NEUROBIOLOGY OF DEVELOPMENT
BIOL. 449: M, W, 8:00 – 9:40 pm; SH C136
SPRING 2012

Instructor: Michael Chen, Ph.D. Office hours: Tues, Thurs, 12:45-3:00 pm;
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General Course Objectives: To understand current concepts of and experimental approaches to the development of the nervous system; as well as the maintenance and remodeling of neuronal connections.

Prerequisites: Biology 380 (Cell Biology), Biology 340 (Genetics)

Textbook:
Development of the Nervous System. Sanes, D.H., Reh, T.A., Harris, W.A. Academic Press, 2006. You will be expected to review the assigned chapter prior to lecture.

Original Scientific Literature:

LECTURES: I will lecture using almost exclusively PowerPoint slides. These can be found on my faculty webpage at www.calstatela.edu/faculty/mchen/.

Course Schedule:			**Book Chapters**
Mon	4/2	General Introduction Introduction to Required Literature Presentation	
Wed	4/4	Neural Induction and Early Neural Morphogenesis	1
Mon	4/9	Patterning and Regionalization of the Nervous System	2
Wed	4/11	Neuronal Determination and Differentiation Introduction to Experimentation in Developmental Biology	4
Mon	4/16	Neuronal Determination and Differentiation (cont'd) **Form groups (4-5) by this date**	4
Wed	4/18	Neuronal Migration in Nervous System Development	3
Mon	4/23	**Midterm Exam 1** **Decide on topic by this date**	
Wed	4/25	Axon Outgrowth and Pathfinding	5
Mon	4/30	Target Selection and Topographic Mapping	6

Wed	5/2	Synapse Formation	8
Mon	5/7	Neuronal Death During Development	7
Wed	5/9	Neurotrophic Factors **Presentation titles/first two references due**	7
Mon	5/14	Neurotrophic Factors (cont'd)	7
Wed	5/16	**Midterm Exam 2**	
Mon	5/21	Synapse Elimination and Remodeling	9
Wed	5/23	Synapse Elimination and Remodeling (cont'd) **Presentation outlines and full bibliography of references due.** **Groups should start meeting with me for approval of presentation.**	9
Mon	5/28	No Class – Memorial Day	
Wed	5/30	Early Experience and Developmental Learning	
Mon	6/4	Behavioral Development	10
Wed	6/6	**Final Examination** (taken exam during regular class period)	
Mon	6/11	**Journal Review Power-Point Presentations 8:00 – 10:30 am** (occurs during scheduled final exam period)	

As instructor, I reserve the right to slightly alter the above topic schedule as time permits.

Grading:

2 Midterm exams	100 points each
Attendance	2 points/class period = 28 points
J. Review presentation	70 points
Presentation participation	30 points
Final Exam	100 points
	~ 428 points total

This point total is an estimate and may not necessarily represent the real outcome, depending on possible assignments, *etc*.

I do not grade on a curve and generally, the bottom and top 3% of a range (e.g., 80-90%) will get "-" and "+" grades, respectively.

Cross-Course Contamination: For those of you who have also been enrolled in my Biol 448 course (Molecular Biology of the Brain) or are currently enrolled in my Biol

436 course (Neurophysiology): Despite the fact that the potential for topic overlap between this course and Biol 448 and 436 is great, I cannot allow students, per University policy, to do the same presentation, assignment, *etc*. for both courses. The 2 presentations must differ significantly. If you have any doubt, please consult with me before proceeding any further. In addition, please do not assume that policies for one course are the same as those in my other courses. Administratively, the courses have nothing to do with each other.

****I don't accept assignments via e-mail, except under dire circumstances.****

Academic Honesty: Students are expected to read and abide by the University's Academic Honesty Policy, which can be found at www.calstatela.edu/academic/senate/handbook/ch5a.htm. Students who violate this policy will be subject to disciplinary action, and may receive a failing grade in the course for a single violation.

Tests: The tests will be a combination of short answer, multiple choice, and perhaps some matching. The final exam will be comprehensive. No make-up tests will be scheduled. With an excused (*i.e*. discussed in advance or doctor's note) absence for the midterm, the value of the final exam will be increased to compensate for the missed test. If evidence of emergency can be provided for a missed final, an Incomplete will be given until the final exam the following summer quarter.

Only ***your own*** medical emergency or illness will excuse you from an exam. Medical emergencies of relatives, friends, relatives of friends, friends of relatives, weddings, anniversaries, parties, rain, traffic, *etc*. are not valid reasons for missing an exam. Nor are they valid reasons for asking me to allow you to take an exam during a time other than the scheduled time.

Attendance: To help ensure that people attend the lectures, I take attendance (2 points/class period).

Journal Review Project:

You are to assemble into teams of 4-5, decide on any topic in ***developmental neurophysiology*** that interests you all, and orally present the most cutting-edge research on that topic. You may choose from the following list or bring another topic to me for my approval. Your references should be current, no older than 10 years old, and should, therefore, cover cutting-edge research from journal articles. You should have no fewer than 10 such references. You may use books to clarify concepts in your mind, but not as a primary source. Presentations should be 10-12 minutes long and will occur during Finals week, Mon, 6/11/12, 8:00-10:30 am.

The Neurobiology of Development is one of the most active and growing fields in the life sciences. I have included, as a required project for this class, the review of one specific area of neurobiology research with relevance to development (the general subjects are listed below). The review will be summarized in a power-point presentation during the

final exam period. Three to five relevant research papers from the *primary* literature will be used in your review. Book chapters and review articles should also be used in your preparation, but do not count toward the 3-5 research papers (you should have about 8 items total in your bibliography). In addition to text (described below), your presentation should include some form of visual aids (such as bullet points/lists, figures from research studies or figures explaining experimental methods), in order to make your presentation clear.

The format of your presentation will include:

Introduction (2-4 slides)
Significance of this research area
Historical background
Hypothesis (or group of related hypotheses) tested in the chosen recent studies

Review of example research studies and key results (4-6 slides)
Purpose of each experiment
Method(s) used
Results obtained
Interpretation of the results (Do they support or refute the hypothesis? What is their significance in light of other studies?)

Conclusions (1-2 slides)
Summarize the advances in this area of research that you have presented, and state their importance to medicine or the understanding of how the nervous system functions.

One important aspect of this exercise will be developing the ability to summarize material in a succinct manner, so that the audience can learn a few key points. Presentations will be prepared and delivered by a team of 3-4 students. At professional meetings/conferences, presentations are limited to 10-12 minutes. If a group reaches the 12-min mark and has not yet finished, I will stop the presentation and everyone in that group lose 5 points from their presentation grade.

Grading:
Presentations will be graded on these points:
- Clarity
- Evidence of understanding
- Efficiency of words, lists or tables
- Quality of visual aids

Your title and references of two chosen research papers will be due during week 6 (due at the beginning of lecture 5/9/12).

Your full bibliography of 3-5 research papers (plus supporting review papers or books) and a two-page outline of your presentation will be due at the end of week 8 (due at the beginning of lecture on 5/23/12).

Peer Evaluations:

You will also be required to evaluate the presentations of your peers. Your evaluations will not go toward your peers' grade, but will be graded themselves on a credit/no credit basis. Briefly evaluate each poster and presentation on these points:

Introduction – What is the purpose of the studies presented? Is there a testable scientific hypothesis stated? Does the presenter clearly state the significance of the studies in relation to recent scientific knowledge?

Review of studies and results – Is it possible to understand the procedures used in the experiments, and are specialized or technical terms well-defined?

Conclusions – What is the "take home" message? Has the presenter demonstrated an understanding of the significance of the results (in terms of their contribution to science or medicine)?

Intra-Group Evaluation: Each member of a group will be required to evaluate each other member of that group in terms of contribution and participation to the presentation. These evaluations will be anonymous and only I will know the results. This will count towards 30% of the presentation grade (30/100 points).

General Topics: (Students will sign up for a topic and presentation group during the second week). Possibilities should be highly focused topics under any of the following:

Neural Induction
Neural morphogenesis
Neuronal differentiation
Neuronal migration
Axon outgrowth
Synapse formation
Synapse elimination or remodeling
Programmed neuronal death
Neurotrophic factors
Developmental learning
Neuronal regeneration and repair
Neurodegeneration

Specific Learning Objectives for Biol 449:

Neural Induction and Early Neural Morphogenesis:

- to be able to describe early embyonic events such as gastrulation and neurulation (in the amphibian embryo, as an example) and identify the developing germ layers.
- to know what structures the germ layers give rise to in the developing animal.
- to be able to identify the "organizer tissue" in amphibian and avian embryos
- to identify key structures in the neurula and understand their developmental function (such as neural groove, neural plate, neural tube, notochord and somites)
- to identify the developing vescicles leading to major parts of the vertebrate brain (prosencephalon, etc.)
- to understand early experiments re: neural induction (i.e. Spemann's experiment) and later problems that arose re: specificity (i.e. the finding of "artificial inducers" or non-specific "activators")
- to understand how a potential inducer could be tested in an experimental system
- to know about the current understanding regarding polypeptide growth factors (substances related to TGF-β, the bone morphogenetic proteins, or BMPs) and the mechanisms of neural induction
- to understand the role of mechanical forces, such as coordinated growth, change in cell shape and cell movement (convergent extension, or C-E) in early neural morphogenesis
- to understand the role of differential cell adhesion in early neural morphogenesis

Patterning and Regionalization of the Nervous System:

- to understand how chemical gradients can participate in establishing positional information and polarity for developing cells and tissues
- to understand how the initial establishment of A/P polarity during early formation of the embryo is established by organizer tissue (i.e. by chordal and prechordal mesoderm)
- to understand how neural inducers promote the development of anterior-like neural tissues, and that inhibitors from the Wnt signaling family allow more posterior tissues to be expressed.
- to understand the concept of segmentation during development, the essential function of this arrangement (why is it beneficial?), and the basic mechanisms thought to establish segmentation.
- to understand how developmental control, or homeobox, genes (Hox genes as the example) direct antero-posterior positional information through their interaction with different concentrations of secreted substances such as retinoic acid (RA).
- to understand how sonic hedgehog (SHH) helps to establish dorso-ventral polarity in the developing neural tube.
- to have a working understanding of the original research study presented in class (purpose, methods, results, conclusions and next directions)

Neuronal Differentiation

- to know and understand the 2 major types of signals, intrinsic cues and extrinsic cues, which can determine cell or tissue fate during development

- to understand several means by which neural determination can be studied in an experimental system (i.e. transplantation, genetic mutation studies, cell/tissue culture and cell ablation)
- to understand the basic two-step mechanism by which neuroectodermal cells are instructed to develop into neural progenitors as opposed to epidermal progenitors in an insect model (expression of proneural genes and neurogenic genes)
- to understand, in a general way, how proneural and neurogenic genes promote postmitotic neuronal differentiation in the vertebrate
- to understand how neuronal vs. glial lineages are produced from common progenitors
- to understand how the extrinsic cues, glucocorticoid hormones and growth factors bFGF and NGF, signal the differentiation of specific cell types (adrenergic sympathetic neurons vs. endocrine chromaffin cells from sympathoadrenal progenitors)
- to understand how cell-cell signaling determines cell fate in the insect compound eye, as well as the vertebrate retina.
- to understand how extrinsic and intrinsic cues for differentiation can change over time during development
- to understand the process of laminar fate determination in the developing cerebral cortex (subject of our paper for discussion)
- to have a working understanding of the original research study presented in class (purpose, methods, results, conclusions and next directions)

Neuronal Migration in Central Nervous System Development:

- to know what the neural crest is, and to identify the variety of tissues and systems these cells give rise to
- to understand examples of how both intrinsic and extrinsic cues direct the migration of neural crest cells
- to know which major CNS structures from the neural tube will be layered in their final development, (and to understand how this laminar structure is essential to the later formation of neuronal circuits)
- to identify the basic embryonic zones which are built in the wall of the neural tube as neurons undergo primary migration outward from the ventricular surface
- to understand the basic defect thought to be present in the mutant mouse, "reeler", causing a disruption in the signals which allow migrating neurons to stop and form layers
- to understand the function of the radial glial cell in assisting primary neuronal migration
- to know our current understanding of the mechanism of neural cell migration along glial fibers
- to have a working understanding of the original research study presented in class (purpose, methods, results, conclusions and next directions.

Axon Outgrowth and Pathfinding

-to be familiar with the general structure of a growth cone and its cytoskeletal components

-to understand the essential mechanism by which a growth cone is thought to advance and move forward

-role of polymerization and depolymerization of actin filaments

-role of the substratum (also: what are thought to be the active components of the substratum, and how do they effect the neuronal cytoskeleton?)

-to understand the concept of growth cone guidance by attractive and repulsive cues

-which model appears more correct: Do axons advance fairly randomly, and are later fine tuned as they get closer to their target, or do they grow along very pre-set (stereotyped) trajectories throughout their progress?

-to understand the concept of stepwise neuronal migration between specific guidepost cells

-to know that, in the development of larger nerve tracts, earlier extending axons ("pioneers") serve as a scaffold for the rest that subsequently grow in

-While navigating each segment, axons respond to a host of attractive and repulsive cues from both local and long range sources. One objective is to understand the general nature and mechanism of three types of cues:

-those that "hem in" the growth of axons along a specific track

-those that "pull" axons in a specific direction

-those that "push" the growth of axons along from behind

-to know several examples of molecules which are thought to mediate the local, as well as long range guidance of developing axons

-extracellular matrix molecules

-cell surface molecules

-semaphorins and netrins

-growth factors

-Ig superfamily proteins

Target Selection and Topographic Mapping

-to understand the concepts and experimental examples presented in the videotape during class

Formation of Synapses

-to review the structural and functional specializations that make up a synapse, such as active zones, synaptic vescicles, post-junctional folds and basal lamina

-to understand that specializations in the post-synaptic membrane, such as clusters of neurotranmitter receptors, are induced by factors coming from the incoming axon (in the neuromuscular junction model)

-to know that the synaptic basal lamina is a "repository" for many of the molecular signals that direct the development of both the presynaptic and postsynaptic elements

-to understand the functions of agrin, a substance deposited into the basal lamina by the developing motor neuron terminal

-to understand the function of MuSK, a tyrosine kinase receptor which binds agrin and mediates it's signals to the post-synaptic cell, and also initiates signals back to the presynaptic (nerve) ending to settle and synthesize it's own specializations

-to understand how scaffolding proteins such as rapsyn participate in the development of post-synaptic specializations such as neurotransmitter receptor clusters

-to understand the role of neuronal activity in synapse formation, both in the neuromuscular junction model and in the CNS

Cell Death During Development

-to know the definition of Programmed Cell Death (PCD) as a normal developmental process (as opposed to injury-induced or pathological cell death)

-to understand the role of retrograde signals from target tissue in cell death, and to know the initial evidence supporting a trophic hypothesis (rather than a recruitment hypothesis) for cell survival

-to understand that PCD can occur at all stages in nervous system development, but is most thoroughly studied the time of synapse formation and establishment (and is less common after synaptic connections are well established)

-to know the essential differences between apoptosis and necrosis as mechanisms of cell death

-to understand the concepts of intrinsic versus extrinsic signals for the "cell fate" of PCD (also referred to as autonomous specification versus conditional specification).

-to know the various sources of trophic signals, in addition to the target tissue (i.e. glial-derived, afferent-derived), which can regulate cell death and survival

-to understand what effect ablation/reduction or increases in target cell populations (as well as afferent inputs) would have on the degree of neuronal death

-to understand that PCD is an active and genetically regulated process (rather than a passive "starvation" due to the absence of certain signals)

-to understand how neurotrophic molecules may function as extracellular signals to inhibit the expression or activity of proteins produced by cell death genes such as caspases, or to increase the expression or activity of cell death inhibiting genes such as bcl-2

-to know the basic intracellular mechanism thought to be involved in the activation of apoptosis (in the worm as well as the mouse)

- to have a working understanding of the original research study presented in class (purpose, methods, results, conclusions and next directions)

Growth Factors

-to review and understand the concept of target-derived neurotrophic signals and their contribution to neuronal survival (the neurotrophic hypothesis)

-to know the story behind the discovery of nerve growth factor (NGF), and to know the growth factors that make up the neurotrophin family

-to know the various receptors that are responsive to neurotrophins, such as the p75 and tryrosine kinase (trkA-C) receptors, and to understand the basic intracellular signaling mechanisms by which neurotrophins can direct gene expression within the neuron (i.e. the PI-3 kinase pathway and the ras-MAP kinase cascade)

-to understand the roles that the neurotrophins and other growth factors play in the development of the peripheral nervous system

-their role in the early establishment of neuronal cell fate
-their role in the survival and maintenance of sensory neurons during development

-to know the other functions besides cell survival signaling which neurotrophins serve in the CNS (both during development and in the adult)

-to know the various sites of neurotrophin synthesis and release in the CNS (both at the level of the cell, and major brain areas)

-to know the major functions of BDNF, NGF, NT3 and NT4/5 in the CNS

-to understand the role of various forms of physiological and neuronal activity in the regulation of neurotrophin transcription and synthesis

-to understand the way that neurotrophins regulate synaptic function in both short- and long-term manners

-to know the major classes and general functions of cytokines (several additional growth factor families) such as:

neuropoietic cytokine family (CNTF, LIF)
TGF superfamily (including GDNF, TGFs, FGFs and IGF)

Synapse Elimination and Remodeling

-to understand that synapse elimination is an important developmental process which refines neuronal input after initial multiple, often diffuse contacts

-to understand the functional reason for synapse elimination in the development of muscle and its innervation

-to understand the concepts of decreased convergence and decreased divergence during development of synaptic connections

-to understand that developmental synapse elimination does not always diminish the total number of synapses for a particular target (redistribution can occur)

-to understand the concept of synaptic strength

-to know the basic mechanisms of synaptic removal (cell death, gradual withdrawal of synapses), and to understand how post-synaptic changes (decreased neurotransmitter receptors, for example) can precede and possibly trigger axonal withdrawal

-to understand how activity level at the synapse can determine synaptic survival or elimination

model from the visual system:
-to understand the basic process of synapse elimination and refinement that goes into the formation of ocular dominance columns, and to know the importance of this arrangement in terms of refining inputs to the brain from each eye, and the formation of retinotopic maps

-to understand how, in general, neuronal activity level determines the “competition” between axons as visual connections are remodeled and ocular dominance columns are formed

Developmental Learning

-to understand the concept of a sensitive period during the development of neuronal connection patterns, and to know the definition and importance of the critical period (a specific and more extreme version of a sensitive period).

-to understand that the receipt of appropriate signals during the critical period is important for the normal processing of information later in life. Therefore, the critical period is key for various types of perception as well as behavior.

-to understand why these neuronal patterns are not coded entirely genetically and "pre-set", but that genetic "filters" may exist to limit the possibilities of responses in an animal.

-to know which neurotransmitter receptor system mediates many of the signals that drive experience-induced plasticity in several example systems.

Example systems:
-to understand, in a general way, how a "map" of auditory space is developed in the midbrain of the barn owl in order that movements of the head and eyes can be coordinated. What are the cues? What is the anatomical pathway?

-to understand how both genetic instruction and learning are integrated in the development of birdsong.

-to know the two critical periods that exist for song memorization and vocal learning, and to understand what will happen if the bird is isolated or deafened during critical periods. In general, what determines the closing of sensitive periods?

-to know, in general, the anatomical pathways involved in birdsong development, and to understand what is known about the influence of sex hormones on the development of birdsong.

-what is known about the role of a sensitive period in shaping the temperament of rats?

-to be able to understand and describe the process of imprinting, and the influence of sensitive periods on this process.

ADA: Reasonable accommodation will be provided to any student who is registered with the Office of Students with Disabilities and requests needed accommodation.