Dopamine–PKA Signaling and Age-Related Changes in Decision-Making Flexibility

Introduction: Learning to adjust behavior based on recent outcomes depends on coordinated interactions between frontal cortex, basal ganglia, and dopaminergic input to the nucleus accumbens (NaC).[1,2] In the NaC, dopamine has been shown to modulate PKA signaling in striatal projection neurons, a pathway required for experience-dependent synaptic plasticity.[3] However, it remains unclear what intracellular signaling conditions determine when phasic dopamine events are sufficient to drive plasticity during ongoing decision-making. **Background & Preliminary Findings:** The two-armed bandit task (2ABT) provides a controlled framework for studying how animals update choice strategies from reward history. (Fig.1A) Using fluorescence-lifetime dopamine measurements, we have found that basal dopamine tone in the NaC changes across the lifespan, while phasic reward-evoked signals remain indiscriminately spread. (Fig.1B) This suggests that aging may alter the *neuromodulatory background* in which learning-relevant signals are interpreted. Additionally, aging is known to induce coordinated transcriptional shifts in NaC neurons and astrocytes, but it remains unknown whether these shifts bias the circuit away from synaptic plasticity in a way that limits behavioral updating. Establishing this link is essential for determining whether neuromodulatory changes with age become stabilized at the level of cell state. To **elucidate how basal dopamine tone sets the intracellular and cellular conditions for behavioral updating**, and how this process changes across aging, I will pursue the following aims:

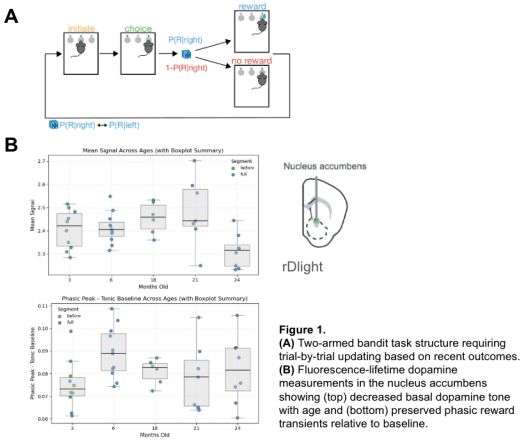

Figure 1.
(A) Two-armed bandit task structure requiring trial-by-trial updating based on recent outcomes.
(B) Fluorescence-lifetime dopamine measurements in the nucleus accumbens showing (top) decreased basal dopamine tone with age and (bottom) preserved phasic reward transients relative to baseline.

Aim 1: Does basal dopamine tone regulate PKA-dependent plasticity during behavioral updating?
Rationale: Dopamine activates PKA signaling in striatal projection neurons (SPNs), and our preliminary fluorescence-lifetime measurements indicate that basal dopamine tone declines with age while phasic reward-evoked transients remain stable. However, it is not known whether reduced basal tone alters the intracellular conditions under which phasic dopamine drives plasticity during updating. **Hypothesis:** Lower basal dopamine in aged animals will reduce PKA activation during update-relevant trials even when phasic dopamine transients are intact, lowering the probability that those transients produce synaptic plasticity in SPNs during behavioral updating. **Experimental Design:** I will perform in-vivo fluorescence-lifetime measurements of tonic dopamine (dLight3.8-FLIPR) and PKA activation (FLIM-AKAR) in genetically identified D1-SPNs, D2-SPNs, and astrocytes during 2ABT.[4,5] I will compare (1) update trials vs repeat trials and (2) young vs aged cohorts. **Anticipated Outcome:** Aged animals will show *reduced* PKA activation during behavioral updating, despite preserved phasic reward prediction signals, indicating that aging-related tonic decrease weakens the intracellular machinery required to convert phasic dopamine into synaptic change.

Aim 2: Do neurons and astrocytes adopt transcriptional states that reduce plasticity readiness in the NaC? Rationale: PKA activation engages transcriptional programs that support synaptic remodeling through CREB and related pathways.[6] If Aim 1 shows that aging reduces PKA activation during update-relevant events, the downstream effect should be a shift in neuron/glial gene expression toward states that favor synaptic stability over remodeling. **Hypothesis:** With age, D1-SPNs, D2-SPNs, and astrocytes will show reduced expression of PKA/CREB-dependent plasticity programs, decreased astrocytic glutamate clearance capacity, and increased complement-associated synaptic stabilization signals. **Experimental Design:** I will perform single-nucleus RNA sequencing on NaC tissue from young, middle-aged, and aged mice matched to Aim 1 cohorts. Cell types will be classified using

canonical markers (D1-SPNs: *Drd1*; D2-SPNs: *Drd2*; astrocytes: *GFAP, Aldh1l1*, *Aqp4*). Differential expression and pathway analyses will focus on gene modules related to PKA/CREB signaling, AKAP scaffolding organization, dopamine receptor effector pathways, astrocytic glutamate transport, and complement-mediated synaptic tagging. To quantify functional shifts, I will derive plasticity-permissive vs plasticity-stable module scores and relate these to behavioral updating performance and PKA activation strength from Aim 1. **Anticipated Outcome:** I expect to identify coordinated neuron–glia transcriptional shifts that reflect reduced NaC plasticity readiness with age.

Aim 3: Is reduced age-related cognitive flexibility reversible by restoring dopamine–PKA signaling gain in the NaC? Rationale: If Aims 1–2 show that aging lowers basal dopamine tone and reduces PKA activation during update-relevant trials, then restoring tonic dopamine should improve behavioral updating. Critically, flexibility should depend on normalizing *tonic* dopamine tone, not *global* dopaminergic stimulation, which induces motor and motivational side effects. **Hypothesis:** Increasing basal dopamine toward young-adult physiological range will enhance PKA activation during update trials and rescue adaptive switching behavior in aged mice. **Experimental Design:** I will use low-gain chemogenetic modulation of VTA dopamine neurons or their upstream RMTg/VP GABA inputs to selectively raise tonic dopamine in the NaC while preserving phasic dopamine transients.[7] Lifetime dopamine measurements will verify the (1) restoration of baseline dopamine and (2) intact phasic event structure. Aged and young adult mice will then perform 2ABT, and behavioral updating will be quantified using previously defined Recursively Formulated Logistic Regression (RFLR) model parameters.[8] **Anticipated Outcome:** Restoring tonic dopamine is expected to increase trial-by-trial updating, reduce perseveration, and shift learning/update parameters in aged mice toward those observed in young adults.

Intellectual Merit: If we show that age-related reductions in flexibility arise from changes in the plasticity state of the circuit, rather than reduced reward representation, this work has the potential to refine our understanding of how the striatum integrates neuromodulatory context during learning. The findings would demonstrate that adaptive decision-making depends not only on cortical computations and phasic dopamine signals but also on slower neuromodulatory conditions that determine the readiness of synapses to change. This framework would further provide a mechanistic basis for how learning capacity is regulated across the lifespan and can inform future studies of value-based choice, motivation, and circuit adaptation in both healthy and disease contexts.

Broader Impacts: Declines in cognitive flexibility affect independence and decision-making in aging populations, yet these changes are often interpreted in moral or fatalistic terms. By identifying how basal dopamine tone sets the intracellular threshold for PKA activation during behavioral updating, this research reframes cognitive aging as a shift in plasticity conditions rather than a loss of capacity. This distinction has meaningful translational implications. Current clinical approaches often attempt to increase dopamine globally, producing limited benefits and side effects. In contrast, understanding how aging alters signaling gain creates the possibility of more precise strategies that support adaptive behavior without overstimulating dopaminergic systems. These include modulation of PKA anchoring domains, tonic dopamine stabilization, or modulation of identified genetic programs (from Aim 2). This work therefore provides a mechanistic foundation for the rational design of future interventions that preserve cognitive agency later in life.

References: [1]Herd S, Krueger K, Nair A, et al. *Cogn Affect Behav Neurosci*. 2021;21:35–57. [2] Stopper CM, Khayambashi S, Floresco SB. *Neuropsychopharmacology.* 2013;38:715–728. [3] Lee SJ, Lodder B, Chen Y, Patriarchi T, Tian L, Sabatini BL. *Nature.* 2021;590:451–456. [4] Lodder B et al. *Neuron* 2025;113:3554–3566. doi:10.1016/j.neuron.2025.08.013. [5]Tilden EI, Maduskar A, Oldenborg A, et al. *Sci Rep.* 2024;14:3054.[6]Sakamoto K, Karelina K, Obrietan K. *J Neurochem.* 2011;116:1–9. [7] Faget L, Oriol L, Lee WC, et al. *Nat Commun.* 2024;15:4233.[8]Beron CC, Neufeld SQ, Linderman SW, Sabatini BL. *PNAS* 2022;119:e2113961119.