OEB 223 Topics in Neurogenetics

Description of the class:

The goal of the class is to achieve an advanced understanding of the molecular and neuronal mechanisms that regulate behavior. We will discuss some key findings in the field, as well as the cutting-edge techniques used in these studies. The topics include human olfaction, motivation, social behavior, sleep regulation, memory formation and extinction, and neurological disorders.

General information

Instructor:

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Teaching fellow:

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G4 graduate student, Department of Organismic and Evolutionary Biology

Meeting time:

One class (75 minutes) on every Wednesday 3pm-4:15pm

Meeting place:

NW B105

Office hour:

To be determined

Class format

The class meets once per week for 75 minutes. Each class consists of the following components:

A ~30-minute lecture from the instructor on the background of the topic,
A ~30-minute presentation from students (assigned at the beginning of the semester) on a selected paper,
~15-minute discussion of one selected paper participated by the class.

Grading and class guidelines

Grading (100 points in total)
Class attendance: 20 points
Homework: 20 points
Leading Discussion: 20 points
Primary presentation: 40 points

There is no Final Exam.
The final letter grades for the class:
A: 85-100 points;
B: 70-84 points;
C: 60-69 points;
Failed: < 60 points.

Class attendance:
All students should attend all classes. Permission from the instructor is needed in advance for missing a class.

1) If an assigned presentation will be missed due to unforeseen reasons, the assigned student presenter needs to work with the instructor and the TF to re-arrange the presentation. Otherwise, the assigned student presenter will lose half of the points for the primary presentation in the final grade (=20 points).

2) If a class without the presentation assignment will be missed, permission from the instructor is needed in advance. In this case, a make-up assignment (usually a three-page single-spaced assay on the selected paper) is required. Missing class without permission will reduce the final grade by 15 points.

Homework:
Home assignment will be uploaded on canvas on Thursday and students are expected to submit homework by the deadline indicated by the TF. Missing one homework assignment will reduce the final grade by 10 points and missing a homework deadline will reduce 10 points for the homework (100 points in total for each homework).

Leading Discussion:
A student will obtain up to 20 points by leading the discussion of one paper presented by other student presenters. It is a good idea for each student that leads the discussion to prepare 2 discussion points/questions and prepare comments and thoughts about them in order to interact with the class during the discussion and share the thoughts and insights with the class. Please feel free to get in touch with the instructor if you have questions on how to prepare to lead the discussion.

Primary presentation:
Each presentation for the selected papers is scheduled for 30 minutes and is expected to include introduction, methods, results and interpretation, impacts and future direction of the study. Student presentations start on Week III.

Syllabus

There will be no student presentation for the first and the second class. TF will present during these two weeks.

The papers for presentation are underlined.

Part I Genes and neural circuits of Behavior

Week I

Genes and neural circuits of Behavior I: Introduction to neurogenetics

Learning goals:
1) A brief overview of the class on learning objectives, class format and the topics.
2) Discussion on genetic underpinnings for interaction between humans and insects.

Reading materials:
TF will present the paper.

1. Blau N, van Spronsen FJ, Levy HL. Phenylketonuria. Lancet 376(9750):1417-27 (2010).

2. McBride CS, Baier F, Omondi AB, Spitzer SA, Lutomiah J, Sang R, Ignell R and Vosshall LB. Evolution of mosquito preference for humans linked to an odorant receptor. Nature 515, 222–227 (2014).

3. De Obaldia ME, Morita T, Dedmon LC, Boehmler DJ, Jiang CS, Zeledon EV, Cross JR, Vosshall LB. Differential mosquito attraction to humans is associated with skin-derived carboxylic acid levels. Cell 185(22):4099-4116 (2022).

4. **Dennis EJ, Dobosiewicz M, Jin X, Duvall LB, Hartman PS, Bargmann CI, Vosshall LB. A natural variant and engineered mutation in a GPCR promote DEET resistance in C. elegans. Nature 562(7725):119-123 (2018).**

Week II

Genes and neural circuits of Behavior II: Combining multiple genetic approaches

Learning goals:
1) The vertebrate olfactory system.
2) Combining multiple genetic approaches to understand olfaction under normal and disease conditions.

Presentations and Readings:
TF will present the paper.

1. Buck L, Axel R. A novel multigene family may encode odorant receptors: a molecular basis for odor recognition. Cell 65:175-87 (1991).

2. Mombaerts, P. Genes and ligands for odorants, vomeronasal and taste receptors. Nat. Rev. Neurosci. 5, 263-278 (2004).

3. Khan M et al. Visualizing in deceased COVID-19 patients how SARS-CoV-2 attacks the respiratory and olfactory mucosae but spares the olfactory bulb. Cell 184(24):5932-5949 (2021).

4. **Zazhytska M, Kodra A, Hoagland DA, Frere J, Fullard JF, Shayya H, McArthur NG, Moeller R, Uhl S, Omer AD, Gottesman ME, Firestein S, Gong Q, Canoll PD, Goldman JE, Roussos P, tenOever BR, Jonathan B Overdevest, Lomvardas S. Non-cell-autonomous disruption of nuclear architecture as a potential cause of COVID-19-induced anosmia. Cell 185(6):1052-1064 (2022).**

Week III

Genes and neural circuits of Behavior III: Optogenetics

Learning goals:
1) How does optogenetics work?
2) Dissecting neural circuits of complex behaviors using optogenetics.

Presentations and Readings:
Student presentation starts this week.

Future presentations will be assigned on this class.

1. Nagel G, Szellas T, Huhn W, Kateriya S, Adeishvili N, Berthold P, Ollig D, Hegemann P, Bamberg E. Channelrhodopsin-2, a directly light-gated cation-selective membrane channel. Proc Natl Acad Sci USA, 100(24):13940-5 (2003).

2. Boyden ES, Zhang F, Bamberg E, Nagel G, Deisseroth K. Millisecond-timescale, genetically targeted optical control of neural activity. Nat. Neurosci. 8(9):1263-1268 (2005).

3. Lima SQ and Miesenböck G. Remote control of behavior through genetically targeted photostimulation of neurons. Cell 121(1):141-52 (2005).

4. **Siciliano CA, Noamany H, Chang CJ, Brown AR, Chen X, Leible D, Lee JJ, Wang J, Vernon AN, Vander Weele CM, Kimchi EY, Heiman M, Tye KM. A cortical-brainstem circuit predicts and governs compulsive alcohol drinking. Science 366(6468):1008-1012 (2019).**

Week IV

Genes and neural circuits of Behavior IV: Host-pathogen interaction

Learning goals:
1) Pathogen infection alters host behavior.
2) The mechanisms underlying pathogen-induced host behavioral changes.

Presentations and Readings:
Student presentation (two relatively short papers)

1. Vyas A. Mechanisms of Host Behavioral Change in Toxoplasma gondii Rodent Association. PLoS pathogens 11(7): e1004935 (2015).

2. Berdoy M, Webster JP and Mcdonald DW. Fatal attraction in rats infected with Toxoplasma gondii. Proc. R. Soc. B: Biol. Sci. 267, 1591–1594 (2000).

3. Poirotte, C. et al. Morbid attraction to leopard urine in toxoplasma-infected chimpanzees. Curr. Biol. 26, R98-R99, https://doi.org/10.1016/j.cub.2015.12.020 (2016).

4. Gering E, Laubach ZM, Weber PSD, Soboll Hussey G, Lehmann KDS, Montgomery TM, Turner JW, Perng W, Pioon MO, Holekamp KE, Getty T. Toxoplasma gondii infections are associated with costly boldness toward felids in a wild host. Nat Commun. 12(1):3842. doi: 10.1038/s41467-021-24092-x (2021).

5. **Wang ZT, Harmon S, O'Malley KL, Sibley LD. Reassessment of the role of aromatic amino acid hydroxylases and the effect of infection by Toxoplasma gondii on host dopamine levels. Infection and immunity 83(3), 1039-1047 (2015).**

6. **Hari Dass SA, Vyas A. Toxoplasma gondii infection reduces predator aversion in rats through epigenetic modulation in the host medial amygdala. Molecular ecology. 2014; 23(24):6114–22.**

Week V

Genes and neural circuits of Behavior V: Genetic encoding of behavior

Learning goals:
1) *Drosophila* as a model organism for behavioral studies.
2) Dissecting neural circuits for behavior and evolution in *Drosophila*.

Presentations and Readings:
Student presentation

1. Vosshall LB. Into the mind of a fly. *Nature*. 450, 193-197 (2007). Review.

2. Yapici N, Cohn R, Schusterreiter C, Ruta V, Vosshall LB. A Taste Circuit that Regulates Ingestion by Integrating Food and Hunger Signals. Cell 165(3):715-29 (2016).

3. Pan Y, Baker BS. Genetic identification and separation of innate and experience-dependent courtship behaviors in Drosophila. Cell 156(1-2):236-48. doi: 10.1016/j.cell.2013.11.041 (2014).

4. Wang K, Wang F, Forknall N, Yang T, Patrick C, Parekh R, Dickson BJ. Neural circuit mechanisms of sexual receptivity in Drosophila females. Nature 589(7843):577-581 (2021).

5. **<u>Seeholzer LF, Seppo M, Stern DL, Ruta V. Evolution of a central neural circuit underlies Drosophila mate preferences. Nature 559(7715):564-569 (2018).</u>**

Week VI

Genes and neural circuits of Behavior VI: Genetic encoding of social behavior

Learning goals:
1) Mouse as a model system for studying genes for behavior.
2) Genetic basis for social behavior in mice.

Presentations and Readings:
<u>Student presentation</u>

1. Ferguson JN, Young LJ, Hearn EF, Matzuk MM, Insel TR, Winslow JT. Social amnesia in mice lacking the oxytocin gene. Nat Genet. 25(3):284-8 (2000).

2. Kimchi T, Xu J, Dulac C. A functional circuit underlying male sexual behaviour in the female mouse brain. Nature 448(7157):1009-14 (2007).

3. **<u>Bendesky A, Kwon YM, Lassance JM, Lewarch CL, Yao S, Peterson BK, He MX, Dulac C, Hoekstra HE. The genetic basis of parental care evolution in monogamous mice. Nature 544(7651):434-439 (2017).</u>**

4. Kohl J, Babayan BM, Rubinstein ND, Autry AE, Marin-Rodriguez B, Kapoor V, Miyamishi K, Zweifel LS, Luo L, Uchida N, Dulac C. Functional circuit architecture underlying parental behaviour. Nature 556(7701):326-331 (2018).

5. Chen J, Markowitz JE, Lilascharoen V, Taylor S, Sheurpukdi P, Keller JA, Jensen JR, Lim BK, Datta SR, Stowers L. Flexible scaling and persistence of social vocal communication. Nature 593(7857):108-113 (2021).

Week VII

Genes and neural circuits of Behavior VII: Human behavioral variance

Learning goals:
1) Genetic underpinnings for human behavior variances.

Presentations and Readings:
<u>Student presentation</u>

1. Jones SE, et al. Genetic studies of accelerometer-based sleep measures yield new insights into human sleep behaviour. Nat Commun. 10(1):1585 (2019).

2. Hall AB, Tolonen AC, Xavier RJ. Human genetic variation and the gut microbiome in disease. Nat Rev Genet. 18(11):690-699 (2017).

3. COVID-19 Host Genetics Initiative. Mapping the human genetic architecture of COVID-19. Nature 600(7889):472-477 (2021).

4. **Shi G, Xing L, Wu D, Bhattacharyya BJ, Jones CR, McMahon T, Chong SYC, Chen JA, Coppola G, Geschwind D, Krystal A, Ptáček LJ, Fu YH. A Rare Mutation of β_1-Adrenergic Receptor Affects Sleep/Wake Behaviors. Neuron 103(6):1044-1055 (2019).**

Week VIII - Spring Recess

Week IX

Genes and neural circuits of Behavior VIII: Motivation

Learning goals:
1) Motivational state.
2) The role of dopamine signaling in regulating motivation.

Presentations and Readings:
Student presentation

1. Bromberg-Martin ES, Matsumoto M & Hikosaka O. Dopamine in motivational control: rewarding, aversive, and alerting. Neuron 68:815–834 (2010).

2. **Zhang SX, Lutas A, Yang S, Diaz A, Fluhr H, Nagel G, Gao S, Andermann ML. Hypothalamic dopamine neurons motivate mating through persistent cAMP signalling. Nature 597(7875):245-249 (2021).**

3. Mohebi A, Pettibone JR, Hamid AA, Wong JT, Vinson LT, Patriarchi T, Tian L, Kennedy RT, Berke JD. Dissociable dopamine dynamics for learning and motivation. Nature 570(7759):65-70 (2019).

4. Wise RA. Dopamine, learning and motivation. Nat Rev Neurosci. 5(6):483-94 (2004).

Part II Mechanisms underlying learning and memory

Week X

Mechanisms underlying learning and memory I: Memory formation and recall

Learning goals:
1) Memory formation and recall.
2) The brain circuits involved in forming and retrieving memories.

Presentations and Readings:
<u>Student presentation</u>

1. Kandel ER, Schwartz JH and Jessell TM. Principles of neural science (2000). Chapter 63.

2. Wu X, Morishita W, Beier KT, Heifets BD, Malenka RC. 5-HT modulation of a medial septal circuit tunes social memory stability. Nature 599(7883):96-101 (2021).

3. **<u>Roy DS, Kitamura T, Okuyama T, Ogawa SK, Sun C, Obata Y, Yoshiki A, Tonegawa S. Distinct Neural Circuits for the Formation and Retrieval of Episodic Memories. Cell 24;170(5):1000-1012 (2017).</u>**

4. Vetere G, Tran LM, Moberg S, Steadman PE, Restivo L, Morrison FG, Ressler KJ, Josselyn SA, Frankland PW. Memory formation in the absence of experience. Nat Neurosci. 22(6):933-940 (2019).

Week XI

Mechanisms underlying learning and memory II: Memory extinction and reconsolidation.

Learning goals:
1) Dynamic memories.
2) Mechanisms addressing how a memory is lost and re-established.

Presentations and Readings:
<u>Student presentation</u>

1. Tonegawa S, Pignatelli M, Roy DS and Ryan TJ. Memory engram storage and retrieval. Curr Opin Neurobiol. 35:101-9 (2015).

2. Keene AC and Waddell S. Drosophila olfactory memory: single genes to complex neural circuits. *Nat. Rev. Neurosci.* **8**, 341-354 (2007).

3. Qasim SE, Miller J, Inman CS, Gross RE, Willie JT, Lega B, Lin JJ, Sharan A, Wu C, Sperling MR, Sheth SA, McKhann GM, Smith EH, Schevon C, Stein JM, Jacobs J. Memory retrieval modulates spatial tuning of single neurons in the human entorhinal cortex. Nat Neurosci. 22(12):2078-2086 (2019).

4. **<u>Lacagnina AF, Brockway ET, Crovetti CR, Shue F, McCarty MJ, Sattler KP, Lim SC, Santos SL, Denny CA, Drew MR. Distinct hippocampal engrams control extinction and relapse of fear memory. Nat Neurosci. 22(5):753-761 (2019).</u>**

5. Felsenberg J, Jacob PF, Walker T, Barnstedt O, Edmondson-Stait AJ, Pleijzier MW, Otto N, Schlegel P, Sharifi N, Perisse E, Smith CS, Lauritzen JS, Costa M, Jefferis GSXE, Bock DD, Waddell S. Integration of Parallel Opposing Memories Underlies Memory Extinction. Cell 175(3):709-722 (2018).

Week XII

Mechanisms underlying learning and memory III: Sleep and memory

Learning goals:
1) How sleep impacts memory – past studies and current understanding.

Presentations and Readings:
Student presentation

1. Diekelmann S and Born J. (2010) The memory function of sleep. *Nat. Rev. Neurosci.* 11, 114–126 (2010).

2. Yang G, Lai CS, Cichon J, Ma L, Li W, Gan WB. Sleep promotes branch-specific formation of dendritic spines after learning. *Science* 344, 1173-1178 (2014).

3. Sawangjit A, Oyanedel CN, Niethard N, Salazar C, Born J, Inostroza M. The hippocampus is crucial for forming non-hippocampal long-term memory during sleep. Nature 564(7734):109-113 (2018).

4. **Izawa S, Chowdhury S, Miyazaki T, Mukai Y, Ono D, Inoue R, Ohmura Y, Mizoguchi H, Kimura K, Yoshioka M, Terao A, Kilduff TS, Yamanaka A. REM sleep-active MCH neurons are involved in forgetting hippocampus-dependent memories. Science 365(6459):1308-1313 (2019).**

Part III Neurological disorders

Week XIII

Neurological disorders I: Disorders associated with defects in learning and memory

Learning goals:
1) Mood disorders, such as general anxiety and post-traumatic stress disorder.
2) Understanding of learning and memory helps to probe the pathology of mood disorders.

Presentations and Readings:
Student presentation

1. Milton AL. Fear not: recent advances in understanding the neural basis of fear memories and implications for treatment development. F1000Res. 8. pii: F1000 Faculty Rev-1948. doi: 10.12688/f1000research.20053.1. eCollection 2019.

2. **Marcinkiewcz CA, Mazzone CM, D'Agostino G, Halladay LR, Hardaway JA, DiBerto JF, Navarro M, Burnham N, Cristiano C, Dorrier CE, Tipton GJ, Ramakrishnan C, Kozicz T, Deisseroth K, Thiele TE, McElligott ZA, Holmes A, Heisler LK, Kash TL. Serotonin engages an anxiety and fear-promoting circuit in the extended amygdala. Nature 537(7618):97-101 (2016).**

3. Luo R, Uematsu A, Weitemier A, Aquili L, Koivumaa J, McHugh TJ, Johansen JP. A dopaminergic switch for fear to safety transitions. Nat Commun. 9(1):2483 (2018).

4. Villano WJ, Kraus NI, Reneau TR, Jaso BA, Otto AR, Heller AS. Individual differences in naturalistic learning link negative emotionality to the development of anxiety. Sci Adv. 9(1):eadd2976 (2023).

Week XIV – (Last day of the spring term class)

Neurological disorders II: Disorders associated with defects in learning and memory

Learning goals:
1) Neurological changes associated with Alzheimer's disease.
2) Understanding Alzheimer's disease and current treatment.

Presentations and Readings:
<u>Student presentation</u>

1. Long JM, Holtzman DM. Alzheimer Disease: An Update on Pathobiology and Treatment Strategies. Cell 179(2):312-339 (2019).

2. Naj AC., et al. Common variants at MS4A4/MS4A6E, CD2AP, CD33 and EPHA1 are associated with late-onset Alzheimer's disease. Nat Genet. 43(5):436-41 (2011).

3. McAlpine CS, Park J, Griciuc A, Kim E, Choi SH, Iwamoto Y, Kiss MG, Christie KA, Vinegoni C, Poller WC, Mindur JE, Chan CT, He S, Janssen H, Wong LP, Downey J, Singh S, Anzai A, Kahles F, Jorfi M, Feruglio PF, Sadreyev RI, Weissleder R, Kleinstiver BP, Nahrendorf M, Tanzi RE, Swirski FK. Astrocytic interleukin-3 programs microglia and limits Alzheimer's disease. Nature 595(7869):701-706 (2021).

4. Blanchard JW, Akay LA, Davila-Velderrain J, von Maydell D, Mathys H, Davidson SM, Effenberger A, Chen CY, Maner-Smith K, Hajjar I, Ortlund EA, Bula M, Agbas E, Ng A, Jiang X, Kahn M, Blanco-Duque C, Lavoie N, Liu L, Reyes R, Lin YT, Ko T, R'Bibo L, Ralvenius WT, Bennett DA, Cam HP, Kellis M, Tsai LH. APOE4 impairs myelination via cholesterol dysregulation in oligodendrocytes. Nature 611(7937):769-779 (2022).

5. **<u>Seo DO, O'Donnell D, Jain N, Ulrich JD, Herz J, Li Y, Lemieux M, Cheng J, Hu H, Serrano JR, Bao X, Franke E, Karlsson M, Meier M, Deng S, Desai C, Dodiya H, Lelwala-Guruge J, Handley SA, Kipnis J, Sisodia SS, Gordon JI, Holtzman DM. ApoE isoform- and microbiota-dependent progression of neurodegeneration in a mouse model of tauopathy. Science 379(6628): eadd1236 (2023).</u>**