CBC | CHICAGO BIOMEDICAL CONSORTIUM

CBC Catalyst Award Proposal Title Page

Title of the proposal *(no more than 100 characters including white space)*

Neural mechanisms of sensory hypersensitivity in autism spectrum disorders

Name, degree, title, institution, and contact information including the email address of each PI

Joseph D. Zak, PhD, Assistant Professor, University of Illinois at Chicago (Lead Contact)
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Chicago, IL, 60607
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Chicago, Illinois 60637
lkay@uchicago.edu, (773) 702-6174

Do you have any current or pending grant applications that potentially overlap with this application? Check ONE:

YES ☐ **NO** ☒

If YES, please identify them.

(ENTER THE OVERLAP HERE)

Explain the overlap in the Biosketch section.

Does the proposed research involve animal subjects?	**Check ONE:**	**YES** ☒	**NO** ☐
Does the proposed research involve human subjects?	**Check ONE:**	**YES** ☐	**NO** ☒
Does the proposed research involve embryonic stem cells?	**Check ONE:**	**YES** ☐	**NO** ☒

(Note: if the data entered exceeds one page, it is acceptable to submit it as two pages.)

Lay Summary (150 words):

Why does the same sensory encounter often elicit different perceptions across individuals? Autism spectrum disorders (ASD) are both diagnosed and defined by overwhelming sensory hypersensitivity (Cermak et al., 2010; Ashwin et al, 2014). These atypical sensory responses are a major detriment to the quality of life for persons with ASD. Therefore, understanding the neural foundation of sensory hypersensitivity is critical for the development of therapeutic avenues and a holistic understanding of sensory processing in healthy and diseased brains. The studies that we propose have the potential to improve our understanding of the basic biology behind sensory processing disorders and will support the development of targeted therapeutics that will aid in the restoration of sensory function in ASD. Our studies will address how sensory encoding is disrupted at the cellular level in autism which holds the promise to directly improve human health.

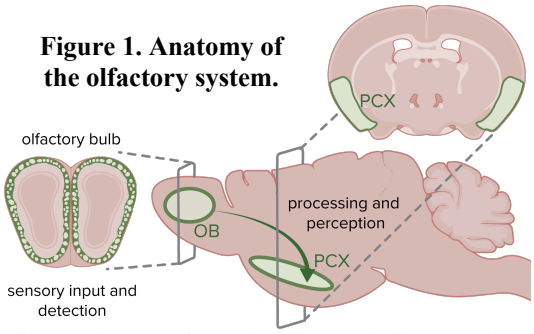
Risk/Reward (200 words):

Investigating disordered sensory processing presents numerous high-risk challenges with respect to understanding neural connectivity and stimulus encoding. Despite the link between sensory hypersensitivity and ASD, the neural factors that contribute to the sensory processing disorder are not known. Neural hyperexcitability may first arise in early sensory processing centers that are responsible for stimulus detection (Shilit Nitenson et al., 2015). Alternatively, hypersensitivity might result from aberrant neural encoding in sensory cortices that are responsible for analytical processing. We will fill this knowledge gap through a multidisciplinary approach combining electrophysiology, functional imaging, and applied mathematics in a mouse model of ASD. Our work will be the first direct examination of sensory processing in ASD through the hierarchy of a sensory system, and the fulfillment of these aims will result in a greater understanding of sensory processing in healthy and diseased brains. A product of our collaboration will be the development of new experimental approaches for understanding neural processing across sensory modalities. At present, our preliminary data is likely insufficient for funding consideration from conventional granting agencies. This award will facilitate the acquisition of the data necessary to obtain federal funding.

Proposed Research:

Our overall objective is to reveal the neural underpinnings of sensory hypersensitivity in autism spectrum disorders. The olfactory system is an ideal model for studying how animals integrate information about external cues and the neural circuits that orchestrate this information extraction. Furthermore, mouse models of autism allow for the monogenic examination of disease phenotypes. We will use the Fragile-X Mental Retardation Protein knockout mouse (*Fmr1*-KO) model of ASD to study sensory processing disorders. ***We hypothesize that sensory hypersensitivity in ASD arises through an imbalance of neural excitation and inhibition at successive stages of the sensory processing hierarchy.*** Our studies will reveal how sensory processing is affected in neurodevelopmental disorders that result in sensory hypersensitivity.

Figure 1. Anatomy of the olfactory system.



Olfactory inputs arrive at the olfactory bulb (OB), where we will study synaptic connectivity using patch-clamp electrophysiology and local field potentials. Sensory information is then routed to the piriform cortex (PCX) where further sensory processing takes place. We will develop a novel approach to measure cellular and population coding in the PCX.

Aim 1: To measure the balance of synaptic excitation and inhibition in the olfactory bulb of a mouse model of autism. Within the olfactory bulb, odor information is initially processed by both local excitatory neurons called external tufted cells (eTCs) and inhibitory periglomerular (PG) cells. The interplay between these two cell types, and their respective excitation and inhibition, helps to determine whether sensory information is routed by mitral cells (MCs) to the piriform cortex where sensory perception occurs (**Figure 1**; Gire et al., 2012). The weakest sensory inputs are generally filtered out by a network of inhibitory cells (Gire and Schoppa, 2009; Zak and Schoppa, 2022). We predict that in *Fmr1*-KO animals the balance of inhibition and excitation in the olfactory bulb is shifted to favor excitation at lower levels of sensory input compared to wild-type (WT) mice. In the Kay lab model (Osinski & Kay, 2016), stronger input excitation should shift the oscillations into the beta band at lower volatilities than normal. We will test this prediction in both excised brain tissue using

single-cell electrophysiology (Zak lab) and in live animals by measuring oscillations in local field potentials (LFP; Kay lab).

The Zak lab is well-equipped for *in-vitro* studies of synaptic physiology and contains multiple microscopes and recording devices for this purpose. We will record synaptic excitation and inhibition at MCs, which transmit sensory information to the piriform cortex. A variable amplitude electrical stimulus will be delivered to olfactory sensory neuron (OSN) axon terminals (**Figure 2A**). We will then isolate excitatory and inhibitory synaptic inputs and compare their relative amplitudes as a function of sensory neuron stimulus strength **(Figure 2B,D)**. The data provided in *Figure 2* demonstrate the feasibility of our approach. We predict that in *Fmr1*-KO animals the balance of excitation and inhibition will be shifted to favor excitation at MCs for weaker levels of sensory input (**Figure 2C,E**), thereby allowing enhanced sensory activity to propagate to the piriform cortex and providing a cellular mechanism behind heightened sensory sensitivity (Bodaleo et al., 2019).

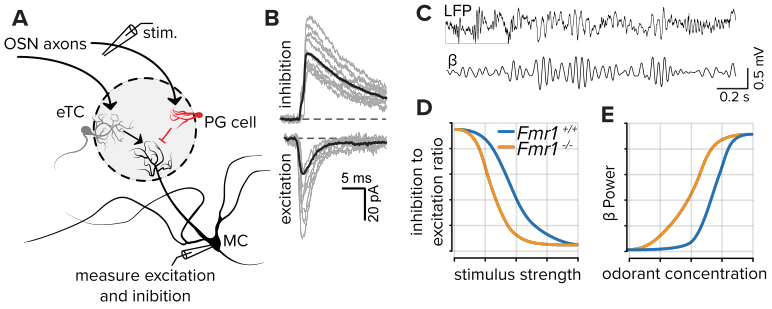


Figure 2. Preliminary data and Aim 1 outcomes.
A. Schematic for measuring excitation and inhibition in the olfactory bulb. **B**. Example recordings of inhibition (top) and excitation (bottom) from an eTC. **C**. Example of a local field potential (LFP; top) and isolated beta frequency band (bottom) during odor sampling. Adapted from Osinski and Kay, 2016. **D**. Predicted results measuring excitation and inhibition in *Fmr1*-KO mice. Excitation exceeds inhibition earlier in knockout animals. **E**. Predicted power in the beta frequency of local field potentials from the same animals.

The outcomes of the in vitro experiments performed in the Zak laboratory will inform work performed using live animals in the Kay laboratory, where LFP oscillations in the beta frequency will be measured. Beta oscillations are an aggregate measure of the balance between neural excitation and inhibition, they scale with the effective concentration of an odorant, and are generated by interactions between the olfactory bulb and cortex (David et al., 2015; Lowry and Kay, 2007; Martin et al., 2006). In the Kay laboratory, odorants will be delivered to mice at increasing concentrations, analogous to the variable amplitude electrical stimulus used in the previous experiment. We predict that power in the beta band of the LFPs will be enhanced in *Fmr1*-KO animals at lower odorant concentration or volatility when compared to WT control animals (**Figure 2D**), thereby indicating a greater degree of excitation in the olfactory bulb and sensory propagation to the cortex of *Fmr1*-KO mice. Our complementary cellular- and network-based approaches will provide valuable insight into sensory gating disorders and how hypersensitivity may arise in early sensory processing areas.

Aim 2: To develop a novel technical approach for recording network activity in sensory processing centers.
We will develop new tools to simultaneously measure cellular and network activity in the piriform cortex of live animals. The recurrent circuit architecture of the piriform cortex normalizes population responses to increasing odorant concentration (Roland et al., 2017; Bolding and Franks, 2018). In WT mice, the neural activity in the cortex remains constant regardless of stimulus concentration due to interactions with a network of local inhibitory cells. We predict that in ASD, normalization becomes ineffective and cortical activity will scale with odorant concentration more than in WT mice – a further potential mechanism of sensory hypersensitivity.

In *Fmr1*-KO and WT mice, we will inject a virus encoding for the calcium indicator jGCaMP7f into the piriform cortex where we will preferentially target excitatory cells. We will then perform a craniotomy and implant a gradient-index (GRIN) lens into the piriform cortex (**Figure 3A**) to provide optical access (Wang et al., 2020). In the same preparation, an electrode will also be implanted into the piriform cortex adjacent to the lens to allow for LFP readouts. These innovative surgical procedures will be a collaborative effort between members of the Zak and Kay laboratories and will allow for the transfer of surgical expertise between personnel in the two groups.

Experimental animals will then be exposed to odorant concentrations while neural activity is measured concurrently using 1) multiphoton microscopy and 2) LFP in the beta frequency. Our approach is both novel

and powerful because it will allow us to not only track the stimulus responses of individual neurons but also the network activity across an entire sensory structure. We predict that in *Fmr1*-KO mice, individual cells of the piriform cortex will show enhanced concentration dependence (**Figure 3B,D**), and concurrently measured neural oscillations in the beta frequency will be enhanced when compared to WT mice. (**Figure 3C,D**).

Together, the aims of our experimental plan will provide novel mechanistic insights into sensory processing disorders associated with ASD. We will also develop novel tools and analysis pipelines that our labs can carry forward for use in future projects. Overall, this proposal has the potential to provide significant, clinically-relevant insights into the neural processing that underlies sensory processing in healthy and diseased brains.

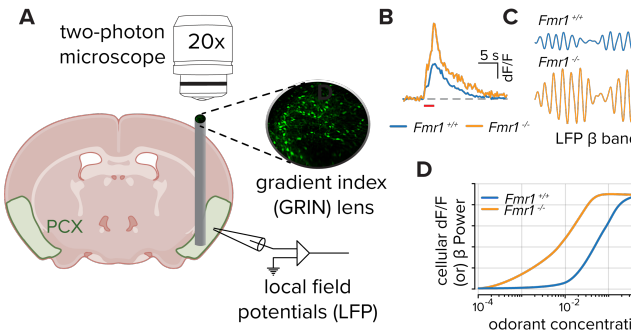


Figure 3. Novel approach to study cellular and population encoding in the piriform cortex.

A. Schematic for concurrently measuring cellular and population activity in the piriform cortex. **B**. Predicted cellular calcium responses to a given odorant concentration in *Fmr1* animals. Red bar is odor delivery. **C**. Predicted field potential responses concurrently recorded the calcium signals in part *B*. **D**. Predicted concentration dependence of cellular activity and oscillatory power in the beta frequency.

<u>Nature of Inter-Institutional Collaboration:</u>

The studies proposed here draw upon the systems neuroscience and physiology expertise of the established investigator Kay (UChicago) and *in vivo* imaging and brain slice recording expertise of junior investigator Zak (UIC). This collaboration will bridge existing gaps between physiological approaches to studying sensory systems and draw on complementary expertise between the two CBC institutions.

The newly established Zak laboratory (2022) houses two custom brain slice electrophysiology setups, behavior testing arenas, and a microscopy suite housing a custom-built two-photon microscope that is currently under construction. The Kay lab (UChicago) is well-equipped for physiological studies of sensory processing and has made seminal contributions to the field of systems neurobiology, including recent studies of oscillations in sensory coding and behavior (Lowry and Kay, 2007; Osinski and Kay, 2016) that are built upon in this proposal. A new recording rig will be purchased that can be transferred to the Zak lab for imaging experiments.

The collaboration forged here will allow for technical and analytical expertise to be transferred from a senior to a junior investigator, thereby broadening biomedical expertise in the Chicago area. This collaboration will also involve training opportunities for graduate, postbac and postdoctoral trainees from the Kay laboratory (Huibo Li & Abigail Stuart) and Zak laboratory (Vaibhav Konanur & Yanti Manurung), each using complementary approaches to studying sensory processing disorders that draw from cellular physiology, systems neurobiology, and applied mathematics. Meetings of our combined research teams have already occurred, and the diversity of expertise brought together will drive our collaborative studies. As the project proceeds, we anticipate significant personnel exchange and interaction at both locations. Experiments will be performed collaboratively, allowing for direct interaction between personnel in the Zak and Kay laboratories.

<u>Criteria for Measuring Success:</u>

We anticipate the outcomes of this collaboration will produce two high-impact publications that will reveal the behavioral and physiological underpinnings of sensory hypersensitivity in ASD and potential therapeutic targets for disorder interventions. The data generated will significantly strengthen submissions for external funding from the NIH by providing high-quality preliminary data and proof-of-concept.

<u>Long-Term Funding Plan:</u>

We will submit an NIH R01 proposal to the National Institute for Deafness and other Communication Disorders (NIDCD) by the 6/2024 (Cycle II) deadline. Our timeline allows for preliminary data collection and analysis for both an initial and a revised application should NIH require it. The proposed NIH award will aim to characterize sensory processing disorders in neurodevelopmental diseases using the approaches outlined here.

References

1. Ashwin C. et al. (2014) Enhanced olfactory sensitivity in autism spectrum conditions. Mol. Autism 5
2. Bodaleo F, Tapia-Monsalves C, Cea-Del Rio C, Gonzalez-Billault C, Nunez-Parra A. Structural and Functional Abnormalities in the Olfactory System of Fragile X Syndrome Models (2019) Front Mol Neurosci. 12:135
3. Bolding KA, Franks KM (2018) Recurrent cortical circuits implement concentration-invariant odor coding. Science. 361:6407
4. Cermak, SA, Curtin C, Bandini LG (2010) Food selectivity and sensory sensitivity in children with autism spectrum disorders. J. Am. Diet. Assoc. 110, 238–246
5. David F, Courtiol E, Buonviso N, Fourcaud-Trocmé N (2015) Competing mechanisms of gamma and beta oscillations in the olfactory bulb based on multimodal inhibition of mitral cells over a respiratory cycle eNeuro 2: 2015
6. Gire DH, Schoppa NE (2009) Control of on/off glomerular signaling by a local GABAergic microcircuit in the olfactory bulb. J Neurosci. 29: 13454-64
7. Gire DH, Franks KM, Zak JD, Tanaka KF, Whitesell JD, Mulligan AA, Hen R, Schoppa NE (2012) Mitral cells in the olfactory bulb are mainly excited through a multistep signaling path. J Neurosci. 32(9):2964-75
8. Lowry CA, Kay LM (2007) Chemical factors determine olfactory system beta oscillations in waking rats. J Neurophysiol 98: 394–404
9. Martin C, Gervais R, Messaoudi B, Ravel N (2006) Learning-induced oscillatory activities correlated to odour recognition: a network activity. Eur J Neurosci 23: 1801–1810
10. Osinski BL, Kay LM (2016) Granule cell excitability regulates gamma and beta oscillations in a model of the olfactory bulb dendrodendritic microcircuit. J Neurophysiol 116: 522–539
11. Roland B, Deneux T, Franks KM, Bathhellier B, Fleischmann A (2017) Odor identity coding by distributed ensembles of neurons in the mouse olfactory cortex. eLife 6:e26337
12. Slilit Nitenson A, Stackpole EE, Truszkowski TLS, Midroit M, Fallon JR, Bath KG (2015) Fragile X Mental Retardation Protein Regulates Olfactory Sensitivity But Not Odorant Discrimination Chemical Senses 40(5) 345–350
13. Wang PY, Boboila C, Chin M, Higashi-Howard A, Shamash P, Wu Z, Stein NP, Abbott LF, Axel R (2020) Transient and persistent representations of odor value in prefrontal cortex. Neuron. 108(1):209-224
14. Zak JD, Schoppa NE (2022) Neurotransmitter regulation rather than cell-intrinsic properties shapes the high-pass signal filtering properties of olfactory bulb glomeruli. Journal of Physiology 600.2:393-417

Program Director/Principal Investigator (Last, First, Middle):

DETAILED BUDGET FOR INITIAL BUDGET PERIOD DIRECT COSTS ONLY	FROM	THROUGH

List PERSONNEL *(Applicant organization only)*
Use Cal, Acad, or Summer to Enter Months Devoted to Project
Enter Dollar Amounts Requested *(omit cents)* for Salary Requested and Fringe Benefits

NAME	ROLE ON PROJECT	Cal. Mnths	Acad. Mnths	Summer Mnths	INST.BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTAL
	PD/PI							
SUBTOTALS →								

CONSULTANT COSTS	
EQUIPMENT *(Itemize)*	
SUPPLIES *(Itemize by category)*	
TRAVEL	
INPATIENT CARE COSTS	
OUTPATIENT CARE COSTS	
ALTERATIONS AND RENOVATIONS *(Itemize by category)*	
OTHER EXPENSES *(Itemize by category)*	

CONSORTIUM/CONTRACTUAL COSTS	DIRECT COSTS	
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*		**$**
CONSORTIUM/CONTRACTUAL COSTS	FACILITIES AND ADMINISTRATIVE COSTS	
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD		**$**

Program Director/Principal Investigator (Last, First, Middle):

BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS	INITIAL BUDGET PERIOD *(from Form Page 4)*	2nd ADDITIONAL YEAR OF SUPPORT REQUESTED	3rd ADDITIONAL YEAR OF SUPPORT REQUESTED	4th ADDITIONAL YEAR OF SUPPORT REQUESTED	5th ADDITIONAL YEAR OF SUPPORT REQUESTED
PERSONNEL: *Salary and fringe benefits. Applicant organization only.*					
CONSULTANT COSTS					
EQUIPMENT					
SUPPLIES					
TRAVEL					
INPATIENT CARE COSTS					
OUTPATIENT CARE COSTS					
ALTERATIONS AND RENOVATIONS					
OTHER EXPENSES					
DIRECT CONSORTIUM/ CONTRACTUAL COSTS					
SUBTOTAL DIRECT COSTS *(Sum = Item 8a, Face Page)*					
F&A CONSORTIUM/ CONTRACTUAL COSTS					
TOTAL DIRECT COSTS					

TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD	**$**

JUSTIFICATION. Follow the budget justification instructions exactly. Use continuation pages as needed.

Program Director/Principal Investigator (Last, First, Middle):

DETAILED BUDGET FOR INITIAL BUDGET PERIOD DIRECT COSTS ONLY	FROM	THROUGH

List PERSONNEL *(Applicant organization only)*
Use Cal, Acad, or Summer to Enter Months Devoted to Project
Enter Dollar Amounts Requested *(omit cents)* for Salary Requested and Fringe Benefits

NAME	ROLE ON PROJECT	Cal. Mnths	Acad. Mnths	Summer Mnths	INST.BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTAL
	PD/PI							
SUBTOTALS →								

CONSULTANT COSTS	
EQUIPMENT *(Itemize)*	
SUPPLIES *(Itemize by category)*	
TRAVEL	
INPATIENT CARE COSTS	
OUTPATIENT CARE COSTS	
ALTERATIONS AND RENOVATIONS *(Itemize by category)*	
OTHER EXPENSES *(Itemize by category)*	

CONSORTIUM/CONTRACTUAL COSTS	DIRECT COSTS	
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*		$
CONSORTIUM/CONTRACTUAL COSTS	FACILITIES AND ADMINISTRATIVE COSTS	
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD		$

Program Director/Principal Investigator (Last, First, Middle):

BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS	INITIAL BUDGET PERIOD *(from Form Page 4)*	2nd ADDITIONAL YEAR OF SUPPORT REQUESTED	3rd ADDITIONAL YEAR OF SUPPORT REQUESTED	4th ADDITIONAL YEAR OF SUPPORT REQUESTED	5th ADDITIONAL YEAR OF SUPPORT REQUESTED
PERSONNEL: *Salary and fringe benefits. Applicant organization only.*					
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OUTPATIENT CARE COSTS					
ALTERATIONS AND RENOVATIONS					
OTHER EXPENSES					
DIRECT CONSORTIUM/ CONTRACTUAL COSTS					
SUBTOTAL DIRECT COSTS *(Sum = Item 8a, Face Page)*					
F&A CONSORTIUM/ CONTRACTUAL COSTS					
TOTAL DIRECT COSTS					

TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD	**$**

JUSTIFICATION. Follow the budget justification instructions exactly. Use continuation pages as needed.

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: Zak, Joseph Donald

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

POSITION TITLE: Assistant Professor of Biological Science

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 Michigan *Ann Arbor, MI*	BSc	05/2008	Neuroscience
University of Colorado Medical School *Aurora, CO*	PhD	05/2015	Physiology & Biophysics
Harvard University *Cambridge, MA*	Postdoctoral	12/2021	Neuroscience

A. Personal Statement

I am an Assistant Professor of Biological Science, and my research is focused on the neurobiology of sensory systems. My research has two objectives: first, to understand how the brain extracts salient information about physical objects in the environment; and second, to understand the mechanisms through which internal neural representations are made from external stimuli. The olfactory system is an ideal model for studying how animals integrate information about external cues, as well as the neural circuits that orchestrate this information extraction.

My training is both broad and multidisciplinary. My research as a graduate student identified specialized neurophysiological circuit properties of the mammalian olfactory system that filter stimuli based on their intensity to enhance sensory contrast. Through these studies, I developed a strong skillset of electrophysiological and analytical tools to study neural circuits. As a Postdoctoral Fellow, I developed a theoretical and computational model of how mixtures of stimuli compete for the same sensory receptors to maximize their collective information transfer and the consequences for stimulus perception. I then empirically tested the model-based hypotheses using cutting-edge biological imaging techniques to measure neural activity in large populations of sensory neurons in live animals. Through these studies, I discovered that sensory neurons in the olfactory system are far from simple relays and contain intrinsic computational power derived from the statistics of receptor-ligand binding interactions. These studies provided new evidence that antagonism in sensory neurons plays a critical role in normalizing sensory input to the olfactory system, which enhances information transfer to downstream neural areas.

My independent laboratory at the University of Illinois at Chicago opened in 2022 and I am excited to continue studying sensory processing in the olfactory system. My previous research training and education puts me in a unique position to tackle intricate questions at the interface of physiology and animal behavior. My laboratory uses a broad range of innovative, experimental techniques ranging from *in vitro* and *in vivo* electrophysiology and pharmacology to *in vivo* imaging, optogenetics, and chemogenetics, as well as computational and quantitative analytical techniques. The combination and implementation of these approaches are necessary to gain novel insight into how neural circuits guide sensory experience and behavior, which is critical for

understanding how experience fundamentally reorganizes neural circuits and their stimulus coding properties. To carry out these studies, I have successfully recruited graduate students and postdoctoral fellows to my research group.

Ongoing and recently completed projects that I would like to highlight include:

Current:
R00 DC017754
Zak (PI)
03/01/20-2/28/23
Learning-mediated plasticity in cortical feedback projections to the olfactory bulb

Completed:
Supplement to R01 DC011291 (Venkatesh N. Murthy)
Zak (co-PI)
6/01/2020-5/31/2021
Alzheimer's disease-related pathology in corticobulbar circuits

K99 DC017754
Zak (PI)
01/01/20-12/31/21
Learning-mediated plasticity in cortical feedback projections to the olfactory bulb

F32 DC015938
Zak (PI)
04/10/17-04/09/20
Information coding in individual olfactory sensory axons

F31 DC013480
Zak (PI)
05/01/13-04/20/16
Balancing excitation and inhibition in olfactory bulb glomeruli

Citations:

1. **Zak JD**, Reddy G, Vergassola M, Murthy VN. (2020) Antagonistic interactions are widespread in freely-breathing mice. ***Nature Communications****,* Jul 3; 11:3350. PMCID: PMC7335155
2. Reddy G**, **Zak JD****, Vergassola M, Murthy VN. (2018) Antagonism in olfactory receptor neurons and its implications for the perception of odor mixtures. ***eLife****,* Apr 24*;* 7:e34958 PMCID: PMC5915184. **Equal Contribution
3. **Zak JD**, Whitesell JD, Schoppa NE (2015) Metabotropic glutamate receptors promote disinhibition of olfactory bulb glomeruli that scales with input strength. ***Journal of Neurophysiology***, Mar 15; 113(6):1907-20. PMCID: PMC4359998.
4. **Zak JD**, Schoppa NE (2021) Optical manipulations reveal strong reciprocal inhibition but limited recurrent excitation within olfactory bulb glomeruli. ***eNeuro****,* DOI: 10.1101/2021.07.21.453150

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2022 – Present	Assistant Professor, Department of Biological Sciences, University of Illinois Chicago, Chicago, IL
2022 – Present	Assistant Professor, Department of Psychology, University of Illinois Chicago, Chicago, IL (affiliate)

2015 – 2021	Postdoctoral Research Associate, Harvard University, Cambridge, MA
2016 – 2021	Teaching Instructor, Harvard College, Cambridge, MA
2018 – Present	Section Editor, Data in Brief
2010 – 2015	Graduate Research Assistant, University of Colorado Medical School, Aurora, CO
2008 – 2010	Research Assistant, The Jackson Laboratory, Bar Harbor, ME

Honors

2021	Polak Young Investigator Award, Association for Chemoreception Science
2020	National Institute of Health K99/R00 Pathways to Independence Award
2017 – 2021	Harvard University Certificate of Distinction in Teaching (six semesters)
2017	National Institute of Health F32 Postdoctoral Fellowship
2013	National Institute of Health F31 Predoctoral Fellowship
2012	Top Poster Presentation, Front Range Neuroscience Group
2013 – 2016	AAAS/Science Program for Excellence in Science
2013	Outstanding Graduate Student Presentation, *28th Annual University of Colorado Research Forum, Aurora, CO*
2014	Travel Award *Association for Chemoreception Sciences Annual Meeting*
2014	Outstanding Graduate Student Presentation *29th Annual University of Colorado Research Forum, Aurora, CO*
2014	Top Student Poster Presentation *Front Range Neuroscience Group (SfN Chapter)*

C. Contributions to Science

1. *Disruption of neural circuit function in autism:* Rett syndrome is a developmental cognitive disorder caused by mutations to the gene MECP2. The focus of my research was to understand the role MECP2 plays in the development of GABAergic synapses in the thalamus of a *Mecp2*-null mouse model. Initially, I learned immunohistochemical techniques to label and quantify the number of GABAergic synapses present at distinct thalamic nuclei. Work on this project sparked my interest in *in vitro* slice electrophysiology, as I began to learn whole-cell electrophysiological techniques. Beyond learning a variety of laboratory techniques, I was able to obtain skills necessary for thoughtful experimental design as well as data analysis. The work I completed contributed to our understanding of neural dysfunction in Rett syndrome pathophysiology and was published in the *Journal of Neurophysiology*.

a. Zhang ZW, **Zak JD**, Liu H (2010) MeCP2 is required for normal development of GABAergic circuits in the thalamus. ***Journal of Neurophysiology***, May 1; 103(5):2470-81. PMCID: PMC2867574.

2. *Signal filtering in the olfactory system:* As a doctoral student in Prof. Nathan Schoppa's laboratory at the University of Colorado Anschutz Medical Campus, my scientific interest shifted toward systems neuroscience and the physiological basis of sensory processing. In Prof. Schoppa's laboratory, my initial work focused on electrical shunting through gap junction-coupled neural networks. I then developed a thesis regarding the specialized synaptic signaling within olfactory bulb glomeruli, where I found that the intrinsic cellular properties of neurons that comprise these structures are uniquely positioned to function as a filter for incoming sensory information. Furthermore, I discovered that glomerular filtering could be modulated by group II metabotropic glutamate receptors, thus expanding its input/output properties. My studies in Prof. Schoppa's laboratory resulted in four manuscripts, which together, describe how sensory information is processed at its earliest stages.

a. Gire DH, Franks KM, **Zak JD**, Tanaka KF, Whitesell JD, Mulligan AA, Hen R, Schoppa NE (2012) Mitral cells in the olfactory bulb are mainly excited through a multistep signaling path. ***Journal of Neuroscience***, Feb 29; 32(9):2964-75. PMCID: PMC3467005.

b. **Zak JD**, Whitesell JD, Schoppa NE (2015) Metabotropic glutamate receptors promote disinhibition of olfactory bulb glomeruli that scales with input strength. ***Journal of Neurophysiology***, Mar 15; 113(6):1907-20. PMCID: PMC4359998.

c. **Zak JD** (2015) A computational framework for temporal sharpening of stimulus input in the olfactory system. ***Journal of Neurophysiology***, Sept 2; 115(4):1749-1751. PMCID: PMC4359998.

d. Gire DH**, **Zak JD****, Bourne JN, Goodson N, Schoppa NE (2019) Balancing extrasynaptic excitation and inhibition within olfactory bulb glomeruli. ***eNeuro,*** Aug 7; 6(4):ENEURO.0247-19.19. PMCID: PMC6709216 **Equal Contribution

e. **Zak JD**, Schoppa NE (2021) Optical manipulations reveal strong reciprocal inhibition but limited recurrent excitation within olfactory bulb glomeruli. ***eNeuro,*** DOI: 10.1101/2021.07.21.453150

f. **Zak JD**, Schoppa NE (2022) Neurotransmitter regulation rather than cell-intrinsic properties shape the high-pass filtering properties of olfactory bulb glomeruli. ***Journal of Physiology***, DOI: 10.1101/2021.09.04.46037

3. *Information coding in olfactory receptor neurons:* In the early phase of my postdoc in Prof. Murthy's laboratory, I began to develop ideas and experimental approaches regarding sensory input to the olfactory system. My studies in Prof. Murthy's laboratory have resulted in two manuscripts to date. As part of the studies proposed in a prior NIH fellowship, in collaboration with Prof. Massimo Vergassola at the University of California, San Diego, I constructed a model describing antagonistic odor-mixture interactions in olfactory receptor neurons that function to normalize input to the olfactory bulb. Within the next year, I will complete a companion manuscript that provides experimental validation for the published model. I recently completed a study that explores the role of the calcium-activated chloride channels (CaCCs) in olfactory transduction, which revealed that, in addition to amplifying transduction currents in olfactory receptor neurons, CaCCs further induce a potent depolarization inactivation of sodium channels to shunt excitation when receptor neurons receive sufficient input. Together the results of these studies provide new insight into how information is encoded by olfactory receptor neurons. The training plan within this application will provide me the opportunity to continue my training in systems neuroscience while providing me the opportunity to expand my intellectual, technical, and analytical repertoire.

a. Reddy G**, **Zak JD****, Vergassola M, Murthy VN. (2018) Antagonism in olfactory receptor neurons and its implications for the perception of odor mixtures. ***eLife,*** Apr 24*;* 7:e34958 PMCID: PMC5915184. **Equal Contribution

b. **Zak JD**, Grimaud J, Li R-C, Lin C-C, Murthy VN. (2018) Calcium-activated chloride channels clamp odor-evoked spike activity in olfactory receptor neurons. ***Scientific Reports,*** Jul 13; 8(1):10600. PMCID: PMC6045664.

c. Albeanu DF, Provost AC, Agarwal P, Soucy E, **Zak JD**, Murthy VN (2018) Olfactory marker protein (OMP) regulates formation and refinement of the olfactory glomerular map. ***Nature Communications,*** Nov 29; 9:5073. PMCID: PMC6265328.

d. **Zak JD**, Reddy G, Vergassola M, Murthy VN. (2020) Antagonistic interactions are widespread in freely-breathing mice. ***Nature Communications,*** Jul 3; 11:3350. PMCID: PMC7335155

e. **Zak JD**. (2022) Longitudinal imaging of individual olfactory sensory neurons in situ. ***Frontiers in Cellular Neuroscience***, July 22, 16:946816 PMCID: PMC9354957

Complete List of Published Work in MyBibliography:
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BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
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NAME: Leslie M. Kay

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

POSITION TITLE: Professor in Psychology and Deputy Dean for Research in the Social Sciences

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
St. John's College, Santa Fe, NM	BA	05/1983	Philosophy and Mathematics (Liberal Arts / Classics)
University of California at Berkeley, Berkeley CA	PhD	11/1995	Biophysics
California Institute of Technology, Pasadena CA	Postdoc	05/2000	Biology & Computational Neuroscience

A. Personal Statement

My career has focused on olfactory behavioral electrophysiology and olfactory psychophysics in small rodents. This includes the influence of olfactory bulb dynamics on cognition. My laboratory studies neurophysiology at the level of system dynamics (local field activity in multiple areas), at the single unit level within the olfactory bulb, and behavioral determination of these effects. My graduate and postdoctoral training at UC Berkeley (Walter J. Freeman) and Caltech (Gilles Laurent) gave me a broad foundation in population dynamics, single unit recording analysis, and comparative approaches across species. I have continued this broad focus in my laboratory at the University of Chicago over the past 22 years. My laboratory specializes in detailed analysis of odor discrimination behavior, odor psychophysics, and electrophysiology of the central olfactory system during odor discrimination learning and performance. I am one of the leaders in the study of olfactory oscillations and contextual modification of early olfactory processing, having begun this work as a graduate student (Kay & Freeman, 1998) and postdoc (Kay and Laurent, 1999). Importantly for this project, my work also addresses the role that the olfactory system plays in multisensory cognition, memory and cognitive health and dysfunction.

1. **Kay, L.M.** and Sherman, S.M. (2006) Argument for an olfactory thalamus. *Trends in Neurosciences,* 30(2):47-53. [This paper selected as recommended reading by Faculty of 1000] [PMID: 17161473]
2. **Kay, L.M.**, Beshel, J., Brea, J., Martin, C., Rojas-Líbano, D. & Kopell, N. (2009) Olfactory oscillations: the what, how and what for, *Trends in Neurosciences*, 32(4): 207-214. [PMC3389991]
3. Heck, D.H., Kozma, R. & **Kay, L.M.** (2019) The rhythm of memory: how breathing shapes memory function. *J Neurophys*, 122(2): 563-571. [PMID: 31215344] [PMC6734396]
4. **Kay, L.M.** (2022) COVID-19 and olfactory dysfunction: a looming wave of dementia? *J Neurophys*, 128: 436-444. https://journals.physiology.org/doi/full/10.1152/jn.00255.2022

B. Positions and Honors

Positions and Employment

1982-85 Summer Intern & Post Bac Researcher, GenBank, Group T10, Los Alamos Natl. Laboratory, NM
1985-86 Graduate Student Researcher, University of California, Berkeley
1986-88 Programmer/Analyst, Applied Risk Management, Oakland, CA
1988 Scientific Reviewer, GenBank, Intelligenetics, Mountain View, CA
1988-90 Sr. Programmer/Analyst, Applied Risk Management, Oakland, CA
1991-95 Graduate Student Researcher, University of California, Berkeley

1995-00 Postdoc Fellow in Biology & Computational Neuroscience, Caltech; Sr. Postdoc Fellow 1998-2000
2000-08 Assistant Professor, Department of Psychology and The College, The University of Chicago
2000- Graduate Committees on Computational Neuroscience and Neurobiology
2008-14 Director, Institute for Mind & Biology, UChicago
2008-15 Associate Professor, Department of Psychology and The College, UChicago
2014-16 Chair, Integrative Neuroscience in the Dept. of Psychology
2015- Member, Grossman Inst. for Neuroscience, Quantitative Biology and Human Behavior, UChicago
2015- Professor, Department of Psychology and The College, UChicago
2017-23 Member, Board of Visitors and Governors, St. John's College, Annapolis & Santa Fe (Chair: Task Force on Diversity and Inclusion for SJC)
2019 Visiting Tutor (Prof), St. John's College, Santa Fe, NM (on leave from UChicago)
2020-22 Director of Graduate Studies, Department of Psychology, The University of Chicago
2022- Deputy Dean for Research in the Social Sciences, UChicago

Other Experience
2004,06 National Science Foundation Advisory Panels on Computational Neuroscience and IOS
2004-06 Program committee for the Organization for Computational Neuroscience annual meeting
2004+ NSF Advisory Panels on Computational Neuroscience and IOS (2004, 2006, 2015, 2016)
2006-09 Board member of the Organization for Computational Neuroscience
2006-16 Editorial Board for Cognitive Neurodynamics, Springer, Netherlands
2007 NSF-Santa Fe Institute advisory meeting on "Brain Science at the Interface of Biological, Physical and Mathematical Sciences, Computer Science, and Engineering: Analysis of New Opportunities"
2007-15 Program committee for the International Conference on Cognitive Neurodynamics (odd years)
2009,11 Site Review Committee, NICHD, October 2009, December 2011, 2013
2008- Consulting editor for Behavioral Neuroscience
2020-22 Counselor, Assoc. for Chemoreception Sciences
2018-22 NIH Study section member, Chemosensory Systems (CSS)
2020- Editorial Board, Chemical Senses
2020- Associate Editor, Journal of Neurophysiology

Professional Memberships
American Association for the Advancement of Science (AAAS); American Physiological Society (APS); Association for Chemoreception Sciences (AChemS); Society for Neuroscience (SFN)

Honors
1981 Annual Mathematics Prize, St. John's College
1982 Bromwell Ault Memorial Scholarship for Academic Excellence, St. John's College
1985 University of California Graduate Fellowship
1986 University of California Graduate Fellowship (declined)
1991-93 USPHS Training Grant in Integrative Biology
1993 NSF Travel Grant to NATO Advanced Study Institute
1995-98 Sloan Foundation Postdoctoral Fellowship in Theoretical Neurobiology
1998-00 Burroughs-Wellcome Computational Molecular Biology Fellowship
2013 Alumni Award of Merit, St. John's College, Santa Fe, NM

C. Contributions to Science

Mechanisms and features of olfactory system oscillations. Several studies have shown and replicated the involvement of gamma oscillations in discriminating very similar odorants (Nusser et al., 2001; Beshel et al., 2007; replicated in Frederick, et al., 2016). Gamma oscillations rely on the reciprocal synapse between mitral and granule cells in the OB. We challenged conventional models that are based on spiking in both neural populations and produced a model based on graded release of GABA from granule cell dendrites (Brea et al, 2009). Our modeling efforts focus on granule cell excitability gating a transition from gamma to beta oscillations (Osinski & Kay, 2016). We have verified model predictions in pharmacological studies (Osinski et al, 2017).

1. Nusser, Z., **Kay, L.M.**, Laurent, G., Homanics, G.E., Mody, I. (2001) Disruption of $GABA_A$ receptor mediated inhibition of GABAergic interneurons leads to increased synchrony of the olfactory bulb network. *J Neurophys* 86(6): 2823-2833. [PMID: 11731539]

2. Brea, J., **Kay, L.M.** and Kopell, N. (2009) Biophysical model for gamma rhythms in the olfactory bulb via subthreshold oscillations. *PNAS*, 106(51): 21954-21959. [PMID: 19996171] [PMC2799880]
3. Osinski, B and **Kay, L.M.** (2016) Granule cell excitability mediates gamma and beta oscillations in model of the dendrodendritic microcircuit. *J Neurophys*, 116(2): 522-539. [PMID: 27121582] [PMC4978795]
4. Osinski, B., Kim, A., Xiao, W., Mehta, N.M., and **Kay, L.M.** (2018) Pharmacological manipulation of the olfactory bulb granule cell modulates beta oscillations: testing model predictions. *J Neurophysiology*, 120(3): 1090-1106. [PMID: 29847235] [PMC6171064] https://doi.org/10.1152/jn.00090.2018

Contextual modification of early stage cortical sensory processing. We have shown at the single unit (Kay and Laurent, 1999) and neural population levels that the context of a sensory stimulus can reconfigure low level sensory representations, even at the level of sniffing behavior. Rats modulate coherence among OB cells as represented in fast cortical oscillations gamma (local field potential/LFP, 40-110 Hz in rats), depending on odor discrimination difficulty (Beshel et al., 2007). Midrange frequency beta oscillations (~20Hz) engage wide areas of the brain, including the hippocampus, as rats learn odor discriminations (Martin et al., 2007). We have examined in parallel go/no-go and 2-alternative choice tasks and show that rats sniff longer in go/no-go, and in both tasks they integrate information over time, adjusting sampling with discrimination difficulty (Frederick et al., 2017). Network modes, defined by changes in neural oscillations, are modified by task, odor, difficulty of discrimination, prior learning status, and the number of tasks that the rats know (Frederick et al, 2016).

5. Beshel, J., Kopell, N. and **Kay, L.M.** (2007) Olfactory bulb gamma oscillations are enhanced with task demands. *Journal of Neuroscience*, 27(31): 8358-8365 [PMID: 17670982].
6. Martin, C., Beshel, J. and **Kay, L.M.** (2007) An olfacto-hippocampal network is dynamically involved in odor discrimination learning. *Journal of Neurophysiology*, 98(4): 2196-2205 [PMID: 17699692].
7. Frederick, D.E., Vujovic, M., Brown, A., Mehta, N., and **Kay, L.M.** (2016) Gamma and beta oscillations define a sequence of neurocognitive modes present in odor processing, *Journal of Neuroscience*, 36(29): 7750-7767. [PMID: 27445151] [PMC4951578]
8. Frederick, D.E., Brown, A., Tacopina, S., Mehta, N., Vujovic, M., Brim, E. Amina, T., Fixsen, B., and **Kay, L.M.** (2017) Task dependent behavioral dynamics make the case for temporal integration in multiple strategies during odor processing. *Journal of Neuroscience*, 37(16): 4416-4426. [PMID: 28336570] [PMC3144557]

Sniffing and hippocampal theta rhythms. Respiratory drive to the OB via receptor neurons in the nasal sensory epithelium produces a respiratory-linked rhythm in the OB (Rojas-Líbano, et al., 2014) that can be further tracked into downstream brain regions, including the hippocampus. Rats modulate the way that they sniff an odor dependent on the physical properties of the odors that they seek in a mixture (Rojas-Libano & Kay, 2012), and sniffing rhythms couple with hippocampal theta rhythms according to the degree to which a rat can perform a difficult odor discrimination task (Kay, 2005). Recent work shows coupling of hippocampal theta and respiratory rhythms among olfactory, hippocampal and visual cortical areas (Sheriff et al., 2021). Coupling patterns depend on spatial context (olfactory or visual) and may scaffold multisensory cognitive processing.

9. **Kay, L.M.** (2005) Theta oscillations and sensorimotor performance. *Proc Natl Acad Sci U S A* 102(10): 3863-3868 [PMID: 15738424] [PMC553293].
10. Rojas-Líbano, D. and **Kay, L.M.** (2012) Interactions between odorant sorptiveness and sniffing behavior in olfactory learning and perception. *J Neurosci*, 32(44):15577-89. [PMID: 23115193] [PMC3495330].
11. Rojas-Líbano, D., Frederick, D.E., Egaña, J.I. and **Kay, L.M**. (2014) The olfactory bulb theta rhythm follows all frequencies of diaphragmatic respiration in the freely behaving rat. *Frontiers in Behavioral Neuroscience*, 8:214. [PMID: 24966821] [PMC4053074]
12. Sheriff A, Pandolfi G, Nguyen VS, Kay LM. (2021) Long-range respiratory and theta oscillation networks depend on spatial sensory context. *J Neurosci*, 41(48):9957-9970. [PMID: 34667070] [PMC8638692].

Odor Mixture psychophysics and physiology. Despite centuries of research into odor mixture quality, we can't predict what two monomolecular odorants will smell like in a mixture. In some cases, mixtures smell like both components (elemental percept), in others like one component (overshadowing) and in many like neither component (configural or synthetic percept). We have tested this theory behaviorally in several studies, first verifying some of its predictions (Kay et al., 2003), and later modifying (Kay et al., 2005) and finally falsifying it (Frederick et al., 2009). We also tested the overlap theory using combined behavior and imaging in mice (Grossman et al., 2008).

13. **Kay, L.M.**, Lowry, C.A., Jacobs, H.A. (2003) Receptor contributions to configural and elemental odor mixture perception. *Behavioral Neuroscience* 117(5): 1108-1114. [PMID: 14570560]
14. **Kay, L.M.**, Crk, T. and Thorngate, J. (2005) A redefinition of odor mixture quality. *Behavioral Neuroscience* 119(3): 726-733. [PMID: 15998193]
15. Grossman, K.J., Mallik, A.K., Ross, J., **Kay, L.M.**, Issa, N.P. (2008) Glomerular activation patterns and the perception of odor mixtures, *European Journal of Neuroscience*, 27(10): 2676-2685. [PMID: 18445053]
16. Frederick, D. E., Barlas, L., Ievins, A., & **Kay, L.M.** (2009) A critical test of the overlap hypothesis for odor mixture perception. *Behavioral Neuroscience*, 123(2): 430-437 [PMID: 19331465].

Olfactory bulbectomy and interactions between the olfactory system, biological rhythms and affective systems. The olfactory system is implicated in most disorders that produce dementia or affective symptoms and has strong influences on limbic and hypothalamic structures. A series of studies in collaboration with Brian Prendergast have quantified seasonally varying affective responses in rats (Prendergast and Kay, 2008) and the variability of olfactory bulb influences (using olfactory bulbectomy) on seasonality across species (Prendergast et al., 2008). In another study, we used olfactory bulbectomy to test a new fast-acting antidepressant that targets the Serotonin 2C receptor (Opal et al., 2014). Newer work on biological rhythms addresses ultradian rhythmicity (Prendergast et al., 2015).

17. Prendergast, B.J. and **Kay, L.M**. (2008) Affective and adrenocorticotrophic responses to photoperiod in Wistar rats, *Journal of Neuroendocrinology*, 20(2): 261-267. [PMID: 18047552]
18. Prendergast, B.J., Pyter, L. M., Galang, J., & **Kay, L. M.** (2008). Reproductive responses to photoperiod persist in olfactory bulbectomized Siberian hamsters (*Phodopus sungorus*). *Behavioural Brain Research*, 198(1):159-164. [PMID: 19027041] [PMC2661624]
19. Opal, M.D., Klenotich, S.C., Morais, M., Bessa, J., Winkle, J., Doukas, D., **Kay, L.J.**, Sousa, N., and Dulawa, S.M. (2014) Serotonin 2C receptor antagonists induce fast-onset antidepressant effects. *Molecular Psychiatry*, 19(10): 1106-1114. *[Note: incorrect author initials Kay, L.J. should be Kay, L.M.]* [PMID: 24166413]
20. Prendergast, B.J., Cable, E.A., Stevenson, T.J., Onishi, K.G., Zucker, I., and **Kay, L.M.** (2015) Circadian disruption alters the effects of lipopolysaccharide treatment on circadian and ultradian locomotor activity and body temperature rhythms of female Siberian hamsters. *Journal of Biological Rhythms*, 30(6): 543-556. [PMID: 26566981] [PMC4900458]

Complete list of publications:
https://www.ncbi.nlm.nih.gov/sites/myncbi/leslie.kay.1/bibliography/41148374/public/?sort=date&direction=descending

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

Big Ideas Generator (B.I.G.) Seed Grant (UChicago) for COVID-19, *Tracking SARS-CoV-2 in the central olfactory system* w/Jay Pinto ($10,000)

Multisensory Cognition in the Nose: Interactions between Olfactory and Trigeminal Senses; Research Collaboration between UChicago and CNRS, collaborative proposal with Claire Martin University of Paris. 2020-24

R01 DC014367 *CRCNS: Dynamical mechanisms of oscillation transitions in the olfactory system* (PI; $1.9 million; CoInvestigator- Thomas Cleland, Cornell) 7/14 - 6/21

DARPA HR0011-18-2-0024: *Context-dependent reconfiguration of an intelligent neural system* 2/18 - 1/20 (PI; $1.2 million; subawards: Christiane Linster-Cornell and Risto Miikkulainen-UT Austin)

Big Ideas Generator (B.I.G.) Seed Grant, University of Chicago. *Redefining sensory information in perceiving brains* ($45,790) 4/15 - 6/16

R01 DC07995 *CRCNS-Multiple olfactory gamma oscillations: roles in sensation and attention*, (PI; Total $1,329,289) 8/05 - 7/11

VP for Research Seed Grant, U of Chicago, *Smelling time: olfactory, visual and auditory interactions in humans* (PI: $8,191) 7/12 - 6/13

Predoctoral NRSA to Jennifer Beshel (graduate student award) 9/06 - 3/08