## RESEARCH PROPOSAL

Dopamine (DA) release from the ventral tegmental area (VTA) contributes to neurotypical survival behavior as well as aberrant behavior that occurs in addiction, depression, and schizophrenia, conditions marked by varying degrees of compulsivity (1). Previous theories of DA function posited that DA contributes to learning only when rewards (i.e., value) are involved (2). We now know this is not the case. In a task where no rewards were involved, and learning could not be accounted for by any sort of reward-related or value mechanism, optogenetic stimulation and inhibition of VTA DA neurons was used to show that DA neuron activity is both necessary and sufficient for learning that is not based on rewards or value (i.e., associative learning). When DA neuron stimulation was used to artificially induce associative learning, subjects acted as if learning occurred under naturalistic conditions (3).

This was shown with behavior. While behavioral responses resulting from natural versus DA stimulation-induced learning may be similar, it is unclear whether the neural responses to naturally versus artificially induced associations are also similar. It is possible that using optogenetics to stimulate learning produces some other pattern of neural response that is quite abnormal yet is able to generate normal behavior. It is also possible this stimulation merely produces a general value signal, rather than true associative learning.

*Here I will approach this question using in-vivo optogenetics and electrophysiology. I will assess neural responses in a cortical target of the VTA DA system that is known to contribute to both neurotypical and compulsive behavior. These experiments will provide additional novel evidence bearing on the biological function of DA signals in learning.*

### *Aim 1. Determine how similar the OFC engram acquired under artificial stimulation is to that acquired during normal learning.*

Here I will replicate the lab's previous findings that DA neuron stimulation produces behavior that appears as if normal associative learning occurred. This will happen in a task where both associative learning or value could account for neural activity, which will be measured in orbitofrontal cortex (OFC), a region known to contribute to compulsive behavior. **This experiment will test the hypothesis that DA neuron stimulation produces associative learning**.

## SIGNIFICANCE

Associative learning and the decision making that depends on it are necessary for species success and survival, and altered associative learning may underlie decision-making deficits in several compulsive conditions, including addiction, depression, and schizophrenia (4).

Associative learning can be easily isolated in sensory preconditioning. In sensory preconditioning, an association between two stimuli that do not predict appetitive or aversive events is learned. These two value-less stimuli are first paired (A→X). If X is thereafter paired with a biologically meaningful stimulus (e.g., food), presentation of A will produce a food-approach response (i.e., A predicts X, which predicts food). This food-directed response demonstrates that subjects formed an associative model in which A predicts X, which can subsequently be mobilized to predict reward when A is presented. Critically, in the preconditioning phase (A→X), no new behavioral responses or values are learned, as no food is delivered, so value or reward learning during this phase cannot explain the later food-directed responding. Additionally, stimuli that have already acquired the ability to predict X can "block" preconditioning of new stimuli. In other words, once animals have learned that A predicts X, if a novel stimulus, B, is presented in compound with A and followed by presentation of X (AB→X), conditioning to B will be blocked because A is already fully predictive of X. This indicates that the stimulus-stimulus learning in this first phase of preconditioning is predicated on errors in predicting X. If DA neurons are stimulated briefly at the start of X under these conditions, the stimulus-stimulus learning is "unblocked", and animals

treat the artificially unblocked cue (B) as if it had been learned about normally (i.e. they respond to the food cup when it is presented). Thus, DA neuron activity is sufficient (and also necessary) for the initial stimulus-stimulus (i.e., associative) learning that occurs in sensory preconditioning, as if DA is the endogenous signal driving stimulus-stimulus associative learning.

While the behavioral responses to the normal and DA-stimulation-unblocked cues are similar, a major question remains: what is the neural engram acquired under these conditions, and how closely does it resemble that acquired naturally? **I will use single unit recording and optogenetics to address this question, directly testing the hypothesis that DA neuron stimulation produces associative learning. If this is true, then the neural ensemble response will most closely resemble that of a stimulus learned about under naturalistic conditions.** I will measure responses to these cues in the orbitofrontal cortex (OFC), a cortical target of the DA system that supports sensory preconditioning. The present studies will probe the nature of the contributions of DA signaling to associative learning, which will further inform our understanding of both normal function and the effects of dysfunction of this system.

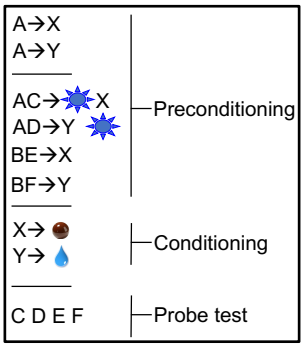


**Figure 1**. Proposed task design. Stimulus C is the artificially unblocked stimulus that will be compared to control stimulus D as well as naturally conditioned stimuli E and F that predict the same and different downstream outcomes.

## APPROACH

**Exp. 1.** Recording OFC neuron electrophysiological responses to naturally versus artificially conditioned cues: TH-Cre Rats (n=10 male, n=10 female) will be infused with a Cre-dependent virus (AAV5-EF1a-DIO-ChR2-YFP) in the VTA that will cause expression of Channelrhodopsin in VTA DA neurons. This light-sensitive membrane protein is a cation channel that will allow me to artificially drive DA neuron activity to induce learning. During this same surgery, rats will also be implanted with optical fibers for light stimulation of Channelrhodopsin in addition to microelectrodes to record OFC neuron activity. We will not include a YFP group that lacks the active opsin, since mere light stimulation itself is not sufficient to cause learning, and our experimental design outlined in **Figure 1** includes ample within-subject controls. In the first stage, rats will learn that A predicts stimuli X and Y, allowing A to block conditioning in the next phase. Light stimulation will be used to "unblock" learning to C. D is the control stimulation cue. Stimuli E and F are naturally conditioned and predict the same and different outcomes as C, respectively. Thus, we have an artificially learned cue I, a control cue (D), a same-outcome natural cue I, and different-outcome natural cue (F). This allows us to test whether the artificial unblocking by DA stimulation produces associative learning, value, or something else. X and Y will be paired with chocolate and vanilla milk, respectively, during the conditioning phase.

It is important to note that the food reward-pairing is a tool to motivate rats to respond to stimuli, so that we can probe the learning that occurred in the preconditioning phase. **Stimuli that subjects learned predict downstream food reward induce food-port entry during probe testing. This food-port entry is the primary behavioral measure. I will measure port-approach latency, duration of time spent in the food port, and food port approach rate**. During probe testing, stimuli C, D, E, and F will be presented in random order. I will measure food-port approach responses and record neural activity during this entire probe session. Verification of opsin expression, fiber placement, and electrode placement, will occur post-hoc using standard blinded histological processing techniques.

*Planned analyses and expected outcomes:* I expect higher food-port responding during stimuli C, E and F, demonstrating we artificially unblocked learning about C, blocked learning about D, and

produced natural learning about E and F. **Behavioral responding will be compared across stimuli by repeated measures ANOVA**.

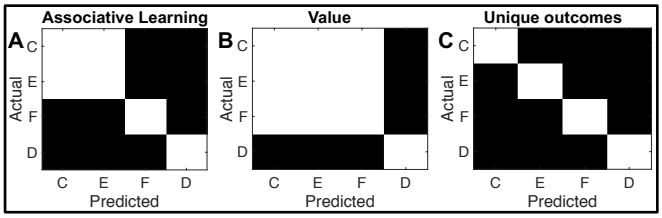


**Figure 2.** Hypothesized results if DA neuron stimulation produces associative learning **(A),** value **(B),** or a unique engram **(C).** Y axis represents the actual stimulus presented during probe testing. X axis represents the stimulus predicted from the pattern of activity across all neurons. **Colors represent proportion of trials classified – black (no trials classified) and white (high proportion of trials classified). White indicates those trial types are more similar.**

Single unit and ensemble decoding analyses will be performed similarly to previous work from the Schoenbaum lab (6-8). This will allow us to measure how well the stimulus presented on a given probe test trial can be decoded from the pattern of firing across neurons, giving a measure of how closely the pattern of neural responses to each of the stimuli resemble each other. Our main analysis will focus on neural data from the probe test, though we will also examine data from other phases. On a logical level, it will consist of comparing responses to stimulus C versus D (artificially unblocked vs blocked), C versus E (naturally conditioned, same outcome), and C versus F (naturally conditioned, different outcome). **Given that the hypothesis is that DA transients drive associative learning** rather than the formation of general value, I expect that the ensemble response to cue C will be most similar to the response to cue E, since cue E predicts the same outcome. If this is the case, then neural activity will correctly identify trials on which C was presented as such, and when the neural activity does not accurately predict C trials, it will miscode E as the presented stimulus. Because C and E predict the same downstream outcome, this finding would support the hypothesis that DA stimulation induces formation of an associative model of downstream events, since this result will show that the engram is closest to that acquired during normal learning of similar information. An alternative outcome is that DA neuron stimulation will produce only value learning. In this case the neural response to cue C will not be differentiable from E and F, which have the same value but predict different outcomes, and decoding will reveal equal prediction of C, E, or F on all C, E, and F trials, but no false prediction of D. A third potential outcome is that the neural response to C will be equally different from E and F and D. This would suggest that the artificial learning, while somehow supporting normal behavior, is quite different from normal learning, as if DA stimulation is a unique outcome that somehow still produces normal behavior. Hypothesized confusion matrices showing each of these three potential classification patterns are shown in **Figure 2**. **I expect the classification pattern obtained to most closely resemble the confusion matrix displayed in Figure 2A.** If DA neuron stimulation instead results in a general value signal, the classification pattern will more closely resemble that presented in **Figure 2B**. If DA neuron stimulation produces a unique engram, then the classification pattern will resemble that in **Figure 2C**. **Standard correlation analyses will be used to test how well the obtained results conform to these hypothesized outcomes, as done previously (8).**

*Alternative strategies, pitfalls, and future directions:* If the proposed behavioral paradigm is too complicated to work, we may default to a simpler task that is proven to work that would allow us to test whether artificially conditioned cue responses are more similar to naturally conditioned responses than to blocked cue responses. We will analyze data from other experimental phases, in addition to testing whether DA-unblocked responding is OFC-dependent in future experiments.

These experiments will test whether the engram induced under artificial DA neuron stimulation, which supports apparently normal associative learning, is also "normal", furthering our understanding of the basic mechanisms of associative learning, which is implicated in several conditions marked by compulsive behavior.

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1. Volkow ND, Wang GJ, Fowler JS, Tomasi D, Telang F. Addiction: beyond dopamine reward circuitry. Proc Natl Acad Sci U S A. 2011;108(37):15037-42. doi: 10.1073/pnas.1010654108. PubMed PMID: 21402948; PMCID: PMC3174598.

2. Schultz W, Dayan P, Montague PR. A neural substrate of prediction and reward. Science. 1997;275(5306):1593-9. PubMed PMID: 9054347.

3. Sharpe MJ, Chang CY, Liu MA, Batchelor HM, Mueller LE, Jones JL, Niv Y, Schoenbaum G. Dopamine transients are sufficient and necessary for acquisition of model-based associations. Nat Neurosci. 2017;20(5):735-42. doi: 10.1038/nn.4538. PubMed PMID: 28368385; PMCID: PMC5413864.

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6. Schoenbaum G, Eichenbaum H. Information coding in the rodent prefrontal cortex. II. Ensemble activity in orbitofrontal cortex. J Neurophysiol. 1995;74(2):751-62. doi: 10.1152/jn.1995.74.2.751. PubMed PMID: 7472379.

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8. Zhou J, Gardner MPH, Stalnaker TA, Ramus SJ, Wikenheiser AM, Niv Y, Schoenbaum G. Rat Orbitofrontal Ensemble Activity Contains Multiplexed but Dissociable Representations of Value and Task Structure in an Odor Sequence Task. Curr Biol. 2019;29(6):897-907 e3. doi: 10.1016/j.cub.2019.01.048. PubMed PMID: 30827919.

**BIOGRAPHICAL SKETCH**

**Provide the following information for the Senior/key personnel and other significant contributors.**

**Follow this format for each person. DO NOT EXCEED FIVE PAGES.**

NAME: Evan Hart

eRA COMMONS USER NAME (credential, e.g., agency login): EVANHART

POSITION TITLE: Postdoctoral IRTA Fellow

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

| INSTITUTION AND LOCATION | DEGREE *(if applicable)* | START DATE MM/YYYY | END DATE MM/YYYY | FIELD OF STUDY |
|---|---|---|---|---|
| University of Connecticut Storrs, CT | BA | 08/2008 | 08/2013 | Psychology |
| University of California, Los Angeles, Los Angeles, CA | PHD | 09/01/2013 | 06/2019 | Psychology |
| National Institute on Drug Abuse Intramural Research Program | Postdoc | 07/01/2019 | present | Cellular Neurobiology |

**A. Personal Statement**

Per the NIH definition set forth in its statement on diversity, NOT-OD-20-031, I am an underrepresented minority in science. Between evictions, my family experienced long bouts of homelessness throughout my childhood, until we received section eight housing benefits. I received free lunches and food stamp benefits throughout middle school and high school, due to a family income below the poverty line. I was raised by a single mother who never went to college. I received a Pell grant to offset the cost of attending college. Other than the aforementioned government benefits, my two sisters, mother, and I received no other financial support. This qualifies me under 5/7 of the “disadvantaged background” criteria. I do not enjoy writing about this, nor is this intended to be a “woe is me” story. However, it must be said, since I am eligible to identify myself as a minority in science in this way, and unlike race and gender, this sort of demographic information, though clearly and explicitly defined as constituting a minority in science, has never been collected as a “box to check” on any fellowship for which I have applied. I simply ask that this be taken into account.

And I believe these life experiences leave me uniquely positioned to further NIH goals in terms of diversity. I know what it is like to have people assume things that are not true based on appearance. I worked 70-hour work weeks at manual labor jobs over summers to pay for college, in addition to part time jobs on top of undergraduate research. I did not even know professors did research prior to my third year of college. Still, I was extremely fortunate to get where I am. I had exceptional mentors who welcomed me into their laboratories where anyone willing to put in the effort to be the best version of themselves was welcome. This is exactly

how I plan to run a lab in the future. Everyone will be included, no matter what their background- women, men, people of color, individuals with disabilities, and those from disadvantaged backgrounds. This active effort for diversity and inclusion is necessary to build a diverse work force, as per the goals laid out in the NIH statement on diversity.

Through many experiences ranging from university coursework to my social life, I have developed a keen interest in studying the neural mechanisms of learning and motivation. These fundamental processes are implicated in nearly every human behavior: how do we decide what to eat for dinner? Is applying for that grant worth the effort? Which stimuli in my environment are meaningful and how was that learned? Importantly, these learning and decision-making processes are impaired in nearly every neuropsychiatric condition. For these reasons, I sought research opportunities that would allow me to pursue my interest in the neural mechanisms of learning and decision-making. As an undergraduate research assistant in Dr. John Salamone's lab at the University of Connecticut, I studied animal models of the motivational symptoms of depression. This work resulted in three publications where I was co-author, and during my time at UConn I was able to hone several bench skills in behavioral pharmacology, neurochemistry, and immunohistochemistry. The research I participated in as an undergraduate focused primarily on dopamine signaling in the striatum. I finished my time at UConn with a desire to explore other brain regions in decision-making from a systems-level approach.

My goals led me to make a cross-continent move to UCLA, where I completed my Ph.D. in Dr. Alicia Izquierdo's laboratory. As a graduate student, I expanded my technical skills and knowledge base to further understand effortful decision-making. I found novel roles of the amygdala and cingulate cortex in effortful choice between qualitatively different options, as well as effects of withdrawal from methamphetamine self-administration. I expanded upon these findings using in-vivo calcium imaging. The final portion of my dissertation entailed finding a neural correlate of effort-based choice. This project pulled from every bench skill in my toolset, and was a rich collaborative effort involving all of my favorite things about science: answering questions, learning new skills, mentoring, and dissemination. This project is complete and in revision. I expect it will be published very soon.

I am well suited to fill my role in this project for several reasons: I have mastered in-vivo single-photon calcium imaging in rats. As far as I know, I am one of less than a handful of people who has successfully done this. I have also mastered in-vivo manipulations using chemogenetics and behavioral testing, as well as the surgical procedures required to do all of the above. The skills I built in graduate school have already facilitated my transition to postdoctoral research. In the eight months since beginning in July of 2019, I have already completed one experiment and acquired large data sets in others. A key component of my training in the Schoenbaum lab and this proposal is learning in-vivo electrophysiology. This is already well underway. I have already learned how to set up and program the behavioral boxes, assemble microelectrode arrays and microdrives, implant arrays, and collect neurophysiological data. Analysis is also underway. The data I have already collected are from a project that is orthogonal to the proposed research from which I can directly translate the skills built. I do not include any preliminary data in the research plan due to space constraints. Critically, all of the research proposed will enhance my training while pulling from several areas in which I already have experience. Being awarded a CCB fellowship will provide an opportunity to build on my strengths and acquire new skills that take my abilities to the next level, further advancing my career in teaching, research, and mentoring.

My productivity, in terms of coursework, suffered during my first year of graduate school (2013-2014). During this time period, I suffered a motor vehicle accident that fractured ten different bones between both my legs, ankles, and feet. I was unable to walk for several months. Fortunately, I was able to make a mostly full recovery. However, my grades during

this time, though passing, were below my personal standards for myself. Please note that, following this period, I did not earn anything below an A.

**B. Positions and Honors**

**Positions and Employment**

2011 - 2012 Undergraduate Research Assistant, UConn
2012 - 2013 Research Technician, UConn
2013 - 2019 Ph.D. Student, UCLA
2019 - present Postdoctoral IRTA Fellow

**Other Experience and Professional Memberships**

2014 - 2019 Graduate Teaching Fellow
2012 - present Member, Society for Neuroscience
2016 - 2018 Member, Society for Neuroeconomics
2017 - 2018 Member, International Behavioral Neuroscience Society

**Honors**

2008 - 2012 University of Connecticut Dean's List
2009 - 2010 University of Connecticut New England Scholar
2011 - 2012 University of Connecticut Babbidge Scholar
2012 University of Connecticut Undergraduate Research Grant
2013 UCLA Distinguished First Year Fellowship
2014 UCLA Graduate Summer Research Fellowship
2016 UCLA Graduate Division Travel Award
2016 UCLA Brain Research Institute Travel Award
2016 - 2017 UCLA Translational Neuroscience of Drug Abuse (T32) Fellow
2017 - 2018 UCLA Neural Microcircuits Training program (T32) Fellow
2018 - 2019 UCLA Dissertation Year Fellowship

**C. Contribution to Science**

**URL to a full list of my published work:**
https://www.ncbi.nlm.nih.gov/sites/myncbi/1z9I8h907CuA2/collections/52968776/public/

**Early Career:** I worked as part of a collaborative team in Dr. John Salamone's lab where we tested whether tetrabenazine, a drug prescribed to humans that commonly induces depressive symptoms, would induce motivational deficits in rats. We also predicted that these deficits could be reversed by drugs that block dopamine transport or adenosine A2A receptors. Using in vivo pharmacology, microdialysis, and immunohistochemistry, we found that tetrabenazine induced deficits in effort output, which were reversible by the dopamine transporter blocker bupropion or the adenosine A2A antagonist MSX-3. These effects were mediated by changes in extracellular dopamine concentration in the ventral striatum and associated signal transduction changes in ventral striatal medium spiny neurons. In a separate line of work, we found that bupropion administration increased baseline effort output in otherwise untreated animals. Finally, we tested the behavioral effects of the pro-inflammatory cytokine interleukin 1-beta in our effortful choice task and found that it decreased effort for the preferred option, similar to tetrabenazine. This effect was also reversible by co-administration of MSX-3. These experiments set the course for future work investigating the behavioral effects of serotonin transporter and norepinephrine transporter blockers in effort as well as experiments probing the mechanism of interleukin 1-beta on effort. They also established the use of animal models of effort as models of the motivational symptoms that occur in depression and other conditions.

**Publications:**

1. Nunes EJ, Randall PA, **Hart EE**, Freeland C, Yohn SE, Baqi Y, Muller CE, Lopez-Cruz L, Correa M, Salamone JD (2013) Effort-related motivational effects of the VMAT-2 inhibitor tetrabenazine: implications for animal models of the motivational symptoms of depression. J Neurosci 33:19120-19130.

2. Nunes EJ, Randall PA, Estrada A, Epling B, **Hart EE**, Lee CA, Baqi Y, Muller CE, Correa M, Salamone JD (2014) Effort-related motivational effects of the pro-inflammatory cytokine interleukin 1-beta: studies with the concurrent fixed ratio 5/ chow feeding choice task. Psychopharmacology (Berl) 231:727-736.

3. Randall PA, Lee CA, Podurgiel SJ, **Hart E**, Yohn SE, Jones M, Rowland M, Lopez-Cruz L, Correa M, Salamone JD (2015) Bupropion increases selection of high effort activity in rats tested on a progressive ratio/chow feeding choice procedure: implications for treatment of effort-related motivational symptoms. Int J Neuropsychopharmacol 18.

**Graduate Career:** The primary focus of my work at UCLA was expanding what is known about the neural mechanisms of effort in regions other than the striatum. When I started at UCLA, I sought to merge my interests in behavior, pharmacology, and systems neuroscience while building strong technical skills. I started by clarifying the roles of the basolateral amygdala and anterior cingulate cortex in effort based choice between qualitatively different options, a behavioral task I gained familiarity with as an undergraduate. My data show that each of these regions is necessary for choosing to work for a preferred reward when a free, less preferred alternative is concurrently available. For both of these projects, I performed the experimental procedures, data analysis, and manuscript preparation. I replicated these findings using chemogenetic silencing techniques (DREADDs) in the Izquierdo lab. In collaboration with Dr. Peyman Golshani and Dr. H. Tad Blair, as well as the rest of the UCLA miniscope community, I recorded ACC calcium activity using in-vivo miniaturized fluorescence microscopy. I was the first person to successfully do so in awake, behaving rats. These data are in revision and expected to be published within weeks.

**Publications:**

1. **Hart EE**, Izquierdo A (2017) Basolateral amygdala supports the maintenance of value and effortful choice of a preferred option. Eur J Neurosci 45:388-397.

2. **Hart EE**, Gerson JO, Zoken Y, Garcia M, Izquierdo A (2017) Anterior cingulate cortex supports effort allocation toward a qualitatively preferred option. Eur J Neurosci.

3. **Hart, E.E**., Gerson, J.O., and Izquierdo, A. (2018). Persistent effect of withdrawal from intravenous methamphetamine self-administration on brain activation and behavioral economic indices involving an effort cost. Neuropharmacology 140, 130-138.

4. **Hart, E.E**., and Izquierdo, A (2019). Quantity versus Quality: Convergent findings in effort-based choice tasks. *Behavioural Processes*.

**Postdoctoral Career:** I began my postdoctoral research in the Schoenbaum lab in July of 2019, approximately eight months ago. My goals for the next three years are as follows: **1.** Learn all the steps required to complete behavioral neurophysiology experiments, from 64 and 128 channel electrode fabrication to analysis in Matlab. **2.** Learn more sophisticated behaviors as well as time-series and ensemble analyses of neural data. **3.** Enhance my public speaking and writing skills. **4.** Apply for a K99 award at the end of my second postdoctoral year. **5.** Apply for and interview for jobs at R1 universities during my third and fourth postdoctoral years. **6.** Bring my calcium imaging expertise to the Schoenbaum lab and train post-bac students, graduate students, and other postdocs in this method. **7.** Involve the general public and disseminate my research, while training a cadre of high-school, undergraduate, and post-bac students, particularly URM and women. The research questions I will answer, broadly speaking, are as follows: **1.** What is the

nature of associative learning, and what sort of changes happen in the brain? Is information "learned" using optogenetics the same as that learned naturalistically? How does associative learning contribute to addictions and other compulsive behaviors? **2.** There are many ways to record "neural activity", for example, calcium and electrophysiology. Do they yield the same results?

In the time since starting in the lab, I have collected data showing effects of optogenetic orbitofrontal cortex inhibition, recorded orbitofrontal cortex calcium activity using miniaturized microscopes during economic decision-making, and recorded anterior cingulate cortex single unit activity during associative learning. I am on track to submit a publication within my first year and have multiple other publications in the pipeline.

**D. Scholastic Performance**

| YEAR | COURSE TITLE | GRADE |
|---|---|---|
| | UC LOS ANGELES | |
| 2013 | Learning and Behavior Seminar | S |
| 2013 | Advanced Psychological Statistics I | B+ |
| 2013 | Instrumental Processes | B |
| 2013 | Physiology of Learning | A |
| 2014 | Neuroanatomy | A |
| 2014 | Presentation of Psychological Material | S |
| 2014 | Advanced Psychological Statistics II | B |
| 2014 | Learning and Behavior Seminar | S |
| 2014 | Biology of Learning and Memory | A |
| 2014 | Advanced Psychological Statistics: Regression | B+ |
| 2014 | Systems Neuroscience | A |
| 2014 | Human Learning and Memory | A- |
| 2014 | Research Methods | A |
| 2015 | Vision Neurobiology | A |
| 2016 | Representational Processes | A |
| 2016 | Dissertation Research | S |
| 2016 | Neuroscience of Drug Abuse Seminar | S |
| 2016 | Pavlovian Processes | A |
| 2017 | Integrity of Scientific Investigation | S |
| 2017 | Neurobiology of Drugs of Abuse | A+ |
| 2017 | Dynamics of Neural Microcircuits | A |
| 2018 | Dissertation Research | S |
| 2018 | Teaching Apprentice Practicum | S |
| 2018 | Dynamics of Neural Microcircuits II | A |
| 2019 | Dissertation Research | S |
| 2019 | Learning and Behavior Seminar | S |
| 2019 | Neural Signal Processing | A+ |

As a graduate student at UCLA many courses were offered on an S/U basis, and S indicates fulfillment of all necessary requirements for the course, including attendance, participation, and completion of any assignments.

**BIOGRAPHICAL SKETCH**

Provide the following information for the Senior/key personnel and other significant contributors. Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Schoenbaum, Geoffrey

eRA COMMONS USER NAME (credential, e.g., agency login): schoenbg

POSITION TITLE: Branch Chief and Distinguished Investigator

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

| INSTITUTION AND LOCATION | DEGREE *(if applicable)* | Completion Date MM/YYYY | FIELD OF STUDY |
|---|---|---|---|
| University of Georgia | BS | 1989 | Biology |
| University of North Carolina Graduate School | PhD | 1994 | Neurobiology |
| University of North Carolina School of Medicine | MD | 1996 | Medicine |
| Yale University | Resident | 1997 | Psychiatry |
| University of North Carolina Psychology Department | Post-doc | 1997 | Psychology |

## A. Personal Statement

I am qualified to support this application by virtue of my expertise in animal behavior, the neural circuits involved in associative learning, judgment and decision-making, and single-unit recording. I have over 20 years of experience implementing relatively complex behavioral tasks to test hypotheses about how neural circuits mediate these simple functions. More recently, the lab has also published a number of studies using optogenetic approaches to manipulate mesocorticolimbic circuits. And we have extensive experience relating changes in these circuits to the loss of behavioral control that characterizes drug addiction. I also have substantial experience as a mentor. Since starting the lab in 2003, I have supervised over two dozen postdocs and graduate students. Three of the students received NRSA awards prior to our move to NIDA, and six have completed their dissertations (avg 4.5 years including ~2 years of coursework, rotations, and quals). Three are working in industry, one is in residency, and one has just taken a tenure-track position at UMB. The postdocs were collectively awarded several private foundation fellowships, six K awards, and one r03 grant. The ten that finished their postdocs with me include two staff scientists (previously in faculty level positions at UMB), a lecturer at JHU, a postdoc at JHU, 5 tenure-track assistant professors, and 1 tenured associate professor. I have also mentored 15 postbacs or postbac-equivalents, nearly all of whom have gone on to PhD, MD, or combined degree programs.

## B. Positions and Honors

*Positions:*

| | |
|---|---|
| 1997-2003 | Associate Research Scientist, JHU, Department of Psychology, Baltimore, MD |
| 2003-2008 | Assistant Professor, University of Maryland, Departments of Anatomy & Neurobiology and Psychiatry, Baltimore, MD; Adjunct, Department of Psychology, University of Maryland Baltimore County, Baltimore, MD |
| 2008-2011 | Professor, University of Maryland, Departments of Anatomy & Neurobiology and Psychiatry, Baltimore, MD; Adjunct, Department of Psychology, University of Maryland Baltimore County, Baltimore, MD |
| 2011-2019 | Branch Chief, Cellular Neurobiology Research Branch; Senior Investigator, Tenured and Chief of the Behavioral Neurophysiology Neuroscience Section, NIDA-Intramural Research Program, Baltimore, MD; Adjunct, University of Maryland, Departments of Anatomy & Neurobiology and Psychiatry, Baltimore, MD; Adjunct, Department of Psychology, University of Maryland Baltimore County, Baltimore, MD |
| 2020-present | NIH Distinguished Investigator |

*Honors:*

| | |
|---|---|
| 1989 | Graduated Summa Cum Laude from University of Georgia |
| 1989 | Full Scholarship, M.D./Ph.D. Program at the University of North Carolina |
| 1996 | Received MD with Honors, University of North Carolina School of Medicine |
| 2007 | Awarded "Best Mentor" by UMB Program in Neuroscience graduate students |
| 2008 | Selected to give Special Lecture at Society for Neuroscience Meeting, Washington DC |
| 2008 | Awarded "Best Mentor" by UMB Program in Neuroscience graduate students |
| 2009 | Awarded Waletzky Prize by SFN and NIDA |
| 2012 | Selected to give Presidential Lecture at the Eastern Psychological Association Meeting |
| 2013 | Selected to give the Abraham Ribicoff Lecture by Yale Psychiatry |
| 2013 | Elected Eastern Psychological Association Fellow |
| 2013 | Elected into the Johns Hopkins University Society of Scholars |
| 2016 | Awarded the Pavlovian Research Award by the Pavlovian Society |
| 2017 | Awarded "Best Mentor" by NIDA-IRP IRTA Trainees |
| 2018 | Selected to give the Plenary Lecturer at the Winter Conference on Brain Research |

## C. Contributions to Science

**Publication Statistics, January 2018:**
ISI Citation Report: 8209 citations on 131 entries, h-index 50
Google Scholar: 12298 citations, h-index 57
http://www.ncbi.nlm.nih.gov/pubmed/?term=schoenbaum+g*

Orbitofrontal contributions to outcome signaling: Beginning with my graduate and postdoc work and continuing in my own lab, I have been involved in a series of papers that have been part of work showing that the orbitofrontal cortex is critical to signaling information about outcomes. We have linked these functions to single unit correlates and the influence of this information on processing in other circuits. More recently we have shown that the orbitofrontal cortex plays a

critical role in both guiding behavior and in supporting learning, due in both cases to its function in signaling information about outcomes. We have also shown that the orbitofrontal cortex signals not just value but other features of outcomes.

- **Schoenbaum**, G., Chiba, A., and Gallagher, M. (1998) Orbitofrontal cortex and basolateral amygdala encode expected outcomes during learning. Nature Neuroscience. 1:155-159.
- Gallagher, M., McMahan, R.W., **Schoenbaum**, G. (1999) Orbitofrontal cortex and representation of incentive value in associative learning. Journal of Neuroscience 19:6610-6614.
- Burke, K.A. Miller, D.N., Franz, T.M., and **Schoenbaum**, G. (2008) The role of orbitofrontal cortex in the pursuit of happiness and more specific rewards. Nature. 454:340-344.
- Jones, J.L., Esber, G.R., McDannald, M.A., Gruber, A.J., Hernandez, A., Mirenzi, A., and **Schoenbaum**, G. (2012) Orbitofrontal cortex supports behavior and learning using inferred but not cached values. Science. 338:953-956.

Role of orbitofrontal dysfunction in addiction: Addiction is characterized by a failure to use information about outcomes to guide behavior. Work in my lab has been critical to showing that this may reflect drug-induced changes in prefrontal and other circuits. We have shown that cocaine and opiate use affect a variety of behavioral functions that we know depend on these circuits, and more recently we have linked these functional changes to changes in single unit information processing in the orbitofrontal cortex and shown that brief stimulation of orbitofrontal cortex is sufficient to restore normal function. Much of this work has replicated or been replicated by work in other labs and species.

- **Schoenbaum**, G and Setlow, B. (2005) Cocaine makes actions insensitive to outcomes but not extinction: implications for altered orbitofrontal-amygdalar function. Cerebral Cortex. 15: 1162-1169.
- Stalnaker, T.A., Roesch, M.R., Franz, T.M., Calu, D.J. and **Schoenbaum**, G. (2007) Cocaine-induced decision-making deficits are mediated by miscoding in basolateral amygdala. Nature Neuroscience 10:949-951.
- Weid, H.M., Jones, J.L., Cooch, N.K., Berg, B.A., and **Schoenbaum**, G. (2013) Disruption of model-based behavior and learning by cocaine self-administration in rats. Psychopharmacology. 229:493-501.
- Lucantonio, F., Takahashi, Y.K., Hoffman, A.F., Chang, C.Y., Chaudhary, S., Shaham, Y., Lupica, C.R., and **Schoenbaum**, G. (2014) Orbitofrontal activation restores insight lost after cocaine use. Nature Neuroscience. 17:1092-1099.

Role of orbitofrontal input to dopaminergic circuits: Dopamine neurons have been shown to signal reward prediction errors in humans, monkeys and rats. Our lab has replicated that finding and further has begun to show how these signals are constructed. In initial work, we showed that these signals are constructed similarly for changes in size versus timing of reward. Subsequently we demonstrated a direct role for the orbitofrontal cortex in inhibiting activity in dopamine neurons and showed that removal of the orbitofrontal input to the midbrain altered error signaling in dopamine neurons in way that was well-modeled by changes in the underlying state representations and associated reward predictions. These data represent the first evidence of how component inputs to the error signaling system are used to construct the errors. We have also linked this error

signaling function with orbitofrontal-dependent learning in novel ways, and we are currently working to link it to changes in orbitofrontal function in addiction.


- Roesch, M.R., Calu, D.J., and **Schoenbaum**, G. (2007) Dopamine neurons encode the more valuable option when rats are deciding between differently sized and delayed rewards. Nature Neuroscience. 10:1615-1624 (also see News & Views highlighting article).

- Takahashi, Y., Roesch, M.R., Stalnaker, T.A., Haney, R.Z., Calu, D.J., Taylor, A.R., Burke, K. A., and **Schoenbaum**, G. (2009) The orbitofrontal cortex and ventral tegmental area are necessary for learning from unexpected outcomes. Neuron. 62:269-280.

- Takahashi, Y.K., Chang, C.Y., Lucantonio, F., Haney, R.Z., Berg, B.A., Yau, H-J., Bonci, A., and **Schoenbaum**, G. (2013) Neural estimates of imagined outcomes in the orbitofrontal cortex drive behavior and learning. Neuron. 80:507-518.

- Takahashi, Y.K., Roesch, M.R., Wilson, R.C., Toreson, K., O'Donnell, P., Niv, Y., and **Schoenbaum**, G. (2011) Expectancy-related changes in firing of dopamine neurons depend on orbitofrontal cortex. Nature Neuroscience. 14:1590-1597.


## D. Additional Information: Research Support and/or Scholastic Performance


The lab is currently supported by intramural funding at NIDA-IRP.

OMB No. 0925-0001 and 0925-0002 (Rev. 03/2020 Approved Through 02/28/2023)

**BIOGRAPHICAL SKETCH**

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Aponte, Yeka

eRA COMMONS USER NAME (credential, e.g., agency login): yekaaponte

POSITION TITLE: Earl Stadtman Tenure-Track Investigator and Unit Chief

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

| INSTITUTION AND LOCATION | DEGREE *(if applicable)* | Completion Date MM/YYYY | FIELD OF STUDY |
|---|---|---|---|
| Universidad Central de Venezuela<br>Caracas, Venezuela | B.S. | 12/2002 | Biology |
| University of Freiburg<br>Freiburg, Germany | Ph.D. | 07/2006 | Natural Sciences |
| University of Freiburg<br>Freiburg, Germany | Postdoctoral Fellow | 07/2007 | Electrophysiology |
| Janelia Research Campus of Howard Hughes Medical Institute<br>Ashburn, Virginia, USA | Postdoctoral Fellow | 12/2012 | Systems Neuroscience |

## A. Personal Statement

My interest is to understand how genetically-identified cell types and their projections drive behaviors essential for survival. Using the mouse as our model system, we apply optogenetics and chemogenetics to manipulate neuronal circuits in awake, behaving mice. In addition, we use a combination of electrophysiology, two- and single-photon fluorescence endomicroscopy, and behavioral assays to elucidate the neuronal basis of survival behaviors, such as feeding, and to determine how these neuronal circuits drive the rewarding and addictive nature of food intake. Evidence for the addictive properties of food has been growing progressively throughout the last decade. Both addiction and overeating are disorders by which individuals learn rewarding associations between stimuli such as drugs of abuse and highly palatable food. Therefore, our laboratory is interested in understanding the addictive aspects of feeding behaviors. We study this topic at the level of neuronal circuits in the context of behaviors, cell types, and synaptic connectivity. Neuronal circuits are composed of diverse collections of cell types, each having a distinct set of synaptic connections and performing specific functions. To understand how neuronal circuits drive behaviors, it is essential to examine the function of specific cell types in the circuit. However, studies have been mostly unable to identify the cell types involved in specific behaviors. Furthermore, experiments to date have largely been unable to determine when specific cell types are active to provide quantitative relationships between circuit activity and behavior. Ultimately, understanding the mechanisms regulating food intake and the rewarding and addictive nature of food will enhance our ability to battle disorders such as obesity, diabetes, anorexia, bulimia, and addiction.

My research program embraces close interactions with members of the NIDA community, the Janelia Research Campus/HHMI, the Department of Neuroscience at Johns Hopkins University, the Department of Physics and Molecular Cell Biology at the University of California, Berkeley, The Netherlands Institute for Neuroscience in Amsterdam, The Netherlands, the School of Biomedical Sciences & Pharmacy at the University of Newcastle, Australia, and both – the KTH Royal Institute of Technology and the Department of Neuroscience at the Karolinska Institute in Stockholm, Sweden. Such collaborations enable the advancement of scientific projects as well as the training of early career scientists *i.e.* students and postdoctoral fellows. I directly supervise two postbaccalaureate students and two postdoctoral fellows. In addition, I participate in the tutoring of the graduate student community at the Johns Hopkins University by lecturing in courses and service of advisory committees.

1. Siemian JN, Borja CB, Sarsfield S, Kisner A, Aponte Y. Lateral hypothalamic fast-spiking parvalbumin neurons modulate nociception through connections in the periaqueductal gray area. Sci Rep. 2019 Aug 19;9(1):12026. PubMed PMID: 31427712; PubMed Central PMCID: PMC6700312.
2. Schiffino FL, Siemian JN, Petrella M, Laing BT, Sarsfield S, Borja CB, Gajendiran A, Zuccoli ML, Aponte Y. Activation of a lateral hypothalamic-ventral tegmental circuit gates motivation. PLoS One. 2019;14(7):e0219522. PubMed PMID: 31291348; PubMed Central PMCID: PMC6619795.
3. Meng G, Liang Y, Sarsfield S, Jiang WC, Lu R, Dudman JT, Aponte Y, Ji N. High-throughput synapse-resolving two-photon fluorescence microendoscopy for deep-brain volumetric imaging in vivo. Elife. 2019 Jan 4;8PubMed PMID: 30604680; PubMed Central PMCID: PMC6338462.
4. Kisner A, Slocomb JE, Sarsfield S, Zuccoli ML, Siemian J, Gupta JF, Kumar A, Aponte Y. Electrophysiological properties and projections of lateral hypothalamic parvalbumin positive neurons. PLoS One. 2018;13(6):e0198991. PubMed PMID: 29894514; PubMed Central PMCID: PMC5997303.

## B. Positions and Honors

### Positions and Employment

| | |
|---|---|
| 2002 - 2003 | Technical Assistant, Instituto Venezolano de Investigaciones Científicas, Caracas |
| 2003 - 2006 | Doctoral Candidate, University of Freiburg, Advisor: Prof. Dr. Peter Jonas, Freiburg |
| 2005 - 2007 | Teaching Assistant, University of Freiburg, Freiburg |
| 2006 - 2007 | Postdoctoral Fellow, University of Freiburg, Principal Investigator: Prof. Dr. Peter Jonas, Freiburg |
| 2007 - 2012 | Postdoctoral Associate, Janelia Farm Research Campus, Howard Hughes Medical Institute, Principal Investigator: Dr. Scott Sternson, Ashburn, VA |
| 2013 - present | Adjunct Assistant Professor, Solomon H. Snyder Department of Neuroscience, Johns Hopkins University School of Medicine, Baltimore, MD |
| 2013 - present | Earl Stadtman Tenure-Track Investigator and Unit Chief, National Institutes of Health (NIH), National Institute on Drug Abuse Intramural Research Program (NIDA IRP), Baltimore, MD |

### Other Experience and Professional Memberships

| | |
|---|---|
| 2006 - present | Member, Society for Neuroscience |
| 2014 - 2016 | Member, NIDA IRP Tenure-Track Investigator Search Committees |
| 2015 - present | Member, Graduate Student Search Committee, Solomon H. Snyder Department of Neuroscience, Johns Hopkins University School of Medicine |
| 2015 - present | Member, Space and Allocation Committee, NIDA IRP |
| 2015 | NIH Study Section Ad Hoc Member, Neuroscience Review Subcommittee (AA-4), National Institute on Alcohol Abuse and Alcoholism (NIAAA) |
| 2016 - present | Journal Ad Hoc Reviewer, Nature Neuroscience, Scientific Reports, The Journal of Neuroscience, and JoVE |
| 2017 | NIH Study Section Ad Hoc Member, Neurobiology of Motivated Behavior (NMB) Study Section, NIH Center for Scientific Review |
| 2018 - present | Member, Diversity and Outreach Committee, NIDA IRP |

### Honors

| | |
|---|---|
| 2003 - 2006 | Deutsche Forschungsgemeinschaft (Graduiertenkolleg 843) Fellowship for International PhD Program, University of Freiburg, Freiburg, Germany |
| 2006 | Graduated summa cum laude with a Doctor of Philosophy in Natural Sciences, University of Freiburg, Freiburg, Germany |
| 2016 | NIH Laboratory Safety Award for Excellence, NIDA IRP, Baltimore, MD, USA |
| 2019 | NIDA Director's Rising Star Award, NIDA IRP, Baltimore, MD, USA |

## C. Contributions to Science

1. During my tenure-track term, my laboratory has been studying the roles of genetically-identified neurons and their projections in behaviors that are essential for survival. Our ultimate goal is to understand how neurons in distinct hypothalamic circuits encode nociception and the rewarding and addictive nature of food intake. Obesity and opioid overuse are global epidemics and major causes of death. Public awareness of the addictive properties of food and opioids has been growing progressively throughout the last decade. Excessive intake of calorie dense palatable food despite negative consequences mimics compulsive drug use. Therefore, my laboratory is interested in understanding the neuronal circuits involved in feeding behaviors and the ways in which these behaviors become compulsive. Beginning with early lesion and electrical stimulation studies, the lateral hypothalamus (LH) has long been considered essential in regulating appetitive and reward-related behaviors. Furthermore, the LH has been hypothesized to regulate food reward through its connections to brain regions associated with reward and goal-directed behaviors, such as the nucleus accumbens (NAc) and the ventral tegmental area (VTA). However, the contributions of LH circuits to other survival behaviors are not well-understood. In part, our lack of knowledge regarding the roles of specific neurons in these behaviors is because the methods to measure their contributions did not exist until recent years. To answer these questions, my laboratory uses a combination of optogenetics, chemogenetics, electrophysiology, two- and single-photon fluorescence endomicroscopy, and behavioral assays to manipulate and measure the activity of these genetically-defined neuronal subpopulations in awake, behaving mice. Our recent studies have shown how two of the lateral hypothalamic neuronal populations identified by the expression of the calcium-binding protein parvalbumin (PVALB; $LH^{PV}$) or leptin receptor (LEPR; $LH^{LEPR}$) modulate nociception and motivation, respectively, in mice. Our work revealed $LH^{PV}$ neurons as regulators of the LH glutamatergic circuitry and identified $LH^{LEPR}$ neurons as modulators of a hypothalamic-ventral tegmental midbrain circuit involved in controlling motivation. Our studies have been recognized by NIH/NIDA as a Science Highlight titled *"New discovery on the brain's reward pathway"* (https://www.drugabuse.gov/news-events/latest-science/new-discovery-brains-reward-pathway).

    a. Siemian JN, Borja CB, Sarsfield S, Kisner A, Aponte Y. Lateral hypothalamic fast-spiking parvalbumin neurons modulate nociception through connections in the periaqueductal gray area. Sci Rep. 2019 Aug 19;9(1):12026. PubMed PMID: 31427712; PubMed Central PMCID: PMC6700312.

    b. Schiffino FL, Siemian JN, Petrella M, Laing BT, Sarsfield S, Borja CB, Gajendiran A, Zuccoli ML, Aponte Y. Activation of a lateral hypothalamic-ventral tegmental circuit gates motivation. PLoS One. 2019;14(7):e0219522. PubMed PMID: 31291348; PubMed Central PMCID: PMC6619795.

2. Throughout all steps of my career, I have made significant advancements in the understanding and technology to study brain function and the role of neuronal circuits in driving behavior. These advancements have become the basis for new research paths by enabling measurements and experiments that were not possible to perform previously. During my postdoctoral work, I studied the contribution of specific cell types in the hypothalamus to feeding behavior using the combination of optogenetics and behavioral methods. First, I developed and characterized a Cre recombinase-dependent viral vector that selectively expresses the light-activated cation channel channelrhodopsin-2 (ChR2) in molecularly-defined neurons in transgenic mice. This tool allowed labeling of specific cell types in a brain area such as the hypothalamic arcuate nucleus (ARC) and permitted the reliable activation of those specific cells using optical methods in both, brain slices and during behavior. Furthermore, we used this method to record, for the first time, long-range synaptic connections of molecularly defined cell types in neuronal circuits that regulate feeding behavior. Prior to my work, it was not possible to specifically label and stimulate genetically-distinct neurons with high efficacy and precision deep in the brain and during behavior. Currently, dozens of laboratories worldwide use our viral vector for their experiments. Moreover, our method has been used in many published papers to study other complex behaviors. Thus, our method has become a standard tool in the systems neuroscience field.

    a. Atasoy D, Aponte Y, Su HH, Sternson SM. A FLEX switch targets Channelrhodopsin-2 to multiple cell types for imaging and long-range circuit mapping. J Neurosci. 2008 Jul 9;28(28):7025-30. PubMed PMID: 18614669; PubMed Central PMCID: PMC2593125.

3. Taking advantage of this tool, I developed techniques to selectively label neurons deep in the brain (~6 mm) and to activate them using light delivered through an implanted optical fiber during feeding behavior in transgenic mice. My

experiments showed that action potential firing in hypothalamic neurons that express agouti-related peptide (AGRP) and pro-opiomelanocortin (POMC) in the ARC is sufficient to trigger and inhibit feeding, respectively. I was the first to show that the activity of AGRP neurons was sufficient to selectively activate feeding (but not drinking). Importantly, this effect was rapid (within minutes) and occurred in untrained mice. The feeding response (magnitude and latency) was proportional to the number of ChR2-expressing AGRP neurons and also to the frequency of AGRP neuron stimulation. Thus, these experiments demonstrated for the first time that AGRP neuron-evoked feeding is directly involved in initiating and maintaining this motivated and complex behavior. My work has driven multiple other labs to pursue studies of feeding behavior using the mouse as a model system. In addition, commentaries summarizing this work have been published in several journals as well as being highlighted in the Faculty of 1000.

a. Aponte Y, Atasoy D, Sternson SM. AGRP neurons are sufficient to orchestrate feeding behavior rapidly and without training. Nat Neurosci. 2011 Mar;14(3):351-5. PubMed PMID: 21209617; PubMed Central PMCID: PMC3049940.

4. During my graduate work, I made new biological insights into the mechanisms by which inhibitory interneurons in the hippocampus generate precise signals for the temporal coding of information in neuronal networks. I performed experiments to measure the functional properties of hyperpolarization-activated cation channels (IH) in fast-spiking interneurons of the rat hippocampus. Prior to my work, H-current was thought to be absent in many neuronal types since in these neurons, the depolarizing sag (the hallmark of neurons expressing IH) was not observed upon injection of hyperpolarizing current pulses. However, I showed that the absence of depolarizing sag is not a sufficient criterion to conclude that IH channels are lacking. By performing whole-cell recordings from dentate gyrus basket cells (BCs) in hippocampal slices, I found that IH channels are expressed in the somatodendritic, axonal and presynaptic regions of those cells. This was the first report showing the presence of IH channels in this neuronal type. My experiments showed that IH channels shape both the integration of synaptic inputs and the action potential firing patterns of BCs. These channels contribute to the repertoire of fast signaling mechanisms in these interneurons and may be involved in the regulation of GABA (γ-aminobutyric acid) release by setting interneuron axonal excitability.

a. Aponte Y, Lien CC, Reisinger E, Jonas P. Hyperpolarization-activated cation channels in fast-spiking interneurons of rat hippocampus. J Physiol. 2006 Jul 1;574(Pt 1):229-43. PubMed PMID: 16690716; PubMed Central PMCID: PMC1817792.

5. I next expanded the study of basket cells signaling to the level of biochemical properties by quantitatively measuring dendritic Ca2+ dynamics in basket cells using whole-cell recordings combined with ratiometric Ca2+ imaging in acute slices. I found that basket cells have a high level of endogenous Ca2+ buffer leading to slow Ca2+ transients that can be summated efficiently. These Ca2+ dynamics likely influence the synaptic plasticity and neurotransmitter release properties of these interneurons. Together these studies provided insight into the mechanisms that regulate how basket cells set precise timing information in neuronal circuits. My work has been highlighted and reviewed by Dr. Erwin Neher, winner of the Nobel Prize in Physiology and Medicine.

a. Aponte Y, Bischofberger J, Jonas P. Efficient Ca2+ buffering in fast-spiking basket cells of rat hippocampus. J Physiol. 2008 Apr 15;586(8):2061-75. PubMed PMID: 18276734; PubMed Central PMCID: PMC2465201.

**Complete List of Published Work in My Bibliography:**
https://www.ncbi.nlm.nih.gov/myncbi/1X7D-hq2ffl5E/bibliography/public/

## D. Additional Information: Research Support and/or Scholastic Performance

### Ongoing Research Support

Intramural Research Program, National Institute on Drug Abuse, National Institutes of Health
Aponte, Yeka (PI)
Neuronal Circuits and Behavior Unit
Role: PI

**Intra-Institute Collaboration**

The proposed experiments require collaboration between the labs of Dr. Geoffrey Schoenbaum (NIDA) and Dr. Yeka Aponte (NIDA). Dr. Geoffrey Schoenbaum will provide funding, space, and all necessary electrophysiological recording equipment and expertise. Dr. Geoffrey Schoenbaum will be the main mentor of Dr. Evan Hart and will oversee all experiments. Dr. Yeka Aponte will provide AAV reagents required for transducing dopamine neurons with Channelrhodopsin, as well as expertise in stimulation parameters of midbrain neurons. Dr. Yeka Aponte, together with Dr. Geoffrey Schoenbaum, will oversee all experiments.