Neuro101X: Stress Resilience and Susceptibility: Mechanisms & Models
Fall 2023 – Spring 2024
Mondays 6:00 PM – 7:15 PM, Location TBA

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Course Description:
Understanding the mechanisms and factors driving resilience or susceptibility to stress is critical for improving psychiatric patient healthcare and quality of life. Stress affects the brain starting prenatally, and thus is a major risk factor for the development of psychiatric and neurological disorders. Although all of us experience stress – whether episodically or chronically, traumatic or otherwise, from psychosocial or physiological sources – not all of us will be diagnosed with Major Depressive Disorder, Generalized Anxiety Disorder, or Post-Traumatic Stress Disorder. This course describes the genetic, molecular, cellular, physiological, and brain circuitry mechanisms that determine how our brains respond to stressors. Focusing on preclinical and animal models, we learn to read and interpret high-impact, primary research journal articles written by the top investigators in this field. Through these examples, we learn how cutting-edge neuroscience methods and techniques such as RNA-sequencing, epigenetic profiling, optogenetics, chemogenetics, and calcium imaging have informed our understanding of stress resilience and susceptibility. With a combination of student-led journal club presentations, brief instructor lectures, class discussions, and written assignments such as research proposals, we develop an understanding of why stress affects us so heterogeneously and what future research can do about it.

Prerequisites:
- MCB/Neuro 80: Neurobiology of Behavior, permission of instructor

Learning Objectives:
- Understand how molecular mechanisms build to behavioral outcomes during and after stress
- Understand and critically evaluate the animal models and techniques used to study stress
- Understand the future priorities of translational neuroscience research
- Interpret and critically evaluate primary research articles
- Efficiently and effectively communicate experimental design, methods, results, and conclusions
- Engage in respectful and constructive discussions

Course Materials:
- No textbook purchase is required for this class
- Instructor will provide PDFs of scientific journal review articles and primary research articles

Course Format:
In a typical meeting, a pair of students will present a scientific journal article in “journal club” format to the class for 50 minutes. You will be responsible for creating and presenting slides featuring and explaining the background, methods, figures, results, and conclusions of the paper. The rest of the class will ask questions to better understand the study and engage in discussion to critically evaluate its rigor, validity, impact, and implications. I will conduct the very first “journal club” myself to set an example on the second week of class, after students have had a chance to read the paper. Afterwards, students will ease into their understanding of high-impact research articles by collaborating in pairs. The students not presenting that week will all be required to submit written assignments that confirm they have done the assigned reading and spent some time thinking critically about it before even

coming to class. You can then share their critiques (positive and negative!) of the paper in group discussion, facilitated and guided by me when necessary. To prepare you for the required reading – both review and research – each week, the last 25 minutes of each class will be a brief, instructor-led lecture to ensure everyone has the same foundational knowledge and refresh prerequisite course material. Finally, in both semesters, students will put together their own miniature research proposals. First, they will submit a single page with two specific aims as a midterm. Then for their final project, they will expand on that in a 2-to-3-page detailed research proposal and slideshow presentation for the class.

Course Policies and Expectations:

- Late work: In unexpected and unusual circumstances, giving the instructor advanced notice may result in a due date extension. Otherwise, written assignments will be penalized 10% each day after the due date.
- Academic integrity: Science is intrinsically collaborative. Students are welcome to work together outside of class to better understand the readings and brainstorm if they explicitly give each other credit for that discussion in written assignments. Written work must be completed independently, however, and plagiarism will not be tolerated. Students must adhere to the Harvard College Honor Code.
- Artificial Intelligence: This course is intended to cultivate and nurture independent and critical thinking. Using ChatGPT or any other generative artificial intelligence tools for ideas, writing, or any other work for this class is explicitly disallowed. Violations of this policy are considered academic misconduct and will not be tolerated.
- Attendance: Each student is allowed one unexcused and one excused absence per semester. Assignments are due on the day of class regardless of absence unless a due date extension has been agreed to as described above.
- Participation: Students are expected to be curious, engaged, and respectful of each other and the instructor. Questions, comments, and responses during class discussion should facilitate the discussion's progress and everyone's intellectual development.
- Accommodations: Students needing any accommodations must inform the instructor as soon as possible for implementation. All such discussions will be confidential except for any necessary involvement of the Accessible Education Office.
- Office hours: Office hours times, location, and Zoom link are TBD.

Workload & Grading:

Semester	Timing	Work	% of Grade	Estimated Workload Hours
Both	Weekly	Reading & Writing	20	4
		Participation	10	in-class
	2x/term	Presentations	20	4
	Midterm	Specific Aims	15	12
	Final	Proposal	20	12
		Presentation	15	12

Work	Description	Grading Rubric

Article Response Writing	• 1-page:
	  ○ succinct description of the research conclusions and implications
	  ○ critique of strengths and weaknesses
	  ○ suggest one additional experiment to support authors' claims
	  ○ suggest one future direction experiment to build on authors' claims
		• Efficient and clear communication
		• Includes each required component
		• Refers to principles or information from assigned review articles
		• Thoughtful and creative suggestions
		• Respectful to authors' work
		• Demonstrates critical thinking skills
		• Understanding of the bigger picture

Participation	• Ask questions • Critique research • Voice skepticism • Share new ideas	• Provides thoughtful commentary that contributes, enhances, and drives discussion forward • Respectful of colleagues

Article Presentation	• Prepare and present slides with
	  ○ background information
	  ○ introduction
	  ○ methods
	  ○ results
	  ○ conclusions
		• Presents each required component
		• States hypothesis & conclusions
		• Explains logical flow of paper
		• Fills allotted time; understandable pace
		• Able to answer audience questions
		• Does not rely on slide text

Midterm Specific Aims	• 1-page summary of "Specific Aims"
	  ○ introduction, background
	  ○ justification
	  ○ hypothesis
	  ○ two distinct experiments
		• Efficient and clear communication
		• Includes each required component
		• Logical foundation for proposed research
		• Reasonable hypothesis
		• Uses methods learned in class
		• Demonstrates clear understanding
		• All references cited

Final Written Proposal	• 2-page mini-grant
	  ○ introduction, background
	  ○ justification
	  ○ hypothesis
	  ○ methods
	  ○ expected results
	  ○ expected conclusion
	  ○ pitfalls & alternatives
		• Efficient and clear communication
		• Includes each required component
		• Logical foundation for proposed research
		• Reasonable hypothesis
		• Uses methods learned in class
		• Graphs/figures/diagrams clear & labeled
		• Demonstrates clear understanding
		• All references cited

Final Proposal Presentation	• Prepare and present slides on mini-grant
	  ○ introduction, background
	  ○ justification
	  ○ hypothesis
	  ○ methods
	  ○ expected results
	  ○ expected conclusion
	  ○ pitfalls & alternatives
		• Presents each required component
		• Clear, logical hypothesis
		• Explains techniques/methods
		• Does not rely on slide text
		• Graphs/figures/diagrams clear & labeled
		• Fills allotted time; understandable pace
		• Able to answer audience questions
		• Demonstrates clear understanding

Satisfactory (Fall Term)						Unsatisfactory (Fall Term)	
		B+	88.0 – 89.9	C+	78.0 – 79.9	D+	68.0 – 69.9
A	94.0 – 100.00	B	84.0 – 87.9	C	74.0 – 77.9	D	64.0 – 67.9
A-	90.0 – 93.9	B-	80.0 – 83.9	C-	70.0 – 73.9	D-	60.0 – 63.9

Tentative Course Schedule:

Class	Due	Journal Club	Required Reading	Optional Reading	Lecture Topic
1: 9/11					mood & anxiety disorders
2: 9/18		*(Instructor-led)* Gammi SC. Evaluation of animal model congruence to human depression based on large-scale gene expression patterns of the CNS. Scientific Reports. 2022.	Otte C. Major depressive disorder. Nature Reviews Disease Primers 2016.	Yehuda R. Post-traumatic stress disorder. Nature Reviews Disease Primers 2015. Vieta E. Bipolar disorders. Nature Reviews Disease Primers 2018.	genetics
3: 9/25		*(Instructor-led)* Wray NR. Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. Nature Genetics 2018.	Feder A. Psychobiology and molecular genetics of resilience. Nature Reviews Neuroscience 2009.	Zhang W. Biological subtyping of psychiatric syndromes as a pathway for advances in drug discovery and personalized medicine.	animal models to measure & induce stress
4: 10/2		Berton O. Essential role of BDNF in the mesolimbic dopamine pathway in social defeat stress. Science 2006.	Russo S. Neurobiology of resilience. Nature Neuroscience 2012.	Gururajan A. The future of rodent models in depression research. Nature Reviews Neuroscience 2019. Bale TL. The critical importance of basic animal research for neuropsychiatric disorders. Neuropsychopharmacology 2019.	transcription: factors, enhancers
10/9	Indigenous People's Day				
5: 10/16		Labonte B. Sex-specific transcriptional signatures in human depression. Nature Medicine 2017.	Krishnan V. The molecular neurobiology of depression. Nature 2008.		transcription: epigenetics
6: 10/23		How to write a specific aims page			
7: 10/30	Midterm	Kronman H. Long-term behavioral and cell-type-specific molecular effects of early life stress are mediated by H3K79me2 dynamics in medium spiny neurons. Nature Neuroscience 2021.	Sun H. Epigenetics of the depressed brain: role of histone acetylation and methylation. 2013.	Yim Y. In vivo locus-specific editing of the neuroepigenome. Nature Reviews Neuroscience 2020.	translation: miRNAs
8: 11/6		Issler O. MicroRNA 135 is essential for chronic stress resiliency, antidepressant efficacy, and intact serotonergic activity. Neuron 2014.	Allen L. MicroRNA mediators of early life stress vulnerability to depression and suicidal behavior. Molecular Psychiatry 2020.		translation: initiation factors
9: 11/13		Ota KT. BICC1 expression is elevated in depressed subjects and contributes to depressive behavior in rodents. Neurospychopharmacology 2015.	Febauer F. Molecular mechanisms of translational control. Nature Reviews 2004.		metabolism
10: 11/20		Lehmann ML. Behavioral sequelae of social defeat require microglia and are	Manji H. Impaired mitochondrial function in psychiatric disorders.		pre-synaptic

		driven by oxidative stress in mice. Journal of Neuroscience 2019.	Nature Reviews Neuroscience 2012.		
11: 11/27		*(Instructor-led)* Treccani G. Stress and corticosterone increase the readily releasable pool of glutamate vesicles in synaptic terminals of prefrontal and frontal cortex. Molecular Psychiatry 2014.	Sudhof TC. Neurotransmitter release: the last millisecond in the life of a synaptic vesicle. Neuron 2013.		post-synaptic
12: 12/4		Barrot M. CREB activity in the nucleus accumbens shell controls gating of behavioral responses to emotional stimuli. PNAS 2002.	Sanacora G. Stressed Synapse 2.0. Nature Reviews Neuroscience 2022.	McEwen B. Mechanisms of stress in the brain. Nature Neuroscience 2015.	Fall Term wrap-up discussion
13: 12/4		How to write a grant proposal			
14: 12/11	Slides	Presentations			
12/18	Proposals	No class			
Winter Break					
15: 1/22					neurotransmitters
16: 1/29		Heshmati M. Depression and social defeat stress are associated with inhibitory synaptic changes in the nucleus accumbens. Journal of Neuroscience 2020.	Duman RS. Altered connectivity in depression: GABA and glutamate neurotransmitter deficits and reversal by novel treatments. Neuron 2019.		neuron types
17: 2/5		Lobo MK. dFosB induction in striatal medium spiny neuron subtypes in response to chronic pharmacological, emotional, and optogenetic stimuli. Journal of Neuroscience 2013.	Francis TC. Emerging role for nucleus accumbens medium spiny neuron subtypes in depression. Biological Psychiatry 2017.		glia
18: 2/12		Koskinen MK: Node of Ranvier remodeling in chronic psychosocial stress and anxiety. Neuropsychopharmacology 2023.	Tsyglakova M. Immune mechanisms of stress susceptibility and resilience: Lessons from animal models.		glia
2/19	President's Day				
19: 2/26		Hodes GE. Individual differences in the peripheral immune system promote resilience versus susceptibility to social stress. PNAS 2014.	Wohleb ES. Integrating neuroimmune systems in the neurobiology of depression. Nature Reviews Neuroscience 2016.		physiology
20: 3/4	Midterm	Morel C. Midbrain projection to the basolateral amygdala encodes anxiety-like but not depression-like behaviors. Nature Communications 2022.	Lin M. Genetically encoded indicators of neuronal activity. Nature Neuroscience 2016.		physiology
3/11	Spring Break				

21: 3/18		*(Instructor-led)* Muir J. In vivo fiber photometry reveals signature of future stress susceptibility in nucleus accumbens. Neuropsychopharmacology 2018.	Hodes GE. Sex differences in vulnerability and resilience to stress across the life span. Biological Psychiatry 2019.		neuroanatomy
22: 3/25		Anacker C. Neuroanatomic differences associated with stress susceptibility and resilience. Biological Psychiatry 2016.	Russo S. The brain reward circuitry in mood disorders. Nature Reviews Neuroscience 2013.		circuitry
23: 4/1		Bagot RC. Ventral hippocampus afferents to the nucleus accumbens regulate susceptibility to depression. Nature Communications 2015.	Fox ME. Molecular and cellular mechanisms of depression: a focus on reward circuitry. Molecular Psychiatry 2019.	Muir J. Wiring the depressed brain: optogenetic and chemogenetic interrogation in animal models of depression. Neuropsychopharmacology 2019.	endocrinology
24: 4/2		McCullough KM. Blood levels of T-cell receptor excision circles provide an index of exposure to traumatic stress in mice and humans. Translational Psychiatry 2022.	Menard C. Immune and neuroendocrine mechanisms of stress vulnerability and resilience. Neuropsychopharmacology 2017.		pain, addiction
25: 4/8		Heller EA. Locus-specific epigenetic remodeling controls addiction- and depression-related behaviors. Nature Neuroscience 2014.	Baliki MN. Nociception, pain, negative moods, and behavior selection. Neuron 2015.	Elman I. Pain and suicidality: insights from reward and addiction neuroscience. Progress in Neurobiology 2016.	new medicine: ketamine
26: 4/15		Brachman RA. Ketamine as a prophylactic against stress-induced depressive-like behavior. Biological Psychiatry 2016.	Duman R. Synaptic plasticity and depression: new insights from stress and rapid-acting antidepressants. Nature Medicine 2016.		new medicine: aticaprant
27: 4/22		Jacobson ML. Kappa opioid receptor antagonist aticaprant reverses behavioral effects from unpredictable chronic mild stress in male mice.Psychopharmacology 2020.	Krystal AD. Randomized proof-of-mechanism trial applying the fast-fail approach to evaluating kappa-opioid antagonism as a treatment for anhedonia. Nature Medicine 2020.		
29: TBD		Presentations			
30: 5/6	Proposals	No class			