

CAPS 426 Course Syllabus

CAPS 426 Nervous System Function in Human Health and Disease (3 Credits)

Academic Calendar Description:

An integrated study of the theory and experimental findings of neuronal synaptic plasticity, including focus on underlying molecular mechanisms and its roles in cellular, systems, behavioral and cognitive biology and disease. [3-0-0]

Prerequisites

CAPS 305, **or** NSCI 200 and NSCI 300

Corequisites: None

Other Requirements

This course is open to CAPS Majors and Honours students, as well as Neuroscience students. Other 4th year students with 3 and 4 year cell biology credits may be considered at the discretion of the Course Director.

Instructional Schedule: 2 weekly 90 min sessions

Student Expectations

Attend all classes and all exams in person. Read all assigned literature. Prepare any requested materials for presentations in class. Actively contribute to all class discussions.

Course Structure

2 SESSIONS PER WEEK (1.5 HOURS EACH). Each session comprises in-person classes. Classes will alternate between lecture-based and student-led debates to guide discussion based on assigned literature centered on contentious issues in the field. In these debate/discussion classes, groups of students will be assigned to defend opposing sides of an issue to initiate and direct in-class discussion. All relevant literature and lecture materials will be provided on CANVAS at the start of term. An exam at mid-term and at end of term will be in person and will examine the respective half of the course.

Learning Materials

All learning and reading material will be provided in PDF format on Canvas prior to the start of term. This will include all assigned reading and Instructor lecture and instructional material. See 'Literature' section below for details of publications.

Course Co-Directors

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Other Instructional Staff

TA's to be updated annually

Acknowledgements

UBC's Point Grey Campus is located on the traditional, ancestral, and unceded territory of the xwməθkwəy̓ əm (Musqueam) people. The land it is situated on has always been a place of learning for the Musqueam people, who for millennia have passed on in their culture, history, and traditions from one generation to the next on this site.

Learning Outcomes

At the successful completion of this course, students will be able to:

- Articulate the theoretical and experimental basis for synaptic plasticity and critique its connection to human learning and memory.
 - Students will understand and be able to both communicate and defend the role of neural activity driven by sensory experience in brain circuit formation.
 - Students will be able to articulate and critique historic and current controversies in the field of neuronal synaptic plasticity.
 - Students will be able to read and analyze published literature to perform a critical
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assessment of a study's strengths and weaknesses.

- Students will be able to formulate new experiments using classical and cutting-edge technologies to address remaining questions in the field of synaptic plasticity.
- Students will be able to make connections between fundamental studies of synaptic plasticity in animal models and the pathophysiological causes of human brain disorders.

Schedule of Topics

INTRODUCTION TO SYNAPTIC PLASTICITY

1 Techniques: Technologies for studying synaptic plasticity

- Describe major technologies used in studying synaptic plasticity and articulate their utility and limitations.

2: Debates in Technologies for studying synaptic plasticity

- *Why Connectomics? Is Optogenetics any good? Cranial Window vs Shaved Skull for in vivo spine imaging?*

LONG TERM POTENTIATION (LTP) AND LONG TERM DEPRESSION (LTD)

3: Models of synaptic plasticity

- The molecular mechanisms underlying LTP and LTD.
- Historic and current debates associated with LTP and LTD and the design of experiments to aid finding solutions.

4: Debates in Models of synaptic plasticity

- *Is LTP Presynaptic or Postsynaptic? How can silent synapses work?*

MOLECULAR MECHANISMS OF SYNAPTIC PLASTICITY 1

5: Molecular and Cellular Mechanisms 1

- The molecular processes that drive plasticity at synapses, and the quality of evidence supporting these models.

6: Debates in Molecular and Cellular Mechanisms 1

- *Do NR2B subunits contribute to LTD? Is AMPA Receptor Trafficking a mechanism of LTP?*

MOLECULAR MECHANISMS OF SYNAPTIC PLASTICITY 2

7: Molecular and Cellular Mechanisms 2

- Students will be able to design novel experiment to address leading-edge question in the molecular mechanisms underlying synaptic plasticity.
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8: Debates in Molecular and Cellular Mechanisms 2

- *Is PKMz a memory molecule?*

SYNAPTIC PLASTICITY IN INTACT CIRCUITS

9. Synaptic plasticity in intact circuits

- Molecular mechanisms of plasticity developed from reduced preparation to question of the role of plasticity within intact circuits.
- Reduced vs intact preparations.

10: Debates in Synaptic plasticity in intact circuits

- *Is LTP physiological? Are LTP and LTD sufficient?*

SESSION CONSOLIDATION AND EXAM

11: Active learning in synaptic plasticity mechanisms.

12. Mid-term exam (1.5hrs in class. Covering material in weeks 1-6)

DEVELOPMENT: BUILDING FUNCTIONAL BRAIN CIRCUITS 1

13: Axonogenesis and navigation

- The major mechanisms of axon guidance during brain circuit development.

14. Debates in Axonogenesis and navigation

- *Whats up with Netrin?*

DEVELOPMENT: BUILDING FUNCTIONAL BRAIN CIRCUITS 2

15: Synaptogenesis

- The role of synaptic plasticity in early neural circuit formation.

16: Debates in Synaptogenesis

- *Can you make and erase memories with optogenetics?*

DEVELOPMENT: BUILDING FUNCTIONAL BRAIN CIRCUITS 3

17: Synaptic plasticity during brain circuit formation

- A role for experience in sculpting brain circuit structure and function: Evidence from studies in animals and humans.

18: Debates in Synaptic plasticity during brain circuit formation

- ***Is activity required for neural circuit formation?***

HIGHER BRAIN FUNCTIONS

Session 19: Synaptic plasticity in consciousness, learning, memory, and sleep.

- Theories for the roles of synaptic plasticity in higher brain functions with evidence from both experimental animals and human studies.

20: Debates Synaptic plasticity in consciousness, learning, memory, and sleep.

- *What is the role of plasticity during sleep?*

DISEASE

21: Synaptic plasticity in disease

- Models of human disease involving aberrant synaptic plasticity as a mechanism of pathophysiology.

S22: Debates in Synaptic plasticity in disease.

- ***Does synapse plasticity play a role in CNS disease?***

SESSION CONSOLIDATION AND EXAM

23: Active learning in developmental and disease-state synaptic plasticity. (All Instructors).

End of term exam (1.5hrs covering material after midterm exam).

Assessments of Learning

- 1) For each debate class, a group of students will be responsible for leading a debate on the assigned literature. Each presenting student will receive 20% of their final course mark based on instructor assessment of their performance, including depth of understanding and ability to articulate findings of the assigned literature, ability to critique strength and limitations of the work, as well as their ability to engage the entire class in a discussion on controversial aspects of the science.
- 2) Two invigilated in person exams. Exam 1 is an in-class midterm and will assess the content of weeks 1-6. Exam 2 takes place after term and will assess the content of weeks 7-12

Grading scheme:

| | |
|------------------|-----|
| Debate | 20% |
| Midterm exam | 40% |
| End of term exam | 40% |

Literature

All learning and reading material will be provided in PDF format on Canvas prior to the start of term. This will include all assigned reading and instructor lecture material.

Session: 1 Techniques: Technologies for studying synaptic plasticity

Session 2: Debates in Technologies for studying synaptic plasticity

Why Connectomics?

- 1) Morgan, J.L., Lichtman, J.W. Digital tissue and what it may reveal about the brain. *BMC Biol* 15, 101 (2017).
- 2) Byrd DT, Jin Y. Wired for insight-recent advances in *Caenorhabditis elegans* neural circuits. *Curr Opin Neurobiol.* 2021 Aug;69:159-169. doi: 10.1016/j.conb.2021.02.009. Epub 2021 May 3. PMID: 33957432; PMCID: PMC8387325.
- 3) Kandel ER, Markram H, Matthews PM, Yuste R, Koch C. Neuroscience thinks big (and collaboratively). *Nat Rev Neurosci.* 2013 Sep;14(9):659-64. doi: 10.1038/nrn3578. PMID: 23958663.

Is Optogenetics any good?

- 1) Malyshev A, Goz R, LoTurco JJ, Volgushev M. Advantages and limitations of the use of optogenetic approach in studying fast-scale spike encoding. *PLoS One.* 2015 Apr 7;10(4):e0122286. doi: 10.1371/journal.pone.0122286. PMID: 25850004; PMCID: PMC4388689.
- 2) Zalocusky KA, Fenno LE, Deisseroth K, Current Challenges in Optogenetics. 2013

Cranial Window vs Shaved Skull for in vivo spine imaging?

- 1) Xu, HT., Pan, F., Yang, G. *et al.* Choice of cranial window type for *in vivo* imaging affects dendritic spine turnover in the cortex. *Nat Neurosci* 10, 549–551 (2007). PMID: 17417634
- 2) Trachtenberg, J., Chen, B., Knott, G. *et al.* Long-term *in vivo* imaging of experience-dependent synaptic plasticity in adult cortex. *Nature* 420, 788–794 (2002). PMID: 12490942

Session 3: Models of synaptic plasticity

Session 4: Debates in Models of synaptic plasticity

Is LTP Presynaptic or Postsynaptic?

- 1) Coan, E. J., W. Saywood, and G. L. Collingridge. "MK-801 Blocks NMDA Receptor-mediated Synaptic Transmission and Long Term Potentiation in Rat Hippocampal Slices." *Neurosci Lett* 80 (1987): 111-114.
- 2) Kerchner, G., Nicoll, R. Silent synapses and the emergence of a postsynaptic mechanism for LTP. *Nat Rev Neurosci* 9, 813–825 (2008). <https://doi.org/10.1038/nrn2501>
- 3) Enoki R, Hu YL, Hamilton D, Fine A. Expression of long-term plasticity at individual synapses in hippocampus is graded, bidirectional, and mainly presynaptic: optical quantal analysis. *Neuron.* 2009 Apr 30;62(2):242-53. doi: 10.1016/j.neuron.2009.02.026. PMID: 19409269.

How can silent synapses work? Depolarizing GABA

- 1) Liao D, Hessler NA, Malinow R. Activation of postsynaptically silent synapses during pairing-induced LTP in CA1 region of hippocampal slice. *Nature.* 1995 Jun 1;375(6530):400-4. doi: 10.1038/375400a0. PMID: 7760933.
 - 2) Isaac JT, Nicoll RA, Malenka RC. Evidence for silent synapses: implications for the expression of LTP. *Neuron.* 1995 Aug;15(2):427-34. doi: 10.1016/0896-6273(95)90046-2. PMID: 7646894.
 - 3) Rivera, C., Voipio, J., Payne, J. *et al.* The K⁺/Cl⁻ co-transporter KCC2 renders GABA hyperpolarizing during neuronal maturation. *Nature* 397, 251–255 (1999). <https://doi.org/10.1038/16697>
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Session 5: Molecular and Cellular Mechanisms 1

Session 6: Debates in Molecular and Cellular Mechanisms 1

Do NR2B subunits contribute to LTD?

- 1) Liu L, Wong TP, Pozza MF, Lingenhoehl K, Wang Y, Sheng M, Auberson YP, Wang YT. Role of NMDA receptor subtypes in governing the direction of hippocampal synaptic plasticity. *Science*. 2004 May 14;304(5673):1021-4. doi: 10.1126/science.1096615. PMID: 15143284.
- 2) Morishita W, Lu W, Smith GB, Nicoll RA, Bear MF, Malenka RC. Activation of NR2B-containing NMDA receptors is not required for NMDA receptor-dependent long-term depression. *Neuropharmacology*. 2007 Jan;52(1):71-6. doi: 10.1016/j.neuropharm.2006.07.005. Epub 2006 Aug 8. PMID: 16899258.

Is AMPA Receptor Trafficking a mechanisms of LTP?

- 1) Hayashi, Y., S. H. Shi, J. A. Esteban, A. Piccini, J. C. Poncer, and R. Malinow. "Driving AMPA Receptors into Synapses by LTP and CaMKII: Requirement for GluR1 and PDZ Domain Interaction." *Science* 287 (2000): 2262-2267.
- 2) Díaz-Alonso J, Morishita W, Incontro S, Simms J, Holtzman J, Gill M, Mucke L, Malenka RC, Nicoll RA. Long-term potentiation is independent of the C-tail of the GluA1 AMPA receptor subunit. *Elife*. 2020 Aug 24;9:e58042. doi: 10.7554/eLife.58042. PMID: 32831170; PMCID: PMC7500950.
- 3) Díaz-Alonso J, Sun YJ, Granger AJ, Levy JM, Blankenship SM, Nicoll RA. Subunit-specific role for the amino-terminal domain of AMPA receptors in synaptic targeting. *Proc Natl Acad Sci U S A*. 2017 Jul 3;114(27):7136-7141. doi: 10.1073/pnas.1707472114. Epub 2017 Jun 19. PMID: 28630296; PMCID: PMC5502653.

Session 7: Molecular and Cellular Mechanisms 2

Session 8: Debates in Molecular and Cellular Mechanisms 2

Is PKMz a memory molecule?

- 1) Shema R, Sacktor TC, Dudai Y. Rapid erasure of long-term memory associations in the cortex by an inhibitor of PKM zeta. *Science*. 2007 Aug 17;317(5840):951-3. doi: 10.1126/science.1144334. PMID: 17702943.
 - 2) Kwapis JL, Helmstetter FJ. Does PKM(zeta) maintain memory? *Brain Res Bull*. 2014 Jun;105:36-45. doi: 10.1016/j.brainresbull.2013.09.005. Epub 2013 Sep 26. PMID: 24076105; PMCID: PMC3966985.
 - 3) Tsokas P, Hsieh C, Yao Y, Lesburguères E, Wallace EJC, Tcherepanov A, Jothianandan D, Hartley BR, Pan L, Rivard B, Farese RV, Sajan MP, Bergold PJ, Hernández AI, Cottrell JE, Shouval HZ, Fenton AA, Sacktor TC. Compensation for PKM ζ in long-term potentiation and spatial long-term memory in mutant mice. *Elife*. 2016 May 17;5:e14846. doi: 10.7554/eLife.14846. PMID: 27187150; PMCID: PMC4869915.
 - 4) Volk LJ, Bachman JL, Johnson R, Yu Y, Hugarir RL. PKM- ζ is not required for hippocampal synaptic plasticity, learning and memory. *Nature*. 2013 Jan 17;493(7432):420-3. doi: 10.1038/nature11802. Epub 2013 Jan 2. PMID: 23283174; PMCID: PMC3830948.
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Session 9: Synaptic plasticity in intact circuits

Session 10: Debates in Synaptic plasticity in intact circuits

Is LTP physiological? STDP

- 1) Bliss TV, Lomo T. Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. *J Physiol.* 1973 Jul;232(2):331-56. doi: 10.1113/jphysiol.1973.sp010273. PMID: 4727084; PMCID: PMC1350458.
- 2) Li CY, Lu JT, Wu CP, Duan SM, Poo MM. Bidirectional modification of presynaptic neuronal excitability accompanying spike timing-dependent synaptic plasticity. *Neuron.* 2004 Jan 22;41(2):257-68. doi: 10.1016/s0896-6273(03)00847-x. PMID: 14741106.

Are LTP and LTD sufficient? Homeostatic plasticity and metaplasticity

- 1) Turrigiano G. Homeostatic synaptic plasticity: local and global mechanisms for stabilizing neuronal function. *Cold Spring Harb Perspect Biol.* 2012 Jan 1;4(1):a005736. doi: 10.1101/cshperspect.a005736. PMID: 22086977; PMCID: PMC3249629.
- 2) Abraham WC, Bear MF. Metaplasticity: the plasticity of synaptic plasticity. *Trends Neurosci.* 1996 Apr;19(4):126-30. doi: 10.1016/s0166-2236(96)80018-x. PMID: 8658594.

Session 11: Active learning in synaptic plasticity mechanisms.

- Students will be able to describe the critical components of synaptic plasticity.

Session 13: Axonogenesis and navigation

Session 14: Debates in Axonogenesis and navigation

Whats up with Netrin?

- 1) Nature. 2017 545:350-354. Floor-plate-derived netrin-1 is dispensable for commissural axon guidance. Dominici C, Moreno-Bravo JA, Puiggros SR, Rappeneau Q, Rama N, Vieugue P, Bernet A, Mehlen P, Chédotal A.
- 2) Long-Range Guidance of Spinal Commissural Axons by Netrin1 and Sonic Hedgehog from Midline Floor Plate Cells. Wu Z, Makihara S, Yam PT, Teo S, Renier N, Balekoglu N, Moreno-Bravo JA, Olsen O, Chédotal A, Charron F, Tessier-Lavigne M. *Neuron.* 2019 Feb 20;101(4):635-647

Session 15: Synaptogenesis

Session 16: Debates in Synaptogenesis

Can you make and erase memories with optogenetics?

- 1) Han JH, Kushner SA, Yiu AP, Hsiang HL, Buch T, Waisman A, Bontempo B, Neve RL, Frankland PW, Josselyn SA. Selective erasure of a fear memory. *Science.* 2009 Mar 13;323(5920):1492-6. doi: 10.1126/science.1164139. PMID: 19286560.
- 2) Ramirez S, Liu X, Lin PA, Suh J, Pignatelli M, Redondo RL, Ryan TJ, Tonegawa S. Creating a false memory in the hippocampus. *Science.* 2013 Jul 26;341(6144):387-91. doi: 10.1126/science.1239073. PMID: 23888038.

Session 17: Synaptic plasticity during brain circuit formation

Session 18: Debates in Synaptic plasticity during brain circuit formation

Is activity required for neural circuit formation?

- 1) Verhage M, Maia AS, Plomp JJ, Brussaard AB, Heeroma JH, Vermeer H, Toonen RF, Hammer RE, van den Berg TK, Missler M, Geuze HJ, Südhof TC. Synaptic assembly of the brain in the absence of neurotransmitter secretion. *Science*. 2000 Feb 4;287(5454):864-9. doi: 10.1126/science.287.5454.864. PMID: 10657302.
- 2) Podgorski K, Toth TD, Coleman P, Opushnyev S, Brusco J, Hogg P, Edgcumbe P, Haas K (2021) Comprehensive imaging of synaptic activity reveals dendritic growth rules that cluster inputs. *bioRxiv* 2021.02.11.430646; doi: <https://doi.org/10.1101/2021.02.11.430646>

Session 19: Synaptic plasticity in consciousness, learning, memory, and sleep.

Session 20: Debates Synaptic plasticity in consciousness, learning, memory, and sleep.

What is the role of plasticity during sleep?

- 1) Lee AK, Wilson MA. Memory of sequential experience in the hippocampus during slow wave sleep. *Neuron*. 2002 Dec 19;36(6):1183-94. doi: 10.1016/s0896-6273(02)01096-6. PMID: 12495631.
- 2) Eagleman DM, Vaughn DA. The Defensive Activation Theory: REM Sleep as a Mechanism to Prevent Takeover of the Visual Cortex. *Front Neurosci*. 2021 May 21;15:632853. doi: 10.3389/fnins.2021.632853. PMID: 34093109; PMCID: PMC8176926.

Session 21: Synaptic plasticity in disease

Session 22: Debates in Synaptic plasticity in disease.

Does synapse plasticity play a role in CNS disease?

- 1) Rubenstein JL, Merzenich MM. Model of autism: increased ratio of excitation/inhibition in key neural systems. *Genes Brain Behav*. 2003 Oct;2(5):255-67. doi: 10.1034/j.1601-183x.2003.00037.x. PMID: 14606691; PMCID: PMC6748642.
- 2) Mills F, Globa AK, Liu S, Cowan CM, Mobasser M, Phillips AG, Borgland SL, Bamji SX. Cadherins mediate cocaine-induced synaptic plasticity and behavioral conditioning. *Nat Neurosci*. 2017 Apr;20(4):540-549. doi: 10.1038/nn.4503. Epub 2017 Feb 13. PMID: 28192395; PMCID: PMC5373847.
- 3) Chapman PF, White GL, Jones MW, Cooper-Blacketer D, Marshall VJ, Irizarry M, Younkin L, Good MA, Bliss TV, Hyman BT, Younkin SG, Hsiao KK. Impaired synaptic plasticity and learning in aged amyloid precursor protein transgenic mice. *Nat Neurosci*. 1999 Mar;2(3):271-6. doi: 10.1038/6374. PMID: 10195221.
- 4) Parsons, R., Ressler, K. Implications of memory modulation for post-traumatic stress and fear disorders. *Nat Neurosci* 16, 146–153 (2013). PMID: 23354388

Session 23: Active learning in developmental and disease-state synaptic plasticity. (All Instructors).

University Policies

UBC provides resources to support student learning and to maintain healthy lifestyles but recognizes that sometimes crises arise and so there are additional resources to access including those for survivors of sexual violence. UBC values

respect for the person and ideas of all members of the academic community. Harassment and discrimination are not tolerated nor is suppression of academic freedom. UBC provides appropriate accommodation for students with disabilities and for religious observances. UBC values academic honesty and students are expected to acknowledge the ideas generated by others and to uphold the highest academic standards in all their actions. Details of the policies and how to access support are available at the Policies and Resources section of the UBC Senate website.

Academic Integrity

The academic enterprise is founded on honesty, civility, and integrity. As members of this enterprise, all students are expected to know, understand, and follow the codes of conduct regarding academic integrity. At the most basic level, this means submitting only original work done by you and acknowledging all sources of information or ideas and attributing them to others as required. This also means you should not cheat, copy, or mislead others about what is your work. Violations of academic integrity (i.e., misconduct) lead to the breakdown of the academic enterprise, and therefore serious consequences arise and harsh sanctions are imposed. For example, incidences of plagiarism or cheating may result in a mark of zero on the assignment or exam and more serious consequences may apply if the matter is referred to the President's Advisory Committee on Student Discipline. Careful records are kept in order to monitor and prevent recurrences.

A more detailed description of academic integrity, including the University's policies and procedures, may be found in the Discipline for Academic Misconduct section of the UBC Academic Calendar.

- No assignment may be submitted to any other instructor of any course for a grade.
- The minimum penalty for plagiarism in any assignment is a zero for the paper; the maximum penalty is a zero for the course.

UBC Grading Standards

Undergraduate Grading Scale

| Percentage (%) | Letter Grade |
|----------------|--------------|
| 90-100 | A+ |
| 85-89 | A |
| 80-84 | A- |
| 76-79 | B+ |
| 72-75 | B |
| 68-71 | B- |
| 64-67 | C+ |

| | |
|-------|----|
| 60-63 | C |
| 55-59 | C- |
| 50-54 | D |
| 0-49 | F |

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