The Role of Dopamine in Hippocampus and Prefrontal Cortex Dependent Learning and Memory *Key Words:Theta synchrony; memory consolidation; short- &long-term memory recall*

Background The hippocampus (HPC) and prefrontal cortex (PFC) play key roles in the acquisition of both short-term (STM) and long-term memory (LTM)[1,2]. These regions form a circuit, with the PFC receiving direct input from the HPC, the HPC receiving indirect input from the PFC and each structure receiving direct projections from the ventral tegmental area (VTA)[3]. Dopamine (DA) from the VTA modulates the activity of the HPC, PFC and their interaction [3-5]. DA is important in mediating synaptic changes, such as long-term potentiation (LTP), that are thought to underlie learning and memory[5,6]. Additionally, *in vivo* recordings in the HPC and PFC have produced strong physiological correlates of learning and memory, such as HPC place cell activity and HPC-PFC theta synchrony[7,8]. HPC place cells are neurons that exhibit increased firing rates in a restricted region of an animal's environment, termed place fields, while theta rhythms (5-12 Hz) are a type of field potential that result from local network activity and occur during exploration[7,8]. While highly suggestive, these physiological phenomena remain correlative and the question of the necessity of these physiological measures in learning and memory remains unaddressed. Additionally, very little is known about the molecular basis of these physiological changes that accompany learning and memory. Here I propose the use of genetically manipulated mice lacking forebrain dopamine-5 receptors (D5-KOs) in order to disturb specific molecular components of these physiological measures of learning and memory as a tool to better understand the basis of these forms of plasticity.

Aim 1: The Role of Dopamine in the Consolidation of CA1 Place Fields The HPC consists of a trisynaptic pathway that includes the dentate gyrus (DG), area CA3 and CA1, with each region contributing to specific aspects of memory[9]. Learning models suggest CA1 compares raw information from cortical inputs with information stored in CA3 in order to detect novelty in the environment and initiate the learning process[4]. This role is reflected in the increase of CA1 activity when an animal encounters a novel stimulus[4]. Novelty also leads to increased activity in the VTA, resulting in a transient release of DA to the HPC and PFC[4,5]. DA is both sufficient and necessary for long-term changes in communication at the CA3-CA1 synapse, referred to as the late phase of LTP (L-LTP)[6]. L-LTP is required for consolidating HPC-dependent memories and pharmacological inactivation of HPC D5 receptors prevents memory consolidation[10]. As a result, novel experiences do not consolidate and previously experienced environments and contexts remain novel. DA may be critical in this process of familiarization, and thus may play a vital role in the consolidation of contextual representation and the place fields that underlie them. Place fields occur in all three regions of the HPC. Mice that lack the NR1 subunit of the N-methyl-D-aspartate receptor (NMDAR), specifically in DG, CA3 or CA1 exhibit broadly tuned place fields[11-13]. Experience rescues this deficit in the DG and CA3 mouse lines, and preliminary data suggests that place field tuning in CA1-NR1 KO mice is rescued by additional experience [11-13]. Although all three lines of mice also show learning and memory deficits, DG and CA3-KOs exhibit a decrease in learning deficits over time, showing a positive correlation between place field tuning and memory consolidation[11,12]. While these results suggest that a loss of NMDAR-mediated plasticity in the network can be overcome, the signal for place field tuning is not known. The D5 receptor is necessary for memory consolidation and for L-LTP, thus D5 receptor activation in CA1 may also mediate place field tuning. To test this idea, the following experiment will be conducted: forebrain restricted D5-KOs (produced in our lab) and control mice will undergo drive surgery for chronic electrode placement in CA1. After reaching CA1, mice will be introduced to a novel linear track and place cell activity will be recorded as the

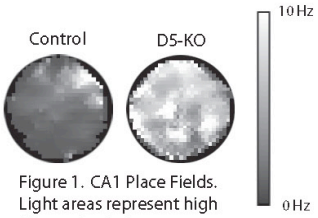

Figure 1. CA1 Place Fields. Light areas represent high firing rate, dark areas represent low firing rate.

animal navigates the track. Mice will be re-introduced to the same environment for three additional days to familiarize the animal to the environment; on day four the animal will be introduced to a novel linear track. The amount of spatial information that each place cell action potential provides during behavior can be used to predict the animal's position, and will be assessed during the behavioral task. Place field consolidation will also be compared across days, between KOs and controls. *I hypothesize that D5-KOs will lack the signal for place field tuning and thus will exhibit broadly tuned place fields and have reduced spatial informational content within each place field in the novel and familiar environments as compared to controls.* Preliminary data is in agreement with this hypothesis; when placed into a circular arena D5-KO place fields are larger than those of control mice on day 1, but it is not known if D5-KO place fields will tune by the next day (Figure 1). If D5-KO place fields do not significantly tune D5-KO mice may also exhibit HPC- and PFC-mediated learning deficits that do not ameliorate over time.

Aim 2: The Role of Dopamine in HPC-PFC Theta Synchrony During Associative Learning Population activity of neurons in the HPC and medial (m)PFC are tightly correlated at the theta rhythm during behavior[8]. Area CA1 leads the activity of mPFC neurons amid mPFC-dependent memory tasks during CA1-mPFC theta synchrony, suggesting information may be sent from the HPC to the mPFC[14]. The source of the HPC theta rhythm relies on input from the medial septum (MS) and lesions of the MS significantly reduce theta power in the HPC[15]. DA modulates the HPC theta signal by acting on MS inputs to the HPC[16], thus *I hypothesize that D5-KO mice will have significantly reduced HPC-PFC theta synchrony and reduced transfer of HPC information to the PFC*. I will record the local field potential from CA1 and PFC of D5-KO and control mice as they acquire the active place avoidance (APA) task. APA is a robust HPC-dependent behavioral task. Mice will be placed on a slowly rotating circular platform that moves the animal to a stationary sector termed the "shock zone" (SZ). When the animal enters the SZ a small foot-shock is administered, and the animal is removed from the apparatus after training. A STM (immediately following training) and LTM retention test (24h later) will be given. After the STM test, mice will be given additional training trials for the LTM test. For each test, I will measure (1) latency to enter the SZ and (2) number of entrances to SZ. Measure (1) reflects memory consolidation and is not affected by within-trial learning or memory extinction. Measure (2) reflects STM, as a single trial is robust enough for initial encoding. During testing, HPC and mPFC local field potentials will be recorded. *I hypothesize that D5-KO mice will enter the SZ as often as control mice during the STM test, but will show shorter latencies to SZ entry in the LTM test. D5-KO mice will also have significantly decreased HPC-PFC theta synchrony during APA memory recall.* These findings would support learning models which suggest that HPC transfer to PFC is required for LTM storage and rule learning[1].

Broader Impact This research will help in understanding diseases such as bipolar disorder, where patients exhibit altered HPC and PFC function that are dependent on DA levels. Additionally, I will mentor undergraduate students on this research project this coming semester. Success in research also depends on diversity and I fully realize the importance and have contributed to diversity during my time at UCLA and MIT.

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I attest to the originality of this research proposal