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The Avian Hippocampal Declarative Memory System

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by

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Abstract

Across Mammalia, memory has long been dissociated into multiple component systems specialized to process specific facets of experience. Among these segregated systems, declarative memory is processed by the hippocampus and surrounding structures, which have collectively been referred to as the hippocampal declarative memory system (HDMS). The HDMS, in turn, can be further divided into parallel streams dedicated to the processing of spatial versus object identity based information, commonly discussed as the 'what' and 'where' streams. While we know that the organization of the HDMS is conserved in humans, nonhuman primates, and rats, evidence outside Mammalia is lacking. Here HDMS homology is tested in Aves, a class known to have sophisticated memory abilities. This dissertation first adapts testing methods well established for dissociating spatial and object recognition in mammals and validates them in multiple avian species (Chapter 2). These methods are then applied to birds undergoing selective lesions along either the mediolateral (Chapter 3) or rostrocaudal (Chapter 4) extent of the HDMS. These data then permit an update of the known functions of the sub-regions of the avian HDMS (Chapter 5). In summary, these data suggest that most of the key features of the mammalian HDMS, including the existence of anatomically separated hierarchical processing streams for object and spatial information, as well as eventual convergence of this information in the hippocampal formation, is conserved across at least these two classes. Given the great survival value of the ability to identify the '*whats'* and '*wheres'* within an environment, this homology may not be surprising. In fact, the HDMS may be conserved across much of the animal kingdom.

Keywords: animal behaviour, avian cognition, avian memory, comparative cognition, hippocampus, multiple memory systems, neuroethology, novelty detection, object memory, spatial memory

Dedication

In loving memory of Kurt Damphousse

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Abbreviations

APH	area parahippocampalis
BIC	binding of item in context
CA	Cornu Ammonis
CDL	dorsolateral corticoid area
CFC	contextual fear conditioning
COR	conjunctive object recognition
DG	dentate gyrus
DL	dorsolateral region of the hippocampal formation
DM	dorsomedial region of the hippocampal formation
DMS	delayed match to sample
DNML	delayed non-match to location
DNMS	delayed non-match to sample
DVR	dorsal ventricular ridge
EC	entorhinal cortex
FA	foraging array
H	hyperpallium
HDMS	hippocampal declarative memory system
Hp	hippocampus proper (CA subfields)
Hf	hippocampal formation (Hp, DG, subiculum)
dHf	dorsal hippocampal formation
cHf	caudal hippocampal formation
vHf	ventral hippocampal formation
rHf	rostral hippocampal formation
LEC	lateral entorhinal cortex
Ma	magnocellular region of the hippocampal formation
MEC	medial entorhinal cortex
MMS	multiple memory systems
MTL	medial temporal lobe
MTDMS	medial temporal declarative memory system
N	nidopallium
NCV	caudoventral nidopallium
NFL	frontolateral nidopallium
NHP	non-human primate
PC	paired comparison
PHC	parahippocampal cortex
PiC	piriform cortex
PoRhC	postrhinal cortex
PRhC	perirhinal cortex
SOR	spontaneous object recognition
SOR-SV	spontaneous object recognition with systematic variation
TE	anterior inferotemporal
TEO	posterior inferotemporal
Tr	triangular part between V-shaped layer
V	V-shaped layer
VPC	visual paired comparison
YMD	Y-Maze discrimination

Chapter 1: General Introduction

The acquisition, storage, and retrieval of different kinds of information is critical for survival. Combining information and storing it within memory allows multiple causative and correlative relationships to be identified, permitting learning from past events and enabling planning for future ones. Considering the implications for survival, it is perhaps unsurprising that memory has been widely studied for centuries. In fact, the idea that memory is not a unitary function (a notion that is particularly relevant to this dissertation) dates back more than two hundred years. French philosopher Maine de Biran wrote in 1804 about the potential for different types of memory, making distinctions between what he called mechanical memory, sensitive memory, and representative memory (Maine de Biran, 1804/1929). In the latter part of the 19th century, American philosopher and psychologist William James differentiated between memory and habit (James, 1890). The proposal of different types of memory continued well into the 20th century with theories such as those of McDougall (1923) differentiating between explicit and implicit recognition, and Tolman (1948) between different kinds of learning.

Considerable evidence exists supporting the idea that the brain contains multiple memory systems (MMS; Poldrack & Packard, 2003; Squire, 2004). Not only does this imply that differing regions within the brain may be disproportionately involved in certain types of memory relative to others (e.g., procedural versus episodic memory), this also implies that different structures within these regions are more involved than others in the processing of certain types of information (e.g., object identity versus spatial information). There is a

considerable literature tying varying components of MMS to specific pathways in the brain. Although these are not covered here, the interested reader is directed to Poldrack and Packard (2003) or Squire (2004) for further reading. The current dissertation will focus on a specific memory system, declarative memory, which can be described as explicit, conscious recollection of facts and events (reviewed in Squire *et al.,* 2004), and its now well characterized association with the medial temporal lobe (MTL).

The MTL, consisting of the hippocampal formation (Hf; made up of the *Cornu Ammonis* (CA) subfields, the dentate gyrus (DG), and the subicular complex), the adjacent perirhinal cortex (PRhC), parahippocampal cortex (PHC), and entorhinal cortex (EC; divided into lateral (LEC) and medial (MEC) portions), is critical for declarative memory. Evidence supporting the MTL's role in memory began to accumulate over a century ago when Russian neurologist Vladimir Mikhailovich von Bechterew described bilateral softening of the Hf in a patient that had exhibited profound memory deficits (von Bechterew, 1900; for review see Maranhão *et al.,* 2015). Although von Bechterew's findings hinted at the role of the Hf in memory, the extent of MTL involvement was not fully appreciated until over half a century later with the work of Brenda Milner. Her systematic documentation of memory deficits associated with the bilateral resection of the MTL in patient Henry Molaison (H.M.; Scoville & Milner, 1957) established several fundamental principles of memory still utilized today (Squire, 2009). First, despite deficits recalling his past, H.M.'s intellectual and perceptual functions remained largely intact suggesting that memory associated with the MTL can be separated from other cognitive functions. Second, H.M.'s ability to remember information over a short period of time implied

that functions supporting short-term memory, such as working memory, must therefore take place outside of the MTL.

At the time of the first descriptions of H.M., little was known about the anatomy of the MTL and less was known about how specific structures within this region might contribute uniquely to memory (Squire *et al.,* 2004). Through the introduction of animal models of H.M.'s amnesia in non-human primates (NHP) and subsequently in the rat, the critical involvement of the MTL in declarative memory became increasingly clear, and a model of the medial temporal declarative memory system (MTDMS) began to emerge (Mishkin, 1982; Zola-Morgan *et al.,* 1983; Squire, 1992a, b). Importantly, the use of different species of animal (primarily humans, NHPs, and rats) allowed for cross-species comparisons of structure, connectivity, and function, offering insight into how the MTDMS system may have been sculpted by selective pressures over the course of evolution. This comparison across taxa is the focus of the current dissertation, and an area in critical need of further research. Much of the research on the MTDMS has focused predominantly on mammals. This focus, while understandable given the application of this knowledge to human health, leaves gaps in our knowledge concerning how the neural infrastructure underlying memory has changed across the animal kingdom. I address a small facet of these shortcomings through a series of experiments on the avian homologue of the MTDMS.

In order to provide context for the experiments outlined in Chapters 2, 3, and 4 of this dissertation, this Chapter will begin with a comparison of the MTDMS in humans and NHPs, our closest relatives within the same order. The model developed will then be expanded to rats, which are arguably the most studied organism within the same phylogenetic class (mammals).

Finally, I will describe the MTDMS in avian models in order to assess potential neuroanatomical and functional homology across classes within the same clade of tetrapod vertebrates (i.e., amniotes). The studies presented within the scope of this introduction will focus largely on macaques (*Macaca mulatta*), rats (*Rattus norvegicus*), and pigeons (*Columba livia*), as these model organisms make up the bulk of the extant literature. It should be noted, however, that there are limitations inherent to such a small fraction of the mammalian and avian taxa making up the bulk of our understanding. For instance, it should be noted that *Rattus norvegicus* represent one species within the Rodentia, which consists of 2277 recognized species (42% of all mammalian diversity), that there are 376 species of primate (Wilson & Reeder, 2005; Molnár & Clowry, 2012), and over 18,000 species of bird (Barrowclough *et al.,* 2016). Considering that morphological and anatomical variations are commonly observed within orders (in mammals; West, 1990; in aves; Sherry *et al.,* 1992; Hampton & Shettleworth, 1996b, Payne *et al.,* 2021), research on species variation would need to increase exponentially for generalizations to be made with confidence. As such, this review is of necessity speculative in many regards. In an attempt to minimize this variation, the research discussed will be restricted to connectivity tracing and the effects of lesions on various tests of memory, as these methods appear to be most consistently applied across all species of interest.

Since the declarative memory system is largely dependent on the Hf and because the location of the Hf, as well as the nomenclature (and even the existence) of some of the associated structures is contentious across species, for the purpose of comparison and for the remainder of this dissertation, I will refer to the structures associated with declarative memory as the *hippocampal declarative memory system* (HDMS).

One feature that characterizes the HDMS across many (perhaps all) species, is the segregation and parallel processing of varying kinds of information, which is eventually integrated in the Hf, at the apex of this system. Computationally, it has been proposed that this type of hierarchical processing would not only allow for more sophisticated information to be represented in a way that minimizes interference, but may also increase both processing speed and storage capacity of the HDMS (e.g., Damasio, 1989; Alvarez & Squire, 1994; McClelland *et al.,* 1995; O'Reilly & Rudy, 2000). Given the apparent ubiquity of this feature, it will be discussed first for each of the model systems.

While establishing a hierarchy of connectivity provides information concerning how information is transmitted within the HDMS, it does not provide details concerning how each structure contributes uniquely to declarative memory. Toward this, many models have been proposed for how information is segregated within the HDMS (see Nadel, 1992, for a historical account of these models), but one distinction that features prominently in the data surrounding the function of the HDMS is space. The importance of the HDMS for dealing with space is perhaps not surprising, given that several regions of the HDMS are thought to be responsible for relational learning, and spatial cognition is inherently relational. This provides the opportunity to understand the role of the HDMS in processing information in general by understanding how it deals with objects embedded in space (Eichenbaum *et al*., 1999). As such, we will focus on how the HDMS handles spatial versus non-spatial information, or what O'Keefe and Nadel (1978, p. 381) describe as, "memory for items or events within a spatio-temporal context" contrasted with "memory for items, independent of the time or place of their occurrence".

1.1 The Primate Hippocampal Declarative Memory System

Arguably the best model species to begin with when constructing a comparative analysis of the HDMS are our closest evolutionary relatives, NHPs. By examining NHPs we can determine if elements of structure and function are evolutionarily conserved, or if certain structures and functions are unique to humans.

This section will describe a hierarchy of connectivity between structures of the HDMS, in which two different kinds of information are processed in parallel, and how structures within the hierarchy contribute uniquely to the processing of this information. An overview of the primate HDMS will lay the groundwork for comparison when later examining this memory system more broadly within Mammalia as well as across classes with Aves.

1.1.1 Hierarchy of Connectivity

The structures that make up the hierarchical processing of the HDMS have been identified largely through the use of NHP models (Squire & Zola-Morgan 1991). Additionally, this work has established the boundaries and connectivity of these areas, revealing bidirectional pathways between the cerebral cortex and structures within the HDMS, termed the 'hierarchy of connectivity' (Lavenex & Amaral, 2000; Witter *et al.,* 2000a; Kerr *et al.,* 2007; **Figure 1**). The hierarchy of connectivity is composed of four main levels: association areas of the cerebral cortex, the parahippocampal region, the EC, and the Hf. Starting with uni- and poly-modal sensory information, higher order association cortices (exclusive of primary sensory or motor regions) send inputs to and receive outputs from the HDMS. Cortical association areas that do not connect directly with Hf connect to a collection of interconnected areas outside of

the Hf, within the parahippocampal region (comprised of the PRhC and PHC). These areas then connect with different portions of the EC and from there converge within the Hf. Outputs from the Hf are then directed back down the hierarchy, moving information from the Hf to the EC and subsequent parahippocampal regions, which in turn project outputs to the areas of the cerebral cortex from which the inputs originated (Eichenbaum & Lipton, 2008).

Information travels to the Hf through the connectivity hierarchy in two partially distinct channels, dividing into segregated non-spatial and spatial information processing pathways, often referred to as the *what* and *where* streams. The PRhC receives inputs from areas that encode the *non-spatial* identity of a stimulus while the PHC receives inputs from areas involved in processing the spatial content of sensory information. Looking to NHP research, the PRhC largely receives inputs from ventral visual pathway areas, important for object recognition, while the PHC receives inputs from dorsal visual pathway areas, important for spatial attention and visuospatially guided actions (reviewed in Eichenbaum & Lipton, 2008). The separation of spatial and nonspatial information is largely maintained throughout the hierarchy as PRhC projects mainly to LEC, and PHC to MEC, before both converge within the Hf.

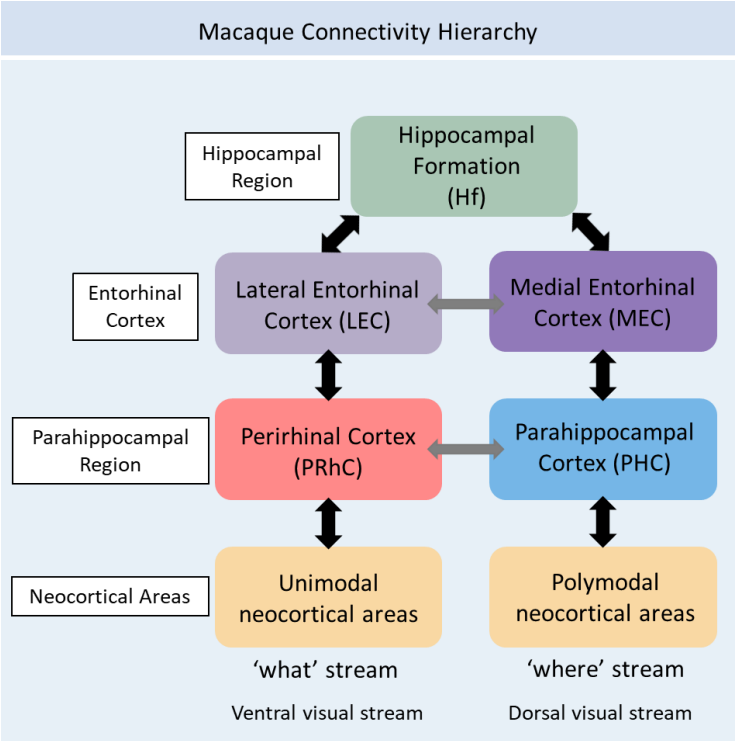


Figure 1. Primate Hierarchy of Connectivity. Separated within two parallel processing streams, sensory information converges in higher order association areas of the neocortex (yellow) before it is passed on to structures within the parahippocampal region [the perirhinal cortex (PRhC, red) or parahippocampal cortex (PHC, blue)]. Information is then relayed to regions of the lateral entorhinal cortex (LEC, light purple) or medial entorhinal cortex (MEC, dark purple) before both streams, which have thus far been processed in parallel, converge within the hippocampal formation (Hf, green). Double-headed arrows indicate bidirectional connectivity. Grey arrows indicate connectivity enabling cross-talk between structures. Black arrows indicate connectivity between levels of the connectivity hierarchy. Adapted from Manns and Eichenbaum (2006).

On the basis of connectivity, dorsal and ventral visual inputs seem to maintain largely segregated processing pathways within the connectivity hierarchy before converging within the Hf. If connectivity is indicative of function, this may imply that non-spatial and spatial information are predominantly processed in parallel throughout the hierarchy. Next, I consider the extent to which data on the functional contributions of individual regions of the HDMS to memory are consistent with this model.

1.1.2 Functional Contributions

Here I consider data collected on the ability of NHPs to perform varying memory tasks following selective lesions to structures within the HDMS. These data reveal the unique structural contributions to functions of the HDMS, and show contributions that are generally consistent with the anatomical account of information processing in this system.

1.1.2.1 Non-Spatial Processing

Non-spatial information refers generally to physical characteristics of an object such as colour, shape, pattern, and size. All of these characteristics can be combined to form a unified representation of the identity of an object in order to support recognition (reviewed by Logothetis & Sheinberg, 1996; Murray *et al.,* 2007).

1.1.2.1.1 Perirhinal and LEC

Non-spatial information carried by the ventral visual stream projects primarily to the PRhC which then projects to LEC. Because of this connectivity, the PRhC and LEC are commonly studied for their contributions to non-spatial memory, especially that involving recognition of objects.

On the basis of lesion studies involving separate components of the MTL, the contribution of the PRhC to visual recognition memory appears to be greater than that of any other single structure (Buffalo *et al.,* 1998). Located at the ventromedial aspect of the primate temporal lobe, the PRhC lies at the interface of the MTL memory system and the ventral visual stream, the 'what' pathway (Bussey *et al.,* 2002). Given that this region receives its heaviest inputs from visual sensory areas [anterior inferotemporal (area TE) and posterior inferotemporal (area TEO); Suzuki & Amaral, 1994a], studies of this area have focused on its role in visual learning and memory. The accumulated data regarding the role of the PRhC to date support its contributions to at least four cognitive functions (reviewed in Murray & Richmond, 2001): 1) PRhC contributes to recognition memory in an automatic fashion; 2) PRhC accomplishes object identification by associating together different sensory features of an object; 3) PRhC associates objects with other objects and with abstractions, and 4) it likely contributes to both perception and memory.

Restricting data to that collected in NHPs, a commonly used paradigm for assessment of PRhC function is the delayed match to sample (DMS) paradigm and its variant, delayed non-match to sample (DNMS; Mishkin, 1978). Briefly, this task usually involves a sample and a choice phase. During sample, the subject is shown a stimulus (or physical object), and then, following a varying delay, there is a choice phase in which the subject is presented with a stimulus identical to the sample alongside a different stimulus. In the DMS paradigm, the subject is rewarded for selecting the choice trial object identical to sample, and for a DNMS paradigm, the subject is rewarded for choosing the other stimulus. In NHP models, PRhC lesions create severe deficits in performance on visual DMS and DNMS tasks (Meunier *et al.,* 1993;

Buckley *et al.,* 1997). Similar findings came from Buckley and Gaffan (1998), using a set of object discrimination problems. During this task, subjects were trained to group images of the same object that had been photographed from different perspectives, called 'set one'. Once this set of images had been learned, a new set, 'set two' was introduced which included photos of the same object but from additional novel perspectives. If 'set two' was learned faster than 'set one', this was thought to be evidence of positive transfer. PRhC lesioned monkeys displayed impaired performance relative to controls. Deficits were also observed by Buckley and colleagues (2001) during an oddity task, in which monkeys were required to identify the 'odd object' (Object B) out of an array of several different views of the same object (Object A).

Another commonly used task to assess declarative memory is a visual paired-comparison task (VPC; Buffalo *et al.,* 1999). VPC typically consists of two phases, sample and choice. During sample, two identical pictures are presented side by side. After a delay, the choice phase consists of two pictures, one being identical to those presented in sample and the other being novel. This task capitalizes on the tendency for primates to prefer novelty and suggests that if (a) the pictures shown during sample are remembered, and (b) the subject can discriminate between the presented stimuli, then the subject should spend more time looking at the novel stimulus relative to familiar one. Buffalo and colleagues (1999) observed PRhC involvement in a VPC task as lesions to the area inhibited performance.

While the majority of inputs to the PRhC are those carrying visual information, approximately one third of its input comes from non-visual unimodal cortices, implying that this region may also be important in combining information across modalities (Suzuki, 1996). Consistent with this, deficits in performance are also observed in PRhC lesioned NHPs during a

tactile recognition task (Buffalo, *et al.,* 1999) and in cross-modal DNMS (tactile-visual; Buffalo *et al.,* 1999; Goulet & Murray, 2001). Additional evidence for PRhC involvement in cross-modal DNMS is seen in human subjects with damage encompassing the PRhC (Taylor *et al.,* 2006). However, data from human amnesic patients should be treated cautiously, as damage typically affects both the Hf and PRhC. Impairments in patients with damage to these areas are typically severe and span many types of memory, so dissociations are rare (Brown & Aggleton, 2001).

Taken together, these findings point to PRhC involvement in forming object identity by associating different perspectives of objects and their multimodal attributes. On the basis of these studies, it appears that PRhC is critically involved in object discrimination, consistent with its implied function following assessment of connectivity alone.

Within the next level of the connectivity hierarchy, the LEC receives direct projections from the PRhC and is one of the two major cortical inputs to the Hf. While there are considerable data on the functions of the PRhC, little is known about how neural representations are transformed between PRhC and LEC in primates. Historically, it has been difficult to dissociate functions of LEC and PRhC as a large number of studies examining PRhC have also lesioned LEC (Meunier *et al.,* 1993; Eacott *et al.,* 1994). Additionally, EC lesions typically encompass both LEC and MEC so assigning specific contributions should be done cautiously. However, EC lesions provide some data in differentiating PRhC and EC function. To the best of my knowledge, in the only experiments exploring EC lesions in NHPs, performance was spared on a DNMS task (Buckmaster *et al.,* 2004), a task on which performance is commonly disrupted following PRhC lesion (Meunier *et al.,* 1993; Buckley *et al.,* 1997). Buckmaster and colleagues (2004) reported deficits in EC lesioned subjects on tasks requiring

conditional discriminations between stimuli with overlapping elements and the learning of predictive relationships.

Although limited, these findings suggest that the PRhC is critically involved in object recognition and simple associations between objects, while the EC may be necessary for flexible manipulations of learned associations (for review, see Garcia & Buffalo, 2020).

1.1.2.2 Spatial Processing

Spatial information refers generally to information about stimuli that is embedded within a spatial context. This context consists of information concerning the stimulus's location both in relation to the subject as well as to other objects (O'Keefe & Nadel; 1978).

1.1.2.2.1 Parahippocampal Cortex and MEC

Spatial information that is carried by way of the dorsal visual stream projects primarily to the PHC, which then in turn projects to MEC. Because of this connectivity, the PHC and MEC are commonly studied for their contributions to spatial memory.

Located along the ventromedial edge of the temporal lobe adjacent to the Hf, the PHC is the interface between the MTL memory system and the dorsal visual stream, commonly referred to as the 'where' pathway. Insight into the function of the PHC may once again be obtained by examining the connections both to and from this structure. The majority of input to the PHC comes from cortical areas mediating spatial information, such as area V4 (Schiller & Lee, 1991) and the posterior parietal cortex (Calton & Taube, 2009), implying that this area may function to represent and retrieve spatial information.

To determine once again if connectivity is predictive of function, the PHC has unsurprisingly been studied extensively for its involvement in spatial processing (for review see Aminoff *et al.,* 2013). To assess the involvement of the PHC on spatial elements of declarative memory, Bachevalier and Nemanic (2008) implemented two variations of the VPC task, a Spatial Location and an Object-in-Place version. In the Spatial Location version, comparison was made between two identical objects presented simultaneously in a novel and familiar location. In the Object-in-Place version, the comparison was between two images, each consisting of the same five objects only in one of the images, the objects had been rearranged. PHC lesioned macaques displayed deficits in both the spatial location and Object-in-Place tasks, supporting involvement of this structure in the 'where' element of declarative memory. Comparable findings were observed by Malkova and Mishkin (2003) in which monkeys with PHC lesions displayed deficits when tasked with a one-trial memory task that relied on remembering object-place associations (object-place trials) or simply a place in an array of three feeding wells (place trials). Monkeys with PHC lesions also displayed deficits on a variation of the DNMS task, in which discrimination was dependent on location (delayed non-match to location; DNML; Alvarado & Bachevalier, 2005).

In the connectivity hierarchy, the MEC receives direct projections from the PHC and is one of the two major cortical inputs to the Hf. By restricting the data presented to that of lesion studies in primates, there is little data investigating dissociable functions between the MEC and PHC that meet the criteria. Evidence for such dissociations is available largely in rat studies which will be discussed in a later section focusing on taxonomic differences in the MTDMS.

Although beyond the scope of this dissertation, functional imaging in primates provides findings comparable to the rat literature (Reagh & Yassa, 2014).

1.1.2.2.2 Hippocampus

The Hf acts as the final stage of convergence for multisensory information received via projections from the adjacent EC, PRhC, and PHC (Lavenex & Amaral, 2000). Since the Hf is the site of 'what' and 'where' pathway convergence, it is likely important in binding disparate event features into an integrated representation. This idea also suggests that tasks that do not require the combining of multiple information streams, such as recognition memory for single items, can instead be accomplished by regions adjacent to the Hf (Tulving & Markowitsch, 1998; Brown & Aggleton, 2001). In examining the functional role of the Hf, I will present two complimentary models concerning how the Hf uniquely contributes to the HDMS relative to other structures within the hierarchy, the Dual-Process model and Binding of Item in Context (BIC).

1.1.2.2.2.1 Dual-Process Model

Reviews of Hf function highlight distinctions between two processes employed in supporting declarative memory, a sense of *familiarity* with previously experienced stimuli (i.e., recognition of an item without retrieval of specific details about the study episode), which can be contrasted with *recollection* (i.e., recognition of an item on the basis of the associations and specific contextual details of a previous study episode; Yonelinas, 1994, 1999; Eichenbaum *et al.,* 2007). Following the Dual-Process model, the PRhC is thought to be critical for familiarity, and the Hf and PHC for recollection (**Figure 2**). It is important to note that the Dual-Process model described here in relation to declarative memory is not to be confused with the Dual-

Process Theory of Thought. While the Dual-Process model describes functional contributions of structures within the MTDMS, Dual-Process Theory of Thought describes two co-existing systems involved in thought, one of which is a quick, automatic, associative, and affective-based form of reasoning, and the other, a slow, thoughtful deliberative process (Sloman, 1996). This dissertation refers to the former and not the latter.

There is considerable evidence in NHPs supporting the suggested roles of the PRhC, PHC, and Hf in the Dual-Process model. Supporting evidence for the role of the PRhC in familiarity comes from studies showing that this region is critically involved in object discrimination (Mishkin, 1978; Meunier *et al.,* 1993; Buckley *et al.,* 1997; Buffalo *et al.,* 1999). Additionally, since the PHC is critically involved in tasks requiring the association of multiple elements such as item and context (Bachevalier & Nemanic, 2008), this could support the idea of the PHC as critical to recollection. Comparable findings to PHC have been noted following lesions to the Hf as lesions to this area have been shown to impair memory for complex associations like those of item and context (for review see Brown & Aggleton, 2001; Rugg & Yonelinas, 2003).

Human studies examining the Dual-Process model support a double dissociation between the PRhC and Hf in that the PRhC appears to be involved selectively in familiarity but not recognition, and the Hf in recollection but not familiarity (Bowles *et al.,* 2010). In studies of patients with transient hypoxia, which causes significant damage to the Hf while sparing structures within the parahippocampal region (i.e., PRhC and PHC), hypoxic patients displayed disproportional deficits in memory for associations or context compared to item familiarity (Mayes *et al.,* 2002; Giovanello *et al.,* 2003; Turriziani *et al.,* 2004; Holdstock *et al.,* 2005). Using

receiver operating characteristic analysis to distinguish familiarity from recollection, Yonelinas and colleagues (2002) showed that mildly hypoxic patients exhibited severe deficits in recollection but not familiarity. Impaired recollection but preserved familiarity has also been reported in patients with selective Hf atrophy caused by meningitis (Aggleton *et al.,* 2005). An example of impaired familiarity but spared recollection comes from extensive studies of patient N.B. who underwent a rare unilateral MTL lesion that spared the Hf (Bowles *et al.,* 2007; Bowles *et al.,* 2010; Köhler & Martin, 2020).

Taken collectively, these lesion studies converge on the idea that the Hf and PHC selectively support recollection (but see Wixted & Squire, 2011; Merkow *et al.,* 2015), while the PRhC supports familiarity.

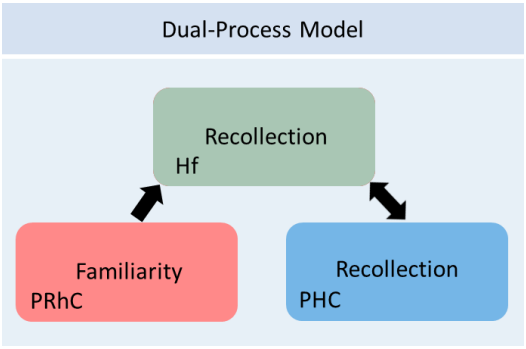


Figure 2. Primate Dual-Process Model. Cognitive account of functional roles of sub-regions within the medial temporal lobe. The hippocampus (Hf) and parahippocampal cortex (PHC) are proposed as supporting recollection (i.e. recognition of an item on the basis of retrieving specific contextual details of the previous learning experience). The perirhinal cortex (PRhC) is proposed as supporting familiarity (i.e. item recognition in the absence of specific details about

the study episode). Double-headed arrows indicate bidirectional communication, single-headed indicate unidirectional communication. Adapted from Opitz (2014).

1.1.2.2.2.2 Binding of Item in Context

In more recent years, the idea that the Hf and PRhC are differentially involved in familiarity and recollection has been challenged. The primary criticism of the Dual-Process model is that it too broadly implies functional differences and that information provided by the MTL connectivity hierarchy should instead be applied for greater specificity. Rather than trying to explain HDMS structural functions in terms of the purely cognitive dichotomy between familiarity and recollection, more recent models separate HDMS structures on the basis of the kind of information thought to be handled by each structure, i.e., item-specific and contextual information. The 'Binding of Item in Context' (BIC) model separates the HDMS on the basis of the kind of information processed within the structures (Diana *et al.,* 2007). Additionally, the BIC model incorporates the 'what' and 'where' parallel processing streams, identifying each hub within the connectivity hierarchy as a site for unique transformations of the information, increasing in refinement as the information is relayed to subsequent structures (**Figure 3**; Manns & Eichenbaum, 2006).

Support for the BIC model can be found in the NHP literature. Recalling the Bachevalier and Nemanic (2008) study, not only did this research identify vital contributions of the PHC to context memory, it also pointed to unique contributions of the PRhC and Hf to the HDMS. Following PRhC lesions, subjects exhibited deficits in a VPC and object-in-place task. However, performance on a spatial location task was spared, supporting the notion that the PRhC contributes object or item information. Lesions to the Hf resulted in deficits in an object in

place association only, suggesting that the Hf may be critically involved in associating information from the PHC and PRhC. The findings of Bachevalier and Nemanic (2008) support the idea that the PHC is critical to context memory, the PRhC to object memory, and the Hf, serving as a site of convergence for both types of information, is vital when task demands require associations between context and object information.

Restricting evidence to human lesion studies, amnesic patients with damage primarily to the Hf displayed a spared ability to differentiate between new and old visual scenes but were unable to distinguish between intact old scenes and old scenes in which particular elements had been displaced (Ryan *et al.,* 2000; Mayes *et al.,* 2004). This suggests that the deficits observed were due to an inability to process the relations of items within a specific context. However, item recognition devoid of spatial information remained intact. This supports the idea that Hf function is dissociable from that of the surrounding cortices and mirrors findings in NHPs. Further supporting the critical role of the PRhC in object memory is the proposal that multiple items sharing cortical representations due to a high degree of feature overlap (e.g., two faces) are associated and stored within the PRhC. In the clinical literature, a People and Doors Test provides a battery to assess a number of memory functions, namely visual and verbal recognition and recall (Baddeley *et al.,* 1994; Morris *et al.,* 1995; Manns and Squire 1999). Using this task, amnesic patients with damage restricted to the Hf displayed spared recognition for items within the same category (e.g., choosing the familiar door out of an array of doors) but deficits in visual recollection (e.g., drawing an item displayed during a previous trial; patient Jon; Vargha-Khadem *et al.,* 1997; patient Y.R.; Mayes *et al.,* 2002). Success during visual recognition implies that the spared PRhC stores specific features of an item rather than

generalizing into broad categories. Greater support for this comes from comparable amnesic patient studies, all with damage restricted to the Hf, demonstrating unimpaired recognition for within-domain or intra-item associations (e.g., differentiating between faces) but compromised performance on between-domain associations (e.g., object-location and face-voice associations; Mayes *et al.,* 2004).

As discussed in the previous sections, primate lesion data informing how structures within the EC contribute uniquely to the HDMS is lacking. Based on the limited findings of Buckmaster and colleagues (2004), we can only infer that EC structural function is dissociable from that of PRhC and that function of the EC appears to involve complex discriminations and associations. This offers little information when describing these structures within the context of the BIC model. However, LEC and MEC are often depicted at the apex of the spatial and non-spatial processing streams, respectively (Manns & Eichenbaum, 2006). Each receives input from regions that (a) contain complex representations and that (b) are sufficient for many forms of recognition memory. How they might further process these representations before they are passed onto the hippocampus, however, remains unclear.

Taken together, the BIC model and associated experimental evidence supports the notion that the PRhC is vital for retrieval of item feature information, supporting recognition, the PHC for context memory, and the Hf in associations of item and context. These findings are also in agreement with the Dual-Process model of familiarity (recognition) versus recollection (recall). However, the BIC view adds greater specificity about the *kind* of information that each structure contributes to memory (Manns & Eichenbaum, 2006).

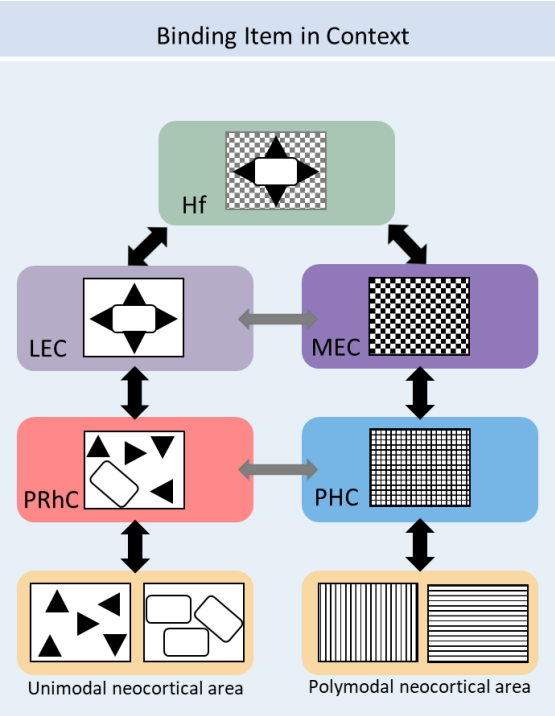


Figure 3. Primate Binding Item in Context (BIC) Model. This model proposes functions for sub-regions of the medial temporal lobe on the basis of the information that they store. The BIC model suggests that the perirhinal (PRhC, red) and the parahippocampal cortex (PHC, blue) support the encoding and retrieval of item-specific and contextual information. Maintained within parallel processing streams, representations reach their highest level of independent processing (i.e. complexity and number of associations between elements), within the entorhinal cortex. Within this region, item information is predominantly processed by the lateral subregion (LEC, light purple), while contextual information is processed by the medial (MEC, dark purple) sub-region. These streams then converge within the hippocampus (Hf, green). The Hf is then thought to store representations of item-context associations. Double-headed arrows indicate bidirectional connectivity. Grey arrows indicate connectivity enabling

cross-talk between structures. Black arrows indicate connectivity between levels of the connectivity hierarchy. Adapted from Manns and Eichenbaum (2006).

1.1.3 Summary

Based only on data from primates (humans and macaques), the HDMS displays a high level of homology between species in regards to both connectivity and function. In terms of connectivity, both species display a hierarchical connectivity pattern between structures within the HDMS, as well as parallel processing of 'what' and 'where' streams that is maintained throughout the hierarchy until converging within the Hf. In terms of functionality, both the human and macaque literatures support the role of the PRhC in encoding item-specific information (Taylor *et al.,* 2006), the PHC in context information (Alvarado & Bachevalier, 2005), and the Hf in forming representations combining the two, forming item-context associations (reviewed in Opitz, 2014).

Since there is a high degree of homology between species belonging to the same order, comparative examination will be expanded to species belonging to the same phylogenetic class, Mammalia.

1.2 The Rat Hippocampal Declarative Memory System

Despite considerable variation in ecological niches (dietary specialization, social structures, means of locomotion, etc.), the anatomy of the Hf across Mammalia is remarkably conserved. For example, of all mammalian species studied to date possess an Ammon's horn, DG, and subiculum (Manns & Eichenbaum, 2006). Considerable neuroanatomical differences arise, however, when comparing the organization of neocortical areas. Since neocortical inputs to the HDMS are predictive of the kind of information being processed, perhaps the HDMS will differ across mammalia in terms of the representation of differing sensory modalities within the connectivity hierarchy. For example, the primate EC shows greater connectivity with visual processing areas (Insausti *et al.* 1987; Kerr *et al.,* 2007) than that of the rat (Schroeder *et al.* 2010). Garcia and Buffalo (2020) postulate that this difference is likely explained by primates primarily exploring environments visually, while rats depend more heavily on olfaction, although there may be other explanations (see general discussion).

While the types of information coming into the mammalian HDMS and their proportions may differ between species, the functions of HDMS structures may remain conserved, particularly when considering that cortical inputs rarely arrive directly at the Hf, but instead arrive indirectly through the parahippocampal region. While in primates the parahippocampal region consists of the PRhC and PHC, in rats, the positions of structures differ and this area is instead comprised of the PRhC and postrhinal hippocampal cortex (PoRhC) rather than PHC.

To aid in the comparison of the HDMS across Mammalia, this section will characterize the connectivity between MTL structures, and present what is known about the functional differentiation of these structures by means of lesion studies in rats.

1.2.1 Hierarchy of Connectivity

The most detailed information on MTL connectivity across Mammalia is available in rat and macaque models. In these models, the connectivity hierarchy appears to be conserved as uni- and polymodal cortical regions project to structures in the parahippocampal regions and converge on the Hf (**Figure 4**; Suzuki & Amaral, 1994b; Burwell & Amaral, 1998a). Although hierarchical pathways are similar, patterns of connectivity differ and rats display connectivity that strictly conforms to this hierarchy less than macaques. For example, in macaques more than two-thirds of input to the EC originates from the parahippocampal region (Suzuki & Amaral, 1994a). By contrast, this proportion is only about one quarter in rats and, instead, a large proportion of inputs to the EC come directly from olfactory cortices, bypassing the parahippocampal region altogether (Burwell & Amaral, 1998a, b; Insausti *et al.,* 2002). The more rigid conformity to processing within the connectivity hierarchy displayed in macaques may suggest that information converging onto the hippocampus is more processed than that converging onto the rat hippocampus (Manns & Eichenbaum, 2006).

Based on data from both rats and macaques, parallel processing of ‘what’ and ‘where’ streams appears to be conserved across Mammalia on the basis of the type of neocortical inputs to the parahippocampal region. For example, the PRhC receives inputs concerning non-spatial identity information while the PHC/PoRhC receives inputs concerning spatial context

(Suzuki & Amaral, 1994a; Burwell & Amaral, 1998a,b). In monkeys, 'what' and 'where' inputs to the parahippocampal area correspond to areas along the ventral and dorsal visual streams, with ventral thought to be important for object recognition and dorsal for visually-guided actions (Suzuki & Amaral, 1994a). In rats, there is no clear-cut segregation of the visual system into dorsal and ventral visual streams. However, PRhC and PoRhC receive disproportionate nonspatial and spatial information (Burwell & Amaral, 1998a, b). In rats, PRhC receives inputs largely from the polymodal ventral temporal association area (TEV) while PoRhC receives prominent spatial inputs from areas like the posterior parietal cortex, approximating the ventral/dorsal visual stream function observed in primates. Despite this difference, the separation of nonspatial and spatial information appears to be maintained between PRC to LEC and PHC/PRoC to MEC (Witter *et al.,* 2000b).

In summary, the evolution of the HDMS across Mammalia is described as a contrast between conserved internal circuitry and diversified neocortical inputs (Manns & Eichenbaum, 2006). When comparing the MTL memory system from an anatomical and connectivity perspective, there appear to be striking similarities from the level of the parahippocampal region and onward to the hippocampus. Differences between mammalian species seem to largely lie upstream of this processing at the level of the neocortex and the resulting connections between neocortical areas and the parahippocampal region. However, how and whether these differing neocortical connections result in differing functions within the MTL cannot be determined by examining anatomy alone.

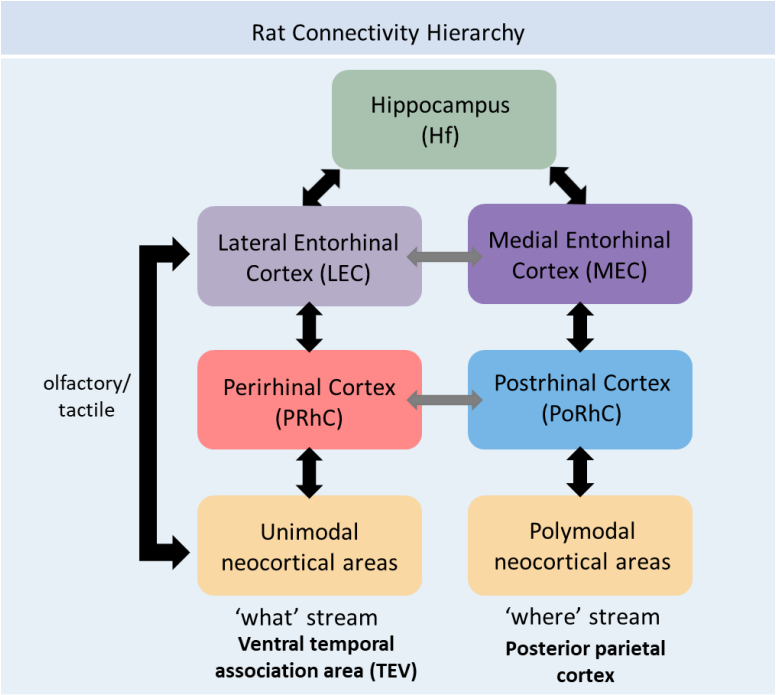


Figure 4. Rat Hierarchy of Connectivity. The rat connectivity hierarchy is separated into two parallel processing streams of 'what' and 'where' information and information converges within the hippocampus (Hf, green) after independent processing occurs within various sub-regions. Within the hierarchy, sensory information converges upon higher order association areas of the neocortex (yellow). It is then passed on to structures within the parahippocampal region (the perirhinal cortex (PRhC, red) or postrhinal cortex (PoRhC, blue), the primate parahippocampal cortex homologue). Information is then relayed to regions of the lateral entorhinal cortex (LEC, light purple) or medial entorhinal cortex (MEC, dark purple) before both streams converge within the Hf. Olfactory and tactile information in rats bypasses parahippocampal regions and converges directly upon the LEC. Double-headed arrows indicate bidirectional connectivity. Grey arrows indicate connectivity enabling cross-talk between structures. Black arrows indicate

connectivity between levels of the connectivity hierarchy. Adapted from Manns and Eichenbaum (2006).

1.2.2 Functional Contributions

In terms of anatomy and the connectivity hierarchy, the Hf and parahippocampal region appear to be highly conserved across the mammals presented. By restricting studies to those demonstrating the effects of lesions on proposed MTL homologues, how these structures compare to one another on a functional basis is explored. This section will focus on tasks that have been adapted for use in multiple species, thus limiting confounds due to differing task demands and providing a more robust comparative framework.

1.2.2.1 Non-Spatial Processing

1.2.2.1.1 Perirhinal and LEC

Based on the primate literature, the PRhC is vital to object recognition memory, as lesioning this area results in profound deficits during DMS and DNMS tasks (Meunier *et al.,* 1993; Buckley *et al.,* 1997), positive transfer (Buckley & Gaffan, 1998), oddity tasks (Buckley *et al.,* 2001), VPC (Buffalo *et al.,* 1999), tactile PC (Buffalo *et al.,* 1999), and cross modal DNMS (tactile-visual; Buffalo *et al.,* 1999; Goulet & Murray, 2001).

When comparing these results to those in rats, the function of the PRhC appears to be highly conserved. Following PRhC lesions, deficits were demonstrated during DMS (Prusky *et al.,* 2004), on oddity tasks (Bartko, *et al.,* 2007a,b; Hales *et al.,* 2015), and during the rat analog of VPC, spontaneous object recognition (SOR; Ennaceur & Delacour, 1988; Winters & Bussey, 2005a,b). While PRhC lesions in primates resulted in deficits in tactile discrimination (Buffalo *et*

al., 1999), this was not the case in rats. Interestingly, and perhaps as a result of a proportion of rat neocortical inputs bypassing the parahippocampal region, terminating instead within the EC (Burwell & Amaral, 1998a,b; Insausti *et al.,* 2002), lesions to the rat PRhC seem to disproportionally affect object recognition when performance depends on visual cues (Albasser *et al.,* 2011). In contrast, recognition on the basis of somatosensory and olfactory cues appear to remain intact (Albasser *et al.,* 2011). When lesions are instead targeted to the LEC, visual recognition remains intact, suggesting that memory for visual object information is mediated primarily by the PRhC (Kesner *et al.,* 2001). This supports the rat MTL connectivity hierarchy model, suggesting that tactile and olfactory inputs may be terminating directly on the EC while visual input is being directed through the PRhC.

Since olfactory input terminates directly onto the LEC, its role in olfactory contributions to declarative memory has been studied extensively. Interestingly, multiple studies using lesions to the LEC suggest that this structure is not required for olfactory discriminations but seems to instead play a role in olfactory learning and associations between multimodal sensory information (Stäubli *et al.,* 1984; Otto *et al.,* 1991; Wirth *et al.,* 1998; Ferry *et al.,* 2006). In a cross-modal learning task involving odour and digging media pairings, LEC lesioned rats were unable to form the required association between olfactory and tactile stimuli (Boisselier *et al.,* 2014). Additional support for this comes from a recent study in which LEC lesioned rats exhibited deficits when the task used required remembering associations between odors and contexts (Persson *et al.,* 2022). However, LEC was not needed when remembering odors or contexts by themselves. This suggests that the LEC in rats may serve to combine multimodal

information with contextual information. This will be discussed in greater depth when comparing functional contributions of HDMS structures within the BIC model framework.

Comparing the primate and rat literatures, functional differences closely mirroring those predicted by neuroanatomical studies are evident. In both rats and primates, PRhC is vital to object recognition. However, in the rat, visual information seems to conform more strictly to processing within the MTL connectivity hierarchy while tactile and olfactory information largely terminate and are processed by the LEC further downstream. Literature from rat studies also provides evidence of the function of the LEC, which was largely unavailable in primates. Although proportions of sensory information may be represented differently within the LEC of different mammals, information from rats suggests that it may be critically involved in combining multimodal sensory information as well as forming associations between sensory information and context.

1.2.2.2 Spatial Processing

1.2.2.2.1 Postrhinal and MEC

Based on the primate literature, the PHC is critically involved in spatial memory, as lesioning this area results in deficits during VPC variants (spatial location and object-in-place; Bechevalier & Nemanic, 2008), and DNML (Alvarado & Bechevalier, 2005). On the basis of anatomy and connectivity, a homologue to this region was identified within the rat brain, the PoRhC. Since structure is similar between rats and primates, studying the function of the PoRhC in rats may help to elucidate the function of the PHC in primates.

A number of studies in rat models confirm that the PoRhC is critically involved in spatial processing. Comparable to the modified VPC studies conducted in primates (Bechevalier & Nemanic, 2008), Norman and Eacott (2005) used a series of modified SOR tasks to assess memory when combining object and context information. This yielded a telling double dissociation between PRhC- and PoRhC-lesioned subjects. PRhC-lesioned rats displayed deficits when the object was to be remembered in combination with a cue in close proximity (called *object as context*), while sparing performance when the object was to be remembered within the overall environment of presentation (called *object in context*). PoRhC lesioned subjects showed spared performance during the object as context condition and displayed deficits during the object in context condition. These findings confirm the involvement of the PRhC in binding visual features to create an object identity, while also suggesting that the PoRhC is vital for discriminating between contexts, showing a functional similarity to primate homologues.

Although considered a hallmark study in determining the functional role of the PoRhC, the findings of Norman and Eacott (2005) should be interpreted carefully as the object in context condition does not solely rely on context differentiation and instead requires a) differentiating between contexts and b) also remembering which item was presented in which context, a function that could also be accomplished by the Hf. Since there are connections providing crosstalk between PRhC and PoRhC, it is possible that PRhC has some level of object representation and can accomplish the object in context condition described in Norman and Eacott (2005). However, this offers little insight into determining how the PoRhC contributes unique functions to declarative memory. This also raises the question of whether the PoRhC is involved in context recognition, spatial processing, or both.

The primate lesion literature offered little insight into the possible contributions of the MEC to memory, with the only evidence coming from Buckmaster and colleagues (2004) suggesting that the EC in its entirety was required for conditional discriminations between stimuli with overlapping elements and the learning of predictive relationships. While rat studies are still somewhat limited, an increase in studies over the past decade has contributed significantly to our understanding of the function of this structure. While the LEC is important for combining multimodal sensory information (non-spatial) as well as forming associations between sensory information and context (spatial), the MEC appears to be critically involved in spatial memory during a water maze task (Van Cauter *et al.,* 2013; Hales *et al.,* 2018), contextual novelty detection (Hunsaker *et al.,* 2013), and fear memory in response to a conditioned context or tone (Hales *et al.,* 2018), extending its role beyond that of strictly the spatial domain. Findings from Hales and colleagues (2018) show that even when Hf remains intact, MEC lesions produce deficits during spatial tasks, suggesting that the MEC contributes unique information to the Hf vital to spatial memory.

The evidence discussed thus far implies that the rat PoRhC/MEC displays comparable functions to those of the primate PHC/MEC. However, in rats functions within the parahippocampal region between PRhC and PoRhC as well as between MEC and LEC do not seem to conform strictly to the 'what' and 'where' pathways of the primate connectivity hierarchy. Instead, it appears that either due to cross talk between regions of the parahippocampal cortex and those of the EC or because of differing neocortical inputs compared to primates, these regions seem to contain differing proportions of 'what' and 'where' information rather than exclusively one or the other.

1.2.2.2.2 Hippocampus

Based on the literature from primate studies discussed earlier, the Hf seems to be critically involved in recollection according to the Dual-Process model (Yonelinas, 1994; Yonelinas *et al.,* 2002; Juola *et al.,* 2019) and in binding item and context information according to the BIC model (Bechevalier & Nemanic, 2008). The following section will explore how the evidence in rats supports each of these models.

1.1.2.2.2.2 Dual-Process Model

By situating functions of the primate MTDSM within the Dual-Process model, the PRhC is critically involved in object recognition (Mishkin, 1978; Meunier *et al.,* 1993; Buckley *et al.,* 1997; Buffalo *et al.,* 1999), the PHC in tasks requiring the association of multiple elements such as item and context (Bachevalier & Nemanic, 2008) and the Hf is selectively involved in recollection but not familiarity (Yonelinas, 1994; Mayes *et al.,* 2002; Giovanello *et al.,* 2003; Turriziani *et al.,* 2004; Holdstock *et al.,* 2005; Juola, *et al.,* 2019).

The Dual-Process model is also supported by the rat data. Comparable to primate findings, the rat PRhC is vital to object recognition (Ennaceur & Delacour, 1988; Meunier *et al.,* 1993; Buckley *et al.,* 1997; Buckley & Gaffan, 1998; Buffalo *et al.,* 1999; Buckley *et al.,* 2001; Goulet & Murray, 2001; Winters & Bussey, 2005a, b), and the PoRhC to combining item and context information (Norman & Eacott, 2005). To examine the role of the rat Hf in recollection, Fortin and colleagues (2004) trained rats to associate odours with different digging media. Following lesions to the Hf, rats had impaired recollection for associations, but odour familiarity remained intact. Interestingly, using a comparable task, Sauvage and colleagues (2008) demonstrated that following Hf lesions, recollection was reduced, but familiarity actually

increased. These findings provide evidence that recollection and familiarity are qualitatively different and that the Hf supports the former but not the latter process.

In comparing findings between primates and rats, it appears that the Dual-Process model can be used to describe functions of three major structures within the MTL; the PRhC in object recognition (familiarity), the PHC (PoRhC in rats) in combining item and context information (recollection) and the Hf in recollection. While this model does not take into account structures of the EC, and therefore provides a rather limited view into the function of structures within the HDMS, it does suggest that function may be conserved between primates and rats.

1.1.2.2.2.3 Binding Item in Context

When exploring the BIC model in relation to structures within the primate HDMS, each structure was shown to have unique functions. For example, the PRhC was shown to contribute uniquely to object information (Vargha-Khadem *et al.,* 1997; Mayes *et al.,* 2002; Bachevalier & Nemanic, 2008), the PHC to context memory (Bachevalier & Nemanic, 2008), and the Hf to associating item and context information (Vargha-Khadem *et al.,* 1997; Ryan *et al.,* 2000; Mayes *et al.,* 2002; Mayes *et al.,* 2004; Bachevalier & Nemanic, 2008). However, limited data on the role of the EC only permitted speculation about its involvement in complex discriminations and associations (Buckmaster *et al.,* 2004).

Dissociating the functions of the rat Hf from that of the PRhC, Winters and colleagues (2004), produced the first known demonstration of a double dissociation between these areas. By lesioning PRhC or Hf and testing subjects using a radial arm maze and SOR (while carefully

controlling for spatial confounds), Winters and colleagues (2004) demonstrated Hf involvement in spatial but not object recognition memory, and PRhC involvement in object recognition but not spatial memory. While these data do not provide evidence of item and context binding in the Hf (only that it is critical to spatial memory), they do support the idea that the PRhC is vital for item information and that spatial information may be obtained by the Hf through the PoRhC.

Determining greater specificity of structural contributions within the BIC model by relying solely on lesion studies has proven to be controversial as rat Hf lesions produce comparable deficits to those observed following PoRhC lesions. For example, lesions to PoRhC resulted in deficits in reference memory during radial arm maze tasks (Liu & Bilkey, 2002; Ramos, 2013), water maze tasks (Liu & Bilkey, 2002; but see Burwell *et al.,* 2004), and in context differentiation during contextual fear conditioning (Bucci *et al.,* 2002). When lesions are restricted to the Hf, deficits in performance were reported on a radial arm maze (Winocur, 1982; Okaichi & Oshima, 1990), water maze (Mumby *et al.,* 1999; Broadbent *et al.,* 2006; Clark *et al.,* 2007) and mixed data emerge from tests of contextual fear conditioning (for review see Gewirtz *et al.,* 2000; Anagnostaras *et al.,* 2001; Sanders *et al.,* 2003). When examining Hf functional contributions at the structural level rather than cellular, PoRhC and Hf are difficult to differentiate. Additionally, inconclusive and conflicting evidence could be arising from slightly different testing parameters. For example, placement (proximal or distal; Parron *et al.,* 2004) and identity of cues (unique or identical; Winocur, 1982; Clark *et al.,* 2007) can lead to different conclusions about the contributions of the Hf to declarative memory. This highlights the need for standardized testing procedures that careful control a wide range of parameters.

To speculate on the role of the rat Hf in the BIC model (**Figure 5**), it is advantageous to explore the functional contributions of other HDMS structures, since the Hf is the site of convergence for the PRhC/LEC and PoRhC/MEC streams. By examining the information being projected to the Hf, it is possible to infer what information is being represented within it.

Beginning with parahippocampal regions, function seems to be largely conserved between primates and rats, with a few key exceptions. When comparing PRhC function within rat models to those of primates, function appears to be highly conserved, as lesions to the PRhC in rats also have profound effects on object recognition (Ennaceur & Delacour, 1988; Prusky *et al.,* 2004; Winters & Bussey, 2005a,b; Bartko, *et al.,* 2007a,b; Hales *et al.,* 2015). An interesting differentiation is that PRhC lesions in rats disproportionately affect visual recognition while leaving tactile and olfactory recognition intact (Albasser *et al.,* 2011), this is not the case in primates as PRhC lesions have been shown to create tactile discrimination deficits (Buffalo *et al.,* 1999). The PHC in primates, and homologous PoRhC in rats, was shown to be critically involved in spatial memory for both species (in primates; Alvarado & Bechevalier, 2005; Bechevalier & Nemanic, 2008; in rats, Norman & Eacott, 2005). When restricting data presented to that of lesion studies only, it appears that the PHC/PoRHC serves a similar function when compared within the BIC model. However, the findings of Norman and Eacott (2005) could suggest that the PoRHC may also represent some amount of 'what' information.

From the perspective of the BIC model, the most profound differences between primate and rat structural contributions come largely from studies differentiating function within the EC. Recall that the primate literature only went as far as suggesting that the EC in its entirety was involved in conditional discriminations between stimuli with overlapping elements and the

learning of predictive relationships (Buckmaster *et al.,* 2004). Rat models greatly improved our understanding of how LEC and MEC contribute uniquely to declarative memory. Beginning with the rat LEC, multiple studies have supported its critical involvement in combining multimodal information with contextual information (Stäubli *et al.,* 1984; Otto *et al.,* 1991; Wirth *et al.,* 1998; Ferry *et al.,* 2006; Wilson *et al.,* 2013; Kuruvilla & Ainge, 2017; Persson *et al.,* 2022). Already, this deviates from what was postulated in the primate BIC model, as 'what' and 'where' information does not appear to be strictly maintained in parallel processing streams and instead seems to differ in the proportion of 'what' and 'where' information represented within the structure. This implies that 'what' information is largely handled within the LEC and 'where' within the MEC, thus 'what' and 'where' information is not exclusive to either EC subdivision.

This speculation was confirmed in a study by Hunsaker and colleagues (2013) in which either the LEC or MEC was selectively lesioned. Lesions to LEC primarily produced deficits in novel object detection while MEC lesions primarily produced deficits in novel context detection, displaying a functional double dissociation between these portions of the EC. What is perhaps most surprising about these findings is that they revealed a graded contribution of the MEC and LEC to the opposing processing stream; that is, LEC appeared to play a minor role in context recognition, and MEC in recognition of novel objects. This finding suggests that the 'what' and 'where' processing streams in the rat MTL system may not be as strictly organized as those in the primate MTL, and, instead, rat LEC and MEC functions differ in the *proportion* of item and context information, albeit much less than that represented when the streams converge within the Hf. Despite apparent dissociable deficits in item and context recognition memory following

LEC and MEC lesions, performance was spared in a condition in which a conjunction of item and context was required for novelty recognition. This finding suggests that although one of the two streams is compromised, the other still contains enough of a combination of item and context information to make the discrimination at levels comparable to shams.

Again in contrast to the primate BIC model, the rat MEC was shown to be critically involved in not only spatial memory (Van Cauter *et al.,* 2013; Hales *et al.,* 2018) and contextual novelty detection (Hunsaker *et al.,* 2013), but also fear memory in response to a conditioned context or tone (Hales *et al.,* 2018). This suggests that in addition to critical spatial information, the rat MEC may also act to form fear responses between both contextual and auditory stimuli.

When comparing the primate HDMS to that of rats using the BIC model, functions seem to be largely maintained, though the rat system appears to have more redundancy in information processing between parahippocampal areas (PRhC/PoRhC) and areas of the EC (LEC/MEC). This could imply that in the rat HDMS, there may be more crosstalk between structures or that there may be more redundancy in neocortical input. Another possibility is that the testing methods and analysis of results are biased toward relying on visual information and fail to acknowledge the multimodal nature of both context and object identification. Rather than thinking that PRhC/PoRhC and LEC/MEC have a poorer division of ‘what’ and ‘where’ streams, it is possible that each structure is accomplishing recognition using a differing sensory modality.

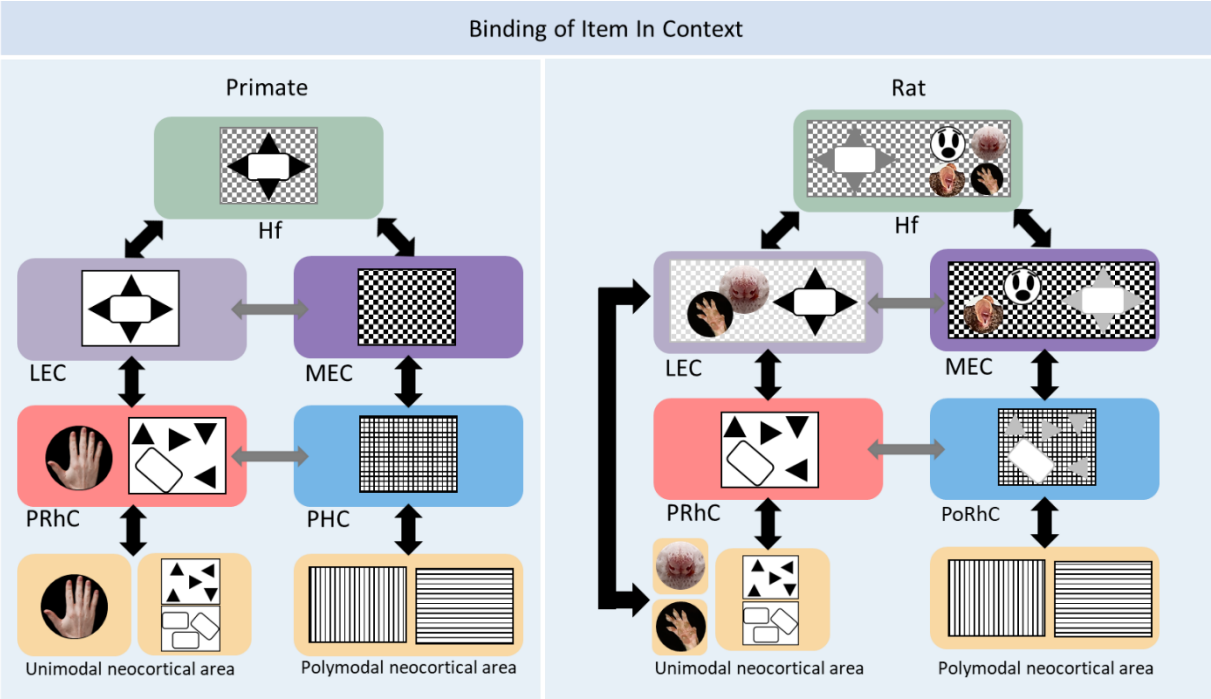


Figure 5. Comparison of Binding Item in Context (BIC) Models between Primates (left) and Rats (right). The BIC model proposes functions for the medial temporal lobe sub-regions on the basis of the uni-modal and poly-modal information that they receive from association cortices (yellow). In both species, the perirhinal (PRhC, red) supports the encoding and retrieval of item-specific information. The primate parahippocampal cortex (PHC, blue), homologous to the postrhinal cortex in rats (PoRhC), supports the encoding and retrieval of contextual information. Maintained within parallel processing streams, representations reach their highest level of independent processing, within the lateral entorhinal cortex (LEC, light purple) and medial entorhinal cortex (MEC, dark purple) before terminating within the hippocampus (Hf, green). The Hf is thought to generate item-context associations. The primate BIC shows strict adherence to 'what' and 'where' streams while the rats BIC depicts less conformity. Multimodal information in primates appears to be processed within the hierarchy while rat olfactory and

tactile information bypass parahippocampal areas and project directly to LEC. Tactile information is represented using a hand (or paw); olfactory, a nose; auditory, an ear; and emotional information using a cartoon face. Object information is represented by rectangles and black triangles. Context information is presented using pattern filled rectangles. Increased complexity in representation is depicted through altering the arrangement of object and contextual elements. Double-headed arrows indicate bidirectional connectivity. Grey arrows indicate connectivity enabling cross-talk between structures. Black arrows indicate connectivity between levels of the connectivity hierarchy. Adapted from Manns and Eichenbaum (2006).

1.2.3 Summary

Following 80 million years of independent evolution between rats and primates, the HDMS across Mammalia can be characterized as a contrast between subcortical circuitry that remains largely conserved and dramatic alterations in neocortical architecture (Manns & Eichenbaum, 2006). This high degree of homology between mammalian species opens the possibility of conserved homology across a wider portion of the phylogenetic tree. To explore this possibility, comparative examination will be expanded to species from different orders in the same clade (amniotes), birds.

1.3 The Avian Hippocampal Declarative Memory System

In examining the evolutionary origins of HDMS, I showed that the available data demonstrate a dramatic homology in both the architecture of the HDMS and in the functional specialization of its components across Mammalia. Now, the neuroanatomical and functional homology of the HDMS will be compared with Aves, as a relatively well-researched example of a non-mammalian Amniote. Since there are 320 million years of evolution separating Mammalia from Aves (Tosches *et al.,* 2018), it is possible that the Hf and other structures of the MTL may have evolved to serve different functions or that an entirely different memory system from that of the mammalian MTL is present (for review see Gupta *et al*., 2012; Gupta *et al*., 2020).

There are considerable anatomical differences between avian brains and those of primates and rats (**Figure 6**). For example, the Hf in rats has a tri-laminar structure with an interlocking DG and Hp (Ammon's horn), and is positioned between the cerebral cortex and thalamus. The Hf in birds, by contrast, appears to be quite simple and is a largely undifferentiated structure situated on the dorsal surface of the brain along the midline. To date, there is no general consensus about which subdivisions of the avian declarative memory system correspond to its mammalian counterparts. At best, the field seems to be converging on the conclusion that the avian Hf contains homologues for at least some of the mammalian MTL. In particular, many researchers conclude that the avian V-shaped region (V) and dorsomedial region of the Hf (DM) are homologues for the DG and Ammon's horn, to some extent (Atoji *et al.,* 2016). In addition, the dorsolateral region of the Hf (DL; Herold *et al.,* 2019; although defined as area parahippocampalis in some atlases; APH; Karten and Hodos; 1967) is often cited

as a homologue of the EC (reviewed in Colombo and Broadbent, 2000; **Table 1**). No literature, to the best of my knowledge, identifies possible homologues of the parahippocampal regions (PRhC and PHC/PoRhC).

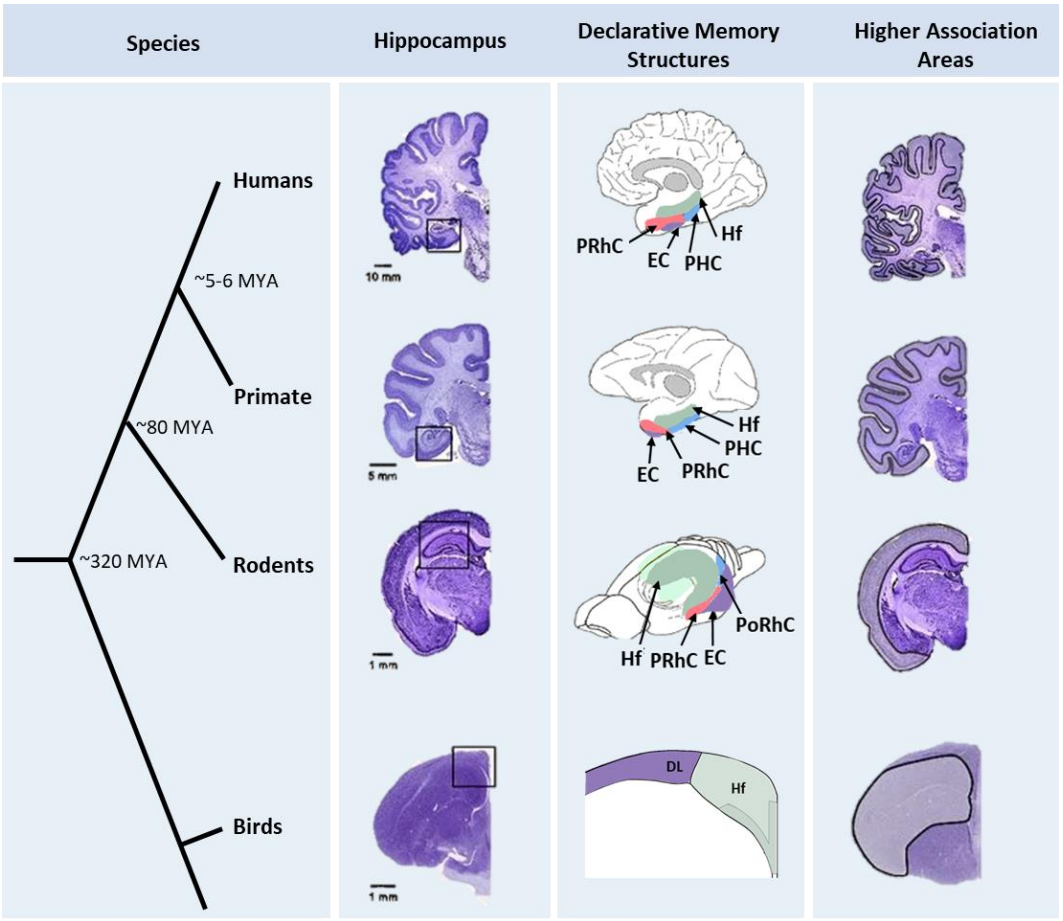


Figure 6. Cross-Species Comparison of Hippocampal Declarative Memory System Structures. A phylogenetic tree is depicted (far left) with date of last common ancestor at each node. Middle left, anatomical comparison of the location of the hippocampus in each species. Note the distinct structures within the mammalian hippocampus compared to the undifferentiated, dorsally situated, avian hippocampus. Middle right, anatomical comparison of the location of structures associated with the hippocampal declarative memory system. Note the conserved

relative locations of structures among species. Far right, comparison of the location of higher association areas. Neocortical areas in mammals and associational areas of the avian dorsal ventricular ridge are outlined. DL, dorsolateral region; EC, entorhinal cortex, Hf, hippocampal formation; PRhC, perirhinal cortex; PHC, parahippocampal cortex; PoRhC, postrhinal cortex. Adapted from Allen and Fortin (2013).

Table 1. Proposed Avian Homologues of Mammalian Hippocampal Declarative Memory System (HDMS) Regions.

Mammalian HDMS Region	Proposed Avian Homologue
Ammon's Horn or Hippocampus Proper (Hp)	Dorsomedial region (DM)[1]
Dentate Gyrus (DG)	V-shaped region (V) [1]
Entorhinal Cortex (EC)	Dorsolateral region (DL) [2]

[1] Atoji and colleagues (2016), [2]Colombo and Broadbent (2000).

In the following section, I will outline connectivity between proposed homologues within the avian memory system. On the basis of this connectivity, I will propose a memory circuit that may be comparable to the mammalian MTL hierarchy of connectivity. Then, I will focus on what is known about the proposed homologous structures on the basis of function via lesion studies.

1.3.1 Hierarchy of Connectivity

Study of the HDMS in Aves presents many challenges. First, there are several different ways of dividing the avian Hf and surrounding areas and a single nomenclature has yet to be agreed upon. In the simplest model, the avian hippocampal memory system was traditionally divided into two areas, the Hf (defined as a V-shaped medial area) and area parahippocampalis

(APH) a thin, poorly delineated structure overlaying the dorsal portion of the lateral ventricle (Karten & Hodos, 1967). Extensive anatomical studies conducted by Atoji and Wild (2006) suggested a different method of division, based on what is known about connectivity in the avian Hf. Atoji and Wild's model defined the avian Hf as the pallial area medial to the paraventricular sulcus (**Figure 7**). When comparing the two models, what Atoji and Wild (2006) proposed as a homologue to the avian Hf (areas DM, V, and the triangular region positioned within V (Tr)) ultimately encompasses Karten and Hodo's (1967) proposed Hf in addition to the medial portion of the APH. While other models have been described (see Székely, 1999), connectivity will be described in reference to the Atoji and Wild (2006) model. In addition to differing regional divisions, the second challenge facing avian memory system studies is the absence of a universally agreed upon nomenclature. For this reason, I will be using nomenclature consistent with Atoji and Wild (2006).

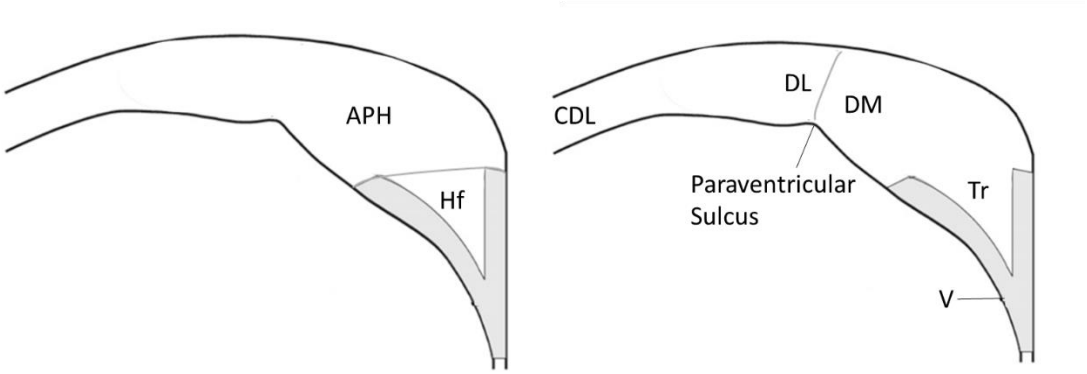


Figure 7. Common Divisions of the Avian Hippocampal Declarative Memory System. Left, Karten and Hodos (1967) divisions. Right, Atoji and Wild (2006) divisions. APH, area parahippocampalis; CDL, dorsolateral corticoid area; DL, dorsolateral region; DM, dorsomedial region; Hf, hippocampal formation; Tr, triangular region; V, V-shaped region.

To review, the HDMS shows strong evidence of homology across Mammalia. Briefly, within this hierarchy, multimodal information enters into parahippocampal regions from association cortices of the neocortex, is passed onto the EC and then terminates within the Hf. From a comparison of primate and rat studies, there is support that the hierarchy of HDMS connectivity and functional specialization are conserved across the mammalian species studied. Differences primarily arise when considering neocortical inputs to the hierarchy of the HDMS from differing modalities as well as how strictly information within the hierarchy conforms to the 'what' and 'where' streams. When comparing mammalian connectivity to avian, the neocortex may provide a useful starting point in examining avian declarative memory systems.

The pallium is the dorsal division of the telencephalon that in mammals gives rise to the neocortex and other cortical and non-cortical structures (Medina & Abellán, 2009). In Aves, the pallium (**Figure 8**) consists of a medially located Hf, a laterally located piriform cortex (PiC), and between the two lies what has long been regarded as the homologue of the mammalian neocortex, the hyperpallium (H, or Wulst; Karten *et al.,* 1973), and the dorsal ventricular ridge (DVR; Karten, 1969, 1997; Butler *et al.,* 2005; Ahumada-Galleguillos *et al.,* 2015)).

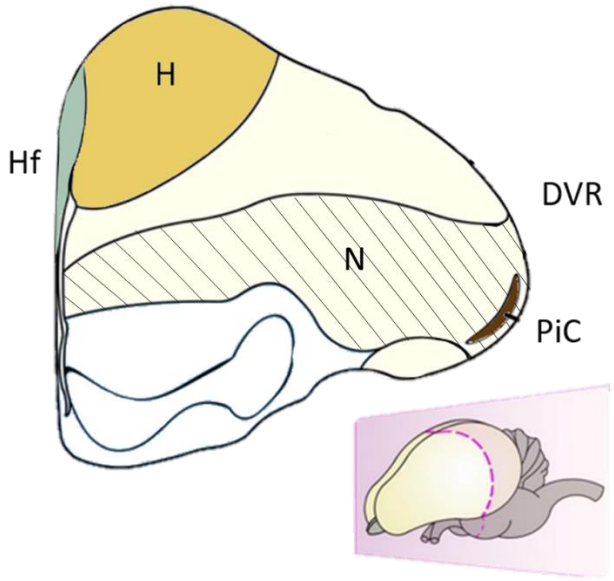


Figure 8. Avian Pallium Divisions. Hippocampal formation (Hf) in green, hyperpallium (H) in gold, dorsal ventricular ridge (DVR) in yellow, the nidopallium (N) of the DVR, striped, and the piriform cortex (PiC) in brown. Figure adapted from Montiel and Molnár (2013).

When examining connections likely to be involved in declarative memory systems, areas within the nidopallium (N) of the DVR, called the caudoventral nidopallium (NCV) and frontolateral nidopallium (NFL), as well as the PiC and H may contribute unique sensory information. The NCV, thought to be equivalent to the avian caudomedial nidopallium described in Kröner and Güntürkün (1999), is likely the avian equivalent of the auditory association cortex in the mammalian temporal lobe (Atoji & Wild, 2005). The NFL appears to be a convergence region for the thalamofugal and tectofugal pathways (Husband & Shimizu, 1999). This is of interest when comparing avian to mammalian literature because the tectofugal pathway was thought to be involved in local stimulus identification, while the thalamofugal pathway has often been attributed to visual information used in spatial learning, potentially comparable to mammalian 'what' and 'where' streams (Budzynski *et al.,* 2002;

Mayer *et al.,* 2013; but see Bischof and Watanabe, 1997). Since both the thalamofugal and tectofugal pathways converge within the association cortex, it is unlikely that these streams are separated and processed in parallel throughout the remainder of the avian declarative system. However, whether there is a different division and maintenance of parallel information processing in the avian brain is unknown.

Another area likely to contribute unique sensory information is the PiC. This structure is critical for avian olfaction (Gagliardo *et al.,* 1997), comparable to its mammalian homologue (Bekkers & Suzuki, 2013) and projects directly to Hf (Atoji and Wild, 2006; but see Striedter, 2016). Finally, the H is a presumptive homologue to the mammalian primary visual and somatosensory cortices (Fernández *et al.,* 2020), receiving inputs from the tectofugal pathway as well as the piriform cortex (Atoji *et al.,* 2016)

While the NCV, NFL, PiC, and H all display a large amount of connectivity, only connections to proposed areas of interest for the study of avian declarative memory will be discussed. Since the DM, Tr, and V are considered to be homologues of the mammalian Hf and since details of connectivity within the Hf were not discussed for primate or mammals, connections with respect to components within the Hf will not be discussed and the region will instead be treated as a whole. Since the literature to date does not make a distinction between homologues of lateral and medial entorhinal cortex, the DL will be treated as homologous to the entire entorhinal cortex (**Figure 9**). Additionally, since the border between the DL and the dorsolateral corticoid area (CDL) is not defined (Atoji and Wild, 2006), connectivity of each will be discussed to see if they differ in a way comparable to that observed between or within mammalian parahippocampal or EC regions.

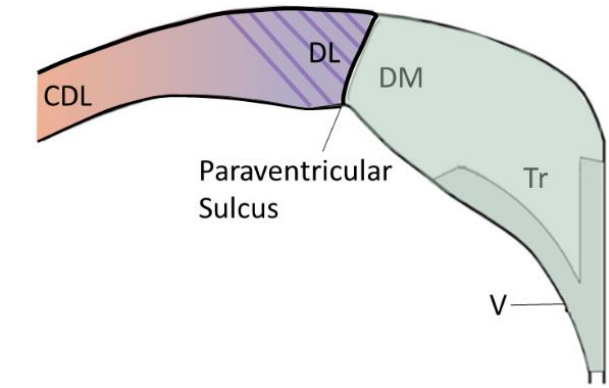


Figure 9. Divisions of the Avian Hippocampal Declarative Memory System Depicting Proposed Homologues. Hippocampal formation (green) and surrounding cortex (purple/orange). Since avian homologues to parahippocampal regions (i.e., perirhinal and postrhinal cortices) and entorhinal (i.e., lateral and medial portions) are unknown, this area is depicted as undifferentiated. CDL, dorsolateral corticoid area; DL, dorsolateral region; DM, dorsomedial region; Tr, triangular region; V, V-shaped region.

To describe the connectivity within the avian HDMS, discussion will progress from the most lateral to the most medial pallial structures, through areas commonly considered to be the backbone of the avian memory system (Behroozi, *et al.,* 2017), the CDL, DL, and Hf. Considering that the mammalian HDMS converges onto the Hf, this will also provide a framework for comparison between Mammalia and Aves. The CDL shows strong connectivity with the Hf (Atoji & Wild, 2005; Herold *et al.,* 2019), making it a likely critical structure in memory formation. The main sources of afferents to the CDL include DVR areas (NCV and NFL), PiC, and H, implying that this area receives multimodal sensory information including that of

'what/where' streams, olfaction, and audition. Another structure receiving input from a large number of pallial areas is the DL, which receives sensory input from the PiC, and H, which also have reciprocal connections with one another (Bingman *et al.,* 1994; Atoji & Wild, 2006). The DL in turn sends inputs to structures within the Hf (Atoji & Wild, 2004). Since the boundaries between CDL and DL are unknown, connectivity between the two regions is difficult to determine. Additionally, whether these structures operate in parallel or in series is unknown. The proposed avian memory system connectivity diagram is shown in **Figure 10**. While this connectivity model does not take into account connections terminating on different portions within structures, this is meant to serve as a starting point for investigating functional differentiation within the avian declarative memory system that may be comparable to those observed in the mammalian MTL.

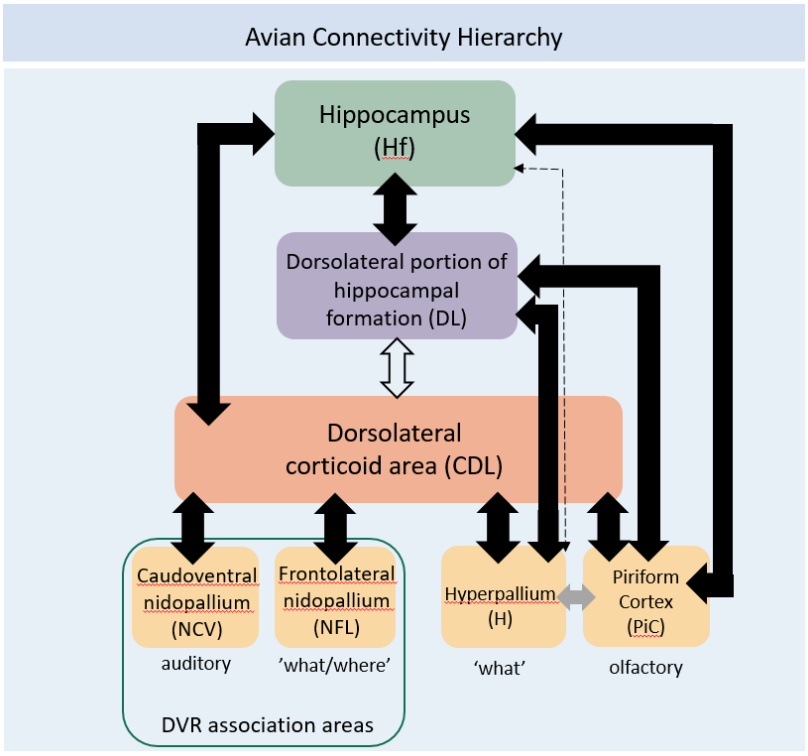


Figure 10. Proposed Avian Hierarchy of Connectivity. Within the hierarchy, sensory information converges upon higher order association areas (yellow); the caudoventral nidopallium (NCV) and frontolateral nidopallium (NFL) of the dorsal ventricular ridge (DVR), hyperpallium (H), and piriform cortex (PiC). NCV, NFL, H, and PiC project to the dorsolateral corticoid area (CDL, orange). H and PiC also send projections to the dorsolateral portion of the hippocampal formation (DL, purple). PiC sends additional projections directly to the hippocampal formation (Hf, green). Streams from CDL and DL then converge within the Hf. Since the border between CDL and DL is undetermined and differentiation may instead follow a gradient, connections between the two regions are depicted using a clear double headed arrow. Double-headed arrows indicate bidirectional connectivity. Black arrows indicate connectivity between levels of the connectivity hierarchy. Dashed arrow indicates a weak connection between the H and DM as noted in Atoji and Wild (2006). Adapted from Allen and Fortin (2013).

When considering connectivity, there is a considerable amount of homology between the avian and mammalian HDMS. In both orders, this system has the following features: 1) information from various sensory modalities converges onto association areas, 2) from these association areas, all outputs are processed through a series of intermediary structures (with olfaction having the least amount of processing, at least in pigeons (Atoji & Wild, 2006) and rats (Mouly & Di Scala, 2006)), and 3) information processed within these intermediary structures ultimately converges on the Hf.

1.3.2 Functional Contributions

Popular nomenclature once again changes when discussing functions of HDMS structures and tends to incorporate regions proposed by Karten and Hodos (1967), with those of Atoji and Wild (2006). In this model (**Figure 11**), the Hf covers the area medial to the paraventricular sulcus, encompassing Atoji and Wild's (2006) DM, Tr, and V. APH extends laterally to the paraventricular sulcus, encompassing Atoji and Wild's (2006) DL. Since the boundaries between CDL and APH are poorly understood, exact coordinates vary according to the atlas and species used but it is, very generally, lateral to the APH (Atoji and Wild, 2005).

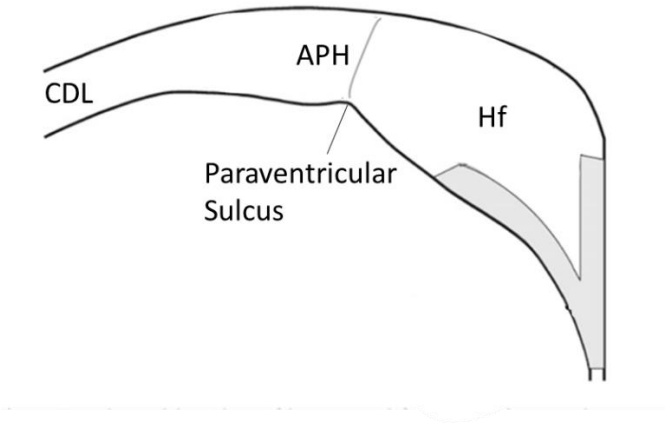


Figure 11. Avian Structural Divisions Commonly Used in Lesion Studies. APH, area parahippocampalis; CDL, dorsolateral corticoid area; Hf, hippocampal formation.

Consistent with the primate and mammal discussions, evidence of functional roles of areas of interest will be restricted to experiments conducted via lesion study. However, within the avian lesion literature, additional problems arise as Hf and APH (as defined in **Figure 11**) are often lesioned together, making it difficult to interpret if and how these structures contribute uniquely to memory. This problem also arises with CDL because lesions involving this structure

are typically included with, or it is damaged in the process of, lesioning structures deeper within the lateral telencephalic wall (Atoji & Wild, 2005). In the only existing study where CDL function was examined, the only conclusion drawn was that lesions to this area did not impair performance during delayed alternation (Gagliardo *et al.,* 1996).

Before beginning a discussion of possible functional contributions to declarative memory, there is another problem in the avian literature that hinders a comparative analysis between amniotes. Since a large proportion of avian research to date has been inspired by behaviours exhibited by a relatively small number of species, such as homing and caching, few testing methods and results are generalizable across the class. Moreover, these species-specific tasks do not provide the framework needed for comparative analysis between amniotes. When limiting avian functional discussion to tasks also used in assessing mammalian memory, an already limited body of literature becomes even more scant. For the purpose of comparison, discussion of avian HDMS functional contributions within the scope of this dissertation will be limited to tasks also used in analysis of mammalian models.

1.3.2.1 Spatial Processing

In the search for avian homologues of structures within the mammalian HDMS, there is, by a wide margin, the most information concerning the avian Hf. To date, there are several lines of evidence supporting homology between the rat and avian Hf (see Atoji and Wild, 2006, for review). For example, similarities between the avian and mammalian Hf are seen during development, as both appear to develop from the same region of the embryonic forebrain (Gupta *et al.,* 2012; Gupta *et al*., 2020); hippocampal afferent and efferent projection patterns are similar (Casini *et al.,* 1986; Székely, 1999); regional neurotransmitters are similar (Krebs *et*

al., 1991; Herold *et al.,* 2014); and function is widely regarded as homologous. As previously stated, results from lesion studies should be treated with caution as it cannot be determined if deficits observed are a result of lesioning Hf or APH.

Similar to the function of the mammalian Hf, the avian Hf and APH are also thought to be critically involved in spatial memory. By lesioning the avian Hf and APH, multiple studies have reported consequent deficits in tasks involving the processing of spatial information (see Macphail, 2002, for review). Such tasks include: spatial discrimination (Hampton & Shettleworth, 1996a; Watanabe, 1999; Broadbent & Colombo, 2000; Watanabe, 2001), spatial DMS (Good & Macphail, 1994); spatial alternation in a T-maze (Reilly & Good, 1987; Hampton & Shettleworth, 1996b); analogues of the Morris water maze (Fremouw *et al.,* 1997; Watanabe & Bischof, 2004); and analogues of the radial maze (Colombo *et al.,* 2001).

1.3.2.2 Non-Spatial Processing

When it comes to non-spatial processing within the avian HDMS, very little is known and, yet again, the only source of data to draw conclusions from are from Hf/APH lesion studies. If a task shows no disruption following Hf/APH lesion, the cognitive demands are likely independent of the structure, or at the very least, the task can be accomplished using an alternate memory system. By carefully controlling for spatial confounds, Hf/APH lesions in birds have been shown to spare performance on visual discrimination and reversal learning (reviewed in Broadbent & Colombo, 2000; Colombo *et al.,* 2001), visual DMS (Good & Macphail, 1994; Colombo *et al.,* 1997a), and concurrent discrimination tasks (Colombo, *et al.,* 1997b). These findings do not point to which structure in the avian HDMS may be critical for these

functions. At best, they suggest that the combination of Hf and APH does not appear to be critically involved in non-spatial processing.

1.3.2.3 Functional Models

1.3.2.3.1 Dual-Process Model

Following the review of the mammalian literature, it is clear that the mammalian Hf is not exclusively involved in spatial memory and is also involved in combining multiple features of an episode to form a multifaceted, even non-spatial, representation critical to recollection. For example, Fortin and colleagues (2004) showed that Hf lesions resulted in impaired recollection for associations of odour paired with digging media but spared odour familiarity.

Thus far, the discussion of avian literature almost exclusively supports the idea that the avian Hf is involved in spatial memory, but its role in recollection when associations are between non-spatial elements remains largely unexplored. Coppola and colleagues (2014) addressed this by testing pigeons on a discrimination task in which both the quality and quantity of a food source was to be associated with a certain colour of food cup. This experiment revealed no difference in performance between sham and Hf lesioned pigeons, leading the authors to conclude that the avian Hf, unlike its mammalian counterpart, is not involved in integrating non-spatial elements into a unified memory (non-spatial recollection). These findings are consistent with a previous study from the same lab in which lesions to the Hf spared performance on a paired associate task (Bingman *et al.,* 1998). However, results from these studies should be treated with caution. Unlike the findings of Fortin and colleagues (2004), which incorporated multimodal elements, the testing procedures outlined in Bingman and colleagues (1998) and Coppola and colleagues (2014) could be accomplished using only

visual information and could therefore, assuming homology with mammalian models, be mediated solely by parahippocampal structures (Bunsey & Eichenbaum, 1993).

1.3.2.3.2 Binding of Item in Context

Since it is unknown if the avian Hf serves as an integration hub for item and context information, evaluating the avian HDMS in terms of the BIC model cannot be accomplished using the available data.

1.3.3 Summary

When comparing the HDMS connectivity across Mammalia and Aves, there are some clear similarities. For example, animals within both classes seem to display a hierarchical structure in which information from various sensory modalities converges within association areas, is then projected to intermediary structures, and ultimately converges within the Hf. How structure translates to function within the avian HDMS is much less clear, with the only consensus being that 1) the avian Hf is critically involved in spatial memory, and 2) that non-spatial memory relies on structures outside of the Hf. While both of these point to some level of homology between Mammalia and Aves, the data is not substantial enough to provide convincing support for conserved function.

1.4 Current Experiments

Throughout this chapter, the connectivity and function of the HDMS have been examined through comparison between primates and rats, as our best understood models from Mammalia, and from Aves, as our most widely-researched non-mammal Amniote. Generally, the literature supports the idea that both connectivity and function in the HDMS is largely

conserved across Mammalia, suggesting that major species differences in declarative memory abilities likely arise as the result of changes in cortical input. There is also evidence of conserved connectivity patterns in Aves, although the data are limited relative to Mammalia, and as a result functional contributions remain largely undetermined in many regards.

Two of the largest obstacles hindering comparisons of the HDMS between Aves and Mammalia are 1) a lack of standardized testing procedures for use across Aves, analogous to procedures used in mammals, and 2) a lack of lesion specificity to establish functional contributions of proposed structural homologues to performance on declarative memory tasks. In regards to the first issue, Chapter 2 of my dissertation aimed to establish testing procedures for studying avian memory within a conventional laboratory setting. Closely mimicking testing conditions under which our knowledge of the rat HDMS has been collected allowed for a more direct comparison of performance between aves and rats.

Using the testing procedures established in Chapter 2, the functional contributions of portions of the HDMS were tested following selective lesions across either the mediolateral axis (Chapter 3) or the rostrocaudal axis (Chapter 4) in an attempt to characterize the functional heterogeneity of the HDMS along these axes. Finally, in Chapter 5 the HDMS models presented here are updated to incorporate the knowledge obtained through these lesions studies and the potential homology between Aves and Mammalia are reassessed.

Chapter 2: Reaction to Novelty as a Behavioral Assay of Recognition Memory in Homing Pigeons and Japanese Quail

2.1 Abstract

Spontaneous novelty preference is apparent in a wide array of animals, including mammals, birds, reptiles, and fish. This provides a powerful behavioral assay to assess whether an animal can recognize a diverse array of stimuli in a common paradigm. Surprisingly, no research has been conducted in birds using novelty approach under conditions comparable to the spontaneous object recognition (SOR) protocols that have become standard across other animals. To correct this, the current study adapts a number of SOR protocols commonly used in mammals to characterize novelty approach in silver king pigeons and Japanese quail. We show that, in general, both quail and pigeons readily approach novel objects or locations when tested using SOR protocols, although pigeons show a neophilic response under some conditions in which quail do not. Neither quail nor pigeons readily approach objects in novel contexts or novel locations. These data show that SOR can be successfully adapted to birds, allowing for more direct comparison between mammals and birds in tasks of shared ecological relevance.

Chapter taken from: Damphousse, C. C., Miller, N., & Marrone, D. F. (2022a). Reaction to novelty as a behavioral assay of recognition memory in homing pigeons and Japanese quail. *Learning & Behavior*, *50*(1), 167-177.

2.2 General Introduction

The novelty detection has broad implications for survival. For example, the investigation of novel places and objects within an environment can create opportunities to gather information (Hughes, 1997). Consistent with this idea, many animals, including mammals, birds, reptiles, and fish, will spontaneously and preferentially spend more time dwelling near and investigating novel objects (Hughes, 1997; Blaser & Heyser, 2015). While investigation of novelty can be beneficial, avoidance of novelty may be favored by selection in predator-rich environments and is thought to drive species specific characteristics such as niche breadth, diet, and home range size (Greggor *et al.,* 2016). Because there are large selective pressures driving the detection of novelty, capitalizing on this ability offers a robust behavioral assay to assess the extent to which different animals will spontaneously recognize an object as novel when either the object's physical characteristics or its relationship to its surroundings is altered.

Here we utilize a series of four tests commonly used to assess novelty detection: Spontaneous Object Recognition (SOR; e.g., Ennaceur & Delacour, 1988; Bevins & Besheer, 2006), SOR with Systematic Variation (SOR-SV; e.g., Burke *et al.,* 2011), Conjunctive Object Recognition (COR; e.g., Eacott & Norman, 2004), and Y-maze Discrimination (YMD, Lalonde, 2002). The SOR and SOR-SV protocols manipulate the physical characteristic of an object (e.g., size, shape, configuration) while COR manipulates aspects of the object relative to its environment (e.g., location, context in which an object appeared). While SOR, SOR-SV, and COR rely on a subject's ability to remember characteristics of an object and detect novel changes within them, YMD relies on the ability to remember familiar spatial locations and demonstrate a reaction when a novel location is made available. For each of these tests, reaction to novelty is commonly described in

one of two ways: a preference to explore the detected novelty (neophilia), or avoidance of novelty (neophobia). In both types of exploration, a deviation from random proximity to an object indicates that change is detected and the subject can differentiate between the novel and familiar stimuli (Bevins & Besheer, 2006).

Although these studies have been conducted over multiple taxa, comparison is difficult as methods and experimental design tend to vary within the literature. For this reason, the current study adapts protocols that have become the *de facto* standard for testing in mammals to characterize novelty approach in two species of birds – pigeons (*Columba livia*) and Japanese quail (*Coturnix japonica*). In many ways, birds are the ideal candidates for broadening standardized novelty detection paradigms to non-mammalian species. Birds (and pigeons in particular) have inspired an immense body of literature studying their perception of objects (reviewed in Soto and Wasserman, 2014). However, no research to date on object recognition in birds has explicitly tried to match testing conditions used within rat studies, despite the potential for these data to provide a direct comparison across orders using a common task. Generating such data facilitates bridging the procedural gaps between the considerable literatures regarding rat object memory and avian object perception.

2.3 Experiment 1: Spontaneous Object Recognition

2.3.1 Introduction

To begin assessing avian novelty detection in a way comparable to existing mammalian literature, we began with the most basic of the tests selected: SOR. The most widely implemented variation of SOR utilizes a sample and choice phase. During the sample phase, the subject encounters two identical objects within an arena. The subject is then removed and placed in a holding cage before returning to the enclosure for the choice phase, in which the subject encounters a familiar object (i.e., an object that is identical to those used during the sample phase) and a visually distinct novel object. If the subject discriminates between the novel and familiar objects, then a behavioral response (typically in the form of novelty approach) is observed.

The simplicity of SOR's experimental design is one of the many reasons this paradigm has become one of the dominant means to assess a wide range of cognitive functions (Blaser & Heyser, 2015). Because SOR tests are predominantly one-trial memory tests that do not require learning, they can be rapidly assessed. Moreover, SOR is well suited for a number of manipulations to evaluate neural function, as this paradigm provides a single unambiguous window within which memory function can be facilitated or impaired (Ennaceur, 2010).

Testing SOR in a variety of mammals, including lab reared rats (e.g., Ennaceur & Delacour, 1988), mice (e.g., Dodart *et al.,* 1997), and domesticated pigs (e.g., Moustgaard *et al.,* 2002), reveals an ability for these subjects to discriminate between objects, commonly showing

a tendency to explore novelty. Testing of avian species explicitly matching the rat protocol outlined by Ennaceur and Delacour (1988), has yet to be conducted. Based on previous alternative tests in birds demonstrating avian novelty detection (Mettke-Hofmann *et al.,* 2013; Saint-Dizier *et al.,* 2008; Sewards & Sewards, 2002) and partially occluded object recognition in chicks (Regolin & Vallortigara, 1995) we predicted that quail and pigeons will react differently to novel and familiar objects during SOR testing. If these species respond to novelty in a way comparable to lab-reared mammals, then we expected to see a neophilic response.

2.3.2 Methods

2.3.2.1 Subjects

22 adult Japanese quail (Spring Creek Quail Farms, Saint Anns, ON) and 26 Silver King pigeons (Cober Farms, Wellesley, ON) were used in this experiment. All birds were group housed on a 12:12 light cycle with ad lib access to food and water. Prior to behavioral testing, all animals were handled 15 minutes per day for at least 7 days. All procedures were approved by the Animal Care Committee of Wilfrid Laurier University and conducted in accordance with Canadian Council on Animal Care regulations.

2.3.2.2 Materials

Testing occurred in a 90 x 90 x 45 cm (l x w x h) open field arena constructed from white corrugated plastic sheeting. The interior of one wall was covered in black Bristol board to serve as an orienting cue. The arena floor was covered in wood shavings which were redistributed between trials to control for scent trails.

Objects were selected using the criteria previously outlined in Winters and Reid (2010) and were an assortment of junk objects (e.g., candle sticks, dog toys) constructed from washable materials including plastic, glass, and aluminum. Careful consideration was taken when selecting objects to ensure all were devoid of biologically relevant features such as eyes and mouths, and likenesses to food or nesting materials. The objects ranged from 10 to 20 cm in height and varied in visual and tactile characteristics. Once an object was selected for use, three copies were obtained to be used across testing sessions so that the same object was never used twice for the same bird. All objects were affixed to the floor of the testing arena using strips of hook and loop tape, preventing object movement during testing. Objects were wiped with 70% ethanol before each phase of testing. All sessions were recorded using an overhead webcam.

2.3.2.3 Testing Procedures

The testing protocol was adapted from testing in rats as described previously (Marrone *et al.,* 2011). Briefly, birds were transported to the testing room in individual cages on a rack containing all subjects. Subjects remained undisturbed on rack for 1 hour prior to testing. Three habituation sessions occurred over three consecutive days during which birds were placed individually into the arena to explore freely for 10 minutes. The experimental protocol (**Figure 12a**) consisted of a sample phase followed by a choice phase. During sample, birds were placed in the open field containing two identical objects. After 5 minutes, the bird was removed and placed into a transport cage for 1 minute. During this time, stimuli in the open field were changed to contain an object identical to those used during sample and a novel object. The subject was then returned to the open field for 5 minutes and exploration was recorded according

to the criteria provided below. The side of the arena in which the novel object was placed was counterbalanced between subjects and objects used were randomized.

2.3.2.4 Behavioural Scoring and Analysis

Exploration was defined as the bird spending time within 30 cm of an object while not preening or pecking at the surrounding walls. The time spent exploring the novel (N) and familiar (F) objects for all birds was converted into a discrimination ratio (DR) as follows: DR = (N - F) / (N + F) (Bevins & Besheer, 2006). The DR scores range from -1 (which indicates that the bird explored the familiar object exclusively) to 1 (all exploration time was spent around the novel object). Finally, a DR of 0 would indicate an equal amount of time around both objects (consistent with random chance).

The DRs were analyzed using a one-way analysis of variance (ANOVA) across species, as well as a one-sample t-test within each species comparing performance to zero (chance investigation).

2.3.3 Results and Discussion

When presented with objects to discriminate between (**Figure 12b**) both quail (t_{21} = 6.08; $p < 0.001$) and pigeons (t_{25} = 1.99; $p = 0.03$) spent significantly more time interacting with the novel object, and no significant difference was seen in the DRs generated by the two species ($F_{1,46}$ = 3.20; $p = 0.08$). These results suggests that quail and pigeons spontaneously discriminate between junk objects in an SOR paradigm, and react by spending a larger proportion of time in exploration actively investigating the novel object, demonstrating a neophilic response similar to that described in mammalian studies (Ennaceur & Delacour, 1988; Dodart *et al.,* 1997; Moustgaard *et al.,* 2002).

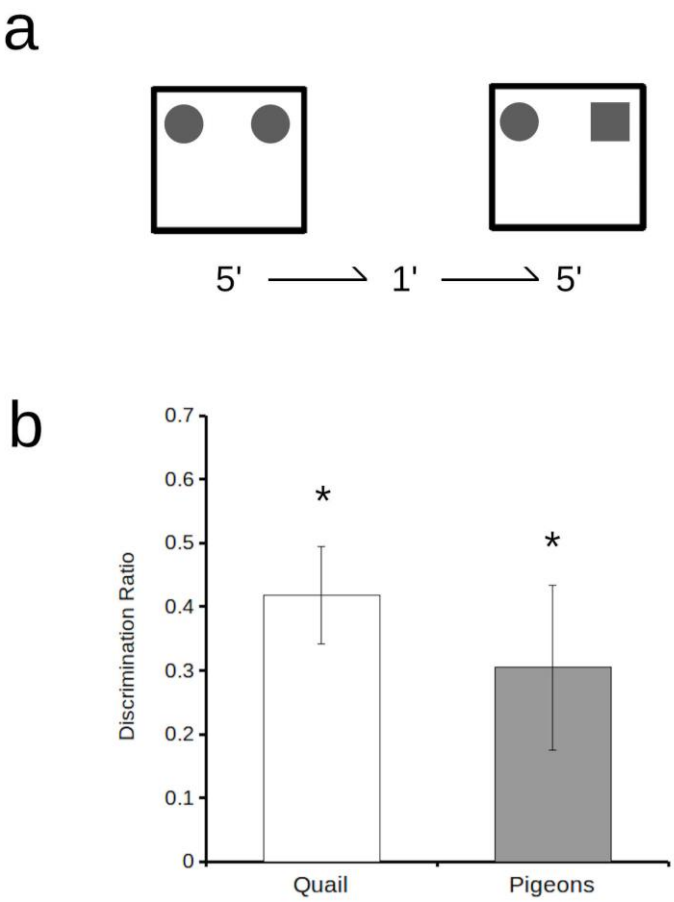


Figure 12. Spontaneous Object Recognition (SOR) in Pigeons and Quail. A schematic (a) demonstrates the placement of objects and timing of trials in SOR. Following 3 days of habituation, birds received their first sample trial (left) in an open-field containing 2 identical novel object (circles) for 5 minutes. After a delay of 1 min, birds received a second sample trial (right) in which an object that is identical to the two previously seen is presented alongside a distinct novel object (square). Calculation of a discrimination ratio (b) shows that both quail (white) and pigeons (grey) spend significantly more time investigating the novel object, since the Discrimination Ratio (DR) is greater than 0 (bars show mean ± SEM; * = $p < 0.05$ significant difference from random chance).

It is important here to stress what can and cannot be concluded from these results. When animals spend more time exploring an object, this can give an indication of what quail and pigeons spontaneously discriminate. However, when they do not differentially explore an object pair, this does not necessarily indicate that an *individual or species* cannot perceive or discriminate the objects. This is because the SOR task does not permit the dissociation of memory processes, perception, motivation, or other cognitive factors that go into performance on this task. Rewarded training would likely be required to attempt such dissociation. However, this task permits the application of novelty detection to a paradigm that is controlled, ecologically valid, and easily applied in a consistent manner across the animal kingdom. This last feature is particularly relevant considering several studies of novelty reactivity in wild-caught birds (e.g., Mettke-Hofmann, *et al.,* 2002; Stowe *et al.,* 2006 a,b; Nilsson *et al.,* 2010; Martin & Sherry, 2019) have generally reported strong neophobia, and many either state or imply that neophobia is endemic to Aves. However, avian studies of novelty reaction have typically involved placing a novel object into the bird's home cage or another location exceedingly familiar to the subject, in which no novel objects had a history of appearing. Under these same testing conditions, both wild (Cowan, 1976) and domesticated (Misslin & Ropartz, 1981) rats are also neophobic, despite their robust neophilic response within a relatively novel testing environment (Ennaceur & Delacour, 1988). This suggests that the extent to which the response to novelty is neophobic or neophilic is the result of the testing protocol, rather than the species studied.

In many respects, the observations from Experiment 1 provide baseline data for further comparison. Objects presented in Experiment 1 differed across many characteristics, including

size, shape, texture, and scent, offering multiple dimensions that could provided the basis for novelty discrimination. Now that it has been established that novelty can be detected under these conditions and elicits approach of the novel object in quail and pigeons, this positive control can be used to make further comparisons. In Experiment 2, we extend our observations by systematically varying stimuli across only the visual dimension.

2.4 Experiment 2: Spontaneous Object Recognition with Systematic Variation

2.4.1 Introduction

Given that both species discriminate novel from familiar objects in simple SOR, next we assessed whether birds are sensitive to the degree of feature overlap in reliably detecting novelty. Although the discrimination in individual subjects is digital, the probability a subject responding changes systematically with feature overlap, and as a result a graded DR is generated across levels of similarity. This graded response across the population can be used to assess manipulations that improve or degrade performance. In an effort to generate comparable graded responses in quail and pigeons, we created objects for the sample and choice phases out of LEGO® building blocks (Aggleton *et al.,* 2010; Burke *et al.,* 2011). This had the advantage of allowing us to assemble a number of identical objects, as well as affording the ability to have a series of objects all made of the same complement of building blocks, but with a set number of these blocks rearranged to create the novel object. To assess the degree of rearrangement needed for objects to be detected as novel, we implemented conditions in which 25%, 50%, and 100% of the blocks making up the structure were rearranged (**Figure 13a**). If the subjects could discriminate between two objects based on the arrangement of building

blocks, then we expected a larger proportion of time to be spent investigating the novel arrangement, comparable to findings in Experiment 1. We anticipated that the greater the percentage of re-arrangement of the building blocks, the more likely subjects would be to differentiate between them.

2.4.2 Methods

2.4.2.1 Subjects

23 adult Japanese quail and 15 Silver King pigeons were used in this experiment. Subjects were purchased from the same suppliers and were housed in the same conditions as those described in Experiment 1.

2.4.2.2 Materials

Testing took place in the same arena as described in Experiment 1. LEGO® objects were constructed so that each percent change condition (25%, 50%, 100%) had three identical sample objects and one novel object. The novel object changed only in the configuration of the top portion of pieces by a given percentage, the rest of the pieces remained identical in placement to those in the sample object.

2.4.2.3 Testing Procedure

Testing was conducted as described in Experiment 1 but with three conditions: a 25% change group in which 25% of the blocks in the LEGO® object were re-positioned, as well as a 50% change group, and a 100% change group (**Figure 13a**). Testing consisted of a sample phase with two identical LEGO® objects followed by a choice phase in which one LEGO® object was identical to those encountered during sample and the other was manipulated based on the

change condition. The order of these conditions was counterbalanced across subjects, and each test was separated by at least 24 hours.

2.4.2.4 Behavioural Scoring and Analysis

Scoring was identical to that outlined in Experiment 1. A two-way mixed ANOVA was conducted comparing similarity (i.e., 25%, 50%, 100%) as a repeated factor, as well as species. In addition, a one sample t-test was conducted for each species at each similarity level relative to a DR of zero (chance exploration).

2.4.3 Results and Discussion

Discrimination performance was affected by the degree of similarity between objects (main effect of similarity: $F_{2,72} = 7.77$; $p < 0.001$, Fig. 2b). The difference between species in this regard was not significant ($F_{1,36} = 1.28$; $p = 0.27$). Single sample t-tests showed that while both quail ($t_{22} = 5.02$; $p < 0.001$) and pigeons ($t_{14} = 9.11$; $p < 0.001$) were able to make this discrimination at the easiest level, in which 100% of the blocks are rearranged, quail did not show a significant preference for the novel object in the 50% condition ($t_{22} = 0.63$; $p = 0.53$), while pigeons did ($t_{14} = 1.99$; $p = 0.03$). In the 25% condition, both quail ($t_{22} = 0.81$; $p = 0.43$) and pigeons ($t_{14} = 0.509$; $p = 0.62$) failed to significantly prefer the novel stimulus.

These results suggest that the reactivity of quail and pigeons to a novel object declines as the objects become more physically similar. As fewer pieces were rearranged, both species investigated the novel object less, suggesting increased difficulty in detecting change or decreased motivation to explore novelty in these conditions. This trend is apparent in **Figure**

13b, however, performance of quail in the 50% and 25% condition were not indicative of novelty detection.

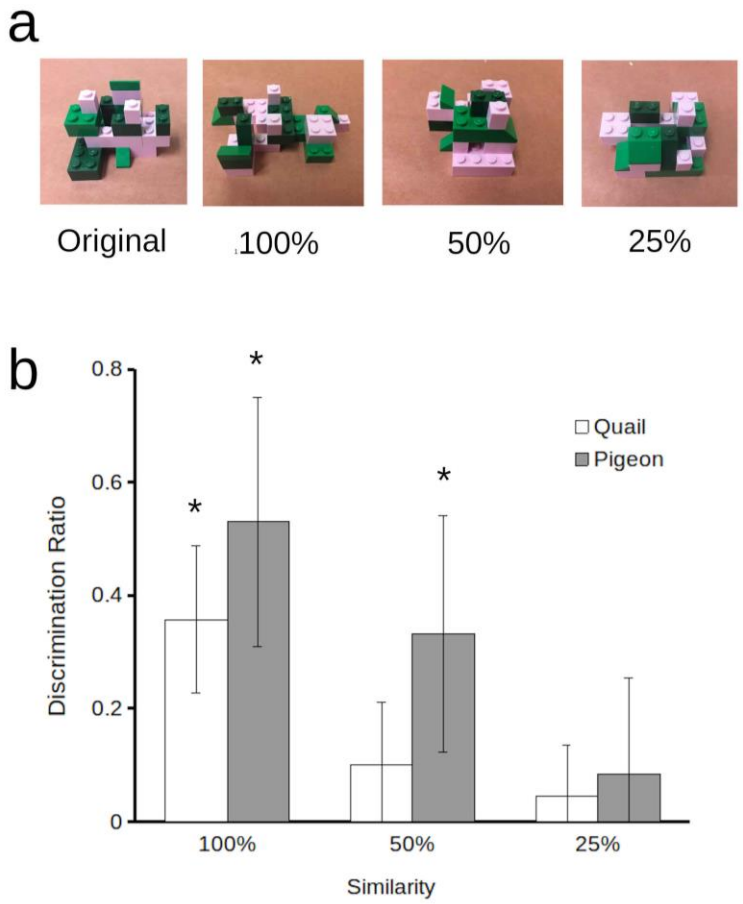


Figure 13. Spontaneous Object Recognition with Systematic Variation**.** Images (a) depict one of the arrangements of LEGO objects making up the sample object (left) and how the blocks were altered to create new objects to be differentiated by rearranging 100%, 50%, or 25% of the component blocks. Testing using the same paradigm described in Figure 12 and calculating a discrimination ratio (DR) shows that (b) both quail (white) and pigeons (grey) differentiate between objects when 100% of the component blocks are rearranged, since the DR is greater than 0. Pigeons, but not quail, differentiate between objects with 50% of the component blocks rearranged from the original, while birds from neither species spend significantly more

time investigating an object which has 25% of the component blocks rearranged relative to the original (bars show mean ± SEM; * = $p < 0.05$ significant difference from random chance).

Previous instrumental conditioning data in both species are consistent with the observed relationship between similarity and object discrimination difficulty. In quail, trials to reach criterion was lowest for a color discrimination (red vs green), moderately higher for a pattern discrimination (horizontal vs vertical lines), and highest for a form discrimination (triangle vs circle). Moreover, as the complexity of the objects increased, quail performance during pattern or form discriminations became worse, requiring more than 1300 trials to reach a criterion of 15 consecutive correct responses in a form discrimination task (Fidura, 1969; Fidura & Grey, 1966). Although pigeons learn these discriminations somewhat faster, they show a comparable trend (Towe, 1954; Williams, 1972), requiring approximately 1000 trials to reach a similar criterion in a form discrimination task. Thus, it is perhaps not surprising that a rearrangement of LEGO® objects, which keeps color consistent while altering form and pattern, creates a stimulus pair that neither bird spontaneously discriminates with limited experience under the most difficult condition. In fact, the observation that a pigeon can discriminate a 50% change in block configuration speaks to the speed with which data can be generated using the SOR paradigm. A single trial under conditions that more closely resemble foraging behaviors in the wild allows birds to demonstrate a discrimination that would require hundreds of instrumental conditioning trials to establish.

It is also notable that the current data mimic the small differences observed between quail and pigeons in instrumental tasks, with pigeons showing a significant preference for the novel configuration in the 50% when quail did not. Differences in performance between quail

and pigeons were small and statistical evidence was mixed. Thus, until a wider array of species can be tested, results must be interpreted cautiously.

Collectively, Experiment 1 and Experiment 2 suggest that both quail and pigeons (a) discriminate between novel and familiar objects, even when novelty is based on the arrangement of components of the same shape and color, (b) generally exhibit neophilia when novelty is detected, and (c) are sensitive to the amount of feature overlap when making discriminations. To further extend our understanding of novelty detection in quail and pigeons, in Experiment 3, we were interested in determining if information about the object can be bound to information about location and context.

2.5 Experiment 3: Conjunctive Object Recognition

2.5.1 Introduction

In a naturalistic setting, the context in which an object is encountered, including its physical location, and its relationships to other objects, is important for object recognition (reviewed by Ennaceur, 2010). To test whether subjects bind these characteristics to form a representation of an object and detect change, we implemented a COR task similar to that described in Eacott and Norman (2004). If the subjects behaved in a way consistent with recognition of important contextual cues in combination with object identity, then we expected them to spend a greater portion of time investigating a familiar object if that object is encountered in a new location or context. For all conditions of COR, **Figure 14** denotes the novel object with an N, this is the object expected to elicit a neophilic response.

2.5.2 Methods

2.5.2.1 Subjects

22 Japanese quail and 26 Silver King pigeons were used in this experiment. Subjects used were the same sample as those used in Experiment 1. Prior experience on Experiment 1 was not considered to affect performance on Experiment 3 as they were separated by several weeks, a different set of objects was used, and spontaneous novelty detection does not require rule learning (Blaser & Heyser, 2015).

2.5.2.2 Materials

This experiment consisted of two arenas, both identical in dimensions to those described in Experiment 1, in two different rooms. These are referred to as Context A and Context B. While one arena was identical to Experiment 1, the other had three dark grey walls and one was covered in green Bristol board. Testing rooms were located across the hallway from one another, and each contained distinct visual cues on the walls. Objects used were selected based on the same parameters outlined in Experiment 1.

2.5.2.3 Testing Procedure

Subjects were habituated to both contexts for 10 minutes a day for three consecutive days. To assess the extent to which approach could be stimulated by conjunctive object recognition (COR), subjects were exposed to novel conjunctions of objects, locations, and contexts, through a series of three conditions (**Figure 14**) adapted from Eacott and Norman (2004).

In the Object/Location condition, subjects were placed in the open field containing two distinct objects for sample training. After 5 minutes, the bird was removed and placed in a transport cage for 1 minute. During this time, one of the stimuli in the open field was exchanged for an object identical to the other sample object, so that now there were two identical objects in the open field. There was now, therefore, an object in the arena that was not novel in itself, and occupied a location in which the bird had previously seen an object, but the conjunction of object and location was novel. The bird was then returned to the open field for 5 minutes and their exploration was recorded.

In the Object/Context condition, birds were placed in the open field containing two identical objects for sample training, this will be referred to as Context A. After 5 minutes, the bird was removed and placed in their transport cage for 1 minute. During this time, the animal was transported to a second room, Context B, with distinct visual cues on the walls and a second open field of the same dimensions as Context A, containing two identical objects that are distinct from those seen in Context A. After 5 minutes in Context B, the bird was removed and placed in a transport cage for 1 minute, before being returned to Context A, which now contained one object identical to the objects encountered in Context A and one object identical to those encountered in Context B. Thus, neither object nor context are novel on their own, but one object is novel in this context. Note here that if the bird responds only to relative novelty, they will spend a lesser proportion of time around the most recently seen item, rather than the item that was not encountered in this context, indicating that the subject was not binding object and context information.

Finally, in the Object/Context/Location condition, birds were exposed to two distinct objects in the open field of Context A. After 5 minutes, the bird was removed and placed in a transport cage for 1 minute. During this time, the animal was transported to a second room (Context B) with distinct visual cues on the walls and an open field of the same dimensions to Context A. Context B contained two objects identical to those observed in Context A, but here they were presented in the opposite orientation (the object on the left in Context A was now on the right and vice versa). After 5 minutes, the bird was removed and placed in a transport cage for 1 minute, before being returned to Context A. The open field now contained two identical objects that are the same as one of the objects previously presented. Although both objects had been seen in both rooms and in both locations, one object had not been seen in this location in this room. The time spent exploring this object was recorded relative to the other object, over the course of 5 minutes. Objects used and the location of the novel object were counterbalanced for all conditions. At least 24 hours elapsed between each COR testing condition.

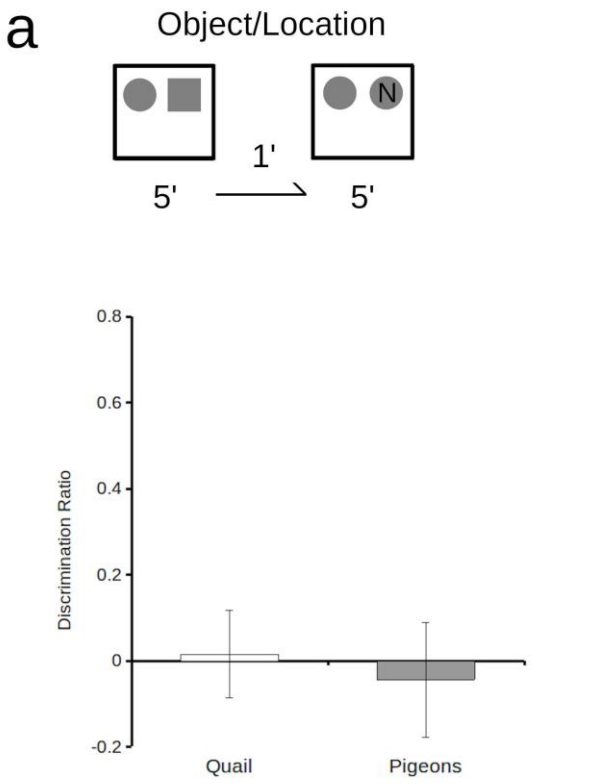
2.5.2.4 Behavioral Scoring and Analysis

Scoring was identical to that outlined in Experiment 1. DRs were analyzed using a 3 (condition: Object/Context, Object/Location, Object/Context/Location) x 2 (species) mixed ANOVA. Each individual species and condition was also evaluated using a one-sample t-test against a DR of zero (chance exploration).

2.5.3 Results and Discussion

Analysis of COR (**Figure 14**) revealed no significant main effect of condition ($F_{2,90} = 1.85$; $p = 0.16$) or species ($F_{1,45} = 0.01$; $p = 0.97$). One-sample t-tests verified that this is because

neither quail nor pigeons approached any novel conjunction of an object with a location and/or context more than expected by chance ($p > 0.05$ in all conditions). In the Object/Location (**Figure 14a**), Object/Context (**Figurer 14b**), and Object/Location/Context (**Figure 14c**) conditions, performance of quail and pigeons did not provide behavioural evidence of novel change detection. The observation that quail and pigeons do not approach novel conjunctions of object with their environment is not consistent with the rat literature. For instance, findings of Eacott and Norman (2004), which provided the basis for our experimental protocol, showed that rats behaved consistently with novel change detection in all conditions, and consistently exhibited a neophilic response. In another comparable study by Dix and Aggleton (1998), rats reliably approached the novel element across a wide range of novelty discrimination tests incorporating elements of object location within an arena, object position relative to an array of objects, and the context in which an object was presented.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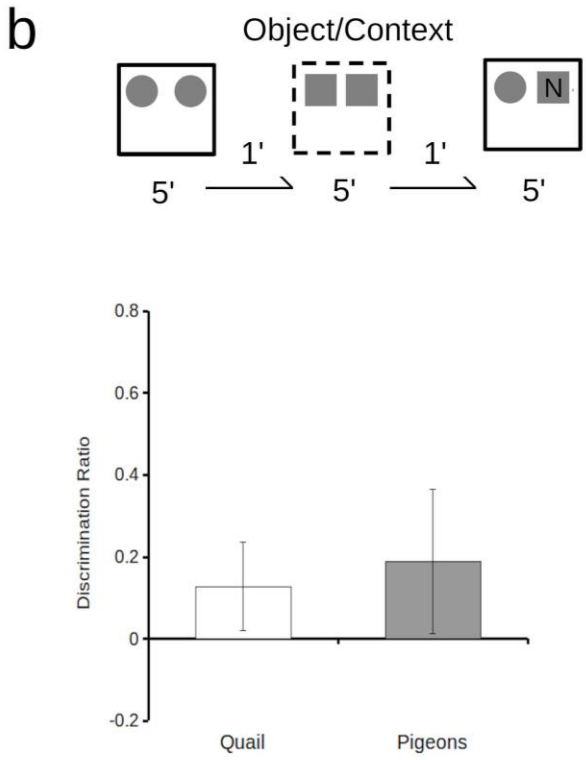
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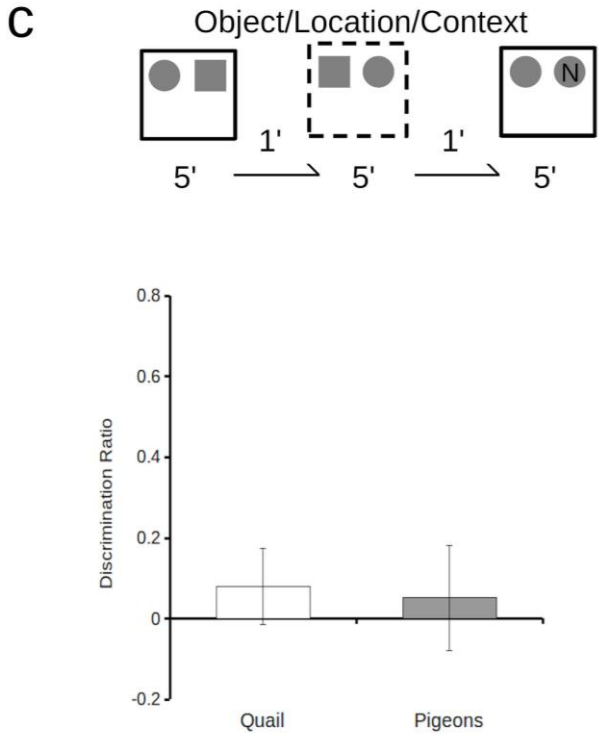


Figure 14. Conjunctive Object Recognition (COR) in Pigeons and Quail. Schematics (top) demonstrate the placement of objects and timing of trials in the Object/Location test (a), the Object/Context test (b), and the Object/Context/Location test (c). Neither quail (white) nor pigeons (grey) spent significantly more time than expected by chance investigating the novel object (N) in any condition.

The current observations lead to two distinct possibilities: (a) that the conjunction of a familiar item with a novel location and/or context does not elicit the motivation to respond with exploration, or (b) that the novelty of these conjunctions of information cannot be detected. Although no comparable data exist testing feature binding in quail, several behavioral experiments in pigeons corroborate the latter interpretation. Although pigeons can be trained

to make discriminations of object location (Leising *et al.,* 2013), their performance decays to chance levels at presentation delays of less than 10 seconds – far less than the delays encountered in SOR. Our findings are also consistent with data on pigeons' performance in a what-where-when memory task (Skov-Rakette *et al.,* 2006). Skov-Rakette and colleagues (2006) showed that, while pigeons could correctly indicate the location, identity, and time of appearance of a single cue, when they were required to respond to more than one of these features of a single item, a successful response on one feature did not predict success in the other. This suggests that although pigeons could retain information about the what, when and where of objects, they did not bind this information together in memory. Similarly, Lazareva and Wasserman (2016) found no evidence of feature binding in pigeons across multiple versions of a change detection task, even with a delay of only 900 milliseconds.

A potential explanation for behavioural observations in this task could point to deficits in detection or an unwillingness to preferentially explore novel spatial locations. Perhaps detection of novelty in quail and pigeons does not extend beyond physical characteristics of the object itself. To test this further, we implemented a test in which novelty detection relied on differentiating between novel and familiar spatial locations in the absence of object information.

2.6 Experiment 4: Y-Maze Discrimination

2.6.1 Introduction

After testing novelty seeking in relation to objects, we investigated if quail and pigeons had similar discrimination reactions to novel spatial locations. Additionally, since neither species responded to novelty via location change in the COR test, we wanted to assess if the lack of response was due to an inability to detect or an unwillingness to preferentially explore novel spatial locations. Toward this goal, birds were tested using two versions of YMD: one utilizing a single Y-maze (**Figure 15a**) and the other incorporating two Y-mazes in two distinct contexts (**Figure 15b**). During commonly used YMD protocols, an arm of the maze is blocked during the sample trial and is opened during the choice trial (Lalonde, 2002). Consistent with mammalian experiments (Kraeuter, *et al.,* 2019; Lalonde, 2002), we were interested in the amount of time that subjects spend in the novel, previously blocked arm, relative to the proportion of time in the familiar, previously open arm. If subjects preferentially explore spatial novelty in addition to the observed object novelty from Experiments One and Two, then we expected them to spend a larger proportion of time investigating the previously blocked arm. In the two Y-maze condition, subjects were challenged with remembering which arm was blocked in each of two contexts and were expected to explore the previously blocked arms in both contexts during the choice trial.

2.6.2 Methods

2.6.2.1 Subjects

15 adult Japanese quail and 15 Silver King pigeons were used in this experiment and were the same sample as those used in Experiment 2. Participation in Experiment 2 was not thought to affect performance on Experiment 4 as they were separated by several weeks, a variety of visual cues within the room and the testing apparatus were changed, and neither task required rule learning.

2.6.2.2 Materials

Two Y-mazes with arms measuring 60 x 20 x 30 cm (l x w x h) were constructed from clear acrylic so that subjects could readily see the distinct visual cues present on all four walls of the rooms. Square rod styrene tracts with removable opaque acrylic guillotine doors were installed in the two exploration arms. The floor was constructed from black haircell acrylonitrile-butadiene-styrene (ABS) and covered with wood shavings.

2.6.2.3 Testing Procedures

The testing protocol used here was adapted from rat testing procedures as described previously in Marrone and colleagues (2011). The YMD tasks consisted of two conditions, a single Y-maze condition, and another in which two Y-mazes were utilized in two separate rooms. In the first single Y-maze condition, subjects underwent three consecutive days of 10 minute habituation sessions. During the sample trial, birds were given 5 minutes of exploration with one arm of the maze blocked off by a guillotine door. Birds were then removed for 1 minute, during which time the door was removed and the bedding in the maze was replaced to remove

scent cues. Birds were then returned to the maze for a 5 minute choice trial. Which arm was blocked during the sample trial was counterbalanced across subjects.

In the two-Y-maze condition, birds were sequentially placed in two different rooms (Context A and Context B) containing distinct visual stimuli. The task consisted of four trials: two sample trials (one in each context), and two choice trials (one in each context), in the same order as during sample. In the first sample trial, the subject was placed in the start arm of the maze in Context A, facing away from the center, while one arm of the Y-maze (either left or right) was blocked with a guillotine door. Subjects were permitted to explore the Y-maze for 5 minutes. After being placed in a transport cage over a 1 minute delay, the same procedure was followed in Context B. Again, after a 1 minute delay, the subject underwent the first choice trial in which they were placed back into Context A but this time with all arms open. Following this, they were removed, placed in a transport cage for a 1 minute delay and underwent the final choice trial in Context B. The sequence of exposure to the two contexts was counterbalanced between subjects. The floor of each maze was covered with bedding, which was replaced between trials in order to eliminate olfactory cues. Recording were taken using an overhead camera.

2.6.2.4 Behavioral Scoring and Analysis

Manual scoring of videos recorded the time that the subject spent in each arm as a proportion of their total exploration time. The subject was considered to be exploring an arm if their entire torso was inside of the arm. The time spent exploring the novel and familiar arm (excluding the start arm) for all subjects was converted into a DR as described in Experiment 1. In the single Y-maze test, DRs were compared across species by one-way ANOVA. In the double-

Y-maze, analysis consisted of a 2x2 mixed ANOVA comparing species in addition to maze as a repeated factor. Each individual species and condition was also evaluated using a one-sample t-test against a DR of zero (chance exploration).

2.6.3 Results and Discussion

The pattern of behavior observed in the COR may suggest that novel spatial information does not elicit a spontaneous approach response in these bird species. Testing this hypothesis with spatial recognition refutes this possibility; both pigeons (t_{14} = 2.51; p = 0.01) and quail (t_{14} = 2.30; p = 0.02) spent more time in the previously blocked arm in the single Y-maze condition (**Figure 15a**) than expected by chance, and the performance of the two species did not differ significantly ($F_{1,28}$ = 0.084; p = 0.77). In the two Y-Maze condition (**Figure 15b**), pigeon performance differed from quail, as shown by a significant species difference ($F_{1,26}$ = 4.51; p = 0.04). One-sample t-tests verify that pigeons significantly preferred the novel arms (mean DR: t_{14} = 3.38; p = 0.002), while quail did not (mean DR: t_{14} = 1.34; p = 0.10).

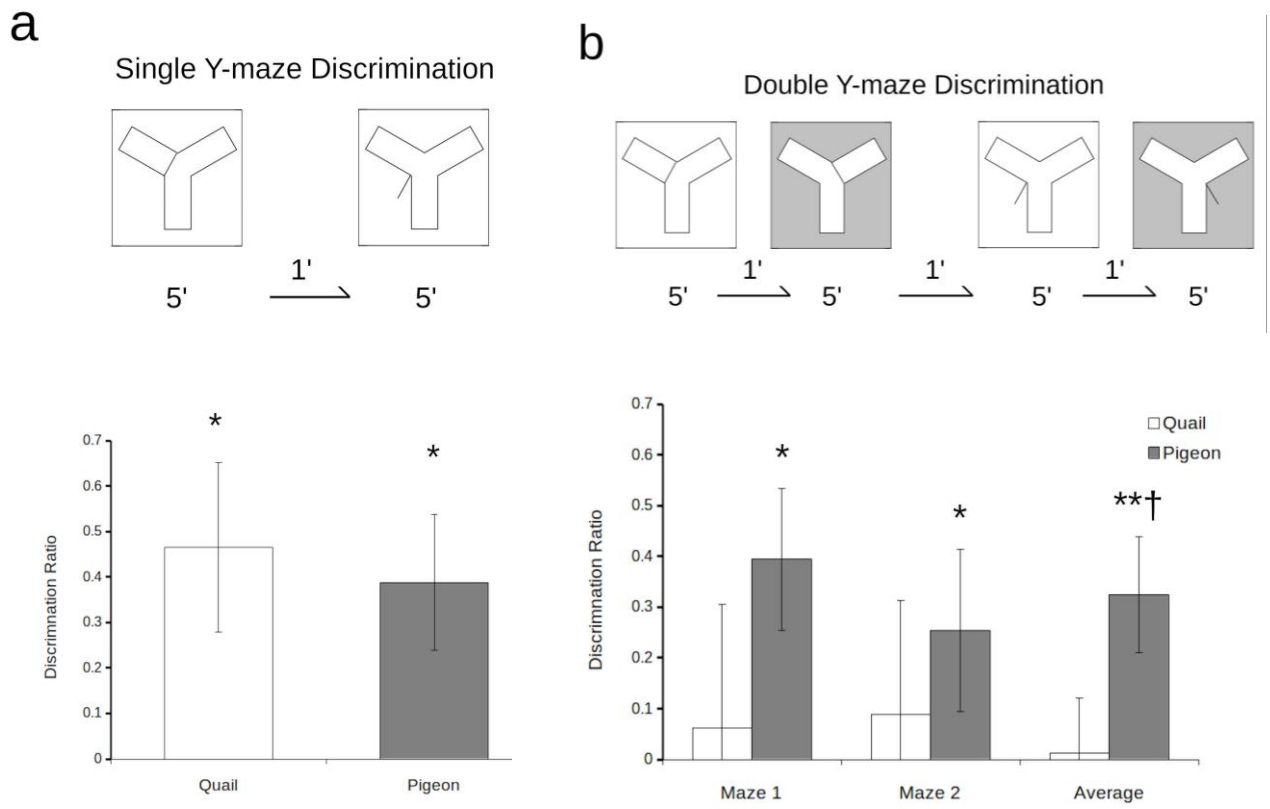


Figure 15. Reaction to Novel Spatial Locations in Pigeons and Quail. Schematics are presented above to demonstrate the timing of trials in each variation of the spatial recognition task, while data are presented below. In the single-Y-maze condition (a), both quail (white) and pigeons (grey) spend significantly more time in the arm of the maze that had previously been blocked. In the two-Y-maze condition (b), pigeons spent significantly more time in the previously blocked arm in both Y-mazes, while quail did not (bars show mean ± SEM; * = $p < 0.05$; **$p < 0.01$, significant difference from random chance; † = $p < 0.05$ significant difference between species).

These results demonstrate that while both quail and pigeons spent a larger proportion of time in the previously blocked arm, consistent with novelty detection and neophilia for novel

spatial locations. This pattern is inconsistent with the suggestions that novel spatial locations cannot be detected or do not elicit approach from birds, corroborating that failures to approach novelty in Experiment 3 were the result of an inability to form novel conjunctions of item and context information.

Notably, only pigeons made this discrimination in the two Y-maze condition. Comparing results to mammalian literature, rats readily discriminate novel from familiar arms within a Y-maze in both a single maze (Kraeuter, *et al.,* 2019; Lalonde, 2002), and two maze condition (Marrone *et al.,* 2011). Until additional species are tested, an explanation of why pigeons preferred the novel arms when presented two Y-mazes while quail did not is purely speculative. However, it is possible that species-related differences in this task may result from species-related differences in foraging strategies (Charnov, 1976; Reiss, 1987). For example, a species with a win-shift strategy might be more likely to investigate the novel arm, while a win-stay species may demonstrate hesitancy. Pigeons have been noted as having a win-shift strategy when tested within a T-maze (Olson & Maki, 1983; but see Hughes, 1989). Although information for Japanese quail is lacking, other Galliformes have a win-stay strategy (Hayes & Warren, 1963). It should be noted, however, that Hayes and Warren (1963) urged caution in this interpretation, positing that exploration of the maze may be a stressful experience and as a result removal from the maze may serve as a reward that reinforces entering the arm that the subject was last removed from on a previous trial.

2.7 General Conclusions

The current findings show that reaction to novelty can be successfully used to assess novelty detection for both discrete objects (Experiment 1 and 2) and spatial locations (Experiment 4) in both pigeons and quail. Observations of novelty detection tests described here, support their use in at least some avian species with minimal changes in protocol relative to that used for rats. Moreover, the fact that these effects are consistently observed in two families of birds (i.e., Galliformes and Columbiformes) suggests that approach to novelty may provide a robust behavioral assay across Aves.

One factor that limits the generalization of these results, however, is the fact that both species of bird tested here are highly domesticated. As pointed out by Blaser and Heyser (2015), domestication is a major predictor for reaction to novelty in rats (Minckler & Peaseh, 1938; Orgain, & Schein, 1953; Bernett, 1958). Similarly, studies of novelty reactivity in wild-caught birds generally reported strong neophobia (e.g., Mettke-Hofmann, *et al.,* 2002; Stowe *et al.,* 2006a,b; Nilsson *et al.,* 2010; Martin & Sherry, 2019), and a bird's neophobia may be predicted by the nature of the habitat from which the bird was caught, migratory strategy and diet breadth (Mettke-Hofmann *et al.,* 2013; Sol *et al.,* 2011). Although there is evidence to suggest that testing procedures may account for this difference (as described in Experiment 1), the neophilic reaction observed in Experiments 1, 2, and 4 should be replicated in wild-caught species. It will be important to assess behavioral differences in domesticated and wild birds during comparable novelty testing – the responses of wild birds under these standardized protocols remains to be addressed.

Despite this open question, it is clear that in Experiments 1, 2 and 4, that both novel objects and novel locations readily elicit a neophilic response in both pigeons and quail. These observations lay the foundation for further apples-to-apples comparisons of the neurobiology of novelty detection across taxa using SOR. The neural circuits underlying these behaviors are very well characterized in rats, in part because of dissociation that can be observed by varying standardized testing protocols. Many of the variations in novelty detection tasks (including those used here) exist in part because interventions that perturb only one of these circuits alter performance on some variations of this task and not others. Searching for similar dissociation in birds can provide unique insight into the functional homologies that exist across taxa and allow the placement of object recognition memory within the framework of an evolutionary basis of multiple memory systems (Sherry & Schacter, 1987).

The fact that our findings show similar results across taxa also raises the question of whether novelty detection and neophilia in general are evolutionarily conserved or if these traits have independently evolved in two classes. The observation of neophilic responses to novel objects in fish, reptiles, amphibians, and a variety of invertebrates (reviewed in Blaser & Heyser, 2015) suggests that this may be a trait shared by much of the animal kingdom. More importantly, it suggests that the response to novelty when it is detected (i.e., approach or avoidance) is likely the product of the exact testing procedures and behavioral history of individual animals. The systematic manipulation of these conditions within the framework of standardized testing holds the most promise of understanding novelty detection and object recognition across taxa. It is the outliers that will provide the greatest insight into the basis for this cognitive ability and the circumstances under which adaptive specialization might sculpt it, in much

the same way that insight into spatial cognition in birds has been gained largely through the study of birds with exceptional spatial abilities, such as food caching (Sherry & Hoshooley, 2007; Sherry, 2014a,b).

Chapter 3: Dissociation of Spatial and Object Memory in the Hippocampal Formation of Japanese Quail

3.1 Abstract

The mammalian temporal cortex can be functionally segregated into regions that encode spatial information and others that are predominantly responsible for object recognition. In the present study, we report comparable functional segregation in the avian brain. Using Japanese quail, we find that bilateral lesions of the hippocampus (Hf) produce robust deficits in performance in a foraging array (FA) spatial memory task, while sparing spontaneous object recognition (SOR). In contrast, lesions to the adjacent area parahippocampalis (APH) compromise both SOR and FA. These observations demonstrate a functional dissociation between Hf and APH that is comparable to the distinctions seen in mammals between the hippocampus and surrounding temporal cortex.

Chapter taken from: Damphousse, C. C., Miller, N., & Marrone, D. F. (2022b). Dissociation of Spatial and Object Memory in the Hippocampal Formation of Japanese Quail. iScience, 103805.

3.2 Introduction

The hippocampus (Hf) and surrounding medial temporal lobe (MTL) structures have long been identified as critical neural circuits supporting memory, especially memory for spatial information (O'Keefe & Nadel, 1970). Recent work has shown that declarative memory can be functionally segregated both within and between structures of the MTL (Lee *et al.,* 2017; Strange *et al.,* 2014; Winters *et al.,* 2004). The hippocampus and each of the surrounding cortical structures, including the entorhinal cortex (EC), make unique contributions to the computations supporting declarative memory function (see van Strien *et al.,* 2009, for review). One important distinction is in the processing of spatial and non-spatial (e.g., object identity-based) information – with the Hf being critical to the former and often unnecessary for the latter (Eichenbaum & Lipton, 2008; Kneirim *et al.,* 2013).

The avian Hf is often proposed as the homologue to its mammalian counterpart because of similarities in development, connectivity and neurotransmitters, and because of its critical role in spatial cognition (see Székely, 1999; Colombo & Broadbent, 2000; Atoji & Wild, 2005 for review). Although many ways of dividing the avian hippocampal formation have been proposed (e.g., Erichsen *et al.,* 1991; Montagnese *et al.,* 1996), two methods are most commonly utilized. The first and most simplistic model describes two subdivisions, the Hf and area parahippocampalis (APH) regions (Karten & Hodos, 1967, Székely & Krebs, 1996). In the second, regions are described as the ventral (V), dorsomedial (DM), and dorsolateral (DL) subdivisions (Atoji & Wild, 2005), although these areas are often further subdivided (Atoji & Wild, 2006). Combining these two models, the Hf is largely comprised of the V and DM areas while the APH corresponds to

the DL. Although the inclusion of more subdivisions is more accurate, here we opt for consistency with the previous lesion studies that inform this research and refer to these areas as simply the Hf and APH. These previous studies have often ignored the boundaries between these two regions and destroyed both Hf and APH (e.g., Good, 1987; Colombo *et al.,* 2001; Kahn & Bingman, 2004; Broadbent & Colombo, 2000; Johnston *et al.,* 2021). This is in part because multiple methods of dividing the avian Hf exist, and in part because of early data demonstrating that damage to either Hf or APH result in comparable spatial memory impairments (e.g., Bingman *et al.,* 1988; Bingman & Mench, 1990). As a result, the issue of whether functional specialization might occur in different regions of the avian hippocampal formation remains largely unexplored, despite anatomical data suggesting that APH may be homologous to the EC (Redies *et al.,* 2001; Abbelan *et al.,* 2004; Zhou *et al.,* 2020; Bingman *et al.,* 1994; Kröner & Güntürkün, 1999; Wild *et al.,* 1993).

To address this, groups of Japanese quail (*Coturnix japonica*) underwent lesion surgery to either the APH or Hf (**Figure 16**) and were tested using a spatial learning task in a foraging array (FA) and a spontaneous object recognition (SOR) task, paradigms well known to require distinct structures of the mammalian memory system.

3.3 Methods

For methods in greater detail, including a materials list and surgical and behavioural procedures, see Damphousse and colleagues (2022d).

3.3.1 Subjects

24 adult female Japanese quail (Spring Creek Quail Farms, Saint Anns, ON), aged approximately 3 months were used in this experiment. All birds were group housed on a 12:12 h light-dark cycle with *ad lib* access to food and water. Prior to behavioral testing, all animals were handled 15 min/day for at least 7 days. All procedures were approved by the animal care committee of Wilfrid Laurier University in accordance with the guidelines of the Canadian Council on Animal Care.

3.3.2 Materials

3.3.2.1 Foraging Array

The FA (see **Figure 17a**) followed testing methods previously described by Lormant and colleagues (2018). Briefly, an octagonal arena (each wall 50 cm in length, 45 cm in height) was constructed using white corrugated plastic sheeting. The flooring was also corrugated plastic sheeting. Eight unique visual cues constructed of black poster board cut into 8 unique geometric shapes were used in the arena. Four cues were placed as local cues on walls within the maze and the other four were used as distal cues attached to the walls of the room near the ceiling so that they were visible to subjects within the arena. Eight food cups were placed in the arena in the configuration depicted in Fig. 2a. Food cups were constructed using a 2 oz plastic cup, with a 1.5 oz cup with a perforated bottom nested within it. The outer cup contained inaccessible mealworms in order to control for scent cues.

3.3.2.2 Object Recognition

The SOR protocol used here was adapted from a previous publication testing Japanese quail (Damphousse *et al.,* 2022a). Testing occurred within a square arena with walls 90 cm wide and 60 cm tall, constructed from painted plywood (see **Figure 18a**). Flooring was corrugated plastic sheeting. A spatial cue was placed onto one wall of the arena. Behaviour was monitored using an overhead webcam and tracking was done in real time using ANY-maze. All subjects encountered the same sets of objects, with object sets differing between test days (**Figure 18b**).

3.3.3 Testing Procedures

3.3.3.1 Surgery

All surgeries were conducted prior to any behavioral testing. Each lesion group consisted of 8 subjects (8 APH, 8 Hf, 8 Sham). Lesions (see **Figure 16**) were conducted in four batches of 6 (2 APH, 2 Hf, 2 Sham). Each batch was tested on the FA, SOR, and sacrificed before the other batch began testing. This resulted in roughly 2 weeks between start dates for each batch.

Quail were anesthetized with isoflurane using a SomnoSuite anaesthesia machine (Kent Scientific, Torrington, CT) and placed in a stereotaxic instrument (Kopf Instruments, Tujunga, CA). Once the head was secured using ear bars and a nose cone, feathers were removed and the area was prepared using antibacterial cleanser (Phenrex®), 70% isopropyl alcohol, and chlorhexidine gluconate solution (Baxedin®). Following subcutaneous injection of lidocaine and epinephrine (Bimeda, Cambridge, ON) along the midline of the skull, a midline incision was made, the scalp was retracted, and a craniotomy was made over the lesion site (1 craniotomy for Hf

lesion, 2 for APH). The Hf and APH were removed by aspiration according to coordinates determined using a published quail brain atlas (Baylé *et al.,* 1974). Coordinates for lesions were determined relative to where the parieto-occipital suture intersects with the midline. For Hf lesions, aspirations were 5 mm anterior to bregma, 3 mm posterior, 1.5 mm on either side of midline, and 3 mm deep. Aspirations for APH lesions were 5mm anterior to bregma, 3 mm posterior, 1.5 mm – 3.5 mm lateral to bregma, 2 mm deep.

Craniotomies were packed using a hemostatic sponge, sealed with bone wax and the skin was sutured. After recovering on a heating pad and regaining mobility, quail were placed into individual cages to recover for 1 week while undergoing antibiotic and analgesic treatment.

Figure 16. Coronal Sections Illustrating the Extent of Hf and APH lesions. Lesion reconstruction of (a) Hf-lesioned and (b) APH-lesioned quail included in the study. The black areas depict damage found in at least five of the seven lesioned quail. Grey areas show damage found in at least two of the seven lesioned quail. Hf, hippocampal formation; APH, area parahippocampalis.

3.3.3.2 Foraging Array

The FA consisted of three phases: habituation, training, and probe. 1 hr prior to beginning all phases of the experiment, food was removed and subjects were transported to the testing room in a rack containing all subjects in individual cages. The rack was surrounded by a curtain and subjects were left undisturbed. There were 5 days of habituation in total. The first 2 days were habituation to transport. Subjects were transported into the testing room from their homeroom and left undisturbed for 1 hr. Over the next 3 days, subjects were habituated to the arena. During arena habituation, subjects were placed into the centre of the arena with all cups baited with one mealworm. Sessions were recorded using an overhead webcam and number of mealworms eaten was scored. Subjects were removed once all mealworms had been consumed or after 600 sec had elapsed.

Subjects received 3 training trials per day (1 hr ITI) over the course of 8 days. During training, only one cup was baited (SW) and this remained consistent throughout all of the training trials. Subjects were placed into the maze at 1 of 3 locations (N, S, E) chosen at random for each trial. Trails were 300 sec in duration or until the subject had retrieved worms from the baited cup. Latency to reach the cup was recorded using ANY-maze tracking software. After 8

days of training trials, subjects underwent a probe trial in which none of the cups were baited and subjects entered the maze from a novel direction (W).

3.3.3.3 Object Recognition

Birds underwent two SOR tests over two consecutive days. Identical to the spatial learning task, food was removed, and subjects were left undisturbed in a covered rack for 1 hr prior to beginning the experiment. Subjects were habituated to the empty testing arena over 3 consecutive days for 300 sec per day. On the first day of testing, subjects underwent a sample phase immediately followed by test. During the sample trial, two identical junk objects were placed into the arena in the centre of the two quadrants furthest from the entry point. Subjects explored the objects and arena for 300 s. The subject was removed and over the course of a 1 min ITI, the choice trial was prepared by placing an object identical to those used during sample (familiar) and a novel object within the arena. The arena was also wiped down with 70% Ethanol to eliminate scent trails and the subject was placed into the arena to explore for 300 s. Exploration was defined as the bird spending time within 30 cm of an object while not preening or pecking at the surrounding walls. The entire body of the subject was to be within the defined 30 cm radius and orientation of the subject toward the object was not required as the field of vision for prey birds, such as quail, is large and an object may be viewed from many positions relative to the head (Martin & Young, 1983; for review see Martin & Osorio, 2008). This criterion successfully demonstrates novelty preference in multiple avian species, including Japanese quail (Damphousse *et al.,* 2022a). While 30 cm is a generous distance, quail have much better visual acuity (4.73 ± 0.35 c/d; Lee & Djamgoz, 1997) than albino strains of rat (0.5 c/d; Prusky *et al.,* 2002) used within protocols from which the SOR task was originally adapted (for review see

Blaser & Heyser, 2015). The time spent exploring the novel (N) and familiar (F) objects for all birds was converted into a discrimination ratio (DR) as follows: DR = (N - F) / (N + F). On the second day of testing, an identical procedure was followed using a second, visually distinct set of objects.

3.3.3.4 Histology

Following SOR, 25 days post-surgery for a given batch, subjects were transported to a procedure room, anesthetized using isoflurane, decapitated, and brains were extracted and flash frozen in 2-methylbutane (Sigma Aldrich, Oakville, ON). Coronal sections were cut at a thickness of 30 µm using a CM3050 cryostat (Leica), thaw-mounted onto Superfrost Plus™ slides (Thermo Scientific, Waltham, MA), dried, and stored at -80°C. Every 6th section was then stained using Nuclear fast red-aluminum sulfate to observe placement and extent of the lesions under a light microscope.

3.3.3.5 Behavioural Scoring and Analysis

In the FA task, the mean latency to reach the target cup as well as the number of trials in which the baited cup was calculated for each day of training. These data were analysed using a repeated measures analysis of variance (ANOVA). Lesion location was the between subject factor and training day was the within subject factor. The probe trials were analysed by comparing the mean proximity of each quail to the previously baited cup relative to the cup on the opposite side of the maze using a paired t-test within each group. In SOR, the mean DR for each quail across both object sets was compared using a one-way ANOVA for lesion location. All

statistical analyses were conducted using JASP (JASP team, 2021) using Tukey's HSD in all post hoc tests.

3.4 Results

3.4.1 Foraging Array

Analysis of latency data in the FA (**Figure 17b**) showed no significant effect of training day ($F_{7,133} = 0.55$, $p = 0.80$) or experimental group ($F_{2,19} = 2.18$, $p = 0.14$), showing that, across the total population, there was no significant difference in latency in FA. This, however, was because 2 of the 3 groups examined showed no decrease in latency – in fact, latency increased over the 8 days of training in both lesioned groups. In contrast, the latency of intact sham quail decreased drastically over this same period, from over 60 sec on Day 1 to less than 10 sec on Day 8, consistent with previous observations (Lormant *et al.,* 2018). This resulted in a significant group by training day interaction ($F_{14,133} = 2.27$, $p < 0.01$). Similarly, in *post hoc* tests, the groups did not differ ($p > 0.60$) on Day 1, but by Day 8 shams were significantly different ($p < 0.05$) from both APH and Hf lesioned birds.

However, the accuracy with which quail selected the baited cup (**Figure 17c**) showed a consistent increase over trials (main effect of training day: $F_{7,133} = 13.87$, $p < 0.001$) suggests that significant learning occurred in all animals. A significant difference was observed across experimental groups ($F_{2,19} = 3.83$, $p = 0.04$). Post hoc tests confirmed that this difference was the result of deficits in both lesioned groups, as both APH ($p = 0.04$) and Hf ($p = 0.02$) lesioned birds were significantly less likely to select the baited cup first relative to controls.

Consistent with these observations, analysis of the probe trial (**Figure 17d**) shows that sham quail spent significantly more time in the vicinity of the previously baited cup when compared to the cup on the opposite end of the arena (t_7 = -3.52; p = 0.01). In contrast, no significant difference was observed in either Hf ($t_.$ = 0.63; p = 0.55) nor APH ($t_.$ = -0.88; p = 0.41) lesioned quail.

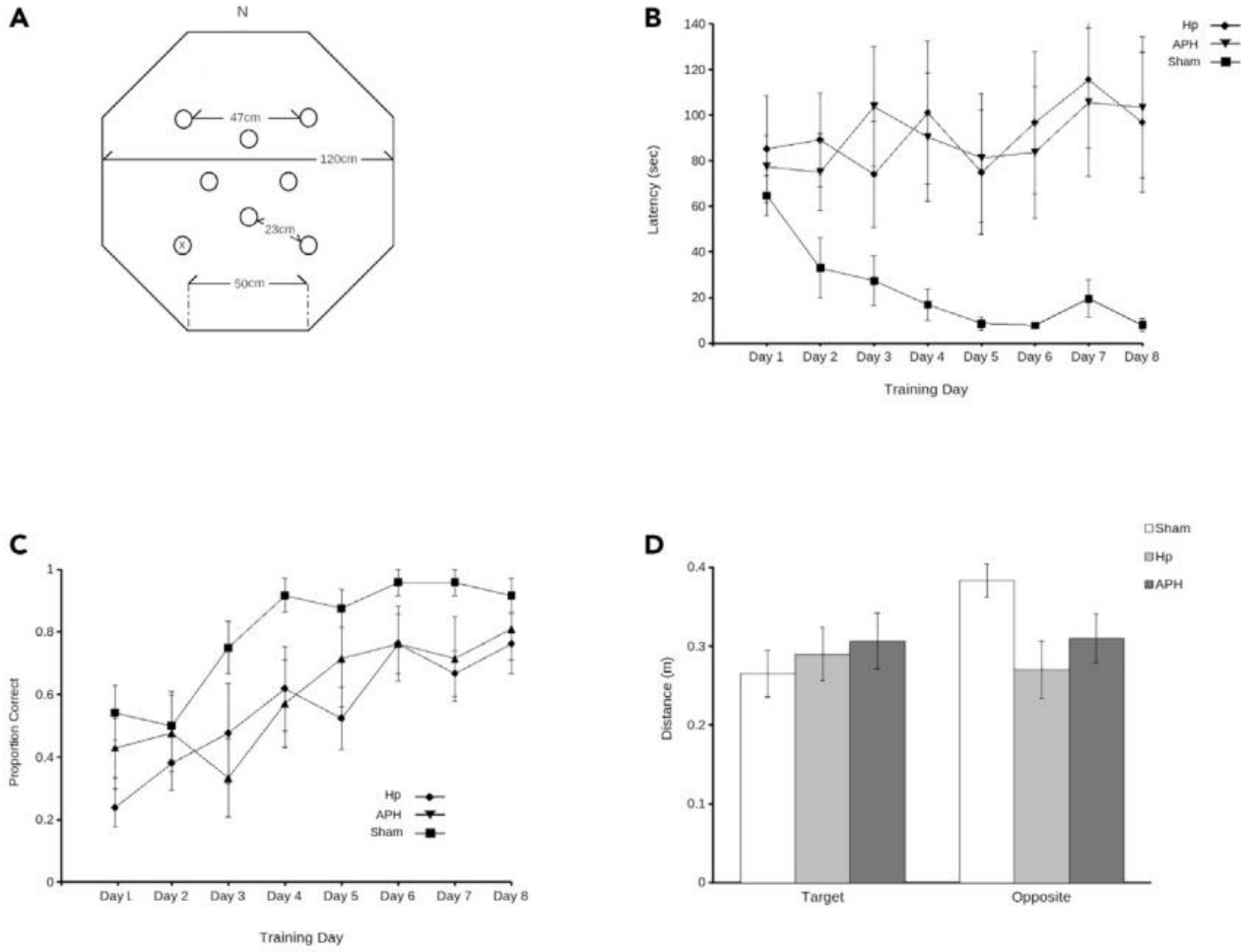
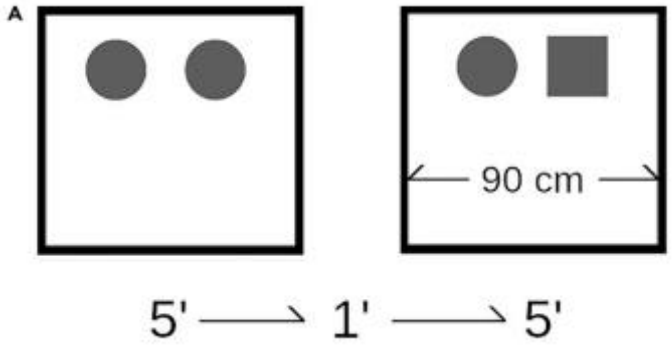


Figure 17. Lesions of Hf or APH Impair Spatial Memory. A schematic (a) shows the placement of reward cups including the baited cup (x) in the foraging array (FA). Calculation of latency to visit the baited cup (b) as well as first choice accuracy (c) show that intact sham quail (square) were

more accurate while requiring less time to retrieve the mealworm from the baited cup relative to Hf-lesioned (diamond) and APH-lesioned (triangle) quail. Similarly, in the probe trials (c) sham quail (white) were significantly closer to the previously baited cup (target) relative to the cup on the opposite end of the arena. This was not true for Hf-lesioned (light grey) or APH-lesioned (dark grey) quail (data represent mean ± SEM).

3.4.2 Object Recognition

Analysis of SOR performance during choice trials showed a significant effect of experimental group (**Figure 18c**; $F_{2,19} = 12.95$, $p < 0.01$) with post hoc tests showing that the performance of APH lesioned quail was significantly worse than either Hf lesioned quail ($p = 0.04$) or sham controls ($p = 0.01$). No significant differences were observed between Hf lesioned and sham quail ($p = 0.59$).


A
90 cm
5'
1'
5'


B

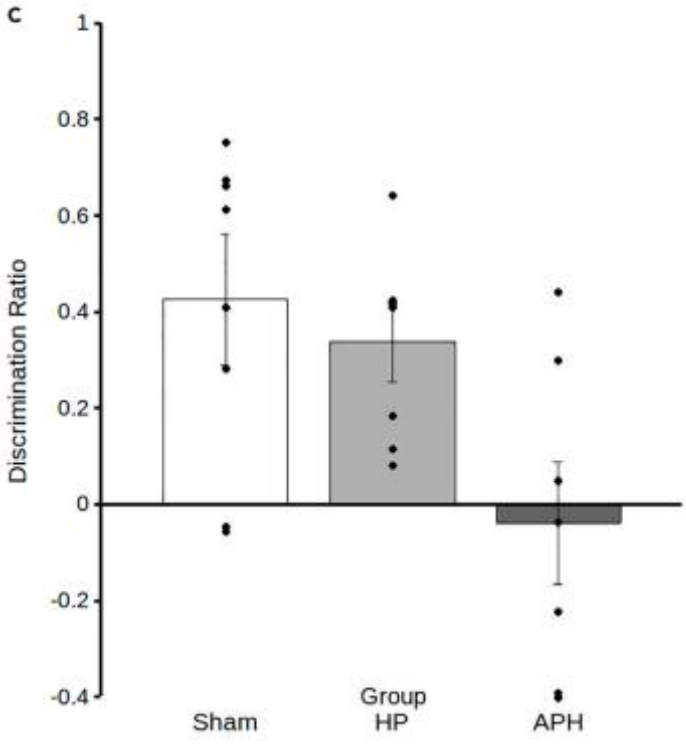

C
Discrimination Ratio
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
Sham
Group
HP
APH

Figure 18. Lesions of APH but not Hf Impair Spontaneous Object Recognition (SOR) Memory. A schematic (a) demonstrates the placement of objects and timing of trials in SOR. Following 3 days of habituation, quail received their first sample trial (left) in an open field containing two identical copies of a novel object (circles) for 5 min. After a delay of 1 min, quail received a choice trial (right) in which a new copy of the same object is presented alongside a novel object (square). Samples of the objects (b) used are also shown. Quantification (c) of discrimination ratios (DR) shows that intact sham quail (white) and Hf-lesioned quail (light grey) spend more time investigating the novel object, as shown by the positive mean DR. APH-lesioned quail, however, have a mean DR that near 0, a value that reflects random chance object investigation (data represent mean ± SEM).

3.5 Conclusions

These data provide the first observation (to the authors' knowledge) of functional heterogeneity across the avian memory system that shows some consistency with the functional differentiation observed in the mammalian temporal lobe. Here we report that while lesions to either APH or Hf induce robust deficits in a spatial learning task. These results are consistent with early studies in pigeons showing spatial deficits after lesions to either of these brain structures (e.g., Bingman *et al.,* 1988; Bingman & Mench, 1990). We also report the novel observation that only lesions to APH induce a deficit in object recognition. It is worth noting here that tasks were not counterbalanced and all quail were trained in the FA task prior to SOR. While counterbalancing remains the ideal, it is unlikely that practice effects from FA that could alter the conclusions drawn from performance in SOR, a task with different cognitive demands that

occurs in a different testing apparatus. In particular, it would be counterintuitive that any effects of practice could differentially benefit quail with Hf lesions and not those with APH lesions. Object recognition and spatial memory are tasks rely on independent neural circuits in mammals. The current observations are consistent not only with these mammalian findings, but also with reports that damage to the avian Hf generally spare performance on visual memory tasks when careful attention is taken to minimize spatial confounds (Colombo *et al.,* 1997; Good & Macphail, 1994; Hampton & Shettleworth, 1996). This evidence strongly suggests a dissociation in the areas of the avian hippocampal formation supporting spatial cognition and object recognition.

Direct comparisons with previous literature are problematic as the nomenclature used changes frequently between papers, often with the same labels describing different regions. Given this variation in terminology, the most conservative conclusion is that the avian Hf, like its mammalian counterpart, is dispensable for object recognition memory, at least within 1mm of the midline. In contemporary nomenclature, this certainly encompasses area V (and its subdivisions) and at least some portion of DM. Moving laterally from the midline, however, there is a point in the avian pallium (perhaps at the division between DM and DL) that also encodes non-spatial information in order to support object recognition. Given this novel observation, many questions remain to be addressed.

For instance, it remains unclear if the APH contains further functional segregation. It is perhaps surprising that APH lesions produced deficits in both spatial and non-spatial tasks, rather than producing a double dissociation between the regions responsible for object recognition and spatial cognition, as is often reported in mammals (e.g., Winters *et al.,* 2004). There

are at least two possibilities that may explain these observations. One is that the APH is less differentiated than its mammalian counterparts and contains both cells that encode spatial information and those that encode non-spatial information throughout its mediolateral extent. The presence of an undifferentiated homologue to the medial temporal cortex (equivalent to a combination of the mammalian entorhinal, perirhinal, and parahippocampal cortices) would be consistent with the lack of clear boundaries between regions of the avian hippocampal formation in general and would be consistent with previous studies that failed to find any mediolateral gradient in spatial information content (Payne *et al.,* 2021). A second possibility, however, is that there are gradients in the activity of APH not captured by the current protocol. The mammalian EC can be functionally separated into a lateral portion that processes non-spatial information about object identity and familiarity, while the medial EC specializes in spatial information (Eichenbaum & Lipton, 2008; Kneirim *et al.,* 2013). Genetic markers provide the basis for dividing the APH into a medial, intermediate, and lateral portion (Abellan *et al.,* 2014) and the homologue of medial EC has been proposed to be the lateral division, perhaps also extending into the corticoid dorsolateral (CDL) area. In this scenario, APH lesions are likely causing spatial deficits by severing fibers of passage from the lateral APH/CDL region to the Hf, explaining why both lesion types effect performance on the spatial task (Rosinha *et al.,* 2009; Kahn *et al.,* 2003). It should be noted, however, that the only study to explicitly examine the behavioural effects of CDL lesions found no spatial deficits in a delayed alternation task (Gagliardo *et al.,* 1996). These inconsistencies will require further studies using selective perturbations to disambiguate, likely in conjunction with cellular markers to more definitively differentiate regions.

Despite these unanswered questions, the current data provide a new perspective on the functional heterogeneity of the avian memory system.

Chapter 4: Functional Dissociation Along Rostrocaudal Axis of Japanese Quail Hippocampus

4.1 Abstract

The mammalian hippocampus (Hf) can be functionally segregated along its septotemporal axis with involvement of dorsal hippocampus (dHf) in spatial memory and ventral hippocampus (vHf) in stress responses and emotional behaviour. In the present study, we investigate comparable functional segregation in proposed homologues within the avian brain. Using Japanese quail, we report that bilateral lesions of the rostral hippocampus (rHf) produce robust deficits in a spatial Y-maze discrimination (YMD) test while sparing performance during contextual fear conditioning (CFC), comparable to results from lesions to homologous regions in mammals. In contrast, caudal hippocampus (cHf) lesions failed to produce deficits in either CFC or YMD, suggesting that, unlike mammals, both cHf and rHf of birds can support emotional behavior. These observations demonstrate functional segregation along the rostrocaudal axis of the avian Hf that is comparable in part to distinctions seen along the mammalian hippocampal septotemporal axis.

Chapter taken from: Damphousse C.C., Miller N., & Marrone D.F. (2022c). Functional Dissociation Along Rostrocaudal Axis of Japanese Quail Hippocampus. *Under Review*.

4.2 Introduction

The hippocampus (Hf) is a structure critical to many forms of memory and spatial navigation across a number of species. Given the many computations that this structure must complete in order to serve these complex cognitive functions, it is not surprising that the Hf is not a unitary structure but is instead segregated into multiple functionally distinct sub-regions. One important functional distinction is along the dorsoventral axis, also referred to as the septotemporal, or "long" axis. Evidence of functional distinctions along this axis have been noted since the earliest studies examining the behavioral effects of Hf lesions (e.g., Kimura, 1958; Hughes, 1965; Nadel, 1968), and numerous studies have confirmed and extended these observations (reviewed in Strange *et al.,* 2014). While the precise nature of the functional domains within the Hf remains a topic of debate (Fanselow and Dong, 2010; Small *et al.,* 2011; Strange *et al.,* 2014), there is consensus that the dorsal Hf (dHf), for instance, is critical for spatial memory in small environments (e.g., Moser *et al.,* 1993; Moser *et al.,* 1995) while the ventral region (vHf) is more critical to emotional behavior and stress responses including contextual fear (e.g., Gray & McNaughton, 1983; Hunsaker *et al.,* 2008; Bannerman *et al.,* 2004; Kjelstrup *et al.,* 2002).

The avian Hf is a proposed homologue of the mammalian Hf for numerous reasons including similarities in development, connectivity and neurotransmitters, and because of its role in spatial cognition (see Székely, 1999; Colombo and Broadbent, 2000; Atoji and Wild, 2005 for review). Similar to functional gradients observed along the dorsoventral axis in mammals, a number of studies have proposed a comparable functional gradient along the rostrocaudal axis of the avian Hf. Studies of connectivity (e.g., gene expression (e.g., Smulders & DeVoogd, 2000;

Abellán *et al.,* 2014), and place cell characteristics (e.g., Payne *et al.,* 2021) all suggest similarities between the rostral pole of the avian Hf (rHf) and the dorsal pole of the mammalian Hf (see Smulders, 2017 for review). What remains unknown is whether the caudal pole of the avian Hf (cHf) is functionally comparable to the ventral pole of the mammalian Hf and if so, is there a functional dissociation between the rostral and caudal poles?

To address this, groups of Japanese quail (*Coturnix Japonica*) underwent selective lesions to either the rostral or caudal pole of the Hf. Subjects were then tested using a contextual fear conditioning (CFC) or Y-Maze discrimination task (YMD), paradigms known to require differing poles of the mammalian Hf.

4.3 Methods

4.3.1 Subjects

Twenty-seven adult female Japanese quail (Spring Creek Quail Farms, Saint Ann's, ON), aged approximately 3 months were used in this experiment. All birds were group housed on a 12:12 h light-dark cycle with *ad lib* access to food and water. Prior to behavioral testing, all animals were handled 15 min/day for at least 7 days. All procedures were approved by the animal care committee of Wilfrid Laurier University in accordance with the guidelines of the Canadian Council on Animal Care.

4.3.2 Materials

4.3.2.1 Contextual Fear Conditioning

This experiment consisted of two visually distinct arenas in two different rooms containing unique local and distal cues, referred to as Context A and Context B (see **Figure 20a**).

Context A consisted of a circular 90 cm diameter arena with 45 cm high walls constructed from white corrugated plastic sheeting, with a floor of the same material covered in butcher paper. Context B consisted of a square arena with 90 cm sides and 45 cm high walls constructed from painted plywood, with flooring of black haircell acrylonitrile-butadiene-styrene (ABS). Behaviour was monitored using an overhead webcam and tracking was done in real time using ANY-maze (Stoelting, Wood Dale, IL).

4.3.2.2 Y-Maze Discrimination

The YMD protocol used here was adapted from a previous publication testing Japanese quail (Damphousse *et al.,* 2021). Briefly, Y-maze arms measured 50 x 17 x 45 cm (L x W x H; **Figure 21a**) were constructed from clear acrylic permitting subjects to readily see distinct visual cues present on all four walls of the room. Square rod styrene tracts with removable opaque acrylic guillotine doors were installed in the two exploration arms. The floor was constructed from black haircell acrylonitrile-butadiene-styrene (ABS) and covered with wood shavings. Behaviour was monitored using an overhead webcam and tracking was done in real time using ANY-maze.

4.3.3 Testing Procedures

4.3.3.1 Surgery

All surgeries were conducted prior to any behavioral testing. Each lesion group consisted of 9 subjects (9 rHf, 9 cHf, 9 Sham). Surgical procedures were modified from those outlined in Damphousse and colleagues (2022). Quail were anesthetized with isoflurane using a SomnoSuite anaesthesia machine (Kent Scientific, Torrington, CT) and placed in a stereotaxic

instrument (Kopf Instruments, Tujunga, CA). Once the head was secured using ear bars and a nose cone, feathers were removed and the area was prepared using antibacterial cleanser (Phenrex®), 70% isopropyl alcohol, and chlorhexidine gluconate solution (Baxedin®). Following subcutaneous injection of lidocaine and epinephrine (Bimeda, Cambridge, ON) along the midline of the skull, a midline incision was made, the scalp was retracted, and a craniotomy was made over the lesion site. The Hf was removed by aspiration according to coordinates determined using a published quail brain atlas (Baylé *et al.,* 1974). Coordinates for lesions were determined relative to where the parieto-occipital suture intersects with the midline. For rHf lesions, aspirations were 1 mm to 5 mm anterior to bregma, 1.5 mm on either side of midline, and 3 mm deep. cHf lesions were 1 mm anterior to bregma, 3 mm posterior, 1.5 mm on either side of midline, and 3 mm deep (**see Figure 19)**.

Craniotomies were packed using a hemostatic sponge, sealed with bone wax and the skin was sutured. After recovering on a heating pad and regaining mobility, quail were placed into individual cages to recover for 1 week while undergoing antibiotic and analgesic treatment.

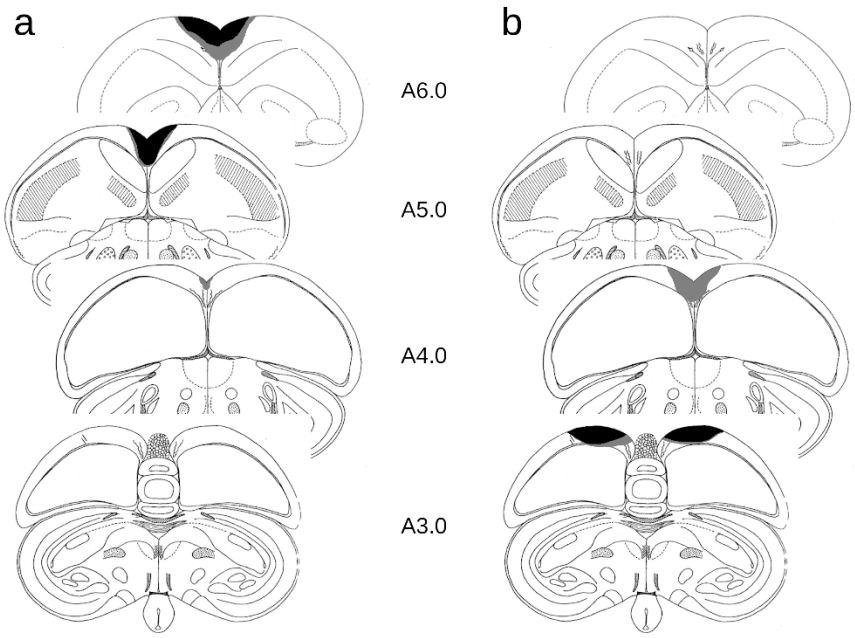


Figure 19. Lesion Reconstruction of (a) rHf-lesioned and (b) cHf-lesioned Quail Included in the Study. The black areas depict damage found in at least six lesioned quail. Grey areas show damage found in at least two lesioned quail. rHf, rostral hippocampal formation; cHf, caudal hippocampal formation.

4.3.3.2 Contextual Fear Conditioning

CFC consisted of four phases: habituation, training, test, and remote test. Prior to beginning each day of the experiment, subjects were removed from their housing room and placed into individual shoebox cages on a rack devoid of food. Each cage was covered by a shroud and subjects were left undisturbed for 1 hour. Subjects were transported individually in their covered cages to the testing room. Habituation, training, and test all occurred on the same experimental day. During habituation, the subject was placed into Context A and allowed to explore freely for 5 min. The subject was promptly removed and the same procedure was

followed in Context B with a 1 min inter-trial-interval (ITI). The subject was then placed back into a covered shoebox cage and left undisturbed for 15 minutes. During training, the subject was again exposed to Context A for 5 min, a 1 min ITI, and was then placed into Context B. After 3 min in Context B, an auditory stimulus (1000 Hz, 95 dB) was delivered for 3 sec, followed by 2 minutes of exploration. The context in which the stimulus was presented was counterbalanced across subjects. The subject was then again placed back into the covered shoebox cage and left undisturbed for 15 minutes. During test, procedures matched those in habituation with 5 min in Context A followed by 5 min in Context B. Following each phase, the arena was wiped down with 70% Ethanol to eliminate scent trails. On the following day, subjects were given a remote test. During remote test, procedures again matched those followed during habituation with 5 min in Context A, a 1 min ITI, and 5 min in Context B.

4.3.3.3 Y-Maze Discrimination

Quail underwent three consecutive days of 10-min habituation sessions. During the sample trial, birds were given 5 min of exploration with one arm of the maze blocked off by a guillotine door. Birds were then removed for 1 min, during which time the door was removed and the bedding in the maze was replaced to remove scent cues. Birds were then returned to the maze for a 5-min choice trial. Which arm was blocked during the sample trial was counterbalanced across subjects.

4.3.3.4 Histology

Following YMD, subjects were transported to a procedure room, anesthetized with isoflurane, decapitated, and brains were extracted and flash frozen in 2-methylbutane (Sigma

Aldrich, Oakville, ON). Coronal sections were cut at a thickness of 30 µm using a CM3050 cryostat (Leica), thaw-mounted onto Superfrost Plus™ slides (Thermo Scientific, Waltham, MA). Every 6th section was then stained using Methyl Green to observe placement and extent of the lesions under a light microscope.

4.3.3.5 Behavioural Scoring and Statistical Analysis

Two quail died during surgery, while another 2 were excluded for lack of movement in at least one of the 2 tests, yielding final data on 25 quail (9 rHf, 7 cHf, 7 sham).

During CFC, quail can be considered freezing when they present a characteristic crouching posture with a) total flexion of the legs and the body in contact with the floor or b) partial flexion of the legs, wide separation between feet/legs and the pectoral region in close contact with one of the walls, with eyes widely opened and accelerated respiration. Such posture, associated with the absence of other observable behaviors, has been repeatedly used to characterize freezing behavior in pigeons (Barnett & Cowan, 1976; Reis *et al.,* 1999; Brito *et al.,* 2006; 2019).

Analysis of CFC data was conducted using a repeated-measures analysis of variance (ANOVA) of the time spent freezing during the first 2 minutes of each trial using context (i.e., acoustically-paired vs. control) and time (i.e., immediate vs. remote) as within-subject factors and group (i.e., rHf, cHf, and control) as between-subject factors. As an additional control, the time spent freezing in each context was also compared before any acoustical stimulation was compared with a 2 (context) x 3 (group) ANOVA.

In the YMD, the time spent within each arm was quantified as a proportion of their total exploration time. The subject was considered to be exploring an arm if their entire torso was inside of the arm. The time spent exploring the novel arm (T_N) and in the familiar arm (T_F) (excluding the start arm) for all subjects was converted into a discrimination ratio (DR) as follows: DR = $(T_N-T_F)/(T_N+T_F)$. These DRs were compared across groups by one-way ANOVA.

Post hoc tests were conducted using Tukey's HSD. All statistical tests were conducted using JASP (JASP team, 2022).

4.4 Results

4.4.1 Contextual Fear Conditioning

Analysis of CFC (**Figure 20b**) showed no significant difference in context ($F_{1,20}$ = 1.12; p = 0.30) or group ($F_{2,20}$ = 1.42; p = 0.27) before acoustic stimulation, showing that the surgeries did not induce any pre-existing differences in freezing behavior. Examining the time spent freezing during the trials following simulation failed to show a significant main effect of time ($F_{1,20}$ = 1.05; p = 0.32) or of group ($F_{2,20}$ = 1.33; p = 0.29). However, a significant effect of context ($F_{1,20}$ = 8.47; p = 0.01) as well as a significant time by context interaction ($F_{1,20}$ = 8.47; p = 0.01) were observed. This pattern of results shows that quail across all groups selectively froze in the context paired with the acoustic stimulus and not in the control environment (paired vs. unpaired context: $p < 0.05$ for all groups), indicating that quail are able to discriminate between the two contexts and retain a memory for the context in which the acoustic stimulus had been presented. In contrast, 24 hours later, freezing had diminished to the point at which no

significant difference could be observed ($p > 0.05$ for all groups), suggesting that the memory had degraded.

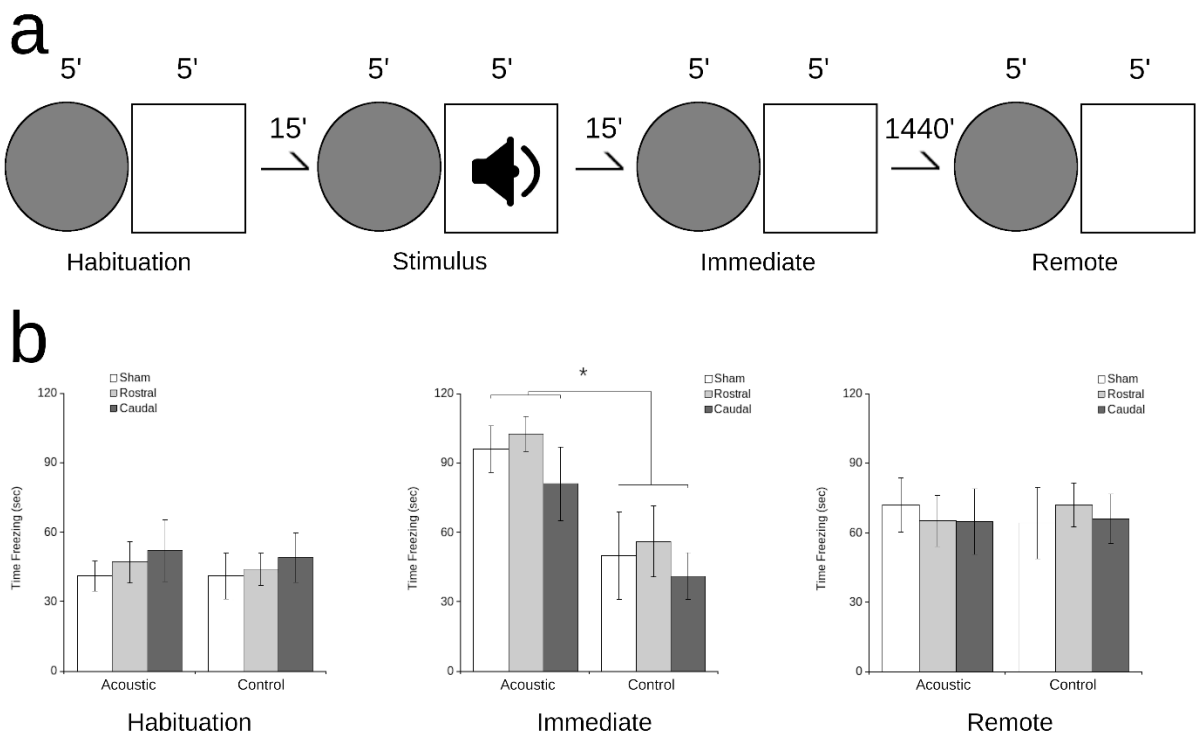


Figure 20. Lesions of rHf or cHf Spare Contextual Fear Conditioning (CFC). A schematic (a) shows the timing and order of CFC in context A (grey) and context B (white). Quail were pre-exposed consecutively to each context for 5 min (pre-exposure), followed by a 15 min delay. Quail were then exposed to each environment for 5 min a second time, during which they were presented with an auditory stimulus (1000 Hz, 95 dB) for 3 sec in one of the environments (stimulus). Following another 15 min delay, quail were again exposed consecutively to each context for 5 min (immediate). After 24 hours, the quail were once again exposed consecutively to each context for 5 min (remote). Analysis of the time spent freezing (b) shows that intact sham quail (white) as well as rHf-lesioned quail (light grey) and cHf-lesioned quail (dark grey) spend comparable time freezing in either environment a baseline (habituation). Following

presentation of the acoustic stimulus, all quail more time freezing in the environment they received the acoustic stimulus in (acoustic) relative to the second environment (control). This difference is no longer apparent 24 hours after the presentation of the stimulus (remote) have a discrimination ratio that is not significantly different from 0, showing exploration of objects equal to random chance (bars show mean ± SEM; * = $p < 0.05$ significant difference between groups).

4.4.2 Y-Maze Discrimination

Analysis of the YMD (**Figure 21b**), yielded a significant effect of condition ($F_{2,20} = 3.99$; $p = 0.03$). Post-hoc tests show that while rHf-lesioned quail performed significantly worse than shams ($p = 0.04$), cHf-lesioned quail did not ($p = 0.12$). This pattern of results suggests that, like mammals, the rHf of quail may disproportionately support spatial learning tasks.

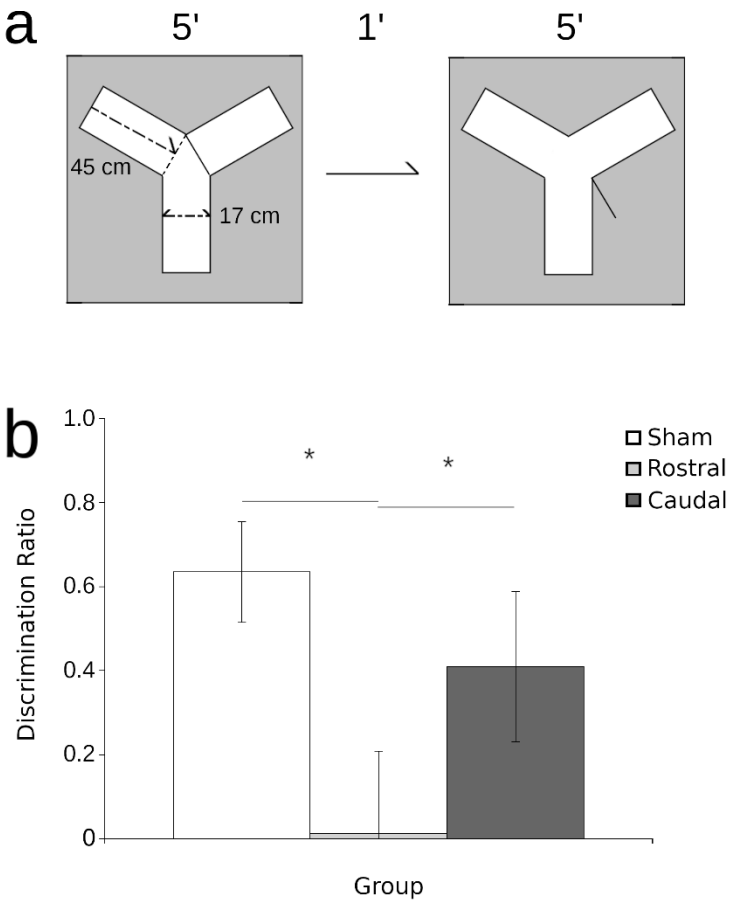


Figure 21. Lesions of rHf but not cHf Impair Y-Maze Discrimination (YMD) Memory. A schematic (a) demonstrates the timing of trials in YMD. Following 3 days of habituation, quail are exposed to the Y-maze for 5 min with one of the arms blocked. Quail are then removed for 1 min and the wall blocking passage to the novel arm is removed before quail are returned for another 5 min. Calculation of a discrimination ratio (b) shows that intact sham quail (white) and cHf-lesioned quail (dark grey) spend significantly more time investigating the novel arm of the maze. In contrast, quail with lesions to rHf (light grey) have a discrimination ratio that is not significantly different from 0, showing exploration of the maze arms equivalent to random chance (bars show mean ± SEM; * = $p < 0.05$ between groups).

4.5 Conclusions

The current results are the first to report functional segregation along the rostrocaudal axis of the avian Hf. These results partially confirm a gradient along the rostrocaudal axis that is in some ways comparable to the mammalian dorsoventral axis. In particular, we observe that the rHf is necessary for identification of spatial novelty during YMD. This observation is consistent with results produced in rats completing comparable tasks following lesions to the dHf (Hunsaker *et al.,* 2008; Lee *et al.,* 2005; but see Dalland, 1976). Moreover, the current results are consistent with reports of a gradient of spatial information content in avian Hf, with the greatest spatial information in principle cells of the rHf (Payne *et al.,* 2021). This pattern, which mirrors the change in information content observed along the rat dorsoventral axis (Kjelstrup *et al.,* 2008) furthers the body of evidence demonstrating that the most rostral extent of the Hf disproportionately supports high-resolution spatial information processing across both Aves and Mammalia.

The observation of intact CFC following either rHf or cHf lesions is inconsistent with data showing homology between cHf and the mammalian vHf (reviewed in Smulders, 2017). Several conclusions are possible given this observation. It is possible a gradient for emotional processing is absent in the avian Hf. That is, the information required to associate an aversive cue with a context may be present along most of the rostrocaudal axis. This suggestion is consistent with anatomical studies in pigeons (Atoji *et al.,* 2002) reporting that input from nucleus taeniae of the amygdala is absent in the rostral third of the HF, but widespread in the caudal two-thirds of this region. These widespread connections may suggest that the majority

of the avian Hf is homologous to the ventral mammalian Hf, and the cHf lesions conducted here were not sufficient to remove this distributed structure in its entirety. Alternatively, the gradient in emotional processing may specifically be absent in the Hf of Japanese quail (or Galliformes in general). This suggestion would be consistent with observations of species differences in spatial information processing, revealing much stronger rostrocaudal gradients in food-caching than non food-caching birds (Payne *et al.,* 2021).

Despite remaining open questions concerning the extent and functional heterogeneity of the cHf, the current results demonstrate that, like its mammalian homologue, the avian Hf is functionally heterogeneous, with its rostral portion specialized to computations that support spatial learning and memory.

Chapter 5: General Discussion

The comparison of the evolutionary origins of HDMS provided in Chapter 1 demonstrated that the critical features of the HDMS are conserved across Mammalia. These key features include: convergence of uni- and poly-modal sensory information onto higher order association cortices, separation of this information into two parallel processing streams of 'what' and 'where' information, hierarchical processing of these streams resulting in progressively more complex, conjunctive representations, and final convergence of both streams within the Hf. Despite these convincing similarities in mammals, a lack of evidence hampered attempts to examine more distant homologies in avian models. While there is considerable evidence of conserved connectivity and function between primates and rats, the existing literature offers little data that could provide definitive conclusions as to whether the structure and function of the HDMS is conserved between Mammalia and Aves. To address the lack of data on this question, in Chapter 2, I developed standardized testing methods, adapted from tests commonly used in mammals, for use in multiple members of Aves; in Chapter 3, I described lesions of proposed homologues of structures critical in the mammalian HDMS; and in Chapter 4, I explored the possibility of functional differentiation within the avian Hf.

Throughout Chapter 1, the Dual-Process and BIC models provided important frameworks for understanding the role of the components of the HDMS in memory. Given the new data in Chapters 2, 3, and 4, it is worthwhile to revisit these theoretical frameworks in order to assess the extent to which they need to be revised given the current data.

5.1 The Dual-Process Model

As described in Chapter 1, the limited experimental evidence suggested that the avian Hf is involved in familiarity but not recollection. More specifically, the collective results of Bingman and colleagues (1998) and Coppola and colleagues (2014), suggested that the avian Hf, unlike its mammalian counterpart, may not be capable of binding non-spatial elements into a unified representation. My findings from Chapter 2 support this claim. Within Chapter 2, Experiments 1, 2, and 4 demonstrate that pigeons and quail can detect, and will subsequently show a preference for, both spatial and object novelty, consistent with a system geared toward familiarity. In Experiment 3 (the COR task), however, no novelty-preference was observed when identification required binding object identity with that object's location, context, or both. These findings support the idea that the avian HDMS is largely involved in familiarity rather than recollection, as failure on these tasks suggests that the avian brain may not bind multiple pieces of information into rich event recollections.

An alternative account for the observed lack of neophilia when recognition required combining multiple elements is that subjects may not have been sufficiently motivated to either attend to the COR task or demonstrate a preference for the type of novelty that this task tests for. To address this, the issue of motivation was considered when designing the behavioural testing in Chapter 4. Since food restriction in the quail during an unpublished pilot study had proven to be an unsuccessful motivator, we instead opted for an abrupt (and potentially stressful) auditory stimulus to maximize the motivation to differentiate the two contexts. Since quail displayed more freezing in the context in which the auditory stimulus was

delivered, this implied that they are capable of at least combining an aversive event with a specific context. While my data do not provide evidence that this is strictly dependent on the avian Hf, it does suggest that given sufficient motivation, Japanese quail are capable of binding stimuli across modalities in order to create complex representations and act appropriately in that context again. This pattern of behavior is consistent with recollection.

Taken together, the current findings allow for the HDMS of Japanese quail to be situated within the Dual-Process model (**Figure 22**). Evidence from Chapter 2 established that quail and pigeons can detect object and spatial novelty (familiarity), Chapter 3 determined that detection of object novelty critically involves the APH and not the Hf, and Chapter 4 established that Japanese quail were capable of associating a multimodal and emotional event with contextual information (recollection). However, the locus of multimodal representations supporting recollection remains unknown and could be a topic of future study.

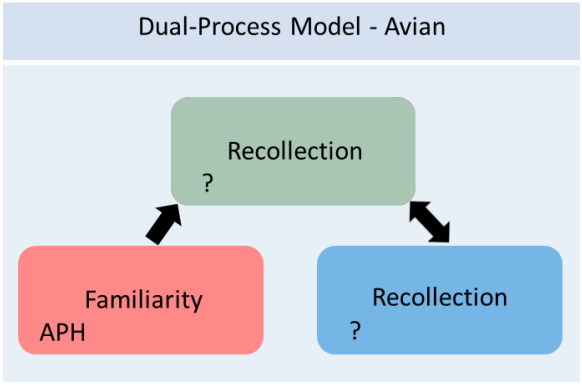


Figure 22. Avian Dual-Process Model. Within the avian hippocampal declarative memory system, area parahippocampalis (APH) seems to support object familiarity. Structures supporting recollection remain unknown, denoted by a question mark. Double-headed arrows indicate bidirectional communication, single-headed indicate unidirectional communication.

5.2 Binding of Item in Context Model

A review of the current literature (Chapter 1) offered little information on how the avian HDMS could be situated within the BIC model. Prior to the current findings, there was a general consensus that the avian Hf was involved in spatial information and that, on the basis of connectivity, the APH/CDL region was possibly an "entorhinal-like" homologue (**Figure 23**). Although the current findings support this role of the avian Hf in spatial memory, they greatly expand the role of the APH. Looking first to Chapter 3, my results support critical involvement of the Hf in spatial memory, but deficits in spatial memory following APH lesions make the distinction between the two structures less clear. While this does not rule out the involvement of the APH in spatial processing, it remains possible that lesions to the APH sever fibers of passage to the Hf, creating the observed deficit. Alternatively, object identity information provided by the APH may be critical in performance during the FA task, as the APH may be essential when discriminating between cues that could be used to locate the baited cup. However, this is unlikely, considering that all the cups were identical. My findings in Chapter 4 confirmed the critical involvement of the Hf in spatial memory, as lesions to the rostral portion of the Hf resulted in deficits in discriminating novel from familiar arms of the Y-Maze. While my data do not support the role of the avian Hf in 'binding item in context', they do affirm its critical involvement in detecting spatial novelty.

On the basis of connectivity, APH/CDL was proposed to be comparable to the mammalian EC. The data in Chapter 3 provide the first demonstration, to the best of my knowledge, of behavioral data consistent with these measures of connectivity. The APH plays a

critical role in SOR, and thus is functionally homologous to the PRhC and/or LEC. These findings are comparable to mammalian studies in which lesions to the PRhC (Norman & Eacott, 2005) or LEC (Boisselier *et al.,* 2014; Persson *et al.,* 2022) also resulted in SOR deficits. Since we are unable to say with certainty whether the APH is critically involved in spatial memory or if the lesions described in Chapter 3 simply severed fibers of passage, it would be conservative and perhaps more accurate to say that the Japanese quail APH *may be* a functional homologue of the parahippocampal region (PRhC and PHC/PoRhC).

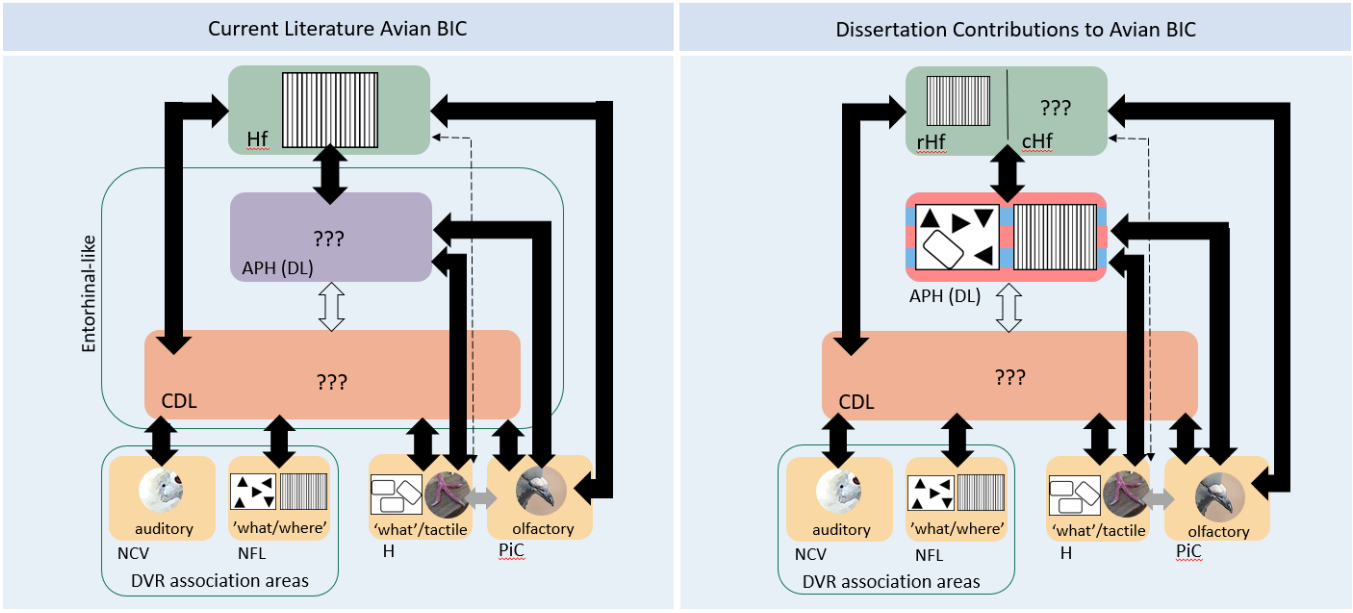


Figure 23. Avian Binding Item in Context (BIC) Model. Proposed BIC model on the basis of previous literature (left) and an updated BIC model incorporating findings of this dissertation (right). The BIC model proposes hippocampal declarative memory system sub-regions can be differentiated on the basis of the information that they store. Based on contributions of the current literature, area parahippocampalis (APH) and the dorsolateral corticoid area (CDL) were proposed as being entorhinal-like, while the hippocampal formation (Hf) was shown to be

involved in spatial memory. Findings from this dissertation contribute to this model by showing APH involvement in object recognition memory and possibly spatial memory, suggesting that this region may be comparable to the mammalian parahippocampal region. Tactile information is represented using a foot; olfactory, a beak; and auditory, an ear. Object information is represented by rectangles and black triangles. Context information is presented using pattern filled rectangles. Increased complexity in representation is depicted through altering the arrangement of object and contextual elements. Double-headed arrows indicate bidirectional connectivity. Black arrows indicate connectivity between levels of the connectivity hierarchy. Dashed arrow indicates a weak connection. Clear arrow indicates possible communication between structures. Adapted from Manns and Eichenbaum (2006). cHf, caudal portion of the hippocampal formation; DVR, dorsal ventricular ridge; H, hyperpallium; NCV, caudoventral nidopallium; NFL, frontolateral nidopallium; PiC, piriform cortex.

The findings presented in this dissertation provide evidence for parallel processing of spatial and non-spatial information within the avian HDMS. In Chapter 3, I observed functional dissociation between Hf and APH, while Chapter 4 demonstrated functional differences within the Hf, along its rostrocaudal axis. Despite the contributions of the current data to the existing literature, when comparing BIC models between primates, rats, and birds (**Figure 24**), we are still unable to say, with certainty, the extent to which the functions of the Hf are conserved across Aves and Mammalia. However, the results of Chapter 4 suggest homology, as the function of the rHf seems to be conserved between rats and several members of Aves, as also noted in previous research (Payne *et al.,* 2021).

In addition to proposing a hierarchy of connectivity for Aves and situating functional findings within the framework of the BIC model, my work provides a critical examination of the BIC across multiple taxa. When comparing the rat BIC model to that of primates, differences within the model have been largely attributed to diversified neocortical inputs (Manns & Eichenbaum, 2006). However, this explanation may not necessarily be correct, and the primate BIC model may instead require updating to consider the extent to which multisensory information is required for the solution of the tasks typically used.

It is intuitive that the natural ecology of individual species may ultimately result in differing proportions of sensory representations being incorporated within the connectivity hierarchy. For example, based on the available literature it is tempting to conclude that the primate HDMS has evolved to process largely visual information. However, the bias may instead lie in the testing methods used with NHPs, since primate studies have largely focused on visual information, usually testing discrimination using images rather than tangible objects, as is most commonly used in rats. Thus, the multisensory nature of discrimination seems to be neglected. What appears to be a BIC system with more overlapping representations within the rat may only appear so because the rat model reflects the response of the mammalian HDMS to real-world objects, while the primate BIC model reflects the HDMS response to 2-dimensional images. Similar testing methods have not been investigated within a primate model, something that would be critical for disambiguating these alternative hypotheses. An updated version of the primate BIC including multisensory information needs to be created in order to allow for more accurate evolutionary comparisons.

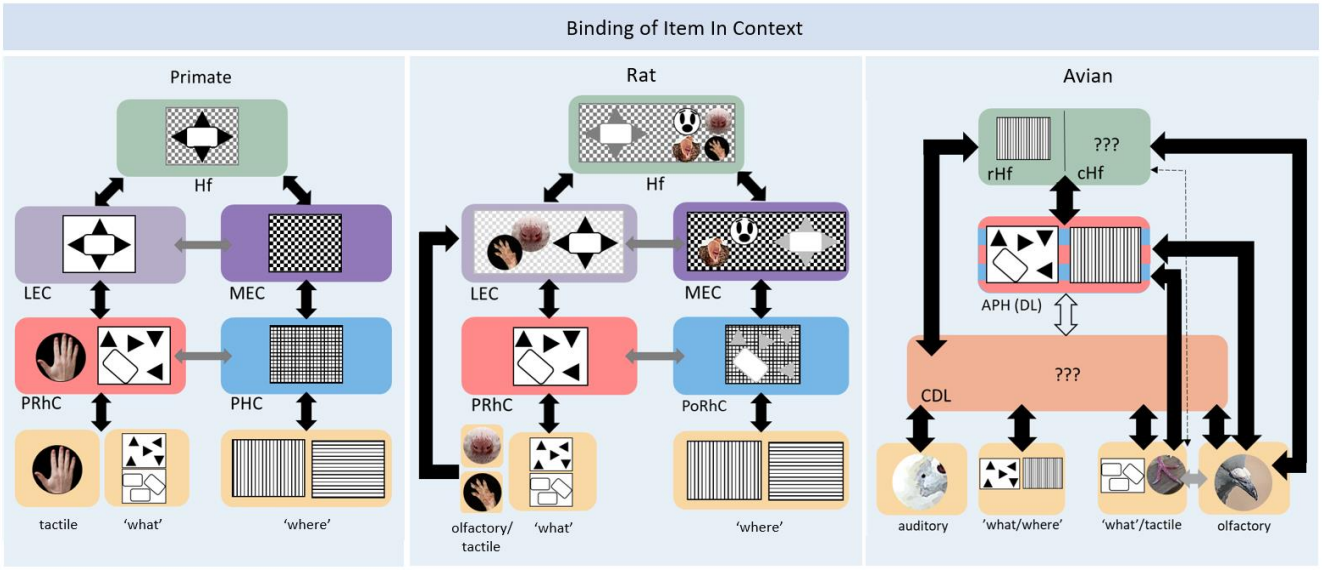


Figure 24. Comparison of Binding of Item in Context (BIC) Models between Primates (left), Rats (center), and Aves (right). BIC models from all three species show similar hierarchical structure as poly- and uni-modal sensory information converges on higher association areas (yellow) and is then passed on to intermediary structures before converging within the hippocampal formation (Hf; green). Tactile information is represented using a hand, paw, or foot; olfactory, a nose or beak; auditory, an ear; and emotional information using a cartoon face. Object information is represented by rectangles and black triangles. Context information is presented using pattern filled rectangles. Increased complexity in representation is depicted through altering the arrangement of object and contextual elements. Double-headed arrows indicate bidirectional connectivity. Black arrows indicate connectivity between levels of the connectivity hierarchy. Dashed arrow indicates a weak connection. Clear arrow indicates possible communication between structures. Grey arrows indicate communication between structures. CDL, dorsolateral corticoid area; cHf, caudal portion of the hippocampal formation; LEC, lateral

entorhinal cortex; MEC, medial entorhinal cortex; PHC, parahippocampal cortex; PoRhC, postrhinal cortex; PRhC, perirhinal cortex; rHf, rostral portion of the hippocampal formation.

5.3 Alternate Theories

While I have described the functions of the HDMS by means of the Dual-Process and BIC models, there are numerous other ways to interpret the current results. For example, an additional way to evaluate these findings is to situate them within the locale and taxon learning systems as described by O'Keefe and Nadel (1978; Nadel 1992, 1994). Note that 'taxon' learning, referring to grouping of learned associations into categories, is not to be confused with 'taxon', in reference to phylogenetic relatedness. To avoid confusion, the former will be referred to as 'taxon learning'. Briefly, when differentiating between locale (dependent on the Hf) and taxon learning (independent of the Hf), Nadel (1992) points to three major distinctions: 1) speed of acquisition, 2) underlying systems of motivation, and 3) stability of the memory. Regarding the speed of acquisition, locale learning is thought to be rapid, but also degrades quickly, and taxon learning is thought to be incremental and slower in comparison. Nadel (1992) suggests that the motivation for locale learning is driven by the desire to investigate novelty, while taxon learning is thought to be motivated by traditional Hullian forces such as hunger and thirst. As evidence for this distinction, Nadel (1992) points to a study in which lesions of the Hf destroy the motivation for information seeking, leading rats to behave in a manner much more tied to reinforcement contingencies (Devenport & Holloway, 1980). Locale learning is thought to yield memory representations with map-like formats as the basis for unique episodes with multiple access routes, while taxon learning is thought to rely on schema-

like representations, emphasizing generalization and similarity between traces, which would be more prone to interference than memory representations in locale learning. The idea of the Hf being tied to information seeking is particularly intriguing given evidence that it is very difficult to get birds to exhibit many "curiosity" driven behaviors such as spontaneous alternation (Hayes & Warren, 1963; Neiburg *et al.,* 1970; Hughes, 1989). These reports are consistent with difficulties I encountered with quail perseverating on arms in radial arm mazes (unpublished observation), which are also consistent with Hughes (1989). Perseveration may occur because removing the subject from the arm reinforces a win-stay strategy, being driven more by contingencies than novelty-seeking. These behavioral patterns, coupled with the idea that Hf activity drives novelty-seeking, may suggest that the output of the HDMS has less relative control of behavior in Aves than Mammalia. This, however, is a question of the interaction of MMS on a scope well beyond the current research.

An additional way to interpret the current findings is to compare them in terms of visual information pathways. Recall that in pigeons, the tectofugal and thalamofugal pathways are thought to be a close approximation of the mammalian 'what' and 'where' (ventral/dorsal) pathways. Within birds, tectofugal and thalamofugal are commonly discussed in terms of processing local (object) and global (spatial) visual information. For a better understanding of these systems, some key features of the pigeon visual system must be discussed. Briefly, the retina of the pigeon contains two foveas, each with enhanced ganglion cell density and differing from one another in the colour of oil droplets present, either red or yellow, which act to enhance spatial resolution (Letelier *et al.,* 2004; Nalbach *et al.,* 1990). The red field fovea, named due to the presence of red oil, mediates high resolution vision in the binocular frontal

visual field and is associated with local information (Hayes *et al.,* 1987). The yellow field fovea mediates high resolution vision in the monocular lateral visual field and is associated with global information (Hahmann & Güntürkün, 1993). Comparable structures are found in many diurnal birds, including Japanese quail (Budnik *et al.,* 1984; Ikushima *et al.,* 1986). Taken together, the tectofugal visual pathway of laterally eyed birds, is associated with information in the red field while the thalamofugal visual pathway primarily mediates visuo-spatial localization and pattern vision associated with the yellow field (reviewed in Clark & Colombo, 2022).

In a recent review by Clark and Colombo (2022), the findings from Chapter 3 in which APH lesions resulted in deficits in both SOR and the FA task were discussed. The authors speculated that the observed impairments may have occurred not because a fiber of passage was severed but because the APH receives 'where' information from the Wulst in addition to 'what' information from the NFL. They speculated that the Wulst may process both shape and spatial information viewed in the yellow field, and relay both types of information to the Hf via the APH. This supports the idea of the APH as an important intermediary structure in potentially processing object information in addition to spatial information upstream of the Hf.

5.3 Future Considerations

The data presented here offer many potential avenues for further exploration of HDMS homology. As mentioned by Clark and Colombo (2022), disambiguating the potential explanations for how the APH contributes uniquely to spatial memory would be of great interest. Toward this, next steps should include reversible knockdown of the APH using methods that spare fibers of passage (e.g., transfection with optogenetic receptors). In

addition, follow-up studies should investigate potential functional differentiation within structures. The study of functional differentiation may be more difficult to investigate in Aves relative to Mammalia, as there are fewer well defined structural borders. This lack of discrete layering also raises the possibility that functional heterogeneity may follow a gradient rather than being contained within discrete anatomical domains. If the avian Hf differs along the rostrocaudal axis, this may also be true for the APH and CDL. In fact, the extensive homology seen in the HDMS suggests this should be the case, as this heterogeneity would resemble mammalian LEC/MEC and PRhC/PHC (PoRHC) distinctions.

Another avenue for further research is the lateralization of the avian HDMS. In a study by Clayton and Krebs (1994), four species of bird displayed a preference for examining object-specific cues with the right eye and spatial cues with the left eye (although species differences have been observed; see Clary *et al.,* 2014). Subsequent studies investigating the neural basis of this behaviour demonstrated preferential involvement of the right Hf in the representation of global environmental space, whereas left Hf was sensitive to local landmarks during a navigation task (Tommasi *et al.,* 2003; Kahn & Bingman, 2004; reviewed in Bingman *et al.,* 2006). Interestingly, the function of each hemisphere may be examined by occluding one eye as the majority of visual information from each eye is maintained within the optic nerves, crossing to the contralateral hemisphere (however, hemispheric functional asymmetry has been shown to decrease with age; Shabro *et al.,* 2022). Since there is evidence of asymmetry at the level of the hemisphere, how and where differing proportions of object and spatial information get integrated within the HDMS could be of interest. In fact, similar hemispheric biases have been seen in human imaging (e.g., Bellgowan *et al.,* 2009), so further investigations of avian

lateralization may bolster the accumulated data establishing homology of the HDMS across classes.

Taken collectively, the results of this dissertation contribute greatly to our understanding of the Japanese quail HDMS. Chapter 2 adapted commonly used mammalian testing procedures for assessment of object and spatial novelty for use in Japanese quail and pigeons. Using these tests to determine HDMS structural involvement, Japanese quail underwent selective lesions along either the mediolateral (Chapter 3) or rostrocaudal (Chapter 4) axis. Results revealed functional differentiation both between (Hf versus APH) and within (rHf versus cHf) structures, permitting an update of the known functions of sub-regions of the avian HDMS (Chapter 5). In summary, these data suggest that most of the key features of the mammalian HDMS, including the existence of anatomically separated hierarchical processing streams, as well as eventual convergence of information in the Hf, is conserved across at least these two classes.

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