

# Research Statement

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My research falls into the broad category of the neuroscience of learning and memory. I am interested in how the brain takes in new information, stores it away for later use and then successfully retrieves that information when it is needed. Memory is a highly adaptive basic competency, as evidenced by the fact that basic memory functions are common to all animals, and yet memory is profoundly complex when studied in detail. The study of learning and memory spans many levels of analysis, from molecular mechanisms to fMRI. I work at the systems level, with a behavioral neurophysiology approach. I think this approach is ideal because it is sufficiently mechanistic to allow for a 'nuts and bolts' kind of understanding of how the brain accomplishes memory functions, but it is always closely coupled to behavior and the theory of memory. All of my research projects have, at their root, questions about how memory works and why it works the way it does.

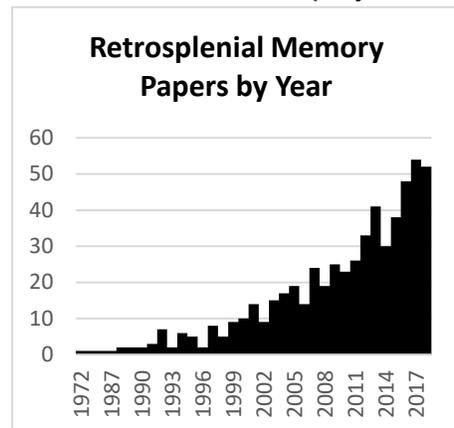
One of the central ideas guiding my work is that complex cognitive processes are not mediated by any single brain region. Instead, these processes require the cooperative interaction of multiple brain regions that form functional circuits. In order to fully understand learning and memory processes, it is necessary to examine how these circuits function as a whole and to examine the computations contributed by each component of the circuit. I address this issue by simultaneously recording neuronal activity in several brain regions and by employing temporary neurochemical inactivation techniques to systematically 'knock out' individual components of the circuit. Another central idea is that understanding behavior is crucial for deciphering the neurophysiological correlates of cognitive functions. Behavior is a critical component of all of my experiments and I use of a variety of techniques from basic conditioning to complex interference paradigms adapted from cognitive psychology. It's only with reference to our behavioral assays that we can make sense of how neuronal activity patterns support memory. My strategy has been to take the sophisticated recording and analysis procedures developed by hippocampal physiologists and adapt them for use in complex behavioral tasks that will allow us to answer key questions about memory functions. Additionally, my laboratory is one of the very few that routinely tracks the development of neuronal response patterns throughout the duration of learning in complex behavioral tasks, an approach that provides valuable insight into the learning process (e.g. Miller et al, 2019).

My research program can be divided into three interrelated interest areas: Retrosplenial Cortical and Anterior Thalamic Contributions to Memory; The Role of the Hippocampus in Contextual Memory; and The Role of the Prefrontal Cortex in Memory and Interference. I describe each of these in more detail below, along with a number of collaborative projects.

## ***Deciphering the Retrosplenial Cortical and Anterior Thalamic Contributions to Memory.***

**Retrosplenial Cortical Memory Representations:** The retrosplenial cortex (RSC) is a key component of the brain's memory and navigation systems. RSC lesions impair spatial navigation, contextual memory, and episodic memory in humans and rodents (for review see Miller et al, 2014). The RSC has also become a target of wide interest among fMRI investigators due to its role in the default mode network, constructive memory processes and imagining the future (e.g. Schacter & Addis, 2007). The RSC is anatomically interconnected with other components of the brain's memory systems, including the hippocampus and anterior thalamus, suggesting that circuit-level interactions between these structures are critical for memory, and recent findings suggest that the RSC is an important consolidation target for hippocampal dependent memories (for a discussion of this issue see Miller et al, 2019).

Despite this, the RSC has gotten relatively little attention from cognitive and behavioral neuroscientists, and this is especially true for behavioral neurophysiologists who have focused primarily on the hippocampus and entorhinal cortex. However, that is rapidly changing: The RSC is becoming a 'hot topic' in neuroscience, as you can see from this plot of published articles on the RSC over time. A major goal of my research program for the next few years will be to establish a foundational set of findings about how the RSC represents memory information in order to help build this new area of inquiry. I believe that any comprehensive account of the neuroscience of memory will need to include a detailed account of the kinds of information that are encoded by the RSC and how the RSC communicates with other components of the brain's memory circuits. At present, there have only been a handful of empirical papers using modern neurophysiological recordings in behaving subjects and we have published four of them. We are therefore uniquely positioned to provide basic neurophysiological data on the RSC, and this was the essential argument of our successful 2018 NIH grant proposal (R01 MH083809).



**Key Findings from My Laboratory:** This line of research has already produced several novel findings. We were the first to simultaneously record single-unit responses in the hippocampus and RSC, and we found that neurons in both regions encode information relevant to contextual memory. However, differences in response properties suggest that while the HPC encodes contexts, the RSC is particularly tuned to the cues that uniquely identify those contexts (Smith et al, 2012, also see my review on this topic: Smith et al, 2019). We have also shown that, consistent with fMRI studies, RSC neurons rapidly develop large-scale responses to important navigational cues (Vedder et al, 2016). In the same study, we found that RSC neurons encode many of the key items needed for successful navigation of a T-maze, including goal locations, and trajectories to the goal. Perhaps our most exciting work to date comes from our recently published study of continuous T-maze alternation (Miller et al, 2019). We recorded RSC

neural activity throughout learning and used a Bayesian decoder approach to examine RSC representations at the neural population level. We found that despite relatively non-specific spatial firing by individual neurons, RSC population activity contains a surprisingly accurate representation of the rat's current position. Moreover, as rats traverse the stem of the T-maze RSC neurons briefly 'simulate' the upcoming goal location. We also found that RSC neurons exhibit so-called 'splitter' firing patterns (i.e. differential firing on the stem of the T-maze for left and right turn trials), which are correlated with memory performance. Each of these findings is a 'first' for the RSC and because we recorded throughout learning, we were able to see that each kind of RSC spatial representation developed slowly, as the rats learned, suggesting that memories may slowly become consolidated into the RSC. Finally, we are also currently preparing a manuscript (Miller et al, in prep), which reports our discovery that the RSC uses a unique rate coding mechanism to represent environmental contexts. Unlike the hippocampus, many RSC neurons fire all over the environment with little spatial specificity, but they reliably fire at a higher rate in one context than another (Fig. 2). This rate code is so robust that we can correctly identify the context more than 95% of the time from a single 250 msec snapshot of firing data from ~50 neurons.

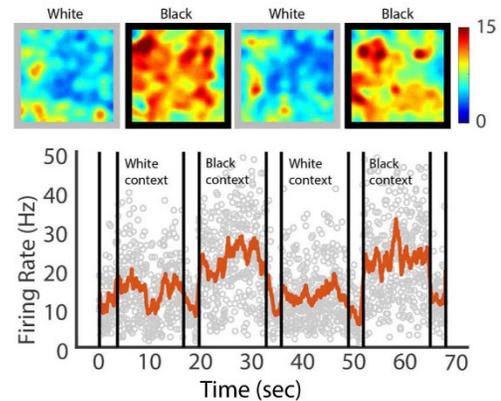


Fig. 2. Example heat maps (top) of a single RSC neuron that fires all over the environment, but fires at a high rate in a black box and a lower rate in a white box. The bottom plot shows firing rates during 250 msec intervals (grey dots) throughout the recording session along with the average firing rate (red line). Despite considerable moment by moment variation, the firing rates were typically higher in the black box.

Theoretical Implications: These studies have revealed that although the RSC shares many functional similarities with the hippocampus, the two structures seem to encode information in very different ways. Hippocampal neurons typically exhibit well-defined place fields with high firing rates inside the field but very little firing elsewhere.

In contrast, RSC neurons have very high background firing rates, they have large and indistinct 'place fields' and each neuron may respond to several different task variables. However, when we examined RSC activity at the population level, we found remarkably specific representations of spatial information (e.g. the rat's current location and the goal location) and task events, such as arrival at a choice point and obtaining the reward. These representations are found all along the ~9mm extent of the RSC in the rat, suggesting that the RSC encodes information using a widely distributed, multi-faceted population code that emerges with learning. We are currently working on a direct comparison of information processing in the RSC and hippocampus, and I think this will be important for establishing a detailed account of how the memory circuits of the brain work.

Anterior Thalamic Contributions to Memory: A rich literature has shown that the anterior thalamic nuclei are critical for memory and navigation. The memory role of the anterior thalamus has primarily been studied using experimental brain lesions (e.g. Langlais &

Savage, 1995; Warburton, Baird, & Aggleton, 1997), while most of the neurophysiology has focused on directional representations found in some of the anterior nuclei (e.g. Taube, 1995). I have a long-standing interest in the anterior thalamus, dating back to my graduate studies on its role in auditory discrimination learning (e.g. Smith et al, 2002) and more recently, we found that the anterior thalamus plays a critical role in contextual memory (Law & Smith, 2012). I plan to make this brain region a larger focus over the next few years. Our goal, as part of our recently funded NIH R01, is to examine how communication between the anterior thalamus and the RSC and hippocampus support memory. I think these studies will help the field to build a more detailed and coherent account of the anterior thalamic contribution to memory.

***The Hippocampal Role in Context Processing.*** One of the major aims of my research program has been to identify the specific role of the hippocampus in memory processes. For the last twenty five years, the two dominant theories of hippocampal function have held that the hippocampus is involved in spatial navigation and in episodic memory. Perhaps my biggest theoretical contribution has been to argue for a third idea, that the hippocampus is involved in encoding contextual information. Contextual information has a profound influence on memory and the context is an unusually potent retrieval cue. The idea that the hippocampus is involved in context processing is not new, but was originally proposed in the 1970s (Hirsh, 1974). My contribution has been to develop the idea that hippocampal firing patterns serve as a neural representation of the context, including non-spatial behaviorally-defined contexts, and that the output of these firing patterns could serve as a means of priming the memories and behaviors that belong to a given context. This provides a mechanistic account of how the context primes memory in such a powerful way (for review see, Smith and Bulkin, 2014).

In our most recent study (Bulkin et al, in press), we examined a dataset of more than 2000 neurons and found that the hippocampus treats different trial epochs as distinct contexts, each with its own unique and highly stable population representation. Interestingly, as the hippocampus transitions from one context to the other, there is a large-scale activity burst which may serve to push the hippocampus from one representational state to the other. In a previous series of studies, I have shown that hippocampal neurons develop highly context specific firing patterns, that these firing patterns develop only when subjects learn to discriminate the contexts and that the loss of the firing patterns in rats with temporary hippocampal lesions blocks the ability to discriminate contexts at the behavioral level (Smith and Mizumori, 2006a, b; Smith et al, 2011). Traditionally, 'context' has referred to the background environment. I have shown that the hippocampus also differentiates more abstract kinds of contexts such as those defined by behavioral demands, strategies and expectations (see Smith and Mizumori, 2006 and Smith, 2008). The hippocampus treats these 'behavioral contexts' the same way that it treats environmental contexts – it generates a new representation for each context the subject encounters. We have also found that the hippocampus represents information about the temporal aspects of memory (Sill and Smith, 2012; Gill et al, 2011).

Theoretical Implications: Hippocampal Context Coding Provides a Mechanism for Preventing Interference. If the firing patterns of hippocampal neuronal populations serve

as context representations, as I have argued above, then it's reasonable to ask why the brain devotes so much energy to the encoding of contexts. One important reason is that contextual information provides a critical mechanism for overcoming interference. As mentioned above, the context is a remarkably potent cue for the retrieval of memories. But how does this work in the brain? I proposed that hippocampal context representations could, through associative learning processes, become linked to extra-hippocampal representations of memories, strategies and behavioral responses that are appropriate to that context (for reviews see Smith, 2008; Smith and Bulkin, 2014). The idea is that when the subject returns to a familiar context, the hippocampal context code is re-expressed and the output of the code primes the relevant memories and behaviors. Because the context-appropriate memories are primed and competing memories from other contexts are not, intrusions of irrelevant memories are minimized and interference is reduced. If this account is correct, then hippocampal processing should be critical when contextual information can be used to resolve interference, but not when there is little potential for interference.

This hypothesis was confirmed in a study using a novel proactive interference task we developed for use in rats (Butterly et al, 2012). In this task, rats learn one list of odor discrimination problems, followed by training on a second list in either the same context where they learned the first list or in a new context. In order to induce interference, some odors are included on both lists, but with their predictive value reversed. Just as with human subjects, control rats that learned the two lists in different contexts performed better than rats that learned the two lists in the same context. However, this contextual advantage was completely abolished in rats given temporary inactivation of the hippocampus. In fact, rats with hippocampal inactivation performed just like rats that learned the two lists in the same context, as if they hadn't noticed that the context changed. We also manipulated the amount of interference in this task, by generating high and low interference versions of the task, using overlapping and non-overlapping lists, respectively. Remarkably, the rats with temporary hippocampal inactivation were entirely unimpaired in the low interference version of the task. These findings confirm that a key benefit of hippocampal context coding is that it provides a mechanism for overcoming interference.

In order to examine the neural mechanisms of this process, we recorded hippocampal neuronal populations while rats were confronted with interference (Bulkin et al, 2016). We trained rats on the task described above and we used population analysis methods to ask questions about the current state of the hippocampal network and its relationship to memory. Specifically, we computed population vectors (a snapshot of the firing rates of all of the recorded neurons) representing neural firing at the time when the rats encountered the odors, made their choice and dug for the reward. In order to determine whether hippocampal representations were related to behavioral performance, we measured the representational state of the hippocampus on a trial by trial basis. Remarkably, we found that when the hippocampal representation was very distinct, the rats were less susceptible to interference and they performed well. In contrast, when hippocampal representations were not so distinct, the rats made lots of errors. These findings suggest that hippocampal representations do, in

fact, provide a critical means of retrieving context-appropriate memories while avoiding interference from memories that belong to other contexts.

**The Role of the Prefrontal Cortex in Memory and Interference.** Dominant theories of PFC function suggest that it is involved in executive functions that allow for behavioral flexibility, such as the ability to shift attention from one feature of a multi-modal stimulus to another (attentional set shifting), the ability to abandon a non-adaptive strategy and adopt a new one (e.g. the Wisconsin card sorting task) and the inhibition of prepotent behavioral response patterns when contingencies change. Much of the rodent work on the PFC has focused on these ideas. However, many of the impairments seen after PFC damage appear to involve an inability to resolve conflicting response tendencies effectively. Memory retrieval also involves conflict, when subjects attempt to retrieve a specific target item from among other similar memory items, resulting in interference. Consistent with this idea, an extensive literature has shown that the PFC plays a role in controlling memory retrieval processes (e.g. Badre & Wagner, 2007; Wimber, Alink, Charest, Kriegeskorte, & Anderson, 2015). This suggests that the PFC may be critically involved in resolving interference, and this has been the focus of our work on the PFC.

We recently used an olfactory matching to sample task to examine the PFC role in interference, separately from any role in strategy selection and rule learning. We found that the PFC is involved in high-interference retrieval situations even when there is no change in the strategic, attentional or working memory aspects of the task (Peters and Smith, in press). Previously, we have also shown that the PFC is critically involved in resolving proactive interference (Peters et al, 2013). These results confirm that the PFC plays a role in resolving interference, but they don't indicate what that role may be. Two additional findings have suggested a specific role in modulating (promoting or inhibiting) the retrieval of particular memories. First, we fortuitously discovered that the PFC seems to 'tag' some memory representations as being particularly important, thereby making them very easy to retrieve in the future. This conclusion comes from findings showing that inactivation of the PFC during the early stages of acquisition of one set of memories actually reduces the tendency for those memories to intrude during attempts to acquire new, conflicting memories up to a week later (Peters et al, 2013). Importantly, this occurs even though the subjects given PFC lesions acquire the first set of memories to the same level as controls. Thus, in intact animals, the PFC must influence the encoding of memories in a manner that promotes their subsequent retrieval. Secondly, we have shown that the PFC is involved in inhibiting the retrieval of potentially interfering items. This idea comes from a recent study in which we developed a new rodent model of the retrieval-induced forgetting (RIF) effect. RIF has been studied extensively in human subjects and the essential finding is that extra practice with some of the items on a study list actually inhibits the retrieval of the non-practiced items, relative to a baseline condition that does not involve any extra practice (Levy & Anderson, 2002). That is, practice with some items inhibits retrieval of the others. Although a bit counterintuitive, the RIF effect is actually a highly adaptive mechanism for dealing with interference. Recently or frequently used items are 'highlighted' for easy retrieval, in part, by suppressing the retrieval of less frequently used items that might otherwise interfere. We adapted the RIF training procedure for rodents by using study

lists of odor cues and we showed, for the first time, that retrieval inhibition is likely a general property of mammalian memory systems and that lesions of the hippocampus or PFC selectively impair the inhibition of the non-practiced, but potentially interfering items (Wu et al, 2014).

**Theoretical Implications:** These findings suggest that the PFC is involved in promoting the retrieval of memory under some circumstances (e.g. particularly important, frequently used items) and inhibiting retrieval in other circumstances (e.g. potentially interfering items). However, the PFC is not a permanent storage site for these memories nor is it critical for the basic processes involved in acquiring memories. Instead, the PFC seems to be involved in modulating the 'retrievability' of memories that are stored elsewhere. Thus, the general role of the PFC in conflict resolution may result from the fact that the PFC modulates how readily a particular item is retrieved. Although we have focused on memory for items (e.g. odors), this may apply equally well to the retrieval of strategies, behavioral responses and attentional targets. If so, this will have important implications for general theories of PFC function. Our ongoing work on this topic is using optogenetic and chemogenetic approaches to study how the PFC influences memory representations in anatomically connected brain areas (e.g. olfactory memory in the anterior olfactory nucleus and piriform cortex).

## **Collaborations**

***Hippocampal Communication with the Olfactory System.*** This ongoing collaboration with Dr. Christiane Linster (Department of Neurobiology and Behavior, Cornell University) is aimed at understanding how hippocampal information about the context might influence memory representations in the olfactory system. We are currently working on a manuscript reporting that the anterior olfactory nucleus acts as a critical interface between the hippocampus and the olfactory processing stream (Levinson et al, in prep). More specifically, hippocampal information about the context is sent to the olfactory system in order to allow subjects to retrieve the correct odor memory for that context. This has been a fruitful collaboration with many important questions remaining, so I expect to continue this line of research for the foreseeable future.

***Hippocampal Representations of the Social Context.*** This ongoing collaboration with Dr. Alex Ophir (Department of Psychology, Cornell University) is aimed at understanding how the hippocampus might encode information about the social context. Previous studies have suggested that the hippocampus, especially the ventral region, is needed for social memory (e.g. memory for individual conspecifics) and given that the hippocampus encodes contextual information, it was likely that hippocampus would represent information about the social context, defined by the conspecifics present in the environment. To examine this, we recorded neurons in the dorsal and ventral hippocampus while rats were exposed to a variety of changes in the social context (e.g. the introduction of familiar males or unfamiliar females into the environment). Much to our surprise, hippocampal place cells appear to be wholly insensitive to these manipulations of the social context, suggesting that the hippocampus must employ some other mechanism for encoding social information. Dr. Ophir and I serve as co-mentors for Dr. Wen-Yi Wu, a postdoctoral researcher who

carried out these studies. These results have been published in abstract form (Wu et al, Society for Neuroscience Abstracts, 2019) and a manuscript is currently in preparation (Wu et al, in prep).

***The Role of Acetylcholine and Norepinephrine in Olfactory Learning.*** The goal of this collaboration with Dr. Christiane Linster (Department of Neurobiology and Behavior, Cornell University) was to understand how neuromodulators influence the processing of olfactory information. Neuromodulators, such as acetylcholine (Ach) and norepinephrine (NE), play a critical role in arousal, attention and learning. More specifically, Ach and NE are known to modulate olfactory perception and neural responses in the olfactory bulb. However, little is known about how Ach and NE neurons respond to odor stimuli in awake behaving animals. To investigate this issue, we recorded recording the responses of Ach and NE neurons in the horizontal limb of the diagonal band of Broca and the locus coeruleus during several olfactory learning tasks.

Dr. Linster obtained NIH funding to support her sabbatical in my laboratory (NIDCD F33 DC009150). After learning the techniques for recording neuronal activity in behaving animals and collecting pilot data, we successfully applied for NIH funding (NIDCD, R21 DC010420). In 2009, we hired postdoctoral research associate Sasha DeVore, who worked full time on this project. Dr. DeVore obtained an NIH postdoctoral training grant to support her work (NIDCD F32 DC011974) and published her findings (DeVore et al, 2016).

***Computational Modeling of Selective Memory Retrieval.*** The goal of this project was to develop a computational model of inhibitory processes that produce a contrast enhancement-like effect for recently used memory items (e.g. the retrieval-induced forgetting effect). This collaboration with Dr. Thomas Cleland (Department of Psychology, Cornell University) has shown that relatively simple mechanisms such as those that produce well-known contrast enhancement functions in the sensory systems can also support selective memory retrieval and can account for the impairing effects of hippocampal or PFC lesions (Wu et al, 2014).

***Adult Hippocampal Neurogenesis and Memory.*** The goal of this line of research was to understand the contribution made by new neurons in the adult hippocampus. One of the most important discoveries in neuroscience of the last 50 years is that new neurons are continually generated in the adult mammalian brain, and one brain region where new neurons are continually added is the dentate gyrus of the hippocampus. This discovery has led to a great deal of speculation about the role these new neurons play in memory. My collaborators on this project, Drs. Suzanna Becker (McMaster University, Hamilton, ON) and Martin Wojtowicz (University of Toronto, Toronto, ON) have proposed, on the basis of computational models and behavioral evidence, that new neurons may play a critical role in overcoming interference. In the resulting paper (Luu et al, 2012), we showed that rats that have had neurogenesis suppressed via focal irradiation of the hippocampus are, in fact, much more susceptible to interference than controls. We also showed that the timescale of the acquisition of the memories had to match the timescale of neurogenesis in order for this mechanism of interference reduction to work. These results were the first demonstration that

hippocampal neurogenesis is important for resolving interference and the first direct support for the idea that the time course is critical.

**Learning in Mosquitos.** The goal of this project was to examine the learning capacities of mosquitos in collaboration with Dr. Ron Hoy (Department of Neurobiology and Behavior, Cornell University). Social insects, such as bees, are known to be capable of associative learning. However, little work had been done with non-social insects such as mosquitos. In this experiment, we showed that mosquitos are capable of inhibitory avoidance learning, whereby they learn to avoid a dark colored region of a container that has been associated with shock (Menda et al, 2012).

## Publications

All of my publications are available at my website:  
<http://people.psych.cornell.edu/~dms248/Publications.html>.

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(Text citations not listed here can be found on my CV)

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