been previously observed in the MWT, with disruptions only being observed in right hemisphere lesions; however, these lesions also disrupted the corpus callosum (Maier, Vitols, Novotny, & Crowne, 1990). This pattern of spared performance is consistent with the performance observed in rats with left hemisphere lesions of the PPC in the current study. As such, the results from the experiment one provide further support for a potential lateralization in spatial processing with the PPC. Aside from the previously described work and the current study, little work has examined the hemispheric specialization of the PPC and its contributions to allocentric processing. Future work should seek to replicate the previously described lateralization of function in the PPC through studying the effects of left vs. right unilateral PPC lesions on performance in a variety of allocentric spatial tasks including the MWT and rodent food hoarding under light conditions. While lateralized differences in function may have mediated the current results, it is also possible that allocentric processing is not dependent on cortical structures, but subcortical structures.

The spared performance observed in the MWT suggests that these cortical structures do not contribute to allocentric processing. Despite the PPC (and to a lesser extent, the AGm) being implicated in allocentric spatial processing, it may be the case that performance in the Morris
water task is dependent on the integrity of other neural structures like the entorhinal cortex, fimbria fornix, medial septum, or hippocampus. For example, anatomical work has shown that the PPC has connections with the medial entorhinal cortex (Burwell and Amaral, 1998). Other work has shown that lesions of these structures impair performance on acquisition and retention in the Morris water task (Morris, Garrud, Rawlins, & O’Keefe, 1982; Hunt, Kesner, & Evans, 1994; Nagahara, Otto, Gallagher, 1995; de Bruin, Moita, de Bradander, & Ruud, 2001). The spared performance across each component of the MWT suggests that the AGm and PPC do not contribute to allocentric processing, but may serve to facilitate acquisition of a spatial strategy, wherein the retention of that spatial information may be mediated by subcortical structures like the hippocampus or entorhinal cortex. Future work is needed to characterize the connections between the AGm and PPC to limbic system structures to better understand the contributions of these cortical structures to allocentric processing. Alternatively, these cortical structures could facilitate the processing of self-movement cue processing. One approach to examining this contribution has been to examine the effects of unilateral damage to the AGm and PPC to the organization of exploratory behavior under dark conditions.
CHAPTER 3
EXPERIMENT 2

Methods – Dark Exploration

Subjects

The same subjects from experiment one were used for experiment two. For reference, a total of 30 female Long-Evans rats (AGm: n = 10, PPC: n = 10, sham: n = 10) obtained from the Northern Illinois University rodent colony served as subjects for the second experiment.

Apparatus

The exploration apparatus consisted of a circular tabletop (2.50 m in diameter) without walls, mounted on a table with ball bearings that permitted it to be rotated between trials. The surface of the table was 0.64 m above the floor. Between each trial, the table was cleaned and rotated in an attempt to displace odor cues. A night vision camera was positioned above the exploration table for recording each rat’s movements. The experimenter used night vision goggles to place rats on the exploration table under dark conditions.

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. All rats were given 40 minutes to explore the table. Rats were tested under dark conditions for two days.

**Data Analysis**

The EthoVision (NOLDUS, Leesburg, VA, USA) motion tracking system was used to quantify exploratory characteristics of rats during four 5-minute consecutive samples throughout the 40-min dark exploratory sessions. The first sample was taken immediately after the first bout of grooming behavior (this usually occurs within 2-5 min of a session; Blankenship, Cherep, Donaldson, Brockman, Trainer, Yoder, & Wallace, 2017). Movement during each sample was broken down into progressions (moment-to-moment speeds of 3.0 cm/sec or greater for at least two frames) and stops (moment-to-moment speeds less 3.0 cm/sec for at least two frames).

Multiple measures were used to characterize group differences in the organization of exploratory behavior. First, general measures of locomotor function were analyzed. These measures included the total distance traveled and total time spent stopping. Next, several measures were used to characterize exploratory progressions. Progression peak speed and distance traveled were analyzed as additional locomotor measures. For these measures, each was calculated for all progressions and averaged for each sample. In addition, the path circuitry of each progression was calculated and averaged for each sample. Lastly, several measures were used to characterize stopping behavior. First, the average stop duration was calculated for each sample. Second, changes in path heading (which typically occur during stops between two progressions) were quantified for each stop and averaged for each sample. Changes in heading involved calculating the angle subtended by the: 1) preceding progression peak speed location, 2)
average stop location, and 3) subsequent progression peak speed location. Finally, a parameter of concentration was calculated to examine the distribution of stopping behavior in the environment. To quantify this measure, Cartesian coordinates (x, y) associated with each stop were converted into polar coordinates (theta, r), and circular statistics were used to characterize the concentration and stability of stops across samples. With the polar coordinates, the duration of each stop was converted into an individual observation at a specific heading (i.e., one second will be equal to one observation). First-order circular statistics (parameter of concentration and average heading) were calculated for all stops for each sample from an individual rat, resulting in a parameter of stop concentrations which were used as a measure of stop density for each sample (Batschelet, 1981). Subsequently, second-order circular statistics were applied to the average heading from each sample, with the resulting parameter of concentration used as a measure of stop stability across samples (Batschelet, 1981).

Repeated measures ANOVAs were used to evaluate main effects of group, day, and group by day interactions for all intended measures. One-way ANOVAs were used to assess group differences on parameters of concentration calculated from average heading across all four samples. All analyses were run with alpha set at 0.05.

**Results – Spontaneous Exploration**

**General Measures of Locomotor Function**

Two measures were used to assess locomotor functioning in the task. First, total distance traveled was calculated across each rat’s 20-minute exploration session. A repeated-measures ANOVA was conducted for total distance traveled with group (AGm vs. PPC vs. sham) as a between-subjects variable and sample (1, 2, 3, & 4) as a within-subjects variable. Lack of
sphericity for total distance traveled across samples resulted in the application of a Greenhouse-Geisser correction (ε = 0.649). The repeated-measures ANOVA revealed a significant main effect of sample [F(1.946, 46.707) = 105.225, p < 0.001, η² partial = 0.814]; however, the main effect of group [F(2, 24) = 0.111, p = 0.895, η² partial = 0.009] and the group x sample interaction [F(3.892, 46.707) = 2.513, p = 0.056, η² partial = 0.179] were not significant. Linear trend analysis of groups’ distance traveled was significant [F(1, 24) = 131.631, p < 0.001, η² partial = 0.846], showing that total distances traveled significantly decreased across samples for all groups (see Figure 13A). In addition, peak speeds were recorded across each sample during the exploratory session. Lack of sphericity in peak speeds across samples resulted in the application of a Greenhouse-Geisser correction (ε = 0.635). The repeated measures ANOVA revealed a significant main effect of sample [F(1.904, 45.698) = 15.209, p < 0.001, η² partial = 0.388]; however, the main effect of group [F(2, 24) = 0.309, p = 0.737, η² partial = 0.025] and the group x sample interaction [F(3.808, 45.698) = 0.171, p = 0.947, η² partial = 0.014] were not significant. Linear trend analysis of groups’ distance traveled was significant [F(1, 24) = 21.822, p < 0.001, η² partial = 0.476], showing that peak speeds significantly decreased across samples for all groups (see Figure 13B).

Sequential Analysis

Progressions

Several measures were used to characterize exploratory progressions. First, average progression path circuitry was calculated for all progressions and averaged for each sample. A repeated-measures ANOVA for path circuitry was conducted with group (AGm vs. PPC vs. sham) as a between-subjects variable and sample (1, 2, 3, & 4) as a within-subjects variable.
Figure 13: Measures of locomotor functioning. Total distance traveled (A) and peak speeds (B) are plotted across four 5-minute samples taken from a 20-minute exploration session. No significant group differences were observed for either measure; however, distance traveled and peak speeds were observed to decrease across samples.
Lack of sphericity in peak speeds across samples resulted in the application of a Greenhouse-Geisser correction ($\varepsilon = 0.762$). The ANOVA failed to reveal a significant main effect of sample $[F(2.287, 54.891) = 2.304, p = 0.084, \eta^2_{\text{partial}} = 0.088]$, group $[F(2, 24) = 0.244, p = 0.785, \eta^2_{\text{partial}} = 0.020]$, or group x sample interaction $[F(4.574, 54.891) = 0.977, p = 0.447, \eta^2_{\text{partial}} = 0.075]$ were not significant. Overall, when exploratory behaviors were segmented into individual progressions, distance ratios associated with progression path circuity were very direct (see Figure 14A). In addition, movement scaling, or the correlation between progression distance and its corresponding peak in speed, was calculated for each sample. The repeated-measures ANOVA for movement scaling revealed a significant main effect of sample $[F(3, 72) = 5.576, p = 0.002, \eta^2_{\text{partial}} = 0.189]$, however the main effect of group $[F(3, 72) = 0.616, p = 0.548, \eta^2_{\text{partial}} = 0.049]$ and the group x sample interaction $[F(6, 72) = 1.521, p = 0.184, \eta^2_{\text{partial}} = 0.113]$ were not significant. Linear trend analysis of groups’ movement scaling correlation was significant $[F(1, 24) = 6.849, p = 0.015, \eta^2_{\text{partial}} = 0.222]$, showing that movement scaling significantly decreased across samples across all groups (see Figure 14B).

**Stops**

Several measures were used to characterize stopping behavior. First, the total time spent stopped was calculated for each group across samples. A repeated-measures ANOVA for average stop duration was conducted with group (AGm vs. PPC vs. sham) as a between-subjects variable and sample (1, 2, 3, & 4) as a within-subjects variable. Lack of sphericity in peak speeds across samples resulted in the application of a Greenhouse-Geisser correction ($\varepsilon = 0.628$). The repeated-measures ANOVA revealed a significant main effect of sample $[F(1.883, 45.199) = 41.259, p < 0.001, \eta^2_{\text{partial}} = 0.632]$; however, the main effect of group $[F(2, 24) = 0.363,$
Figure 14: Sequential analysis of progressions. Progression path circuity (A) and movement scaling (B) are plotted across four, five-minute samples taken from a 20 minute exploration session. No significant group or sample differences were observed for progression path circuity with paths being very direct through the exploration session for all groups. Movement scaling, or the correlation between progression distance traveled and peak speeds, was observed to significantly decrease across samples; however no significant group differences were observed.
p = 0.699, η²_partial = 0.029], and group x sample interaction [F(3.767, 45.199) = 0.265, p = 0.265, η²_partial = 0.022] were not significant. Linear trend analysis of groups’ total stop time was significant [F(1, 24) = 124.523, p < 0.001, η²_partial = 0.838], showing that total time spent stopped significantly increased across samples for all groups (see Figure 15A). Next, the average time for stops was calculated for each group across samples. Lack of sphericity in average stop times across samples resulted in the application of a Greenhouse-Geisser correction (ε = 0.380). The repeated-measures ANOVA revealed a significant main effect of sample [F(1.139, 27.347) = 7.161, p = 0.010, η²_partial = 0.230]; however, the main effect of group [F(2, 24) = 0.093, p = 0.911, η²_partial = 0.008], and the group x sample interaction [F(2.279, 27.347) = 0.319, p = 0.757, η²_partial = 0.026] were not significant. Linear trend analysis of groups’ average stop durations was significant [F(1, 24) = 11.324, p = 0.003, η²_partial = 0.321], showing that the average duration of a stop significantly increased across samples for all groups (see Figure 15B). In addition to examining stop durations, average angular changes in path heading between two progressions were calculated at each stop. The repeated-measures ANOVA for change in heading revealed a significant main effect of sample [F(3,72) = 9.567, p < 0.001, η²_partial = 0.285], group [F(2, 24) = 4.937, p = 0.016, η²_partial = 0.291]; however, the group x sample interaction [F(6,72) = 1.731, p = 0.126, η²_partial = 0.126] was not significant. Linear trend analysis of groups’ change in heading was significant [F(1, 24) =22.248, p < 0.001, η²_partial = 0.481], showing that changes in heading between progressions significantly decreased across samples. In addition, post hoc analysis revealed that although average angular change in heading decreased across samples, AGm lesion rats were observed to exhibit significantly larger changes in heading when compared to sham and PPC lesion rats (HSD p < .05; see Figure 15C). Further, a parameter of concentration was calculated to examine the distribution of stopping behavior in the environment. First-order
Figure 15: Sequential analysis of stopping behavior. Stops were observed to increase across samples as illustrated by increases in stopping behavior (A) and average stop duration (B). Changes in heading were observed to decrease across samples; however, AGm lesion rats were observed to exhibit significantly higher changes in heading than sham or PPC lesion rats (C). No significant differences were observed in parameters of stop concentrations within (D) and between (E) samples.
circular statistics (1\textsuperscript{st} r; parameter of concentration and average heading) were calculated for all stops within each sample. The repeated-measures ANOVA for first order parameter of stop concentrations revealed a significant main effect of sample \([F(3,72) = 5.704, p = 0.001, \eta^2_{\text{partial}} = 0.192]\); however the main effect of group \([F(2, 24) = 0.248, p = 0.783, \eta^2_{\text{partial}} = 0.020]\) and the group x sample interaction \([F(6,72) = 1.316, p = 0.261, \eta^2_{\text{partial}} = 0.099]\) were not significant. Linear trend analysis of groups’ concentrations of stops within samples was significant \([F(1, 24) = 8.563, p = 0.007, \eta^2_{\text{partial}} = 0.263]\), showing that the strength of stop concentrations significantly increased across samples for all groups (see Figure 15D). Lastly, second-order circular statistics were applied to the average heading from each sample, with the resulting parameter of concentration serving as a measure of stop stability across samples. The one-way ANOVA for second order parameter of stop concentrations failed to reveal a significant main effect of group \([F(2,25) = 0.481, p = 0.624, \eta^2_{\text{partial}} = 0.037]\). No significant group differences were observed in the concentrations of stops across samples of exploration (see Figure 15E).

**Discussion of Experiment 2 Results**

Examining the organization of exploratory behaviors under dark conditions served as an assessment of self-movement cue processing. After applying a sequential analysis, segmenting exploratory behavior into stops and progressions, all groups demonstrated similar patterns of movement. Specifically, all groups traveled similar distances during the exploration session, exhibited similar peaks in movement speed, and displayed relatively direct progressions. Moreover, all groups displayed similar patterns in home base establishment, having demonstrated consistent concentrations of stopping behavior within each sample of exploration. Lastly, all groups were observed to maintain stable home base locations as stop cluster
concentrations were located in the same relative direction across all four exploration samples. One exception to these results is that unilateral AGm damage was observed to produce significantly higher changes in heading between stops; however, this difference may reflect disruptions in egocentric processing rather than self-movement cue processing, which will be discussed later. Together, these data suggest that unilateral lesions of the left hemisphere AGm or PPC did not disrupt the organization of exploratory behavior. These results will be considered relative to previous work examining contributions of cortical structures to self-movement cue processing.

The observation that unilateral AGm damage produced increased changes in heading between stops is consistent with previous work demonstrating that the mPFC contributes indirectly to the organization of individual exploratory trips (Blankenship et al., 2016). This work involved taking the first five exploratory trips and analyzing them individually, whereas the analysis for the current study examined all behaviors sequentially. When trips were individually analyzed, lesions of the mPFC produced significantly larger homeward segment heading errors relative to control rats. These impairments were not specific to lighting condition, being observed under light and dark conditions, suggesting that this structure does not directly contribute to self-movement cue processing. Although this study employed bilateral lesions, these data suggest that the AGm (a subcomponent of the mPFC) may play an indirect role in coordinating movement and direction estimation, which may be related to egocentric processing. Relatively little work has directly examined the role of the AGm in self-movement cue processing. Further work is needed to determine whether the increases changes in heading under dark conditions were due to egocentric processing impairments or disruptions of self-movement
cue processing. While damage to the AGm was observed to minimally influence the organization of exploratory behavior, damage to the PPC was observed to spare this organization.

Despite being implicated in self-movement cue processing, unilateral damage to the left hemisphere PPC was not sufficient to disrupt the organization of exploratory behaviors. These results are inconsistent with previous work showing that damage to the PPC disrupts performance in self-movement cue-based spatial tasks. This work has demonstrated that damage to the PPC disrupts performance during a food hoarding task under dark conditions. In particular, PPC damage affected a rat’s ability to make accurate return trips back to their home base (Save, Guazzelli, & Poucet, 2001; Parron & Save, 2004). Two important distinctions between the current study and previous work may account for these differences.

One important distinction between the current study and previous work is the use of unilateral vs. bilateral lesions. In particular, the current study utilized unilateral pial stripping of the PPC, whereas previous work that has shown performance deficits in dead reckoning tasks has used bilateral aspiration lesions of the PPC. As discussed above, differential patterns of behavioral disruptions have been observed following unilateral vs. bilateral damage to the parietal cortex (King & Corwin, 1992). It may be the case that unilateral damage to the PPC is not sufficient to produce visible impairments in performance on dead reckoning tasks when compared to bilateral lesions of this structure. It may be that the intact hemisphere is able to compensate for the impaired hemisphere, allowing for mostly successful self-movement cue processing. As this is the first study to directly examine the effects of unilateral PPC damage on self-movement cue processing, future work is needed to further understand the consequences of unilateral vs. bilateral lesions of the PPC on dead reckoning. In addition to comparing the effects
of unilateral vs. bilateral lesions, the results of the current study could have been mediated by differences in behavioral task demands.

Limited work has examined the contributions of the parietal cortex to self-movement cue processing. A majority of this work has used adaptations of the previously described food hoarding task to examine such processing. While several variations of this task exist, performance in the task involves examining the accuracy of food foraging return trips to an established home base. When lighting conditions are manipulated such that environmental cues are restricted under completely dark conditions, it is believed that performance is dependent on the processing of self-movement cues. Previous work has shown that damage to the parietal cortex disrupts the accuracy of return trips under such conditions (Save, Guazzelli, & Poucet, 2001; Parron & Save, 2004). It is important to note, however, that in these studies, rats were not run under completely dark conditions. Rather, the apparatus was surrounded by an opaque curtain and the room was semi-lit. This difference may have actually recruited other types of spatial processing, like allocentric processing, which has been shown to be disrupted following damage to the PPC. Regardless, it may be the case that potential motivational differences between the tasks (e.g. foraging for food during food hoarding may require more motivation than what is required to facilitate exploration of an environment) could have accounted for the different pattern of results obtained. As of yet, no work has directly examined the effects of unilateral PPC damage on food hoarding performance. Future work should seek to use the food hoarding task under completely dark conditions to examine the effects of left vs. right unilateral PPC damage to self-movement cue processing. Aside from these two methodological distinctions, it appears that unilateral damage to the AGm and PPC spares the ability to process self-movement cues.
Given the extensive connections between the AGm and PPC and the current results suggesting that the AGm produces selective disruptions in egocentric processing, it may be the case that the PPC plays a similar role. Therefore, these structures may not contribute to self-movement cue processing; rather, these results suggest that the AGm and PPC (and the proposed neural network they are a part of) may engage in the parallel processing of contextual information (like establishing a frame of reference) that indirectly contribute to the use of differing spatial strategies, like dead reckoning. As such, the disruptions observed may reflect disruptions in egocentric processing (which is thought to be one component of processing self-movement cues) or could potentially reflect a disruption in temporal processing (which could alter the moment-to-moment processing of self-movement cue information). To evaluate the contributions of these structures to egocentric and temporal processing, rats were run in the food protection task, which possesses the capacity to dissociate between egocentric spatial processing and temporal processing within the interval timing range.
CHAPTER 4

EXPERIMENT 3

Methods – Food Protection

Subjects

The same subjects from experiments one and two were used for the last experiment. For this task, seven naïve female rats were included as robbers, resulting in a total of 37 female Long-Evans rats (AGm: n = 10, PPC: n = 10, sham: n = 10, & robbers n = 7). Rats were pair housed in plastic cages with the colony room temperature being maintained at 21 +/- 2 degrees Celsius. Rats were held on a 12 h light/dark cycle and with free access to water, but food was restricted during food protection to maintain an 85% free-feeding body weight.

Apparatus

The food protection apparatus consisted of a transparent Plexiglas cylinder (45 cm high and 44 cm in diameter). The cylinder was located atop a table with a transparent top. A mirror was located beneath the transparent tabletop and positioned at an angle such that the rats were be filmed from below (Martin et al., 2008; Pinel et al., 1992).
Procedure

Two weeks post-surgery, rats were habituated to food items in their home cages. Following exploration testing, all rats were food restricted for approximately 7 days or until they were 85% of their normal free-feeding weight. During this time, all rats were habituated to banana-flavored sucrose pellets (1g) to prepare them for food protection. Once rats were adequately food restricted to 85% of their free-feeding weight, all rats experienced three days of habituation within the food protection apparatus. Each day of habituation consisted of a 20-minute session where rats were allowed to explore the apparatus alone and were fed food items via tongs. Rats were recorded eating a food item on the final day of habituation. Following the third habituation day, rats began testing. Testing consisted of a once-daily session in which three trials were recorded. The first two trials consisted of the dodger receiving a food item via tongs in the presence of a conspecific (randomized across days). If the conspecific succeeded in stealing the food item from the dodger, the conspecific was removed from the cylinder, the pellet removed from the conspecific and given back to the dodger, then the conspecific was placed back in the cylinder. A trial was considered to have ended upon complete consumption of the pellet by the dodger. The third trial of the session consisted of the dodger being recorded eating a food item in the cylinder without the presence of a conspecific. Testing continued for five days.

Data Analysis

For each food protection session, the total time it took a dodger to eat the food item was calculated and then divided by five to result in five equal time samples. Each behavior (dodge, brace, and theft) was recorded during each food protection trial. For each behavior, the side of approach and the distance between the dodger and robber’s noses was recorded. The distance
between the noses was calculated using a series of concentric circles. The width of each concentric circle is approximately .33 cm with a distance of 0 for the central circle. When determining distances, the central circle was placed on the dodger’s nose and the distance between the dodger and robber was determined by the number of rings between to the two noses (see Figure 16).

Repeated-measures ANOVAs were used to evaluate main effects of group, day, and group by day interactions for all intended measures. All analyses were run with alpha set at 0.05.

**Results**

**Motoric and Motivational Factors**

In order to determine whether lesions produced disruptions in gross locomotor or motivational factors, several measures were used. First, all rats’ first day of habituation to the apparatus served as an open field session. The Noldus motion tracking system was used to analyze total distance traveled and average speed for each open field session. The one-way ANOVA conducted for total distance traveled failed to reveal a significant group difference \([F(2,25) = 0.860, p = 0.435, \eta^2_{\text{partial}} = 0.064]\). No significant group differences were observed in the total distance traveled during the open field session (see Figure 17A). Further, the one-way ANOVA conducted for average peak speed also failed to reveal a significant group difference \([F(2,25) = 0.257, p = 0.776, \eta^2_{\text{partial}} = 0.020]\). No significant group difference was observed in peak speeds for the open field session (see Figure 17B). In addition to open field measures, the time to consume the food item in the absence of the conspecific was used as a measure of motivation to eat the food item. The one-way ANOVA conducted for average time to eat failed to reveal a significant effect of
Figure 16: Concentric circles used to measure the distance between noses of the dodger and robber. The width of each concentric circle is approximately 0.5cms with a distance of 0 for the central circle. When determining distances, the central circle will be placed on the dodger’s nose and the distance between the dodger and robber will be determined by the number of rings between to the two noses.
Figure 17: Motoric and motivational factors of food protection. No significant group differences were observed for total distance traveled (A) or peak speed (B), suggesting that AGm and PPC lesions did not affect locomotor processing required to protect a food item. In addition, the lack of significant group differences for the time to consume the food item in the absence of the robber (C) and total number of behaviors elicited (D) suggest that all groups, including robbers, were sufficiently motivated to consume the food item.
group \( F(2, 25) = 0.617, p = 0.548, \eta^2_{\text{partial}} = 0.047 \). No significant group differences were observed, suggesting that all groups were equally motivated to consume the food item (see Figure 17C). Lastly, the total number of food protection behaviors elicited was used as a measure of robber motivation to approach the dodgers. The one-way ANOVA conducted for total number of food protection behaviors failed to reveal a significant effect of group \( F(2, 25) = 0.841, p = 0.443, \eta^2_{\text{partial}} = 0.063 \). No significant group differences were observed, suggesting that the robbers were equally motivated to approach a dodger to attempt to steal the food item (see Figure 17D).

**Spatial Characteristics of Food Protection**

Several measures were used to examine egocentric spatial processing and the ability to protect a food item from theft. First, the distance between the noses of the dodger and robber, analyzed relative to the robber’s side of approach were examined. The repeated measures ANOVA for distance between dodger and robber noses by side of robber approach revealed a significant effect of side \( F(1, 25) = 13.471, p = 0.001, \eta^2_{\text{partial}} = 0.350 \); however, the main effect of group \( F(2, 25) = 1.126, p = 0.882, \eta^2_{\text{partial}} = 0.010 \) and side x group interaction \( F(2, 25) = 0.078, p = 0.926, \eta^2_{\text{partial}} = 0.006 \) were not significant. All groups were observed to let the robber get closer when it approached the dodger on the right side (see Figure 18A). The presence of a lateralized bias in responding in the sham group is inconsistent with previous work examining food protection in control rats (Blankenship, Cheatwood, & Wallace, 2016). To further investigate this response bias, asymmetry scores were examined. Asymmetry scores were calculated by subtracting the average distance between noses for the impaired (right) side from the intact (left) side. The one-way ANOVA for asymmetry scores failed to reveal a significant
Figure 18: Spatial characteristics of food protection. Robbers were observed to get closer to all dodgers when they approached on the right side when compared to approaches on the left (A). When these distances were converted into an asymmetry scores, all groups demonstrated a below 50% and the proportion of behaviors that were braces increased above 50%. The average sample consistent bias toward responding on the right side (B). Further, no significant differences were observed when numbers of thefts by robber’s side of approach were examined (C).
group effect \[ F(2,25) = 0.078, \ p = 0.926, \ \eta^2_{\text{partial}} = 0.006 \]. All groups had negative asymmetry scores, suggesting a shorter distance between noses when the dodger was approached on the impaired or right side, consistent with the significant effect of side discussed previously (see Figure 18B). One rat in the sham group possessed a score that was beyond two standard deviations from the group mean. This outlier was removed and a paired samples t-test was run for the sham group regarding the distance between noses for left and right approaches. The paired samples t-test was no longer significant after the removal of this outlier case \( t(8) = 2.028, \ p = 0.077, \ d = 0.526 \). Although removing this case abolished the significant difference between noses by approach for shams, the repeated measures ANOVA for distance between noses, rerun with the outlier sham rat excluded, still produced a significant main effect of side \( F(1,24) = 10.906, \ p = 0.003, \ \eta^2_{\text{partial}} = 0.312 \) while not observing a significant main effect of group \( F(2,24) = 0.020, \ p = 0.980, \ \eta^2_{\text{partial}} = 0.002 \) or a significant side x group interaction \( F(2,24) = 0.307, \ p = 0.738, \ \eta^2_{\text{partial}} = 0.025 \). These results suggest that groups were observed to let the robber get closer when it approached the dodger on the right side, independent of group membership. Lastly, the number of thefts, based on the robber’s side of approach, were recorded. The repeated measures ANOVA for thefts by robber’s side of approach failed to reveal a significant effect of side \( F(1,25) = 2.909, \ p = 0.101, \ \eta^2_{\text{partial}} = 0.104 \), group \( F(2,25) = 1.085, \ p = 0.353, \ \eta^2_{\text{partial}} = 0.080 \), and side x group interaction \( F(2,25) = 0.167, \ p = 0.167, \ \eta^2_{\text{partial}} = 0.013 \). No significant group differences were observed in the ability to protect the food item from theft, regardless of the robber’s side of approach (see Figure 18C).
In addition to examining the spatial characteristics of food protection and the ability to protect the food item, the organization of food protection behaviors was examined as an assessment of temporal processing within the seconds to minutes range or interval timing. Specifically, the proportion of each behavior was recorded and averaged for each sample across days to determine which sample behavioral transitions occurred. Specifically, a behavioral transition was considered to have occurred when the proportion of total behaviors that were dodges decreased that this occurred in was recorded for each rat (see Figure 19A-C). Levene’s test indicated unequal error variances \( F = 5.605, p = 0.010 \) so a Brown-Forsythe test of equality (0.143) was used to adjust degrees of freedom from 25 to 19.077. The one-way ANOVA for behavioral transitions failed to reveal a significant group effect \( F(2, 19.077) = 0.060, p = 0.942, \eta^2_{\text{partial}} = 0.005 \). All groups were observed to transition between dodges and braces around the third sample of a given food protection trial (see Figure 19D).

**Discussion of Experiment 3 Results**

Examination of the organization of food protection evaluated the contributions of the AGm and PPC to egocentric spatial and temporal processes. This is possible because the ability to protect the food item is dependent on a dodger attending to an incoming conspecific and subsequently, eliciting an appropriate behavioral response (like dodging or bracing) that protects the food item from theft. It is believed that the capacity to protect the food item is dependent on egocentric spatial processing (Blankenship, Cheatwood, & Wallace, 2017). Further, the organization of food protection behaviors has been shown to be dependent on temporal processing related to a rat’s estimate of time to consume their food item (Whishaw & Gorny, 1994). Therefore, the food protection task offers the possibility to dissociate between spatial and
Figure 19: Temporal characteristics of food protection. The organization of dodging and bracing behavior is plotted for AGm (A), PPC (B), and Sham (C) rats across five equal time samples. When behavioral transitions were examined, all groups were observed to transition from dodges to braces around the third sample of a given food protection trial (D).
temporal processing. The following subsections will consider the results of the current study, related to spatial and temporal characteristics of food protection, or their relation to egocentric spatial processing and interval timing.

Examination of egocentric processing in the food protection task focused on the dodger’s ability to attend to and protect a food item from an approaching conspecific. One measure that evaluated the dodger’s ability to attend to the robber included measuring distance between noses. As previous work has shown that unilateral damage to the AGm or PPC produces lateralized disruptions in attending to multimodal stimuli, it was anticipated that unilateral lesions of the AGm or PPC would produce lateralized disruptions in attending to a robber’s approach on the contralesional (right) side. When the distance between the noses was examined, there was a significant effect of side with all three groups (AGm, PPC, and sham) demonstrating significantly closer distances between noses when the robber approached the dodger on the right side when compared to approaches on the left; however, this trend in the sham group was attenuated with the removal of a group outlier. The absence of a significant interaction, however, limits the ability to argue that unilateral damage to the AGm or PPC produced a lateralized difference in distance between dodger and robber noses. In addition to examining the average distance between dodger and robber noses, the number of robber thefts by side of approach was examined. No significant differences were observed for number of thefts between groups or by side of approach. All three groups were equally likely to protect the food item from an incoming conspecific regardless of the robber’s side of approach. Taken together, these data suggest that unilateral damage to the AGm or PPC did not disrupt the spatial characteristics of food protection. This finding is inconsistent with what has previously been observed following unilateral damage to the DCS (Blankenship, Cheatwood, & Wallace, 2017). Specifically,
unilateral DCS damage was observed to produce a lateraled impairment in the ability to protect a food item from theft when the robber approached on the contralesional side. This difference may reflect one of two possibilities. First is that cortical (AGm and PPC) and subcortical (DCS) structures differentially contribute to mediating behavior related to protecting the food item from theft. It may be that the AGm and PPC serve to integrate multimodal sensory stimuli and do not directly contribute to spatial or temporal processing. Conversely, the DCS is a convergence zone that receives input from several structures, including integrating cortical information from the AGm and PPC. This interpretation is consistent with previous work demonstrating that unilateral lesions of the AGm or PPC produce disruptions in attending to multimodal stimuli presented to the contralesional side of the body that is associated with hemispatial neglect (Corwin et al., 1986; Crowne & Pathria, 1982; King & Corwin, 1990; King & Corwin, 1993; Burcham et al., 1997; VanVleet et al., 2000; 2003). Alternatively, these differences could suggest that unilateral damage to these structures is not sufficient to disrupt spatial and temporal processing and that the intact hemisphere or the integrity of the DCS was able to compensate for the damage produced. Previous work has shown that the integrity of the DCS is critical for mediating or facilitating spontaneous recovery following unilateral damage to the AGm (VanVleet et al., 2000; 2003). This explanation is more likely than the possibility that the AGm or PPC do not contribute to spatial and temporal processing given the extensive evidence implicating these structures in such processing; however, future work is needed to determine the extent to which compensation is possible following unilateral lesions of the AGm or PPC to better characterize the contributions of these structures to the spatial characteristics of food protection. In addition to examining the spatial characteristics of food protection, the current study also examined the effects of unilateral AGm or PPC damage on the temporal characteristics of food protection.
Temporal processing was assessed through examining the organization of food protection behaviors. The likelihood of engaging in a dodge vs. a brace is dependent on a dodger’s estimate of time to consume their food item (Whishaw & Gorny, 1994). Previous work has shown that intact, naïve rats tend to transition from dodges to braces around the third sample (midpoint) of a given trial and shifts in the location of behavioral transitions are associated with changes in a rat’s subjective passage of time (Wallace, Wallace, Field, & Whishaw, 2006; Blankenship, Cheatwood, & Wallace, 2017). When the organization of food protection behaviors was examined, no significant group differences were observed. All groups were observed to transition from dodging to bracing around the third sample of a given trial. While no differences were observed in behavioral transitions, it may be that damage to the AGm or PPC produced increases in the variability of behavioral transition locations and that the current measure is not sensitive enough to detect it. Further work is needed to characterize this potential variability in transitioning. Taken together, this pattern of results suggests that unilateral lesions of the AGm or PPC are not sufficient to disrupt the organization of food protection behaviors. This sparing suggests that these structures do not contribute to temporal processing associated with the interval timing range. It may be the case that these results are due to hemispheric differences in temporal processing or that compensation is occurring in the intact hemisphere.

Limited work has attempted to dissociate the contributions of the left vs. right hemisphere AGm and PPC to temporal processing. Of this work, results suggest that there may be some degree of hemispheric specialization. This work has shown that disruptions or damage to the right hemisphere frontal or parietal cortices produces significant impairments in temporal processing tasks. For example, examination of this relationship in humans noted that impaired timing was observed in patients with right hemisphere damage to prefrontal, premotor, and
parietal cortices, whereas patients with left hemisphere damage to these structures was observed to spare this processing (Harrington, Haaland, & Knight, 1998). More recent work has provided support for this argument. Repeated transcranial direct current stimulation (tDCS) of either the left or right PPC was observed to produce differential influence performance on a temporal reproduction task. Repeated tDCS of the right PPC produced deficits in temporal accuracy, resulting in participants overestimating temporal intervals, whereas tDCS of left PPC decreased the variability in responding to different temporal intervals (Vicario, Martino, & Koch, 2013). Aside from these two human studies, no rodent work has attempted to examine the effects of left vs. right hemispheric damage of the AGm or PPC to temporal processing. As such, future work should seek to examine how damage to the right hemisphere AGm or PPC influences the organization of food protection behaviors. Relatedly, it is also important to consider the consequences of employing unilateral vs. bilateral damage to examine temporal processing.

As discussed, very little work has examined the effects of unilateral damage to the AGm or PPC to temporal processing. Conversely, a majority of the work examining the effects of cortical damage to temporal processing in rodents has used a bilateral approach. As of yet, no work has examined the effects of bilateral lesions of the AGm or PPC to temporal processing, rather most of this work has employed coarse lesions of large cortical areas like the mPFC. In many cases, bilateral inactivations or damage to the mPFC produced significant shifts in responding during interval timing tasks (Meck et al., 1987; Dietrich et al., 1997; Broersen & Uylings, 1999; Risterucci et al., 2003; Narayanan, Horst, & Laubach, 2006; Smith, Horst, Liu, Caetano, & Laubach, 2010). These studies suggest that maintaining an accurate awareness of the passage of time requires bilateral activation of the frontal (and potentially parietal) cortex. Future work is
needed to examine the effects of bilateral damage to the AGm and PPC to performance in interval timing tasks and the organization of food protection behaviors.
CHAPTER 5

GENERAL DISCUSSION

The current series of experiments examined the contributions of the medial agranular cortex (AGm) and posterior parietal cortex (PPC) to allocentric and egocentric spatial processing as well as interval timing. Specifically, the current study examined the effects of unilateral pial strip lesions of the left hemisphere AGm and PPC on performance in the Morris water task (MWT), the organization of exploratory behaviors under dark conditions, and food protection behavior. Overall, unilateral damage to the left hemisphere AGm or PPC was not observed to disrupt aspects of spatial or temporal processing. Despite spared performance across tasks, several selective disruptions in performance were observed. Specifically, unilateral damage to the AGm was associated with significantly more distance traveled across the first two days of place learning in the MWT and significantly higher changes in heading during dark exploration. Neither lesion was observed to influence the ability to learn the location of the hidden platform, protect a food item from theft, or impact the organization of food protection behaviors. Taken together, the results from these three studies suggest that, unilaterally, that these structures do not contribute to spatial and temporal processing. While this may be the case, the following sections will consider evidence that supports a role for the AGm and PPC in spatial and temporal processing and discuss whether the spared performance observed in the current studies could
have been attributed to hemispheric differences in connectivity, compensation from cortical or subcortical structures, or that these structures may serve to mediate attentional processing.

**Lateralization of Information Processing**

One possible explanation for the spared performance observed is that the processing of spatial and temporal information is lateralized, such that it is mediated by structures in the right hemisphere and that left hemisphere structures only support or maintain this processing. The results from the current series of studies provide support for this claim. Damage to the left hemisphere AGm or PPC were observed to either spare performance in tasks or produced selective impairments that suggest more indirect contributions to spatial and temporal processing. The decision to damage the left (vs. the right) hemisphere of these structures was predicated on previous work showing inconsistencies in the pattern of deficits observed following unilateral damage (Corwin et al., 1986; Crowne & Pathria, 1982; King & Corwin, 1990; King & Corwin, 1993; Van Vleet, Heldt, Pyter, Corwin, & Reep, 2003). In particular, unilateral damage to the left hemisphere of the AGm and PPC was associated with more consistent neglect impairments whereas unilateral damage to the right hemisphere produced less consistent impairments and, in some cases, rats with right hemisphere damage demonstrated shifts in the laterality of neglect symptoms and displaying allesthesia and allokinesia (Vargo, Corwin, King, & Reep, 1988; King & Corwin, 1992). As such, producing damage to the left hemisphere was expected to produce more consistent impairments rather than producing more robust, but inconsistent, impairments during behavioral testing. In many cases, the sparing of behavior or the selective disruptions observed were consistent with previous work demonstrating lateralized differences in left vs. right hemisphere damage to these cortical structures. In the current series of studies, unilateral left hemisphere PPC damage was observed to spare
performance in the MWT. This observation provides further support for a potential lateralized contribution of the PPC to allocentric processing. Previous work has shown that unilateral damage to the left PPC spared performance in a dry analogue of the MWT, the cheeseboard task, while unilateral damage to the right hemisphere was associated with slower acquisition of the task (King & Corwin, 1992). Moreover, lateralized differences have been observed following unilateral disruption of the PPC in timing tasks (Vicario, Martino, & Koch, 2013). Left hemisphere disruption was observed to increase variability in responding to a temporal reproduction task while right hemisphere disruption was observed to produce a rightward shift in responding. Together, the results of the current study and those of previous work suggest that there may be hemispheric differences in function and, as such, contributions to spatial and temporal processing. These differences in function may be due to differences in structure or connectivity within each hemisphere.

Lateralized differences in performance on spatial and temporal tasks could be attributed to hemispheric differences in cortical structure or connectivity. Several studies, conducting neuroanatomical tract tracing, have shown that the AGm, PPC, and DCS are highly connected structures (Reep, Corwin, Hashimoto, & Watson, 1984; Reep, Corwin, Hashimoto, & Watson, 1987; Reep, Godwin, & Corwin, 1990; Chandler, King, Corwin, & Reep, 1992; King & Corwin, 1993; Reep, Chandler, King, & Corwin, 1994; Reep, Corwin, & King, 1996; Bucci, Holland, & Gallagher, 1998; Cheatwood, Reep, & Corwin, 2003; Reep, Corwin, Cheatwood, Van Vleet, Heilman, & Watson, 2004; Reep & Corwin, 2009; Wu, Corwin, & Reep, 2009). Specifically, the AGm and PPC are highly interconnected with one another but also send dense projections to the DCS, a proposed integrator of cortical information. This work has provided a strong foundation for examining these connections; however, no work has directly compared left vs. right
hemisphere connectivity in the AGm or PPC. This gap in the literature may be due to limitations in the capabilities of examining hemispheric differences in connectivity simultaneously. Such examination of hemispheric differences may illustrate that right hemisphere structures display stronger projections to the DCS or may have more diverse connections with other structures like the nucleus basalis or thalamic nuclei. Such differences in connectivity could mediate the results observed in the current studies. To further examine potential hemispheric differences in spatial and temporal processing, future work should compare the effects of left vs. right unilateral, as well as bilateral, damage of the AGm and PPC on food protection behaviors. Results from this study could provide further support for bilateral contributions of the AGm and PPC to egocentric processing, but also characterize the specific contributions of the left and right hemispheres of each structure to this processing and also temporal processing associated with the organization of food protection behaviors. While hemispheric differences in function may have contributed to the results of the current study, it may also be the case that compensation from the intact hemisphere or the integrity of the DCS may have facilitated the ability to process spatial and temporal information.

**Compensation and the Integrity of Subcortical Structures**

Unilateral damage of the AGm or PPC did not disrupt measures of spatial and temporal processing. This spared performance may have been due to compensation from ipsilesional cortical structures, the intact contralesional hemisphere, or the integrity of subcortical structures like the DCS. As discussed, bilateral disruptions of the AGm and PPC have been shown to produce robust impairments in egocentric and allocentric processing respectively (Kolb & Walkey, 1987; Kesner et al., 1989; King & Corwin, 1992). Bilateral damage or inactivation of these structures has also been observed to disrupt interval timing (Meck, Church, Wenk, &
Olton, 1987; Dietrich, Frederick & Allen, 1997; Smith et al., 2010). Conversely, unilateral disruptions have been associated with small to moderate disruptions to these processes (King & Corwin, 1992; Vicario, Martin, & Koch, 2013). In the current series of studies, unilateral lesions minimally influenced performance in the MWT and exploration under dark conditions while sparing the ability to protect the food item from theft and the organization of food protection behaviors. It may be the case that the integrity of the ipsilesional AGm or PPC or the cortical structures in the intact contralateral (right) hemisphere were able to provide sufficient compensatory input to subcortical structures, like the DCS or entorhinal cortex, which allowed for spared performance in the tasks. Future work is needed to determine whether the integrity of other ipsilesional cortical structures (e.g. the PPC for AGm lesioned rats and the AGm for PPC lesioned rats) provides compensation for spatial and temporal processing. One approach to address this question would be to produce damage to the left hemisphere in both the AGm and PPC. Potentially, damage to both structures would be sufficient to directly impact the ability to process spatial or temporal information. Previous work has shown that severing the connections between these two structures via knife cuts produced robust impairments in responding to contralesional stimuli (Burcham, Corwin, VanVleet, 1997). Perhaps it is the case that producing focal damage to one structure (and leaving its connections to the other intact) is not sufficient to produce observable impairments in spatial or temporal processing. As such, damaging both structures may produce salient disruptions in one or both of these cognitive processes. Moreover, this work will further characterize the connectivity between the AGm and PPC. While compensatory processing in ipsilesional or contralesional cortical structures may have mediated the spared performance in the current series of tasks, it is also important to consider the influence of the DCS in mediating these results.
The integrity of the DCS may have mediated the results of the current series of the studies. Previous work has shown that this area of the striatum receives dense projections from the AGm and PPC (Cheatwood, Reep, & Corwin, 2003; Cheatwood, Corwin, & Reep, 2005). As these structures have been shown to differentially contribute to spatial processing, with AGm contributing to egocentric processing and PPC contributing to allocentric processing, the DCS may serve as an integrator of types of cortical spatial information. Moreover, as the AGm and PPC have also been implicated in interval timing, the DCS may also serve as an integrator of temporal information from these cortical structures. These neural connections provide the framework for understanding the patterns of food protection behavior and deficits observed following unilateral damage to the AGm, PPC, or DCS. For example, unilateral damage to the AGm or PPC spared the ability to protect the food item as well as the organization of food protection behaviors. Conversely, unilateral damage to the DCS has been shown to disrupt both spatial and temporal aspects of food protection (Blankenship, Cheatwood, & Wallace, 2017). Unilateral DCS damage produced a lateralized impairment in protecting a food item from theft when the robber approached a dodger on the contralesional side. Further, this damage produced a rightward shift in the organization of food protection behaviors. Lesion rats were observed to engage in significantly more dodging behavior, transitioning significantly later than their sham counterparts. This differential pattern of results suggests that the DCS may be a significant contributor to spatial and temporal processing whereas the cortical structures, which send dense projections to the DCS, may provide more subtle contributions to these processes. Therefore, it is plausible that the integrity of the DCS influenced the results of the current series of studies. In particular, it may be the case that the integrity of the DCS provided adequate compensation to
maintain spatial or temporal processing. Alternatively, the DCS could have mediated recovery of function following the unilateral damage to the AGm or PPC.

It has been shown previously that the integrity of the DCS is critical for mediating spontaneous recovery from neglect following unilateral damage to the AGm, whereas unilateral damage to the DCS does not produce this type of recovery (VanVleet et al., 2000). When the glutamatergic connections are disrupted, by way of administering a glutamatergic antagonist into the DCS, rats were observed to manifest contralateral neglect (Schuller, Tran, & Marshall, 1998). Moreover, the glutamatergic connections have been observed to mediate spontaneous recovery of neglect following unilateral AGm damage. In particular, changes in NMDA and kainate receptors in the ipsilesional DCS are highly correlated with spontaneous recovery (Vargo and Marshall, 1996a; 1996b). Compared to densities in the intact hemisphere of unilateral AGm-ablated rats, kainate and glutamatergic binding to NMDA receptors were significantly lower in the lesioned hemisphere of rats that did not demonstrate spontaneous recovery. Conversely, receptor densities were observed to normalize or even increase in the lesioned hemispheres of rats that demonstrated spontaneous recovery. This suggests that an upregulation in striatal glutamatergic or kainate receptors may be a compensatory response to the loss of cortical glutamatergic inputs following the unilateral lesions. It may be that for the current series of studies, deficits associated with unilateral damage to the AGm or PPC were buffered by receptor changes in the ipsilesional DCS. Going forward, it would be advantageous to examine densities of NMDA and kainate receptors following unilateral damage to the AGm and PPC and using them as a covariate for task performance. This approach may provide further insight into the cortical and subcortical connections and the influence of subcortical structures on recovery of function following cortical damage. In addition to mediating spontaneous recovery following
unilateral cortical damage, the integrity of the DCS is also critical for observing the therapeutic effects of dopaminergic agonists in rats with unilateral AGm damage where infusion of apomorphine into the DCS has been shown to produce dramatic, dose-dependent recovery in attending to contralesional stimuli following unilateral AGm damage (VanVleet et al., 2003). Future work should examine the effects of DCS infusions of apomorphine on improving performance in spatial tasks, like the MWT or food protection, following unilateral damage to the AGm and PPC. This work could further characterize the connections between cortical structures and the DCS which may translate into valuable insight into developing effective treatments in patients with neglect. As discussed, it is possible that spared performance was due to lateralized differences in cognitive processing or the DCS providing compensation. One other possibility is that these cortical structures do not contribute to spatial and temporal processing. Rather, they may function to mediate attentional responding to multimodal stimuli.

**Cortical Contributions to Attention**

While unilateral lesions of the AGm or PPC did not produce disruptions in spatial and temporal processing, it may be the case that the selective disruptions observed reflect disruptions in attentional processes. The ability to successfully detect the passage of time and engage in coordinated sequences of events is dependent on an organism’s ability to attend to particular aspects of their internal and external environment (Gibbon, Church, & Meck, 1984; Meck, 1996; Meck & Benson, 2002). Although tentative, the interpretation that these structures mediate attending to and integrating multimodal sensory stimuli is consistent with previous work showing disruptions in orienting toward contralateral stimuli following unilateral damage (Corwin et al., 1986; Crowne & Pathria, 1982; King & Corwin, 1990; King & Corwin, 1993; Burcham et al., 1997; VanVleet et al., 2003). In many cases, though, gradients of neglect
symptomology have been observed. Some rats exhibited severe neglect while other rats only displayed minimal disruptions, despite similar lesion extents. Therefore, it may be that the lesions in the current series of studies would not have produced neglect symptomology. One way to attempt to determine whether unilateral lesions disrupt attention vs. spatial or temporal processing would be to conduct neglect testing prior to other behavioral task running. The major concern with this approach is that the nature of neglect testing, restraining the rat until they are motionless in order to present sensory stimuli, has the potential to produce emotional responding and freezing in control rats, confounding behavioral data (Burcham, Corwin, Stoll, & Reep, 1997). Nevertheless, levels of neglect exhibited prior to testing could mediate performance in tasks like the MWT, exploration under dark conditions, and food protection. Observing that unilateral lesions of the AGm or PPC produce lateralized impairments in attending to multimodal stimuli during neglect testing but spare performance in the MWT, the organization of exploratory behaviors under dark conditions, and food protection would provide support for a dissociation in the function of these structures in that they may mediate attentional rather than spatial or temporal processing. Conversely, rats that display severe neglect could also exhibit significant performance disruptions in these behavioral tasks. If this pattern of results is observed it would provide further support for connectivity of the proposed cortico-striatal system of structures mediating the processing of spatial-attentional information and the ability to orient attention to a specific stimulus or between various stimuli.

**Other Factors That Could Have Influenced Performance**

As discussed, the spared performance in the series of studies could have been attributed to hemispheric differences in cognitive processing, compensation from the intact hemisphere or DCS, or that these structures mediate attention rather than spatial or temporal processes;
however, other factors could have influenced the results. One factor to consider is that the order of testing influenced performance. Recall that for this series of studies, the same groups of rats were run through all three studies. It is possible that the order of testing in each behavioral task could have influenced the results. The choice to run rats through the MWT, then dark exploration, and finally food protection was predicated on previous work. The MWT was chosen to be run first because previous work has shown that non-spatial pretraining or prior experience with spatial tasks influences performance (Perrot-Sinal, Kostenuik, Ossenkopp, & Kavaliers, 1996; Hoh & Cain, 1997; Beiko et al., 2004; Anderson, Moenk, Clarke, & Matuszewich, 2013). For example, rats that were first run through a food hoarding task prior to testing in a MWT were observed to learn the task quicker, as evidenced by faster latencies to locate the hidden platform across the first two days of testing, when compared to rats that were initially run in the MWT and subsequently run through the food hoarding task (Köppen et al., 2015). To avoid influencing performance in the MWT, it was important to initially run rats in this task. Further, it is possible that testing rats in exploration under dark conditions, may have fostered spontaneous recovery. While tenuous, it is possible that the extra hour a day of complete darkness, across the two days of testing, could have increased the likelihood that light deprivation contributed to spontaneous recovery (Corwin & Vargo, 1993; Burcham & Corwin, 1998; Vargo, Lai, & Marshall, 1998; VanVleet et al., 2003). In many of these cases, however, light deprivation was administered immediately following surgery and lasted for 24-28 hours. While highly unlikely, it is possible that these two extra hours of light deprivation, occurring almost four weeks following surgery, could have potentially contributed to increased recovery from neglect. Lastly, the choice to run the rats through food protection last was dependent on the fact that they needed to be food deprived to 85% of their free-feeding weights to increase motivation for protecting a food item.
Previous work has shown that food deprivation or caloric restriction influences performance in
the MWT (Stewart, Mitchell, & Kalant, 1989). Specifically, rats that were placed on 60% ad lib
food restriction diets were observed to perform better on an eight-arm radial maze and MWT
when compared to rats that were not food restricted. Moreover, food restriction was also
observed to increase resistance to MWT deficits following intrahippocampal kainate injections
(Bruce-Keller, Umberger, McFall, & Mattson, 1999). To minimize the influence of food
restriction on the other two tasks, the decision was made to run rats through the food protection
task last. Related to the order of testing, it is possible that the length of time from surgery to the
completion of behavioral testing allowed for some degree of recovery to occur.

The length of time from surgery to completion of behavioral testing was approximately
40 days or almost 6 weeks. This included a two week recovery period followed by nine days of
testing in the MWT, two days of dark exploration testing, nine days of food deprivation, and
finally 8 days of food protection training and testing. It is possible that during this time, some
gradient of recovery occurred in the lesion rats, which may have buffered the expected deficits in
performance. In many cases, attentional deficits associated with neglect are assessed the day
after surgery (Corwin et al., 1986; King & Corwin, 1990; 1993; Burcham et al., 1997). It may
have been the case that spontaneous recovery could have occurred within the two week recovery
period; however, this is unlikely to be the case considering such cases of recovery typically occur
over the course of weeks to months (Corwin et al., 1986; King & Corwin, 1990; 1993).
Moreover, while some gradient of recovery can occur within this time frame, deficits observed
following unilateral damage to the AGm or PPC usually carry out past three weeks of neglect
testing (Corwin et al., 1986; King & Corwin, 1990; 1993; Burcham et al., 1997). Similarly,
unilateral damage to the sensorimotor cortex produces deficits that persist beyond 70 days of
testing (Blackwell, Widick, Cheatwood, Whishaw, & Wallace, 2018). Other work has shown similar ranges in the persistence of deficits following more widespread damage, produced via hemidecortication (Whishaw & Tomie, 1988). Specifically, lateralized deficits in protecting a food item from theft were observed to persist past 60 days of testing following hemidecortications. Taken together, these data suggest that without interventions, like administration of DA agonists of light deprivation, deficits should persist through at least three weeks post-surgery and potentially continue to manifest beyond 70 days post-surgery. As such, it should have been the case that deficits in spatial processing should have been observable, at a minimum, for the duration of place learning of the MWT. The spared performance suggests that if recovery had occurred, it took place during the two-week recovery period. While this possibility cannot be fully ruled out, it would be advantageous going forward, to have a cohort of rats set aside that are dedicated to determining the level of recovery that occurs during this two week recovery period. Specifically, future work should examine the course of recovery during this time by examining the histology of lesion brains at two days, 1 week, and 2 weeks post surgery to determine whether the recovery period should be decreased or that testing should occur closer in time to the surgery day. In addition to considering the order of testing and the possibility of spontaneous recovery occurring prior to testing, it also important to consider the influence of the sex of the rats on the current studies’ results.

The current series of studies only utilized female rats. Hormonal factors, like the estrous cycle have previously been observed to influence performance on spatial tasks, like the MWT (Frye, 1995; Warren & Juraska, 1997); however, the nature of this relationship continues to be debated. Other work has failed to find effects of estrous cycle on water maze performance (Rubinow, Arseneau, Beverly, & Juraska, 2004) or self-movement cue spatial tasks like food
hoarding (Köppen et al., 2015). Moreover, we have recently published using females in the food protection task showing deficits following unilateral DCS lesions (Blankenship, Cheatwood, & Wallace, 2017). Further, the prolonged timeframe of running the MWT and food protection tasks allows female rats to fully cycle from proestrus, estrus, and diestrus throughout the course of testing. Finally, the choice to use females over males is predicated on previous pilot work demonstrating that food deprived Long Evans male rats can behave aggressively toward one another when protecting a food item from theft. Specifically, male robbers were more likely to engage in biting behaviors which produced emotional responding in their dodger counterparts, dramatically reducing the motivation to protect the food item from theft. Taken together, these lines of evidence suggest that the estrous cycle should not have significantly influenced the spared performance observed in this series of studies. One last factor to consider is the influence of rats’ development and the factors associated with litter effects.

It was possible that litter effects mediated the spared performance observed. Previous work has shown that differences in maternal care of pups can directly influence cognitive development. Specifically, mothers that exhibited high levels of pup licking and grooming had pups who exhibited increased levels of brain-derived neurotrophic factor (BDNF) mRNA, were observed to have significantly increased cholinergic innervation of the hippocampus, and exhibited enhanced spatial learning and memory when compared to offspring reared with low licking mothers (Liu, Diorio, Day, Francis, & Meaney, 2000). As such, potential differences in cognitive development, associated with rearing conditions of specific litters, could have accounted for spared performance observed; however, this is very unlikely to have been an issue. Such effects were controlled for by choosing rats that from over 10 different litters, with each
litter contributing no more than 3 rats to a given condition. This precaution should have controlled for the effects of one specific litter significantly contributing to the overall results.

**Conclusions**

Together, this collection of studies sought to dissociate the contributions of the AGm and PPC to spatial and temporal processing. Overall, unilateral AGm and PPC lesions to the left hemisphere were observed to spare performance in the Morris water task, exploration under dark conditions, and food protection. The only exceptions to this spared performance were subtle differences observed for AGm lesion rats. Specifically, rats in this group displayed longer travel distances across the first two days of place learning in the MWT and demonstrated significantly higher changes in heading between progressions during dark exploration. These results suggest that, unilaterally, the left hemisphere AGm and PPC do not contribute to spatial and temporal processing. This spared performance may have been due to lateralizations in functioning between hemispheres, compensation from the intact contralesional hemisphere and/or DCS, or that these structures mediate attentional, rather than spatial or temporal processing. Future work is needed to further investigate the functional organization of the cortico-striatal-thalamic network of structures examined in the current study. In particular, it would be advantageous to examine the effects of unilateral vs. bilateral damage of the AGm and PPC on performance in these spatial tasks. In addition, the unilateral contributions of these structures need to be examined using tasks that specifically assess attentional processing. Lastly, future work needs to continue to characterize the contributions of the DCS and its role in mediating recovery from neglect following unilateral cortical damage. Such work would further characterize the individual contributions of the AGm and PPC to allocentric, egocentric, and temporal processing.
and may ultimately influence the development of novel treatments for promoting recovery of function from neglect-like impairments.


