Topics in Neurobiology and Behavior: Focus on Autism-related Research G4440
Fall 2017, Mondays 4.10-6PM
Schermerhorn 405
Instructor: Helen Brew, PhD
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Office hours: Wednesday 3-5pm, Schermerhorn 356

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 (15%): 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. Ideally, obtain help with your presentation from Dr. Brew well before class, e.g. during Wednesday office hours.

Research proposal or review paper (30%): 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 13th.

Short presentation based on term paper (5%): Each student will give a **ten minute presentation** of an interesting aspect of their term project paper on December 11th, the final day of class.

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. Papers in parentheses are optional extras).

Week 1. September 11th. 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.

> 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. An example of a neurobiologically measured difference between male adolescents with autism and controls.
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> (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). The first paper to suggest this as the neural cause of autism. This paper introduced one of the well-known theories of autism: excitatory/inhibitory imbalance. The fact that epilepsy is a common co-morbidity with ASD means this was not all that controversial. The heterogeneity of ASD means it is unlikely to be true of all ASD.

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

(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). Another well-known theory of autism: abnormal connectivity.

Week 2. September 18th. The behavioral neuroscience of autism.
Biological motion perception, face recognition, studies of baby siblings of kids with ASD, movement abnormalities.

Klin, A., Lin, D., Gorrindo, P., Ramsey G., & Jones, W. (2009) Two-year-olds with autism orient to non-social contingencies rather than biological motion. *Nature*, 459(7868), 257-263.

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. A possible biomarker for early screening.

Week 3. September 25th. The genetics of ASD. How much of the risk for ASD is inherited? Specific genes conferring risk. Chromosomal deletions and duplications conferring risk.

Willsey et al., (2013) Co-expression networks implicate human midfetal deep cortical projection neurons in the pathogenesis of autism. *Cell*, 155(5): 997–1007.

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 2nd. 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 9th. 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 16th. Mouse models of two syndromes associated with ASD: Fragile X syndrome and Rett syndrome. Short mid-term exam.

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 23rd. 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 8. October 30th. Characteristics of autism in females

Frazier T.W. *et al. J. Am. Acad. Child Adolesc. Psychiatry*53, 329-340 (2014) Behavioral and cognitive characteristics of females and males with autism in the Simons Simplex Collection.

Head A.M. *et al. Mol. Autism* 5, 19 (2014) Gender differences in emotionality and sociability in children with autism spectrum disorders.

Jacquemont S. *et al. Am. J. Hum. Genet.* 94, 415-425 (2014) A higher mutational burden in females supports a "female protective model" in neurodevelopmental disorders.

……the first and third are two papers from SFARI list of notable papers 2014.

Monday November 6th is an academic holiday.

Week 9. November 13th. The vaccine story.

There is a huge amount of literature on this whole story, which is more sociology (scare journalism, mass hysteria, conspiracy theories) than psychology, let alone neuroscience. Most importantly please read one or both of the epidemiology studies (papers 1 and 2). If someone feels like volunteering to present topic 3….an overview of the whole vaccine scare….great! If not I will lead a structured discussion on various aspects.

1. Jain A[1], Marshall J[1], Buikema A[2], Bancroft T[2], Kelly JP[1], Newschaffer CJ[3]. (2015) Autism occurrence by MMR vaccine status among US children with older siblings with and without autism. *JAMA*, Apr 21;313(15):1534-40.

2. Smeeth L, Cook C, Fombonne E, Heavey L, Rodrigues LC, Smith PG, Hall AJ (2004) MMR vaccination and pervasive developmental disorders: a case-control study. *Lancet,* Sep 11-17;364(9438):963-9.

3. The retracted Wakefield et al paper and commentaries since:

Eggertson, L, (2010) Lancet retracts 12-year-old article linking autism to MMR vaccines. *CMAJ*, Mar 9;182(4):E199-200.

This is a link to a series of papers by the main journalist uncovering what went wrong…….

http://briandeer.com/solved/bmj-secrets-series.htm

RETRACTED Wakefield AJ[1], Murch SH, Anthony A, Linnell J, Casson DM, Malik M, Berelowitz M, Dhillon AP, Thomson MA, Harvey P, Valentine A,Davies SE, Walker-Smith JA (1998). Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet*. Feb 28;351(9103):637-41

Week 10. November 20th. Maternal infection…….immune and gut things….probiotics
(relevant to microglia, synaptic pruning, mTOR)

Lee et al (2015) Maternal hospitalization with infection during pregnancy and risk of autism spectrum disorders. Brain Behav Immun. Feb;44:100-5…..this is a study of 2.4 million people showing risk of autism increases by 37% if Mom hospitalized with infection.

Hsiao et al (2013) Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. Cell. 2013 Dec 19;155(7):1451-63.

Week 11. November 27th. Treatment approaches suggested by mouse models of ASD

Berry-Kravis et al (2012) Effects of **STX209** (arbaclofen) on neurobehavioral function in children and adults with fragile X syndrome: a randomized, controlled, phase 2 trial. Sci Transl Med. 2012 Sep 19;4(152).

Owen-Smith et al (2015) Prevalence and Predictors of Complementary and Alternative Medicine Use in a Large Insured Sample of Children with Autism Spectrum Disorders. Res Autism Spectr Disord. Sep 1;17:40-51.

(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 4th. Can cells in dishes help find ASD treatments?

Mariani J, Coppola G, Zhang P, Abyzov A, Provini L, Tomasini L, Amenduni M, Szekely A, Palejev D, Wilson M, Gerstein M,Grigorenko EL, Chawarska K, Pelphrey KA, Howe JR, Vaccarino FM (2015). FOXG1-Dependent Dysregulation of GABA/Glutamate Neuron Differentiation in Autism Spectrum Disorders. *Cell*, Jul 16;162(2):375-90.

The two news blurb urls below are from the SFARI.org news site, and relate to the Mariani et al article and the general use of induced stem cells, respectively.

https://spectrumnews.org/news/lab-spun-spheres-reveal-common-biology-in-boys-with-autism/

https://spectrumnews.org/opinion/viewpoint/promise-and-pitfalls-of-induced-stem-cells-for-autism/

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 11th. 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.