Topics in Neurobiology and Behavior: Focus on Autism-related Research G4440
Spring 2018, Mondays 4.10-6PM
Schermerhorn 405
Instructor: Helen Brew, PhD
Email: hbrew@mac.com
Office hours: Wednesday 3-5pm, Schermerhorn 356

Course overview: Research on autism spectrum disorder, or ASD, is highly multi-disciplinary, because it is a behaviorally defined disorder known to depend strongly on genetics, with some single candidate genes and their protein products having strong effects. We will explore the nature of ASD by examining studies in genetics, epidemiology, neurobiology and behavior. We will examine the results from neurobiological experiments on animal models of ASD at the behavioral, systems, cellular, molecular and genetic levels. Questions to be considered will include: Is ASD really a single disorder? Which theories of ASD causation are the most compelling? Has there really been a rise in ASD prevalence? 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? Will the future bring "personalized medicine" with dedicated animal or human stem cell models for every person with ASD? 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 direct 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 (20%): You will be expected to carefully and thoroughly read and understand two 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. Each week, Dr Brew will also present relevant background material.

Presentation of two papers (40%): Each week, 2 student leaders will each 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 or more papers during the semester. 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.

Short mid-term (5%): The students take a half-hour long **written midterm quiz** covering the material presented by Dr Brew, in the papers and the class discussions. 15 minutes will be multiple choice questions,

and 15 minutes will be a short essay chosen from three topic options. This will take place on Monday 5th March, and will be with open notes. The main reason for having it is to give me an idea of your writing skills and how well you are keeping up factually, so that I can help you choose an appropriate term project topic.

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, 3,000-5,000 words). 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 March 19th.

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 April 23rd, 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 listed in parentheses are optional background reading……omit or read at any depth…..skim-read to get overview and perspective, or delve further if it suits your particular areas of expertise).

Week 1. January 22nd. What is ASD? Plus introduction to seminar format

Information on: course format, evaluation, discussion board posts, presentation of papers, class discussion, term paper. **Students will select at least one of their presentation topics today.** Please choose one paper from weeks 2-7, the other from weeks 8-12. Everyone will thoroughly read the two papers selected for presentation. (Dr Brew will usually briefly include the remaining one or two papers in her weekly presentations of background material).

Introduction to ASD and theories of autism The clinical definition and diagnosis of ASD, including broadening definition and changes in diagnostic criteria over time. The strong genetic basis of autism, concordance. Theories: Excitatory-inhibitory imbalance, theory of mind, neural disconnection, overgrowth,

male brain, noisy brain, synaptic dysfunction, faulty synaptic pruning, striatum/cerebellum/frontal cortex, environmental effects, (vaccines).

1. 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.

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, in broad terms. However, E/I imbalance must be thought of with caution because a large majority of epileptics do not have ASD.

2. Sztainberg Y, and Zoghbi HY (2016) Lessons learned from studying syndromic autism spectrum disorders. *Nat Neurosci*. Oct 26;19(11):1408-1417.

(Ben-Shalom R1, Keeshen CM2, Berrios KN3, An JY4, Sanders SJ4, Bender KJ5 (2017) Opposing Effects on NaV1.2 Function Underlie Differences Between SCN2A Variants Observed in Individuals With Autism Spectrum Disorder or Infantile Seizures. *Biol Psychiatry*. Aug 1;82(3):224-232). This is quite neuro heavy.

Week 2. January 29th. Examples of behavioral and neurobiological abnormalities in ASD.
Biological motion perception, abnormal cerebrospinal fluid volume, empathy versus social cognition, noisy brain, language. Baby sib studies/biomarkers.

1. 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.

2. Shen MD, Kim SH, McKinstry RC, Gu H, Hazlett HC, Nordahl CW, Emerson RW, Shaw D, Elison JT, Swanson MR, Fonov VS, Gerig G, Dager SR, Botteron KN, Paterson S, Schultz RT, Evans AC, Estes AM, Zwaigenbaum L, Styner MA, Amaral DG, Piven J; Infant Brain Imaging Study Network; Infant Brain Imaging Study Network (2017) Increased Extra-axial Cerebrospinal Fluid in High-Risk Infants Who Later Develop Autism. *Biol Psychiatry*. Aug 1;82(3):186-193).

(Amaral DG, Li D, Libero L, Solomon M, Van de Water J, Mastergeorge A, Naigles L, Rogers S, Wu Nordahl C (2017) In pursuit of neurophenotypes: The consequences of having autism and a big brain. *Autism Res* May;10(5):711-722).

(PSYCH: Swanson MR1, Shen MD1, Wolff JJ2, Boyd B1, Clements M3, Rehg J3, Elison JT2, Paterson S4,5, Parish-Morris J5, Chappell JC1, Hazlett HC1, Emerson RW1, Botteron K6, Pandey J5, Schultz RT5, Dager SR7, Zwaigenbaum L8, Estes AM7, Piven J1; IBIS Network (2017) Naturalistic Language Recordings Reveal "Hypervocal" Infants at High Familial Risk for Autism. *Child Dev*. 2017 Mar 10).

(PSYCH fMRI: Bird G, Silani G, Brindley R, White S, Frith U, Singer T. (2010) Empathic brain responses in insula are modulated by levels of alexithymia but not autism. *Brain*. 2010 May;133(Pt 5):1515-25).

(NEURO fMRI: 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).

(NEURO fMRI: 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 3. February 5th. The genetics of ASD. Chromosomal deletions and duplications conferring risk. Syndromic autism versus "idiopathic" autism. Specific genes conferring risk. Abnormal expression of networks of synaptic genes and microglia genes.

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

2. 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.

(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).

(Sanders SJ, He X, Willsey AJ, Ercan-Sencicek AG, Samocha KE, Cicek AE, Murtha MT, Bal VH, Bishop SL, Dong S, Goldberg AP, Jinlu C, Keaney JF 3rd, Klei L, Mandell JD, Moreno-De-Luca D, Poultney CS, Robinson EB, Smith L, Solli-Nowlan T, Su MY, Teran NA, Walker MF, Werling DM, Beaudet AL, Cantor RM, Fombonne E, Geschwind DH, Grice DE, Lord C, Lowe JK, Mane SM, Martin DM, Morrow EM, Talkowski ME, Sutcliffe JS, Walsh CA, Yu TW; Autism Sequencing Consortium (2015) Insights into Autism Spectrum Disorder Genomic Architecture and Biology from 71 Risk Loci. *Neuron*. Sep 23;87(6):1215-1233).

(Bernier R. et al (2014) Disruptive *CHD8* Mutations Define a Subtype of Autism Early in Development. *Cell* Volume 158, Issue 2, p263–276, 17 July 2014)

(Kong SW, Sahin M, Collins CD, Wertz MH, Campbell MG, Leech JD, Krueger D, Bear MF, Kunkel LM, Kohane IS (2014) Divergent dysregulation of gene expression in murine models of fragile X syndrome and tuberous sclerosis. *Mol Autism*. 2014 Feb 24;5(1):16).

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

Weeks 4 and 5. February 12th.and February 19th. What makes a good animal model? Is it possible to model ASD? Specific syndromes associated with ASD and

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? Repetitive behaviors and social abnormalities. Consideration of developmental age, and species and strain differences. Advances due to CRISPR techniques. Mouse models of synaptic-associated genes implicated in ASD: Fragile X syndrome, Dravet syndrome, Timothy syndrome, *SCN1A* and *SHANK* genes. ASD-related genes that seem less directly related to synapses: Rett syndrome, *CHD8, PTEN, Ube3a*

For these two weeks the four student presenters may pick whichever papers they like the look of:

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.

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.

Selimbeyoglu A, Kim CK, Inoue M, Lee SY, Hong ASO, Kauvar I, Ramakrishnan C, Fenno LE, Davidson TJ, Wright M, Deisseroth K. (2017) Modulation of prefrontal cortex excitation/inhibition balance rescues social behavior in CNTNAP2-deficient mice. *Sci Transl Med*. 2017 Aug 2;9(401).

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.

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.

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.

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*, *32*(5), 1643–52.

VERY PRELIMINARY MONKEY DATA. Zhao H, Tu Z, Xu H, Yan S, Yan H, Zheng Y, Yang W, Zheng J, Li Z, Tian R, Lu Y, Guo X, Jiang YH, Li XJ, Zhang YQ. (2017) Altered neurogenesis and disrupted expression of synaptic proteins in prefrontal cortex of SHANK3-deficient non-human primate. *Cell Res* Oct;27(10):1293-1297.

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. This is also suited to week 12.

Week 6. February 26th Characteristics of autism in females

The two behavioral papers go together, in terms of posting or presenting.

1. 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.

2a. 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.

2b. Head A.M. *et al*. *Mol*. *Autism* 5, 19 (2014) Gender differences in emotionality and sociability in children with autism spectrum disorders.

Week 7. March 5th. Short mid-term quiz for first half hour of class (see Course Requirements section above for more details).

Do particular parts of the brain show structural or functional abnormalities in ASD? Where in the brain should we look, based on behavioral evidence from people with ASD? Social brain areas? Movement areas? Which parts of the brain are abnormal in ASD or mouse models of ASD? (E.g. striatum, forebrain, cerebellum).

1. 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.

2. 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.

Monday March 12th is spring recess.

Week 8. March 19th. The vaccine story. ALSO TERM PAPER OULINE DUE DATE.

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 and post on one or both of the epidemiology studies (papers 1a and 1b). If someone feels like volunteering to present topic 2….an overview of the whole vaccine scare….great! If not I will lead a structured discussion on it.

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

1b. 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.

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

The RETRACTED paper: Wakefield AJ, 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

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

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

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

Week 9. March 26th. Biomarkers and early diagnosis, further baby sib studies

1. 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.
2. Emerson RW, Adams C, Nishino T, Hazlett HC, Wolff JJ, Zwaigenbaum L, Constantino JN, Shen MD, Swanson MR, Elison JT, Kandala S, Estes AM, Botteron KN, Collins L, Dager SR, Evans AC, Gerig G, Gu H, McKinstry RC, Paterson S, Schultz RT, Styner M; IBIS Network, Schlaggar BL, Pruett JR Jr, Piven J. (2017) Functional neuroimaging of high-risk 6-month-old infants predicts a diagnosis of autism at 24 months of age. *Science Translational Medicine.* Jun 7;9(393).

Week 10. April 2nd. Maternal infection…….immune system and gut….probiotics

(also relevant to microglia, synaptic pruning, mTOR)

1. 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.
2. Maternal gut bacteria promote neurodevelopmental abnormalities in mouse offspring. Kim S, Kim H, Yim YS, Ha S, Atarashi K, Tan TG, Longman RS, Honda K, Littman DR, Choi GB, Huh JR (2017) *Nature*. Sep 28;549(7673):528-532. (Plus companion paper Yim et al and prior study Choi et al).

(Hsiao et al (2013) Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. Cell. 2013 Dec 19;155(7):1451-63). This paper helps to explain the topic two papers.

Week 11. April 9th. Treatment approaches from classroom to clinic

For this week, each presenter will pick a pair of papers from the pairings below and present them together…..they are short. Also you can pick which pair you post on.

1. TWO PAPERS ON CLASSROOM TREATMENTS

Shire SY, Chang YC, Shih W1, Bracaglia S, Kodjoe M, Kasari C (2017) Hybrid implementation model of community-partnered early intervention for toddlers with autism: a randomized trial. J Child Psychol Psychiatry. May;58(5):612-622.

Kasari C, Rotheram-Fuller E, Locke J, Gulsrud A. (2012) Making the connection: randomized controlled trial of social skills at school for children with autism spectrum disorders. J Child Psychol Psychiatry. 2012 Apr;53(4):431-9.

2. TWO PAPERS ON PMD 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

3. TWO PAPERS ON FRAGILE X

Gantois I, Khoutorsky A, Popic J, et al (2017) Metformin ameliorates core deficits in a mouse model of fragile X syndrome. Nat Med. 2017 Jun;23(6):674-677.

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).

Week 12. April 16th. Can cells in dishes help find ASD treatments?

1. 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.

2. 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.

(If Krey et al was not presented in weeks 4 and 5, that will be an option this week).

Week 13. April 23rd. 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.