PSYC G4440x sec.3 (Brew) Preliminary Syllabus

Topics in Neurobiology and Behavior: Focus on Autism-related Research G4440
Fall 2015, Mondays 4.10-6PM
Schermerhorn (room number TBD)
Instructor: Helen Brew, PhD
Email: hbrew@mac.com
Office hours: Wednesday 3-5pm, Schermerhorn (room number TBD)

Course overview: We will explore the relationship between neurobiology and behavior, specifically considering how far neurobiological experiments can elucidate a human behavioral disorder, using as our main example autism (autism spectrum disorder, or ASD). We'll look at studies on both animals and humans, at the behavioral, systems, cellular, molecular and genetic levels. Questions to be considered will include: What makes a good animal model of ASD? Can neurobiological experiments on animals lead to treatments for ASD? Can any oddities of animal behaviors be considered directly analogous to those comprising a human behavioral disorder? Due to the large number of genes implicated in ASD, will the future bring "personalized medicine" with dedicated animal or human stem cell models for every person with ASD? Which of the various theories of autism are most compelling? What types of environmental insult contribute to ASD? What are the links between the immune and nervous systems in ASD? How do current behavioral findings from people with ASD drive neurobiological research?

Prerequisites: Mind, Brain and Behavior (Psych 1010) or an equivalent biological-based psychology class is required. Courses in statistics, research methods or genetics would be helpful, but are not required. The permission of the instructor is required in order to register.

Course objectives: This course fulfills the Seminar Requirement for the Psychology Major and the Advanced Seminar Requirement for the Neurobiology and Behavior Major.

The goals of this course are:

- to gain an advanced understanding of neurobiological research related to ASD by reading primary scientific literature
- to gain an advanced understanding of current knowledge on the neurobiology of ASD
- to read, understand and orally present primary scientific literature from psychology and neuroscience journals
- to be able to critically evaluate published research and discuss its merits, caveats and alternative interpretations
- to develop a review commentary or research proposal on a research topic by reading and evaluating published research

Course requirements: Weekly readings/assignment and participation (25%): You will be expected to carefully read two or three scientific research papers each week. The chosen papers will usually be primary research reports from seminal findings on the topic of the week. Some basic background knowledge of the topic is expected. In some cases, this may need to be supplemented through textbooks or other references cited in the assigned reading. Everyone will post a substantial comment, thought or question on the paper before class on the Discussion Board of Courseworks, which will serve as a basis for discussion during class.

Presentation of two papers (40%): Each week, 2 or 3 of you will present one of the assigned readings in an approximately 30 minute slide presentation and initiate a short discussion of the paper. Each student will present 2 papers during the semester. Written feedback will be provided one week following the presentation.

Research proposal or review paper (35%): A term project will be required, on a topic of your choosing from material covered during the seminar (~10-15pg). It may consist of either a research proposal or a research review paper. Detailed information will be given at the start of the course. The project will require that you meet individually with the instructor to get approval on the topic and outline. Outline due November 16th, for a ten minute presentation of your paper on December 14th, the final day of classes.

Class policies: Attendance: You are expected to come to class each week prepared to discuss the assigned papers. Your unexcused absence will be noted and reflected in your participation grade. Make-up 'participation' for preapproved excused absences will be arranged on an individual basis.

Assignments: Paper presentations are assigned based on solicited preferences during the first week of the semester and once assigned may not be changed. In the case of a documented medical or family emergency, alternate arrangements will be made to present the paper individually during office hours. The due date for the term paper is firm, and as such, one letter grade will be deducted for each day it is late.

Academic Integrity: "The intellectual venture in which we are all engaged requires of faculty and students alike the highest level of personal and academic integrity. As members of an academic community, each one of us bears the responsibility to participate in scholarly discourse and research in a manner characterized by intellectual honesty and scholarly integrity. . . . In practical terms, this means that, as students, you must be responsible for the full citations of others' ideas in all of your research papers and projects; you must be scrupulously honest when taking your examinations; you must always submit your own work and not that of another student, scholar, or internet agent." From the Faculty Statement on Academic Integrity - www.college.columbia.edu/academics/integrity-statement. Cheating on assignments or exams and plagiarism are very serious violations within the academic community. Students are expected to do their own work on all tests and assignments for this class. You are expected to always act in accordance with the Columbia honor code. Any student found cheating or plagiarizing in this class will be reported to Columbia's Office of Judicial Affairs and Community Standards for evaluation and academic discipline. If you have questions about any aspect of academic integrity at Columbia, please refer to the following link: www.college.columbia.edu/academics/integrity and if you have specific questions about the judicial process, please see www.college.columbia.edu/academics/disciplinaryprocess.

Class Schedule

(Please note that readings and topics may be subject to change based on enrollment number and student preferences. And that September 7th is Labor Day, so no class).

Week 1. September 14th. ASD and theories of ASD.

Introduction to seminar, including information on: course format, evaluation, discussion board posts, presentation of papers, class discussion, term paper. Introduction to ASD: the clinical definition and diagnosis of ASD; syndromic versus non-syndromic ASD. Theories of autism: excitatory-inhibitory imbalance, theory of mind, (vaccines), environmental effects, neural disconnection, overgrowth, male brain, noisy brain, synaptic dysfunction, pathological mTOR activation.

Rubenstein, J. L. R., & Merzenich, M. M. (2003). Model of autism: increased ratio of excitation/inhibition in key neural systems. *Genes, brain, and behavior*, *2*(5), 255–67.

Lázaro, M. T., & Golshani, P. (2015). The utility of rodent models of autism spectrum disorders. *Current opinion in neurology*, *28*(2), 103–9.

Dinstein, I., Heeger, D. J., Lorenzi, L., Minshew, N. J., Malach, R., & Behrmann, M. (2012). Unreliable evoked responses in autism. *Neuron*, *75*(6), 981–91.

Hahamy, A., Behrmann, M., & Malach, R. (2015). The idiosyncratic brain: distortion of spontaneous connectivity patterns in autism spectrum disorder. *Nature Neuroscience*, *18*(2), 302–9.

Week 2. September 21st. The behavioral neuroscience of autism.

Biological motion perception, face recognition, studies of baby siblings of kids with ASD, movement abnormalities.

Damiano, C. R., Nahmias, A., Hogan-Brown, A. L., & Stone, W. L. (2013). What do repetitive and stereotyped movements mean for infant siblings of children with autism spectrum disorders? *Journal of autism and developmental disorders*, *43*(6), 1326–35

Elsabbagh, M., Mercure, E., Hudry, K., Chandler, S., Pasco, G., Charman, T., Pickles, A., et al. (2012). Infant neural sensitivity to dynamic eye gaze is associated with later emerging autism. *Current biology : CB*, *22*(4), 338–42.

Week 3. September 28th. The genetics of ASD. How much of the risk for ASD is inherited? Specific genes conferring risk. Chromosomal deletions and duplications conferring risk.

Gaugler et al. (2014) Most genetic risk for autism resides with common variation. Nature Genetics, Aug;46(8):881-5.

Chang, J., Gilman, S. R., Chiang, A. H., Sanders, S. J., & Vitkup, D. (2014). Genotype to phenotype relationships in autism spectrum disorders. *Nature Neuroscience*, *18*(2), 191–8.

Week 4. October 5th. What makes a good animal model? Is it possible to model ASD?

Face validity, construct validity and predictive validity. Which is most important for which type of testing? Which (if any) animal behaviors are analogous to human ASD behavioral symptoms? Consideration of developmental age, and species and strain differences.

Ellegood, J., Anagnostou, E., Babineau, B. A., Crawley, J. N., Lin, L., Genestine, M., DiCicco-Bloom, E., et al. (2015). Clustering autism: using neuroanatomical differences in 26 mouse models to gain insight into the heterogeneity. *Molecular psychiatry*, *20*(1), 118–25.

Drapeau, E., Dorr, N. P., Elder, G. A., & Buxbaum, J. D. (2014). Absence of strong strain effects in behavioral analyses of Shank3-deficient mice. *Disease models & mechanisms*, *7*(6), 667–81.

Week 5. October 12th. What do we know about the neurobiology of ASD?

Stoner, R., Chow, M. L., Boyle, M. P., Sunkin, S. M., Mouton, P. R., Roy, S., Wynshaw-Boris, A., et al. (2014). Patches of disorganization in the neocortex of children with autism. *The New England journal of medicine*, *370*(13), 1209–19.

Voineagu, I., Wang, X., Johnston, P., Lowe, J. K., Tian, Y., Horvath, S., Mill, J., et al. (2011). Transcriptomic analysis of autistic brain reveals convergent molecular pathology. *Nature*, *474*(7351), 380–4.

Week 6. October 19th. Mouse models of syndromes associated with ASD, part I: Fragile X syndrome and Rett syndrome

Henderson, C., Wijetunge, L., Kinoshita, M. N., Shumway, M., Hammond, R. S., Postma, F. R., Brynczka, C., et al. (2012). Reversal of disease-related pathologies in the fragile X mouse model by selective activation of GABAB receptors with arbaclofen. *Science translational medicine*, *4*(152), 152ra128.

Chao, H.-T., Chen, H., Samaco, R. C., Xue, M., Chahrour, M., Yoo, J., Neul, J. L., et al. (2010). Dysfunction in GABA signalling mediates autism-like stereotypies and Rett syndrome phenotypes. *Nature*, *468*(7321), 263–9.

Derecki, N. C., Cronk, J. C., Lu, Z., Xu, E., Abbott, S. B. G., Guyenet, P. G., & Kipnis, J. (2012). Wild-type microglia arrest pathology in a mouse model of Rett syndrome. *Nature*, *484*(7392), 105–9.

Week 7. October 26th. Mouse models of syndromes associated with ASD, part II: Angelman syndrome, Timothy syndrome.

Wallace, M. L., Burette, A. C., Weinberg, R. J., & Philpot, B. D. (2012). Maternal loss of Ube3a produces an excitatory/inhibitory imbalance through neuron type-specific synaptic defects. *Neuron*, *74*(5), 793–800.

November 2nd is an academic holiday.

Week 8. November 9th. Are particular parts of the brain abnormal in ASD?

Where in the brain should we look, based on behavioral evidence from people with ASD? Which parts of the brain are abnormal in mouse models of ASD? (E.g. striatum, forebrain, cerebellum).

Peça, J., Feliciano, C., Ting, J. T., Wang, W., Wells, M. F., Venkatraman, T. N., Lascola, C. D., et al. (2011). Shank3 mutant mice display autistic-like behaviours and striatal dysfunction. *Nature*, *472*(7344), 437–42.

Han, S., Tai, C., Westenbroek, R. E., Yu, F. H., Cheah, C. S., Potter, G. B., Rubenstein, J. L., et al. (2012). Autistic-like behaviour in Scn1a+/- mice and rescue by enhanced GABA-mediated neurotransmission. *Nature*, *489*(7416), 385–90.

Xiong, Q., Oviedo, H. V, Trotman, L. C., & Zador, A. M. (2012). PTEN regulation of local and long-range connections in mouse auditory cortex. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, *32*(5), 1643–52.

Week 9. November 16th. Other mouse models of ASD.

Genes: Cdh8, Adno, Ank2, Cntnap2 (Shank3, Pten, Scn1a already covered above). Pathways: mTOR. Chromosomal deletions and duplications. BTBR mouse strain. Non-rodent models.

Peñagarikano, O., Abrahams, B. S., Herman, E. I., Winden, K. D., Gdalyahu, A., Dong, H., Sonnenblick, L. I., et al. (2011). Absence of CNTNAP2 leads to epilepsy, neuronal migration abnormalities, and core autism-related deficits. *Cell*, *147*(1), 235–46.

Han, S., Tai, C., Jones, C. J., Scheuer, T., & Catterall, W. A. (2014). Enhancement of inhibitory neurotransmission by GABAA receptors having α2,3-subunits ameliorates behavioral deficits in a mouse model of autism. *Neuron*, *81*(6), 1282–9.

Week 10. November 23rd. Which brain mechanisms are abnormal in ASD?

Synaptic pruning, neuronal migration, neuronal overgrowth, neuronal connections. Evidence from mouse models. The relationship between the immune system, brain development and ASD.

Tang, G., Gudsnuk, K., Kuo, S.-H., Cotrina, M. L., Rosoklija, G., Sosunov, A., Sonders, M. S., et al. (2014). Loss of mTOR-Dependent Macroautophagy Causes Autistic-like Synaptic Pruning Deficits. *Neuron*, *83*(5), 1131–43.

Durand, S., Patrizi, A., Quast, K. B., Hachigian, L., Pavlyuk, R., Saxena, A., Carninci, P., et al. (2012). NMDA receptor regulation prevents regression of visual cortical function in the absence of Mecp2. *Neuron*, *76*(6), 1078–90.

Won, H., Lee, H.-R., Gee, H. Y., Mah, W., Kim, J.-I., Lee, J., Ha, S., et al. (2012). Autistic-like social behaviour in Shank2-mutant mice improved by restoring NMDA receptor function. *Nature*, *486*(7402), 261–5.

Week 11. November 30th. Treatment approaches suggested by mouse models of ASD

Huang, H.-S., Allen, J. A., Mabb, A. M., King, I. F., Miriyala, J., Taylor-Blake, B., Sciaky, N., et al. (2012). Topoisomerase inhibitors unsilence the dormant allele of Ube3a in neurons. *Nature*, *481*(7380), 185–9.

Bozdagi, O., Tavassoli, T., & Buxbaum, J. D. (2013). Insulin-like growth factor-1 rescues synaptic and motor deficits in a mouse model of autism and developmental delay. *Molecular autism*, *4*(1), 9.

Kolevzon, A., Bush, L., Wang, A. T., Halpern, D., Frank, Y., Grodberg, D., Rapaport, R., et al. (2014). A pilot controlled trial of insulin-like growth factor-1 in children with Phelan-McDermid syndrome. *Molecular autism*, *5*(1), 54

Week 12. December 7th. Can cells in dishes help find ASD treatments?

Shcheglovitov, A., Shcheglovitova, O., Yazawa, M., Portmann, T., Shu, R., Sebastiano, V., Krawisz, A., et al. (2013). SHANK3 and IGF1 restore synaptic deficits in neurons from 22q13 deletion syndrome patients. *Nature*, *503*(7475), 267–71.

Paşca, S. P., Portmann, T., Voineagu, I., Yazawa, M., Shcheglovitov, A., Paşca, A. M., Cord, B., et al. (2011). Using iPSC-derived neurons to uncover cellular phenotypes associated with Timothy syndrome. *Nature medicine*, *17*(12), 1657–62.

Krey, J. F., Paşca, S. P., Shcheglovitov, A., Yazawa, M., Schwemberger, R., Rasmusson, R., & Dolmetsch, R. E. (2013). Timothy syndrome is associated with activity-dependent dendritic retraction in rodent and human neurons. *Nature neuroscience*, *16*(2), 201–9.

Week 13. December 14th. Which theories of ASD are the most compelling? Which research should be most urgently funded?

Presentations of Term Papers: Persuade the class of your opinion or convince the class that we should fund your research proposal (10 minutes each). No assigned reading this week.