Our Core Research Mission and Approach:

We build and empirically test computational theories of striatal and hippocampal function in human learning and decision-making, and apply this basic research to improving our understanding and treatment of brain disorders. Three core questions at three distinct levels of inquiry drive our research:

1. **Behavior Processes**: How do we learn from past experience and use this to inform future decisions?
2. **Brain Substrates**: What do different brain systems contribute to learning and decision-making?
3. **Clinical Applications**: Can our understanding of these brain systems for cognition inform our ability to diagnose and treat neurological and psychiatric disorders?

To address these three questions, our lab employs a broad range of interdisciplinary methods, including clinical neuropsychological studies of human behavior, brain imaging, animal studies, behavioral genetics, and neurocomputational modeling to understand two key brain systems for learning:

1. **The Striatum (and Basal Ganglia)** and its role in learning new associations, skills, habits, and how these functions are modulated by dopamine and serotonin.
2. **The Hippocampus (and Medial Temporal Lobes)** and its role in supporting new learning by providing contextual and representational constraints on what is learned.

Our Heuristics for Selecting Research Projects:

We focus our efforts on research projects for which we feel we can maximally leverage our competitive strengths, including: (1) computational modeling that links brain systems with cognition, (2) application of theories and paradigms from animal learning to the study of human cognition, (3) extensive experience in cognitive psychology developing human learning tasks that assess information processing capabilities of the brain, (4) cross-disciplinary collaborators who are world-leaders in their fields and have domain expertise and prominence that compliments our own, (5) a broad network of clinical collaborators with whom we study diverse neurological and psychiatric patient populations, (6) unique access to local and international populations, including those in Israel, the West Bank/Palestinian Territories, Hungary, Turkey, Italy, Great-Britain and China, where we can find patients or other research subjects not available locally, (6) opportunities for research that arise synergistically from our two community outreach and infrastructure building programs, the Rutgers/Al-Quds Brain Research Exchange which supports the development of a Palestinian Neuroscience Initiative at Al-Quds University Medical School in the West Bank, and the African-American Brain Health Initiative in Newark, NJ.

Our Current Research Programs and Specific Ongoing and Pilot Projects:

Given the questions we ask at the behavioral, brain, and clinical levels, and the two brain systems of interest to us, the research in our lab can be organized into three broad programs of research, each of which has multiple subprojects:

1. **Cognitive Correlates of Striatal and Hippocampal Dysfunction in Psychopathology.**
2. **Individual Differences in Cognitive Deficits in Parkinson’s Disease.**
3. **Lifestyle and Genetic Influences on Cognitive Health Across the Lifespan.**

Further details on these three inter-related programs of research and the various grants that fund them are described in the pages that follow. Included as well are brief sketches of several preliminary pilot projects recently initiated for which we plan to apply for additional funding in the coming years.

Striatal and hippocampal dysfunction is key to several psychiatric disorders, including clinical depression (also known as major depressive disorder, MDD) and post-traumatic stress disorder (PTSD). In the four projects summarized below we employ a mix of methods to understand how the striatum and hippocampus are affected in these disorders, what happens when patients are treated with antidepressants, how traumatic brain injury increases risk for mental health problems, and how computational modeling can help us understand the links between brain, behavior, and psychopathology.

1.1 Collaborative Research on Cognitive Correlates of Clinical Depression

**Funded:** NIH/NIMH & Fogarty International 1 R21 MH095656-01A1 (PI: Gluck). 2012-2014

**Key Lab Personnel:** Herzallah

**Collaborators:** Al-Quds University Medical School, Abu Dis, West Bank/Palestinian Territories

Major Depressive Disorder ("clinical depression") is the leading mental health problem in the Palestinian West Bank, affecting approximately 24% of men and almost twice as many (45%) women, rates that are two to three times higher than in the USA. Focusing on clinical depression targets a critical regional mental health issue and provides us with the opportunity to take advantage of unique cultural, environmental, familial, and genetic aspects of depression among West Bank Palestinians to advance the science and treatment of depression through three aims:

**Aim #1:** Further develop the environment, personnel, and infrastructure at Al-Quds University for neuroscience research.

**Aim #2:** Study the cognitive correlates of depression among West Bank Palestinians, focusing on how the disorder and antidepressant medications alter learning and decision making.

**Aim #3:** Use the collected data and expected infrastructural growth at Al-Quds as the basis for a future proposal to the NIH Brain Disorders in the Developing World program for a larger and longer program of collaborative neuroscience and psychiatric research between Rutgers and Al-Quds.

**Future Plans:** In February, 2014, we plan to submit a follow-up grant as a 5 year R01 proposal to build on the successes of this current R21. The scope will expand to include projects in line with NIMH RDoC initiative, and include new aims with genetics and structural imaging.

**Pilot Research Projects in Psychopathology**

1.2 Predicting Future Comorbid PTSD and MDD in Individuals with Mild TBI/Concussion Using Computer-Based Cognitive Assessment

**Submitted and Pending:** Department of Defense, CDMRP 2014-2015 (PIs: Gluck, Herzallah).

**Key Lab Personnel:** Herzallah

**Collaborator:** CAPT Jack Tsao, MD, U.S. Navy Bureau of Medicine and Surgery (BUMED)

1.3 Cognitive and Biological Markers of PTSD

**Key Lab Personnel:** Herzallah

**Collaborator:** Charles Marmar & Adam Brown, NYU Psychiatry Department PTSD Clinic

1.4 Collaborative Modeling of Neurocognitive Axes of Individual Differences in Patients with Major Depressive Disorder

**Key Lab Personnel:** Herzallah, Moustafa

**Collaborator:** Catherine Harmer, Oxford University. England.

2. Individual Differences in Cognitive Deficits in Parkinson’s Disease.

The striatal circuits for processing positive feedback (reward) and negative feedback (punishment) during associative learning are disrupted in Parkinson’s disease (PD) by the loss of
dopaminergic inputs to the striatum as well as by the dopaminergic drugs given to treat motor dysfunction. Given our lab’s long history of studying error-correction feedback-learning through computational modeling and empirical studies (beginning with Gluck’s PhD thesis in 1987), we seek to leverage this past work to enhance our understanding of individual differences in the heterogeneous range of cognitive deficits seen in PD.

2.1 Functional Brain Networks: A Novel Approach to Address Clinical Challenges in Parkinson’s Disease

**Funded:** NIH/NINDS: #P50 NS 071675-02 (PI: Eidelberg, NSLIJ Feinstein; Co-I: Gluck). 2010-2015

**Key Lab Personnel:** Simon, Herzallah

**Collaborator:** David Eidelberg, NSLIJ

The major goals of this 5-year NIH/NINDS Center of Excellence are to illustrate the physiological and behavioral contribution of various brain networks to the progression of Parkinson’s disease (PD). The center is based in the neurology department of the Feinstein Institute at the North Shore Long Island Jewish (NSLIJ) Medical Center, and headed by our collaborator, David Eidelberg. Our lab contributes to this center in two ways. First, we are the Cognitive and Behavioral Core that supports the design, development, and analysis of psychophysical tasks to assess frontostriatal circuit functioning in Parkinson’s disease. We also support, through our Core activities, the development of neurocomputational and mathematical models of feedback-driven reinforcement learning and neuroeconomic decision-making in PD. Second, we collaborate with NSLIJ on a specific brain imaging project that seeks to delineate the effects of dopaminergic treatment on dynamic cognitive processing and associated activation responses. This project uses the differential Rewards/Punishment learning task developed at Rutgers, in which it was previously shown that drug-naïve PD patients are selectively impaired at reward learning while patients on medication are impaired at punishment learning but normal at reward learning.

**Pilot Research Projects in Parkinson’s Disease**

2.2 Cognitive Correlates of Hippocampal Dysfunction in PD patients with Impulse Control Disorders

**Key Lab Personnel:** Simon

**Collaborators:** Melissa Nirenberg, NYU Neurology, & Daniel Weintraub, Univ. of Penn. Neurology.

2.3 Effects of genotype on cognitive function in medicated and unmedicated Parkinson’s patients

**Key Lab Personnel:** Simon, Herzallah

**Collaborators:** Al-Quds University; Shanghai Biological Sciences, China; UMDNJ, NJ

2.4 Effects of Laterality of Motor Disorders on Cognition in PD Patients.

**Key Lab Personnel:** Herzallah

**Collaborator:** Yuyan Chen, Shanghai, China; M. T. Pellechia, Salerno, Italy.

2.5 Effects of Levodopa Medication on Cognition in Medication-naïve PD Patients

**Key Lab Personnel:** Herzallah

**Collaborator:** Al-Quds University, West Bank.

2.6 REM Sleep Behavior Disorder (RBD) and Cognitive Deficits in Parkinson’s Disease

**Key Lab Personnel:** Lerner

**Collaborator:** Lama Chahine, University of Penn. Neurology & Sleep Laboratory.

2.7 Instrumental vs. Pavlovian Learning Deficits in Parkinson’s Disease

**Key Lab Personnel:** Herzallah

**Collaborator:** Szabolcs Kéri, Semmelweis Hospital, Budapest, Hungary.

2.8 Interactions between Depression and Cognition in Parkinson’s Disease

**Key Lab Personnel:** Herzallah

**Collaborator:** Roseanne Dobkin, Rutgers-NB Neurology, RWJ Medical School
3. Lifestyle and Genetic Influences on Cognitive Health Across the Lifespan

What are the life-style and genetic factors that influence individual differences in learning and memory across the lifespan, especially those capabilities that rely on striatal and hippocampal systems? Both striatal and hippocampal circuits change with aging, and hippocampal-region dysfunction is among the first brain regions affected in the earliest (probably prodromal) stage of Alzheimer's disease.

3.1 Long-term Mobile Monitoring and Analysis of Sleep-Cognition Relationship

**Funded:** National Science Foundation #1231515 (PI: Gluck). 2012-2015

**Key Lab Personnel:** Lerner, Peters, Cannella

This study utilizes smart and wireless technologies to monitor sleep and test cognition over a long period of time to investigate correlations between the quality/quantity of sleep and cognitive performance in various domains. Our main goal is to use mobile sleep-monitoring devices in combination with cognitive assessments of learning and memory to investigate the relation between sleep and cognition over consecutive weeks. Traditional lab research of sleep and cognition, with few exceptions, based on Polysomnography (PSG) measures of sleep requiring subjects to spend a night in a sleep lab. These settings have two major disadvantages: First, these lab or hospital settings preclude monitoring sleep for long periods (e.g., few weeks). Second, the unnatural environment of sleep labs is known to influence sleep characteristics compared to sleep at home, thus reducing the validity of the findings. These two weaknesses can now be addressed by recent developments in self-monitoring technology focusing on measurement of sleep by mobile devices. We give participants sleep-measuring devices together with a tablet computer running cognitive tasks specifically designed to assess certain types of memory and learning, as well as tasks designed to assess aspects of emotional processing. Participants will measure their sleep every night, and perform the cognitive tasks twice a day upon waking and before going to bed, for several consecutive weeks. These data allow us to examine the relations between sleep patterns, cognitive performance and emotional well-being and answer our main research questions. Using such devices, our project aims to answer two core questions in the field which are not easily addressed by the traditional PSG-based approach:

**Aim #1:** What is the cumulative effect, over many days, of fluctuations in sleep patterns on cognitive and emotional well-being?

**Aim #2:** What are the effects of sleep on the gradual consolidation of memory in activities which require ongoing practice for days or weeks to master?

An additional key component of this project is the parallel development of computational models of how sleep stages (especially REM and nonREM) differentially impact cortico-striatal-hippocampal circuits for learning and memory. These models will be used to integrate and synthesize past data in the literature as well as inform and interpret the new data collected by our lab within this study. Additionally, the models will be used to develop theory-based functional interpretations of sleep disruption in various psychiatric and neurological disorders.

3.2 Effect of Genetics on Reward Learning and Generalization of Associations in Aging

**Pending and Reviewed (rated top 7%):** NIH/NIA R03 AG044610-01A1 (PIs: Gluck, Simon).

**Key Lab Personnel:** Simon

This study will examine the effects of aging on reward-based associative learning and generalization and how these relationships vary by common genetic polymorphisms. It focuses on frontostriatal-based learning (i.e., acquiring new associations from feedback) and hippocampal-based generalization (i.e., context-dependent transfer). Our focus on the dissociation between learning and generalization is particularly relevant to older adults because these processes call on different brain regions that are differentially affected by healthy aging. Understanding the mechanisms underlying individual differences in vulnerability to cognitive decline may, in turn, inform cognitive training and pharmacological treatment programs aimed at maximizing cognitive functioning in old age. A sample of both younger and older adults will complete a variety of learning and generalization tasks that have been validated to assess frontostriatal and hippocampal function, as we seek to address three aims:

**Aim #1:** Older adults are predicted to show greater age-related deficits on learning than generalization, adding to data that healthy aging affects the striatal system more than the hippocampus.
Aim #2.1: It is expected that a functional polymorphism in DAT1 will predict individual differences in frontostriatal learning, whereas a functional polymorphism in BDNF will predict individual differences in hippocampal generalization.

Aim #2.2: We will examine whether healthy aging modulates these genetic effects on cognitive function, by testing a recent hypothesis that aging magnifies the functional significance of genetic variants on cognition. We predict that genotypic differences on cognition will be larger in older than younger adults.

**Pilot Research Projects in Genetics and Lifestyle Influences**

3.3 Familial Alzheimer’s Disease
   Key Lab Personnel: Simon
   Collaborator: John Ringman, UCLA, & Catherine Myers (VAMC, NJ)

3.4 Lifestyle, Personality, and Genetic Influences on Cognitive Health Across the Lifespan in African Americans
   Collaborators: Diane Hill, Rutgers-Newark Vice Chancellor for Community Relations, Brandon Alderman, Rutgers-NB Department of Exercise Science, American Heart Association/American Stroke Association, NJ Alzheimer’s Association.

3.5 The Cognitive Neuroscience of Hippocampal Function in Generalization
   Collaborators: Mauricio Delgado, R-N; Passamonti & Fera, Italy; Nanthia Suthana, UCLA.