NTP/Physiology 629; Fall 2016. Cell and Molecular Mechanisms of Memory.

Lecture 1. September 6. (start with very brief discussion of structure of the class,grading, etc.)

Major concepts in memory and in synaptic memory. (Synaptic Memory denotes the changes in synapses that are the underlying bases for memory.)

Essential synaptic changes for memory formation in a cell assembly according to Hebb's postulate. How these allow formation of memory.
Concept of Pattern Completion.
Long Term Potentiation and Long term Depression. Synaptic Memory Models.
Different durations of memory; different processes
The hippocampal slice used to study these and formulate important properties of LTP and LTD.
Outlines of Events at the synapse that cause LTP or LTD. The key role of calcium. The key role of new receptor insertion.
Outline of Molecular structure at the synapse and how it can be altered.
This as essence of the course.

Lectures 2,3. September 13, 20.

Calcium and synaptic plasticity. Kinetics of calcium at the synapse and the properties of glutamate receptors.

The synapse components.
Measuring calcium in cells and synapses.
Calcium movements and homeostasis at 'resting' synapse.
Properties of the different types of post synaptic glutamate receptors; their roles in calcium movements.
Calcium movements as a result of neuronal and synaptic activity.
Calcium changes associated with LTP. Roles of key types of glutamate receptors in LTP generation.
Principles of how calcium causes changes in protein functions-calcium binding proteins.
Specific role of calmodulin and neurogranin. Regulation of calmodulin.

Lecture 4. September 27

Signaling molecules at the synapse. Protein Kinases, Protein Phosphatases, small GTPases and other Calcium-binding proteins.
These are the molecules which, in general, are regulated by calcium or metabotropic receptors and which act on the proteins involved in synaptic function to cause the events of LTP or LTD.
Important Kinases, phosphatases and GTPases:
how they are activated; how they are localized to critical spots in the synapse Some important targets of these signaling molecules.

Lectures 5,6 . October 4,11.

Spine Structure and the Post Synaptic Density. The synaptic proteins that are critical for basal function and LTP.

Overview of the spine and post synaptic structures..

Optical techniques for measuring the identities, the interactions and the dynamics of proteins in the spine and post synaptic density and dendrites. Focus on the many types of measurements using fluorescence.
Detailed structure of the post synaptic density and spine. Focusing on the different classes of proteins that make up the synapse.
Scaffolding Proteins (e.g.PSD95,AKAP), Structural/Action Proteins (e.g. Actin), Transmitter Receptors, Transmitter Receptor Auxilliary Proteins (e.g. the TARPS), Protein Kinases (e.g. CaMKII).
How the synaptic molecules are put together to maintain stability and how molecular changes are able to alter these molecules in response to neural activity. The roles of protein palmitoylation.

Lecture 7. October 18
Spine Actin and the PSD during neural activity.
Dynamics of actin in the resting state and how actin polymerization and structure is altered by synaptic activity during LTP (and LTD).
'Structural' LTP and the role of actin in LTP.
The role of microtubules during LTP.
Structural changes in the PSD during stimuli that relate to LTP.

MID TERM EXAM HANDED OUT OCTOBER 20. Due back October 24th. Will include material from Lecture 7.

Lecture 8 October 25
Basal Regulation of the AMPA receptors (also known as GluR's).
Synthesis and cycling of the GluR's, exocytosis and endocytosis in the spine membrane and movement through the PSD.
The roles of receptor binding scaffolding proteins (e.g. GRIP) and of the auxiliary proteins, TARPS (e.g. Stargazin) in this process and on the transmission properties of the receptors.
Roles of protein kinases CaMKII , PKC, and PKA in this process.

Lecture 9,10 November 1,8.
The full sequence of events that occur after the LTP stimulation that lead to e-LTP.
Go through the processes that contribute to the final insertion and maintenance of the GluR's in the PSD following the initial LTP stimulus. Focus on tetanic stimulation but also consider TBS and STDP. In these two lectures we integrate what we have learned about synaptic structure and function and regulation, and add in new information, to put together a reasonable description of how LTP occurs. We orient the discussion of the processes that occur, starting with the activation of the NMDA and metabotropic glutamate receptors by the released glutamate, towards explaining LTP as well as possible. We focus on the insertion and the maintenance, removal and regulation of added GluR's. We will revisit some of what we have done before but put it all into an "action framework" trying to clarify the many interactive processes.

Nov 15. No Lecture. Society for Neuroscience Meeting.

Lecture 11,12 November 22,29

Long lasting LTP (l-LTP).

The mechanisms overlap somewhat with those of e LTP but there are additional events, resulting from the strong stimulus, that dramatically alter the protein changes to allow for prolonged maintenance of the LTP. There is a great deal that is still unknown about this process. (I am hoping to bring back some new info from the Neuroscience Meeting!!) Major ideas involve the requirement for new mRNA and protein synthesis; the thorough and intriguing identification of a candidate molecule which very strongly determines the prolonged persistence of LTP (Protein Kinase M zeta); and postulates of several other candidates, including CaMKinaseII interaction with the NMDA2B receptor, and the Prion-like CPEB molecule..

Discuss for both e-LTP and l-LTP how strong the evidence is that these processes do underlie memory.

Lecture 13,14, December 6,13.

Long Term Depression (LTD).

Overview of the mechanisms that lead to long term depression at the synapse, both short term and long term. These involve many of the same players as involved in LTP, but many that are unique to LTD. In contrast to LTP, LTD largely involves destabilization and removal of the receptors. Mechanisms are very different from those that lead to LTP and are somewhat more exotic!!

FINAL EXAM WILL BE HANDED OUT THURSDAY DECEMBER 15th. DUE IN BY THE END OF FINALS WEEK.

That's it for now.

Description of the Course

General Approach

This is an advanced course in how memories are created at the level of the synapses- how the molecular composition of the synapse is changed to allow memories to be formed. A memory, which is a sensation, is the result of a change in interactions between different regions of the brain. However, this change at the systems level is a result of increases and decreases in the strengths of a vast number of participating synapses. These strength changes result from complex changes in the molecular compositions of synapses and the subject matter of this course is to understand the causes and the details of these molecular changes. This 'molecular' approach is distinguished from a 'systems' approach (taught in NTP/Physiology 630) in which the molecular and synaptic changes are taken as occurring and memory is understood in terms of alterations in brain activity patterns.

I call the course 'advanced' for a few of reasons. The first is that I assume that you are all energetically tracking, as best you can, the class. Doing the reading, keeping up with the lectures etc. The second is that the readings are almost all from published writings: either

review articles or original papers. There is some textbook or WEB background material but that is all for your background. It should be helpful but almost all the specific knowledge in the course is derived from published work, some as recently as last month!.. The third reason is that you will, to a significant degree, be working a bit over your heads and working with experimental results.. You will need to understand difficult papers, with techniques that are new to you and present material that we haven't necessarily covered in lecture, and you will need to talk about these, to me and your fellow-students. This being said, I am cognizant of your levels, and my major aim is that you get a lot out of the course, at the level you are able. That is, I know the stuff is hard, but my goal is that you get an understanding that is rewarding to you. I am hoping to help you appreciate the nature of experimental neurobiology, as it is being practiced now, and the exciting things we are finding out. For that reason the course is very much oriented towards learning to understand, and start thinking about past and current experimental results, with an emphasis on the latter. The structure of the course, where there is a lot of face to face time between me and all of you, is nice and conducive to this.

Overall Goal

This is pretty simple, in what it states, and is that I am hoping that you each get an appreciation of the 'amazingness' of biology and, in this course, of the ability we have to form memories! The way I hope this happens is for you to learn about and think hard about, and be creative about, the complexity of how synapses are regulated to be able to form and erase memories, and to hold memories for hugely varying amounts of times. These events involve biological principles about how biological molecules 'work' of which we have almost no understanding, and can hardly believe. We want to get insight here into what those principles might be and how they are put into play by the interactions between molecules at the neuronal synapse. Ultimately I'd like you all to get a satisfactory (to you) idea of how, indeed, we may actually form memories- they are not a figment of our imagination!! (or are they???).

Overall Course Structure

The course has Four components.
1. The lectures. 11-12:50 on Tuesdays
2. Quizzes. 1 per week
3. Discussion Groups. 1 session for each student per week. There are 6 discussion groups each with 12 students.
4. Mid Term and Final Take Home Exams.

Lectures.

The lecture schedule is at the end of this posting. Lectures are in **Rm 290 Nutritional Sciences**. This is a kind of a little known treasure of a building with a very nice lecture room. When you are all there it will be pretty much full. There is a screen for power points and a blackboard, which I tend to use a great deal. In general, the power points are used to illustrate complex structures or to illustrate experiments and models-mostly for experiments.

In general we will take a 10 minute break sometime in the near middle of class where you can indulge your needs or desires.
Expectations for you are that you do attend all the lectures but no attendance will be taken. It is also hoped that you will ask and answer questions in class. **PLEASE be encouraged to ask any questions; I love them.**

Quizzes
Each week except the first there will be a paper handed out that is relevant to the next week's lecture that you should read before the lecture. This will generally be a review paper or sometimes a chapter from a text. It will be handed out on the **Thursday** before the lecture and you will have till **Tuesday morning** before the lecture to answer a short WEB quiz, which is aimed at making sure you have read some key points of the paper. **The Quiz will be posted by Friday at 5 p.m.** These will be questions which you can answer from the reading alone, though you may have to put some things together to get the answer. Of 4 questions three will always be very straightforward Just extract from the reading) and one may need to be thought about a bit. **These will be for 20% of the grade.**

Discussion Groups
General Format These are all in Rm 116 SMI.
Each student will go to one discussion group per week- the one you signed up for when you registered. **Please Check you are in the right one**! Except for the first week the discussion groups will be centered around your individual presentations of the **Paper Improvements (PI's).** Every other week you will be a **Presento**r in which you present your PI. In the alternate weeks you will be a **Responder**; in these you will be expected to comment on one of the answers that was presented by another student. I'll let you know which particular one you should comment on before the class starts so you can be sure to be 'on it' for that one. **Presentors** will each have a max of 5 minutes to present your PI to the group. Responders will have about 2 minutes and we'll have a minute or so for a group discussion. I will set out a schedule early in the semester so you know which weeks you will be a presentor and which weeks you will be a responder.
The PI's will be for 30% of the grade; presentors and responders will each be graded.

Details of the Paper Improvements (In the first week I will do mock PI's.)
Presentor. On the Thursday of the week before your discussion group each student will receive the same published paper. If you are a **presentor** your job will be to read the paper, and to come up with an experiment, or a discussion point, that will "improve" the paper. Improve for our purposes means to add on something which you think makes the paper more interesting, or better (if you see a flaw). For example, this could be an experiment they didn't think of, or didn't do, that you think would add something interesting to the paper by enhancing the conclusions they could draw. Or it could be a slightly (or very) different interpretation of the results than the ones the authors made. Or it can be something new in the Introduction that makes the resuts of the experiment more interesting to do. These can be quite 'far out'; the only criterion is that they have some

feasibility (you cannot propose doing the same experiment on Mars for example.). I am very much looking for creativity, but it is not at all essential and competency is equally rewarded! You can have notes etc of course but grading will be done entirely on the oral presentation and discussion-no power points. **NOTE. In the first week I will do mock PI's to illustrate these different approaches!**
I realize these will be difficult, particularly if you have trouble speaking in public, or have very little or no familiarity with actual research. The idea is not to 'down' you, but to use these as a learning experience and to **look carefully at improvement through the semester**.

Expectation and Grading for Presentors of PI's.
These will all be graded on the spot, tho' silently, by me. In order for me to do this you will need to all try to have a similar structure to your PI's.
1.Why are you choosing what you choose to do? (What is the gap you are filling? What is the new thing you want to know?)
2.Describe what you will do.
3.Provide some experimental detail (essential detail).
4.Describe what you expect to find.
5.Short summary of what will have been accomplished with respect to why you chose to do the experiment.
Note an unusual but somewhat feasible idea is the best and will always get high marks. However, an overall good job can also get high marks.

Responder (Note: You should have read he paper and thought about it before the Discussion Group.)This is actually the more difficult of the two roles as you are suddenly presented with something new and have very little time to prepare a question. (And in some cases the presentation may have been quite confused.) Thus, expectations are not great. The main thing is that you ask a question that in some way relates to what the presentor said. This might well be to explain something more clearly, or 'what would happen if you had added X first instead of after etc.?) The expectation is that it will not just be random but will reflect having listened to and tried to understand what has been said. The more clearly pertinent the question, the higher the grade.

Take Home Mid Term Exam
I will hand out the mid term on **THURSDAY OCTOBER 20**. It will be a timed take home mid term and you will have 2.5 HOURS to do it, from the time you first look at it. You can select any **continuous** 2.5 hour period between when it is handed out and Midnight on **MONDAY, OCTOBER 24th**. It will be a short answer exam and you'll have a choice of 3 questions out of 6. It will be timed so that you should be able to finish in about two hours. You can use any reading material including the WEB. (ALL answers must be in your own words!!)
This will be for 20% of your grade.
THERE WILL BE NO QUIZ HANDED OUT FOR THE TUESDAY 25th LECTURE.

Take Home Final Exam

This will be roughly the same format as the mid term, with the same ground rules. It will be handed out on THURSDAY DECEMBER 15th and you can do it any time between then and the end of finals week. It will be comprehensive but questions will all be focused on the last half of the course. (They may involve some factual material from the first half.)
This final exam will be for 30% of the grade.

Overall Letter Grades.
The class will not be curved. After the mid term is graded a letter grade-numerical grade schedule will e distributed.

Note on Faculty-Student Interactions There is no TA for this class. The only effect this will have on you is that the mid term grade will not be gotten back to you til about 3 weeks after you take the exam…oh, and also, and you have no one to complain to about me!!! SO,.PLEASE COMPLAIN TO ME!!!. I am very anxious to hear your comments about how well I am communicating the material and dealing with the WEB etc. This can be during class, either in lecture or in the breaks, or can be at any other time if we arrange office hours. I have no official office hours but am generally very amenable to meeting with any of you, either alone or in groups.

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