CCB Fellowship Application 2021

Role of orbitofrontal cognitive map representations in flexible and inflexible behavior

Applicant

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Research Proposal

Orbitofrontal cortex (OFC) dysfunction is a consistent neuropathology that underlies aberrant and inflexible behaviors that occur in many disorders of compulsivity such as cocaine addiction[12], and obsessive-compulsive disorder[3]. For example, subjects with a history of cocaine use exhibit repetitive and inflexible behavior[5] during reversal learning, which correlates with impoverished representations of the task structure in OFC[6] Such activity in OFC is thought to encode a cognitive map of state space[4], however in a typical reversal learning task, features of the task that identify task-state specific information critical to cognitive mapping are confounded with actual changes in cue-reward relationships, temporal order, and behavioral inhibition, each of which are also proposed as OFC functions[7]. Therefore, it is unclear whether cocaine use disrupts accurate representations of task states in OFC that are necessary for flexible behavior in reversal learning tasks. Occasion setting (OS) tasks share many features with reversal learning tasks but can be used to isolate the neural correlates of cognitive map representations by using explicit cues to signal cognitive map changes. Here I will use an OS task to directly test whether a history of cocaine use causes inflexible behavior by disrupting cognitive map representations in OFC, and whether any such effects can be mitigated by dopamine D3 receptor (D3R) antagonists, which have been proposed as a novel pharmacotherapy strategy for treatment of cocaine use disorders.

Aim 1. Determine whether remapping of task representations in OFC during OS is disrupted in rats with a history of cocaine use. Rats will undergo a cocaine self-administration procedure known to cause OFC dysfunction and behavioral inflexibility[5,6] or a sucrose self-administration control. After a withdrawal period, these two groups of rats will be implanted with microelectrodes targeting OFC and trained on an occasion setting (OS) task. Analyses will focus on identifying correlates of cognitive mapping in OFC and testing whether they are disrupted by prior cocaine use.

Aim 2. Test whether a novel D3R antagonist can mitigate impaired behavioral flexibility and associated changes in neural correlates in OFC in cocaine treated rats. Rats will undergo the same procedure described in Aim 1, except that prior to each OS training session, half the rats in each group will receive injections of vehicle or the selective D3R antagonist *R*-VK4-40[8,9]. Analyses will focus on whether a novel drug therapy can improve behavioral flexibility, whether improvement is specific to cocaine-experienced rats, and how it relates to changes in neural correlates in OFC caused by cocaine use.

Significance. Disturbances to OFC function and deficits in reversal learning, a marker of behavioral inflexibility, are consistent features of many disorders of compulsivity in patients as well as translational animal models[10–12]. Drug-induced deficits in reversal learning in animal models of addiction are thought to reflect deficits in the creation and maintenance of cognitive map representations in OFC [4]. Key support for this comes from studies from this lab showing that rats with a history of cocaine use, known to cause compulsivity, exhibit inflexible behavior in reversal learning tasks and have impoverished and inflexible neural representations in OFC[5,6,14]. However, in these tasks, the signal to switch to a new cognitive map - the reversal - is confounded with changes in the actual cue-reward associations. As a result, representations of cognitive maps in OFC cannot be disentangled from representations of the new associations, representation of value, or even response inhibition, each of which has also been argued to depend on OFC.

To resolve these confounds and more specifically identify whether OFC supports flexible behavior through a mapping function, it is necessary to use a behavioral approach that dissociates the cue that triggers changes in the task map being used from these other features. One such task is occasion setting (**OS**). In an OS task, subjects are presented with a sequence of two discrete cues, first an OS cue which indicates whether a second target cue predicts reward i.e., OS -> Target -> Reward (**Figure 1**). For example, target cue A is rewarded on X -> A+ trials, and non-rewarded

on Y-> A- trials. This creates two cue-reward maps similar to the alternative maps that might be used in rapid reversal learning, except they are signaled by the X and Y cues, which isolate the information relevant to the alternative map states and are not confounded by changes in associative learning, value, or responding.

Here I will use an OS task modeled after the reversal task used in prior work to test whether reversal learning deficits in rats with a history of cocaine reflect impoverished cognitive map representations in OFC. If this is established, I will then test the efficacy of *R*-VK4-40, a promising D3R antagonist, to treat this behavioral inflexibility, and its neural correlates in OFC, in cocaine experienced rats. Drug compounds that target dopamine D3-receptor antagonists have been shown to have significant potential to treat aberrant behaviors in disorders of compulsivity that are also characterized by dysfunction of dopaminergic signaling[1,8]. *R*-VK4-40 is a highly selective D3R-antagonist that reduces psychostimulant use and relapse behaviors in rodent models[8]. However, its efficacy in treating long-term behavioral inflexibility caused by a history of cocaine use has not been tested. These findings will advance our understanding of how OFC dysfunction contributes to behavioral inflexibility in disorders of compulsivity, and how such dysfunction might be treated.

Experiment 1.

Hypothesis: A history of cocaine use causes behavioral inflexibility in tasks like reversal learning and OS by disrupting the formation and accuracy of cognitive map representations in the OFC.

Predictions: Behavioral accuracy in an OS task will correlate with the strength and fidelity of cognitive map representations, such that more distinct cognitive map representations will predict higher behavioral accuracy. Furthermore, rats with a history of cocaine use will have lower behavioral accuracy and less distinct representations in OFC compared to control rats.

Procedure: Long Evans rats will undergo a standard cocaine (n = 8) or sucrose (n = 8) control self-administration protocol for 2 weeks followed by 30 days of withdrawal[5]. Rats will then be water deprived and given standard pretraining to become familiar with responding for odors and 10% sucrose reward in behavioral testing chambers. Next, drivable microelectrodes will be implanted in OFC to record neural activity according to established lab procedures[15]. Following recovery, rats will be trained with a novel set of cues on the OS task outlined in **Figure 1**. On each trial, the rat will initiate cue presentation by entering the odor port, then a brief auditory cue (1000 ms) followed by an odor (500 ms) will be presented. On rewarded trials, responding to the food port below the odor port will be rewarded. Correct performance will be defined as entering the food port on rewarded trials and withholding responding on non-rewarded trials. Each session will consist of 25 presentations of each trial type, presented in pseudorandom order. Criterion accuracy will be defined as 75% accuracy in a session, acquisition as criterion in 3 sessions in a row. Neural analyses will focus on sessions post-acquisition.

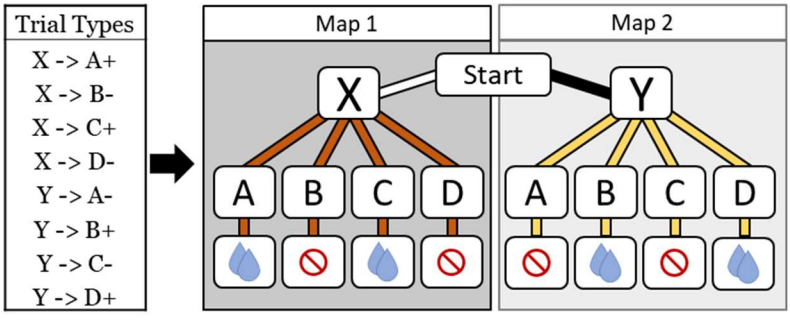

Figure 1. Proposed occasion setting (**OS**) task design. *(Left)* On each trial, OS cues X and Y uniquely identify whether the following Target cue (A-D) predicts reward (+) or no reward (-). *(Right)* Cognitive map illustration of task structure predicted in OFC representations.

Neural activity will be processed using methods established for analyzing activity in prior work in similar tasks[6,16]. Analyses will examine both single-unit and population level neural correlates of

task features expected to reflect aspects of cognitive map representations. I will define the strength of unique state representations as, for example, the proportion of single units that selectively increase firing to one of these cue conditions, or the percentage accuracy of a classifier to predict which cue was presented on a given trial. It is difficult to discuss all the possible results from an electrophysiological experiment such as this, so only key predictions will be presented.

Expected Results. Given the hypothesis that activity in OFC reflects cognitive map representations rather than isolated cue-reward value learning, I expect unique neural representations that discriminate between OS cues X and Y. Cues X and Y do not differ in predicting the next cue, responding, or whether the trial will be rewarded, so differential activity cannot reflect value or even simple associative information. Differences might reflect the distinct physical properties of X and Y; to rule out this possibility I will compare activity between the target cues that come after cues X and Y, that is A+ vs A-, B- vs B+, C+ vs C-, and D- vs D+. Differential activity to A+ vs A- must reflect information about future reward based on whether the previous cue was X or Y, i.e. a unique state/position along a path within a cognitive map. If activity to OS cues in OFC signals which cognitive map to use to correctly interpret the meaning of the target cues, then more accurate/unique representations of OS cues X and Y will predict more accurate/unique representations of target cues A-D on rewarded vs non-rewarded trials. Together, these analyses can determine the strength and accuracy of the neural correlates of cognitive maps i.e. differential representation of (1) OS cues X vs Y and (2) target cues on rewarded vs non-rewarded trials (A+ vs A-, B- vs B+, C+ vs C-, D- vs D+), and (3) the correlation between them. Additionally, for each of the three neural correlates described above, stronger correlates of cognitive map representations should predict higher behavioral accuracy in a given session or portion of a session.

By contrast, if cocaine experience disrupts flexible behavior by affecting the mapping function of OFC, then cocaine experienced rats should require more sessions to learn the OS task to criterion accuracy compared to control rats, their post-criterion performance may be less accurate than controls, and the three neural correlates of cognitive maps in OFC will show reduced fidelity and/or correlations in cocaine rats compared to control rats.

Experiment 2.

Procedure: I will use the same procedure described in Experiment 1, except that sucrose and cocaine groups will receive an injection of either vehicle (25% 2-hydroxypropyl-β-cyclodextrin) or *R*-VK4-40 (3 and 10 mg/kg, i.p.) 15 mins prior to each OS session, i.e., six groups (n = 8 each) for simplicity: sucrose/vehicle, sucrose/*R*-VK4-40, cocaine/vehicle, and cocaine/*R*-VK4-40.

Expected results: In cocaine rats, *R*-VK4-40 is predicted to mitigate the behavioral inflexibility and underlying disturbances to cognitive map representations in OFC described in Experiment 1, making cocaine/*R*-VK4-40 more similar to sucrose/vehicle. Of relevance in interpreting any effect will be whether *R*-VK4-40 affects behavior or cognitive map representations in sucrose control rats. This will indicate whether *R*-VK4-40 generally promotes behavioral flexibility, or if it is treating the specific impairments induced by a history of cocaine use. It is also possible that *R*-VK4-40 will only modify behavior but not disrupted OFC representations in cocaine rats. This would suggest that a different target system is being affected.

Alternative strategies, pitfalls and future directions. One possible outcome is that rats pretreated with cocaine will not show behavioral deficits and/or their neural correlates in OFC. While this is unlikely, this finding would still provide interesting and meaningful information that address aim 1. In this scenario, I will also use this established reversal task to assess the treatment efficacy of *R*-VK4-40 in Experiment 2.

References

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3. Graybiel AM, Rauch SL. Toward a neurobiology of obsessive-compulsive disorder. Neuron. 2000 Nov;28(2):343–347. PMID: 11144344

4. Wilson RC, Takahashi YK, Schoenbaum G, Niv Y. Orbitofrontal cortex as a cognitive map of task space. Neuron. 2014;81(2):267–279. PMID: 24462094

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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: Panayi, Marios Chris

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

POSITION TITLE: Postdoctoral IRTA Visiting 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)*	Completion Date MM/YYYY	FIELD OF STUDY
University of New South Wales (UNSW), Sydney, Australia	BA(Hons)	03/2010	Psychology
University of New South Wales (UNSW), Sydney, Australia	PHD	07/2015	Psychology
University of New South Wales (UNSW), Sydney, Australia	Teaching	12/2015	Psychology
University of Oxford, Oxford, United Kingdom	PostDoc	02/2020	Learning and Decision Making
National Institute on Drug Abuse Intramural Research Program	Visiting Fellow	Present	Cellular Neurobiology

A. Personal Statement

Through many experiences in my academic and personal life, I have developed a keen interest in studying the neural and psychological mechanisms of learning, motivation, and behavior. In particular, how do we come to learn about informative cues in our environment, and how do these representations inform our moment-to-moment behavior? Why am I checking the refrigerator? Why am I refreshing my twitter feed? These processes are fundamental to neurotypical and maladaptive learning and behavior characteristic of most neuropsychiatric disorders. I focused on these issues in my first independent undergraduate research thesis in the lab of Dr. Simon Killcross at UNSW, Australia. There I studied how failed feedback from informative cues could be used to model compulsive behaviors in animal models of obsessive-compulsive disorder. This work received the Australian Psychological Society prize and helped me establish a strong background in designing and testing novel behavioral procedures. A desire to understand these processes further led me to study the orbitofrontal cortex (OFC) in the same laboratory, where I learned stereotaxic surgery to perform lesions and micro infusion techniques. My graduate thesis was awarded the The Paxinos Neuroscience Prize and resulted in publications demonstrating greater contribution of the OFC to basic learning phenomena than had previously been thought, and the existence of novel subdivisions within classically defined OFC subregions. During this time, I also collaborated with Dr. Fred Westbrook and Dr. Nathan Holmes to understand how other neural and neurochemical systems contribute to cue-based control of behavior such as the role of benzodiazepines in extinction therapy, oxytocin signaling in the amygdala regulates fear, and

nicotine self-administration which resulted in co-authorship on three publications. Throughout my graduate career I also acquired a strong background in statistics and research methods, which started with teaching in undergraduate and postgraduate courses, and led to being hired to develop and teach a new course in statistics and critical thinking.

My graduate experience left me with a desire for a finer grained understanding of the relationship between the brain and behavior. This led me to move continent to Europe where I joined the labs of Dr. Mark Walton and Dr. David Bannerman at the University of Oxford to learn how to record real-time dopamine signaling using fast-scan cyclic-voltammetry (FCV) in striatum, to understand how cue learning is disrupted in genetically modified mouse models of aberrant attention in schizophrenia. While some of this work is ongoing, a number of publications from this work have been written up and submitted to journals and I expect they will be published soon. I directly supervised a number of graduate students during my postdoc and continued to teach statistics and research methods. During this time, I also acquired new skills to extend the findings from my graduate work which resulted in three publications. I learned neuroanatomical tracing techniques to provide further evidence of novel subdivisions within OFC and collaborated to develop a novel computational model of OFC function.

I am well suited to fill my role in this project for several reasons. First, I have expertise in animal behavioral testing, including extensive experience developing successful novel behavioral assays. I also have experience with behavioral pharmacology and translational models of neuropsychiatric disorders. I have mastered stereotaxic surgery in rats and mice to lesion, infuse viruses and tracers, implant cannula, and FCV microelectrodes for stable chronic in-vivo recordings. Indeed, there are very few labs that have been able to successfully record FCV signals in freely behaving mice. I also have experience and statistical expertise working with large and complex multivariate data sets that are generated when continuously recording signals from a behaving animal. Finally, I have expertise in studying OFC function. A key component of my training in the Schoenbaum lab and this proposal is learning in-vivo electrophysiology. Since accessing the laboratory, I have already begun pilot testing behavior and learning to assemble and implant microelectrode arrays and microdrives. Critically, all the research proposed will enhance my training while building on many areas of in which I already have experience. Being awarded a CCB fellowship will provide me with an opportunity build on my strengths and acquire new skills to advance my career in research, teaching and mentoring.

My productivity has been impacted by the SARS-CoV-2 pandemic. I moved continent to start a second position as a NIDA IRP Visiting Fellow and flew into the US on March 16th, 2020 a day before international travel restrictions. I was then required to quarantine for two weeks. During this time, in person government services were suspended, which prevented me from acquiring a social security number and access to NIDA facilities until early November of 2020. During this time my productivity and access to necessary computing resources was significantly limited. I am aware that many have been significantly impacted by this pandemic, I only raise this to highlight the additional barriers that I experienced because of the unfortunate timing of moving to a new country during the pandemic.

B. Positions and Honors

Positions and Employment

2010 - 2014	Undergraduate course tutor and lecturer, UNSW
2014	Teaching and Research Fellow, UNSW
2015	Curriculum Development and Postdoctoral Fellow

2016 - 2020	Postdoctoral Research Associate in Learning and Decision Making, University of Oxford
2020 - present	Visiting Fellow, Division of Intramural Research, National Institute of Drug Abuse

Other Experience and Professional Membership

2009 - 2010	Member, Australian Psychological Society
2012	Member, Society for Neuroscience
2012	Member, Society for Neuroeconomics
2012	Member, Pavlovian Society

Honors

2008 - 2009	The Faculty of Science Dean's List, UNSW
2009	Graduated Hons. Class 1, and awarded the University Medal in Psychology, UNSW
2009	The Australian Psychological Society Prize
2010 - 2013	Australian Postgraduate Award
2010 - 2013	UNSW Research Excellence Award
2012	Postgraduate Research Support Scheme Travel Award, UNSW
2012	Postgraduate Research Competition, UNSW
2016	The Paxinos Neuroscience Prize, PhD thesis UNSW
2017	Vice-Chancellor's Award for Outstanding Contributions to Student Learning, UNSW
2018	Monitoring Molecules in Neuroscience Short Oral Communication Award

C. Contributions to Science

URL to a full list of my published work:
https://pubmed.ncbi.nlm.nih.gov/?term=Panayi+MC&cauthor_id=30044220

The role of the orbitofrontal cortex in simple and complex environments. My graduate work tested the dominant idea that the orbitofrontal cortex (OFC) is critical for behavioral flexibility in complex environments, with changing contingencies or multiple cues and/outcomes, but not for simple, single cue-outcome learning. First, I addressed this using both pre- and post-training excitotoxic lesions and muscimol-inactivation of rodent lateral OFC in a simple single Pavlovian cue-reward procedure. I found that pre-training lesions enhanced behavior, whereas post-training lesions and inactivation suppressed behavior. Importantly, given the surprising nature of these results to the field, I demonstrated the reliability and relevance of these effects confirming other standard OFC effects in this preparation and replicated it multiple times with multiple cue modalities. I then confirmed these effects on behavioral expression rather than learning using an associative blocking design. In a separate study, I found that inactivation of OFC disrupted a simple cue-no outcome extinction learning between-sessions, but not within-session extinction, contrary to OFC model predictions. During my postdoc, I sought out a collaboration with Dr. Mehdi Khamassi at the Sorbonne Université to develop a computational model to account for these findings by proposing the OFC as an arbitrator between model-based and model-free reinforcement learning mechanisms. This work has been accepted and will be published in the next edition of the journal. For all these projects I performed all procedures, data analysis, and manuscript preparation.

- **Panayi MC*,** Killcross S. Orbitofrontal cortex inactivation impairs between- but not within-session Pavlovian extinction: An associative analysis. Neurobiol Learn Mem. 2014;108:78–87. PMID: 23954805

- **Panayi MC*,** Killcross S. The role of the rodent lateral orbitofrontal cortex in simple Pavlovian cue-outcome learning depends on training experience. Cereb Cortex Commun. 2021;(November 2020):1–14.

- **Panayi MC*,** Khamassi M*, Killcross S. The rodent lateral orbitofrontal cortex as an arbitrator selecting between model-based and model-free learning systems. Behav Neurosci. 2021; *In Press*.

Defining novel anterior and posterior subregions within the lateral orbitofrontal cortex. The rodent lateral orbitofrontal cortex (LO) is the primary experimental target of most orbitofrontal cortex (OFC) research. During my graduate work, I showed that discrete anterior and posterior LO lesions had dissociable effects on the two cardinal OFC sensitive tasks, outcome devaluation and reversal learning. I followed up this work during my postdoc at Oxford using retrograde tracing, by showing that projections to anterior and posterior LO are as distinct as projections to the anatomically adjacent ventral OFC. I conceived of the experiments, performed all procedures, data analysis, and manuscript preparation for these studies. The neuroanatomical work was shared in collaboration with a graduate student I was supervising. These findings are the first demonstration of functionally and neuroanatomically distinct subregions within LO along the anterior-posterior axis and the implications of these findings were proposed in a review. We argued that the field of OFC research often fails to distinguish between classically defined OFC subregions (e.g. ventral, lateral, dorsolateral, and medial), which may account for conflicting results that have been reported. Furthermore, there is now emerging evidence that there are functionally and anatomically distinct OFC subregions along the anterior-posterior axis in rodents, and primates that must also be considered. These ideas will refine how OFC research is conducted and performed. I co-wrote the manuscript as the senior author with the graduate student. This work has been accepted and will be published in the next edition of the journal.

- **Panayi MC***, Killcross S. Functional heterogeneity within the rodent lateral orbitofrontal cortex dissociates outcome devaluation and reversal learning deficits. Elife. 2018 Jul 25. PMID: 30044220

- Barreiros I V*, **Panayi MC*,** Walton ME. Organization of Afferents along the Anterior-posterior and Medial-lateral Axes of the Rat Orbitofrontal Cortex. Neuroscience. 2021 Apr 15; 460:53–68. PMID: 33609638

- Barreiros I V*, Ishii H, Walton ME, **Panayi MC.** Defining an orbitofrontal compass: functional and anatomical heterogeneity across anterior-posterior and medial-lateral axes. Behav Neurosci. 2021; *In Press*.

Glutamatergic and dopaminergic models of aberrant salience in psychosis and schizophrenia. The primary focus of my postdoctoral work at Oxford looked explored aberrant salience, a model of inappropriate attention to cues that is thought to underly psychosis in schizophrenia. Aberrant salience models predict that patients fail to reduce attention to irrelevant cues. In my first project, I created a novel task to measure levels of attention paid to specific cues or contexts in models of psychosis. My data show that classic dopaminergic models like amphetamine caused general increases in arousal and attention, whereas glutamatergic models

like GluA1-receptor KO mice (GluA1-KO) and MK-801 (dizocilpine; an NMDA receptor antagonist) caused stimulus specific increases in attention. In my second project, I found novel evidence showing how dopaminergic dysfunction in psychosis can be a secondary consequence of glutamatergic dysfunction. Measuring striatal dopamine using fast-scan cyclic voltammetry in anaesthetized and awake behaving animals, I found that administration of metabotropic glutamate receptor agonist LY354740 in rats and GluA1-KO mice had abnormally high dopamine responses that correlated with abnormally high attention to specific cues. These findings show for the first time how glutamatergic dysfunction can lead to a behaviorally relevant hyperdopaminergic phenotype thought to underlie increased attention in aberrant salience. In a third project, I showed that the aberrant salience phenotype found in GluA1-KO mice can lead to the formation of inappropriate associations between cues using a sensory preconditioning paradigm. I found that GluA1-KO mice were more likely to form inappropriate associations between cues when there were multiple cues within the session, but enhanced association formation when no competing cues were present. Together, these projects show how glutamatergic dysfunction thought to underlie psychosis can create increased attention to specific cues that is tied to hyperdopaminergic midbrain signaling and inappropriate cue i.e. direct tests of the mechanisms thought to underlie aberrant salience in schizophrenia. During these projects I supervised 4 masters students and a graduate student. I performed all procedures, data analysis, and manuscript preparation in these studies independently as well as in collaboration with the graduate student. These projects have recently been completed and manuscripts have been completed or submitted. Corresponding presentation of these projects at conference proceedings cited below.

- **Panayi, M. C.*,** Jahans-Price, T., Boerner, T., Huber, A., Harrison, P. J., Walton, M. E., Bannerman, D. M., (2017). Glutamatergic dysfunction leads to a hyper-dopaminergic phenotype: Aberrant salience and aberrant actions. Associative Learning Symposium (XXI), Gregynog Hall, Cardiff, UK.

- **Panayi, M. C.***, Jahans-Price, T.*, Boerner, T., Huber, A., Walton, M. E., Bannerman, D. M., (2018). Glutamatergic dysfunction leads to a hyper-dopaminergic phenotype: Linking dopamine to aberrant salience. Monitoring Molecules in Neuroscience, Oxford, UK.

- Blackmore, T., Stahr, L. B., Samborksa, V., Gilmour, G., Walton, M. E., Bannerman, D. M., **Panayi, M. C.** (2019). Fractionating aberrant salience in rodent models of psychosis. Society for Neuroscience, Chicago, IL, USA.

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

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 NIH 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. 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. Postdocs training in the lab were collectively awarded several private foundation fellowships, six K awards, and one R03 grant and 12 have transitioned successfully into academic research/instructional positions (including 4 tenured and 4 tenure-track). I have also mentored several dozen 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-present	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
2019-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
2019	Named as NIH Distinguished Investigator

C. Contributions to Science

Publication Statistics, January 2021:
Google Scholar: 18659 citations, h-index 69
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, leading to current ideas about the role of this region in cognitive mapping and schema formation.

- **Schoenbaum**, G., Chiba, A., and Gallagher, M. (1998) Orbitofrontal cortex and basolateral amygdala encode expected outcomes during learning. Nature Neuroscience. 1:155-159.

- 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.

- Zhou, J., Jia, C., Montesinos-Cartagena, M., Gardner, M.P.H., Zong, W., and **Schoenbaum**, G. (2020) Evolving schema representations in orbitofrontal ensembles during learning. Nature. Advanced Online Publication.

Role of orbitofrontal input to dopaminergic circuits: Dopamine neurons have been shown to signal reward prediction errors in humans, monkeys and rats. Our lab was among the first to extend that finding to rats and has contributed to showing how these signals are constructed and deployed to affect learning and behavior. In initial work, we showed that they similarly encode changes in size versus timing of reward but that under free choice conditions, signals can initial represent optimal rewards even when not selected. Subsequently we demonstrated direct and distinct roles for orbitofrontal and ventral striatal input in determining the underlying state representations and associated reward predictions used by dopamine neurons to calculate 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., 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.

- Takahashi, Y.K., Langdon, A.J., Niv, Y., and **Schoenbaum**, G. (2016) Temporal specificity of reward prediction errors signaled by putative dopamine neurons in rat VTA depends on ventral striatum. Neuron. 91:182-193.

Dopaminergic error signaling and its contribution to learning: In addition to replicating the classic error signals in rats, our lab has also contributed to new ideas regarding the role of dopaminergic signals in learning that goes beyond value and classic RPE signals. This includes the first demonstration that dopamine neurons exhibit error-like responses reflecting model-based estimates of value as well as value-neutral shifts in expected sensory information. This work joins other data showing error-like signals to shifts in state, new information, and even movement, showing that value-based error signaling may be a special case of a more general function.

Consistent with this, we have published causal data showing that dopamine transients are both necessary and sufficient for value-neutral sensory learning.

- Sadacca, B.F., Jones, J.L., and **Schoenbaum**, G. (2016) Midbrain dopamine neurons compute inferred and cached value prediction errors in a common framework. eLIFE. 5:e13665.
- Takahashi, Y.K., Batchelor, H.M., Liu, B., Khanna, A., Morales, M., and **Schoenbaum**, G. (2017) Dopamine neurons respond to errors in the prediction of sensory features of expected rewards. Neuron. 95:1395-1405.
- Sharpe, M.J., Chang, C.Y., Liu, M.A., Batchelor, H.M., Mueller, L.E., Jones, J.L., Niv, Y., and **Schoenbaum**, G. (2017) Dopamine transients are sufficient and necessary for acquisition of model-based associations. Nature Neuroscience. 20:735-742.
- Stalnaker, T.A., Howard, J.D., Takahashi, Y.K., Gershman, S.J., Kahnt, T., and **Schoenbaum**, G. (2019) Dopamine neuron ensembles signal the content of sensory prediction errors. eLIFE. 8:e49315.

Role of orbitofrontal and dopaminergic dysfunction in addiction: Addiction is characterized by a failure to use information about outcomes to support learning and guide behavior. Work in my lab has shown that this may reflect drug-induced changes in prefrontal and dopaminergic circuits. We have shown that cocaine and opiate use affect a variety of behavioral functions that we know depend on areas, and more recently we have linked these functional changes to changes in single unit information processing in the orbitofrontal cortex, dopamine neurons, 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, and we are working now to extend these studies into normal humans and patients.

- **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.
- 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.
- Takahashi, Y.K., Stalnaker, T.A., Marrero-Garcia, Y., Rada, R.M., **Schoenbaum**, G. (2019) Expectancy-related changes in dopaminergic error signals are impaired by cocaine self-administration. Neuron. 101:294-306.

D. Research Support

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

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: Newman, Amy Hauck

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

POSITION TITLE: Acting Scientific Director and Chief, Molecular Targets and Medications Discovery Branch and Medicinal Chemistry Section

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
Mary Washington College	B.S.	05/1980	Chemistry
Medical College of Virginia, Virginia Commonwealth University	Ph.D.	05/1985	Medicinal Chemistry
NIDDK, National Institutes of Health	Postdoctoral	12/1987	Medicinal/Organic Chemistry

A. Personal Statement

My research effort is focused on the design and synthesis of novel ligands to study the structure and function of selected G-protein coupled receptors and monoamine transporters associated with substance use disorders. Highly selective compounds are prepared for characterization of these molecular targets and to develop structure-activity relationships within diverse chemical classes of drugs. In addition, specific tools such as fluorescent and radiolabeled ligands are synthesized for receptor or transporter structure-function studies. My research program is currently studying the monoamine transport systems and the dopamine D_2 receptor family (D_2/D_3) through the design, synthesis and pharmacological evaluation of novel ligands. The combination of state of the art synthetic organic chemistry, computational biophysics and interpretation of pharmacological data has resulted in the discovery of important molecular probes for studying these neurochemical targets. It is envisioned that ultimately this multidisciplinary approach will provide new leads toward the development of potential pharmacotherapeutic agents for the treatment of substance use disorders. Over the years the strong collaborations I have established with many respected researchers in the field have led to the significant advancement of potential therapeutic agents in preclinical studies of drug abuse and medication development. These collaborative efforts have yielded >280 publications in peer-reviewed journals and 13 U.S. patents or patent applications, several of which have been licensed by pharmaceutical companies.

B. Positions and Honors

Positions and Employment

1985 - 1988 NRSA Post-doctoral fellow, Section on Drug Design and Synthesis, NIDDK, Bethesda, Maryland

1988 - 1990	Research Chemist, Department of Applied Biochemistry, Walter Reed Army Institute of Research, Washington D.C.
1991 - 1994	Senior Staff Fellow, Psychobiology Section, NIDA-IRP, Baltimore, Maryland
1994 - 1999	Investigator (tenure track), Psychobiology Section, NIDA-IRP, Baltimore, Maryland
1999 -	Senior Investigator (tenured) and Chief, Medicinal Chemistry Section, NIDA-IRP, Baltimore, Maryland
2011 -	Deputy Scientific Director; Chief, Molecular Targets and Medications Discovery, Branch and Director, NIDA-IRP Medication Development Program, Baltimore, Maryland
2018 -	Acting Scientific Director, NIDA-IRP
2020-	Scientific Director, NIDA-IRP

Honors

1998	Sato International Memorial Award - Awarded by the Pharmaceutical Society of Japan in March 1999, Tokushima, Japan
2004	NIDA Director's Award of Merit
2006	NIDA Director's Award for EEO, Diversity and Quality of Worklife
2009	1st recipient of the NIDA/NIH Women Scientists Advisory Achievement Award
2010	NIDA Director's Award of Merit
2010	Elected member of the American College of Neuropsychopharmacology
2012	1st recipient of the NIDA Scientific Director's Innovators Partnership Program Award
2013	NIDA-IRP Diversity Mentoring Award for Faculty
2014	Marian W. Fischman Lectureship Award, College on Problems of Drug Dependence
2015	NIDA Director's Innovation Award
2016	Philip Portoghese Lectureship Award, Division of Medicinal Chemistry and the Journal of Medicinal Chemistry, American Chemical Society (first woman recipient)
2018	NIH OD Honor Award - as a member of the NIH Tenure-Track Mentoring Program and a co-leader of the NIDA-NIA TTI Mentoring Program
2018	Honored as a "Remarkable Woman in Medicinal Chemistry" at the 255th American Chemical Society National Meeting
2018	NIH Office of the Director Honor Award - as a member of the NIH Tenure-Track Mentoring Program and a co-leader of the NIDA-NIA TTI Mentoring Program
2019	NIH Ruth L. Kirschstein Mentoring Award, NIH Office of the Director

C. Contributions to Science

1. Design, synthesis, structure-activity relationships (SAR) and in vivo development of novel dopamine D3 receptor antagonists and partial agonists for the treatment of substance use disorders. Developing novel ligands and SAR for the D2-like family receptors, and especially for the D3 receptor has not only provided important preclinical tools for potential translation, but critical information to put into context the structure and function of this receptor subtype. PG01037, from the Newman lab, is now commercially available. Two patents have recently been licensed for development of lead molecules toward opioid use disorders.
    a. Kumar, V., Bonifazi, A., Ellenberger, M. P., Keck, T. M., Pommier, E., Rais, R., Slusher, B. S., Gardner, E.; You, Z.-B.; Xi, Z-X.; Newman A. H. (2016) Highly

selective D_3R antagonists and partial agonists based on eticlopride and the D_3R crystal structure: new leads for opioid dependence treatment. Journal of Medicinal Chemistry, 59(16), 7634-7650. PMID: 27508895

b. You, Z.-B., Bi, G., Galaj, E., Kumar, V., Cao, J., Gadiano, A., Rais, R., Slusher, B.S., Gardner, E.L., Xi, Z.X., & Newman, A.H. (2019). Dopamine D3R antagonist VK4-116 attenuates oxycodone self-administration and reinstatement without compromising its antinociceptive effects. Neuropsychopharmacology, 44(8), 1415-1424. PMID: 30555159

c. Shaik, A. B., Kumar, V., Bonifazi, A., Guerrero, A. M., Cemaj, S. L., Gadiano, A., Lam, J., Xi, Z.-X., Rais, R., Slusher, B. S., Newman A. H. (2019) Investigation of novel primary and secondary pharmacophores, and 3-substitution in the linking chain of a series of highly selective and bitopic dopamine D_3 receptor antagonists and partial agonists. *Journal of Medicinal Chemistry*, *62(20),* 9061-9077. PMID:31526003

2. The development of biased or allosteric GPCR ligands has become an exciting strategy toward discovering novel molecules that may have therapeutic applications in treating neuropsychiatric disorders. We have recently discovered a series of D2-like agonists that are G-protein (over beta-arrestin) biased and a second series of bitopic molecules that exhibit allosteric pharmacology at D3R.

   a. Bonifazi, A., Yano, H., Ellenberger, M. P., Muller, L., Kumar, V., Zou, M., Cai, N.S., Guerrero, A.M., Woods, A.S., Shi, L., & Newman, A.H. (2017). Novel bivalent ligands based on the sumanirole pharmacophore reveal dopamine D2 receptor (D2R) biased agonism. Journal of Medicinal Chemistry, 60(7), 2890-2907. PMID: 28300398

   b. Bonifazi, A., Yano, H., Guerrero, A.M., Kumar, V., Hoffman A.F., Lupica, C.R., & Newman, A.H. (2019). Novel and Potent Dopamine D2 Receptor Go-Protein Biased Agonists, ACS Pharmacology and Translational Science, 2(1), 52-65. PMCID: PMC6371206

   c. Newman, A. H., Battiti, F. O., Bonifazi, A. (2020) 2016 Philip S. Portoghese Medicinal Chemistry Lectureship: Designing Bivalent or Bitopic Molecules for G-protein Coupled Receptors - The Whole is Greater Than the Sum of its Parts. Journal of Medicinal Chemistry, *62(20)* 9061-9078. PMID: 31499001

3. Translating the atypical dopamine uptake inhibitor hypothesis with R-modafinil and novel analogues. We identified R-modafinil as a unique dopamine uptake inhibitor that has the potential of translation to the clinic as a medication to treat psychostimulant abuse and the cognitive impairment that develops with chronic drug abuse. We have synthesized hundreds of novel analogues of modafinil and identified several lead agents that are superior to the parent molecule, in animal models of psychostimulant abuse.

   a. Loland, C. J., Mereu, M., Okunola, O. M., Cao, J., Prisinzano, T. E., Mazier, S., Kopajtic, T., Shi, L., Katz, J.L., Tanda, G., & Newman, A.H. (2012). R-modafinil (armodafinil): A unique dopamine uptake inhibitor and potential medication for psychostimulant abuse. Biological Psychiatry, 72(5), 405-413. PMID: 22537794

   b. Cao, J., Slack, R. D., Bakare, O. M., Burzynski, C., Rais, R., Slusher, B. S., Kopajtic, T., Bonifazi, A., Ellenberger, M. P., Yano, H., He, Y., Bi, G.-H., Xi, Z.-X., Loland, C. J., Okunola-Bakare, Y., Newman, A. H. Novel and High Affinity 2-[(Diphenylmethyl)sulfinyl]acetamide (Modafinil) Analogues as Atypical Dopamine Transporter Inhibitors. Journal of Medicinal Chemistry, 59(23), 10676-10691. PMID: 27933960

c. Newman A. H., Cao, J., Keighron, J.D., Jordan, C.J., Bi, G., Liang, Y., Abramyan, A.M., Avelar, A.J., Tschumi, C.W., Beckstead, M.J., Shi, L., Tanda, G., & Xi, X-Z. (2019). Translating the atypical dopamine uptake inhibitor hypothesis toward therapeutics for treatment of psychostimulant use disorders. Neuropsychopharmacology,44(8), 1435-1444. PMID: 30858517

4. Discovery of the benztropine class of atypical dopamine uptake inhibitors as pharmacotherapies for psychostimulant abuse. In addition to pioneering this area of research, we developed several lead compounds as potential pharmacotherapies. Two patents have been licensed by Pharma and several benztropine analogues are commercially available for preclinical investigation.
    a. Newman, A. H., Kline, R.H., Allen, A.C., Izenwasser, S., George, C., & Katz, J.L. (1995). Novel 4'-substituted and 4',4''-disubstituted 3-alpha-(diphenylmethoxy)tropane analogs as potent and selective dopamine uptake inhibitors. Journal of Medicinal Chemistry, 38(20), 3933-40. PMID: 7562926
    b. Hiranita, T., Soto, P.L., Newman, A.H., & Katz, J.L. (2009). Assessment of reinforcing effects of benztropine analogs and their effects on cocaine self-administration in rats: Comparisons with monoamine uptake inhibitors. Journal of Pharmacology and Experimental Therapeutics, 329(2), 677-686. PMID: 19228996
    c. Hiranita, T., Wilkinson, D., Hong, W., Zou, M., Kopjtic, T., Soto, P., Lupica, C.R., Newman, A.H., & Katz, J.L. (2014). 2-isoxazol-3-phenyltropane derivatives of cocaine: Molecular and atypical system effects at the dopamine transporter. Journal of Pharmacology and Experimental Therapeutics, 349(2), 297-309. PMID: 24518035
    d. Zou, M.F., Cao, J.J., Abramyan, A.M., Kopajtic, T., Zanettini, C., Guthrie, D.A., Rais, R. , Slusher, B.S., Shi, L., Loland, C.J., & Newman, A.H. (2017). Structure-activity relationship studies on a series of 3 alpha-[bis(4-fluorophenyl)methoxy]tropanes and 3 alpha-[bis(4-fluorophenyl)methylamino]tropanes as novel atypical dopamine transporter (DAT) inhibitors for the treatment of cocaine use disorders. Journal of Medicinal Chemistry, 60(24), 10172−10187.PMD: 29227643

5. Development of novel DAT, SERT or D2- Dopamine receptor selective photoaffinity and/or fluorescent ligands for structure function studies. These tools have proven highly useful in numerous laboratories for structure-function and visualization studies. They have also provided the basis for developing similar tools in numerous other labs. Several of our fluorescent ligands, such as JHC1-064, are currently being used for single molecule fluorescence studies.
    a. Hansen, F. H., Skjorringe, T., Yasmeen, S., Arends, N., Sahai, M., Erreger, K., Andreassen, T.F., Holy, M., Hamilton, P.J., Neergheen, V., Karlsbor, M., Newman, A.H., Pope, S., Heales, S.J.R, Friberg, L., Law, I., Pinborg, L.H., Sitte, H.H., Loland, C., Shi, L., Weinstein, H., Galli, A., Hjermind, L.E., Moller, L.B., & Gether, U. (2014). Missense dopamine transporter mutations associate with adult parkinsonism and ADHD. Journal of Clinical Investigation,124(5), 3107-3120. PMID: 24911152
    b. Silm, K., Yang, J., Marcott, P. F., Asensio, C. S., Eriksen, J., Guthrie, D. A., Newman, A.H., Ford, C.P., & Edwards, R.H. (2019). Synaptic vesicle recycling pathway determines neurotransmitter content and release properties. Neuron,102(4), 786-800. PMID: 31003725
    c. Guthrie, D. A., Herenbrink, C. K., Lycas, M. D., Ku, T., Bonifazi, A., DeVree, B. T., Mathiasen, S. Javitch, J. A., Grimm, J. B., Lavis, L., Gether, U., Newman A. H. (2020) Novel Fluorescent Ligands Enable Single-Molecule Localization Microscopy of the Dopamine Transporter. ACS Chemical Neuroscience, 11(20) 3288-3300. PMID: 32926777

Complete List of Published Work in My Bibliography:
https://www.ncbi.nlm.nih.gov/pubmed/?term=Newman+AH

D. Additional Information: Research Support

As a senior investigator at the NIDA-Intramural Research Program since 1991, my research budget is funded entirely and directly through the NIDA-IRP.

Ongoing Research Support

ZIA DA000389 Newman (PI) 10/01/1991 – Ongoing
NIDA Novel and Atypical Dopamine Uptake Inhibitors

ZIA DA000424 Newman (PI) 10/01/1999 – Ongoing
NIDA Novel Dopamine D3 Receptor Ligands

Z1A DA000609 Newman (PI) 10/01/2016 – Ongoing
NIDA Dopamine D2-like Functionally Selective Agonists

Z1A DA000610 Newman (PI) 10/01/2016 – Ongoing
NIDA Monoamine Transporter Nanoprobes

Intra-Institute Collaboration

The proposed experiments require collaboration between the labs of Dr. Geoffrey Schoenbaum (NIDA) and Dr. Amy Newman (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. Marios Panayi and will oversee all experiments. Dr. Amy Newman will provide the dopamine D3-receptor antagonist *R*-VK4-40, expertise in drug dose and timing parameters, as well as rats trained to self-administer cocaine. Dr. Amy Newman, together with Dr. Geoffrey Schoenbaum, will oversee all experiments.