ALZHEIMER'S DISEASE, SPRING 2020

DR. JANE FLINN

THE GOAL OF THIS COURSE IS TO UNDERSTAND THE BIOLOGICAL CAUSES OF ALZHEIMER'S DISEASE, THE BEHAVIORS ASSOCIATED WITH THE DISEASE, AND POSSIBLE THERAPEUTIC APPROACHES.

SYLLABUS

JAN 21,23. Overview
History of AD. Different types of memory
AD is characterised by cognitive impairments and the presence of deposits, plaques and tangles, in the brain. There are different forms of memory which depend on different brain regions. Functional anatomy of the brain.
Maurer,1997, Julia vignettes in Decoding Darkness.

JAN 28/30. Correlation of brain pathology and behavioural changes in AD.
Assessment of behavioural changes seen in AD.
Speaking our Minds. Aging with Grace, pp 4-7, 34-35, 140-152.

FEB 4/6. Stains and Imaging; Localization of brain damage .
How do you know what brain damage there is and where the amyloid and tau are? Different types of amyloid; cerebral amyloid angiopathy (CAA). Tangles are another marker for AD. Histological studies, Imaging studies. fMRI and PET. AD may begin much earlier than we thought.

Braak and Braak, 1991**.** Cohen and Klunk, 2015; Kirby 2015; Marquie et al., 2015.

FEB 11/13. Some risk factors for AD,
My mother has Alzheimer's disease.
Aging with Grace, pp 38 -43, 156,

FEB 18/20. Where does amyloid come from?
Amyloid is produced from APP. Enzymes involved with APP and the production of amyloid.
The search for the genes underlying AD. There are 2 forms of AD, early-onset and late-onset.
Decoding Darkness. Hardy & Selkoe, 2002.
FEB 24, LAST DAY TO DROP WITHOUT PENALTY OF "F"

FEB 25/27. Other factors involved in AD
The role of tau. APOE4 a late-onset gene. The blood brain barrier may play a role and interact with APOE4.
Decoding Darkness. Aging with Grace, Chapter 8. Yu et al. 2014. (Zlokovic, TBA,)

MAR 3/5 AD may begin much earlier than we thought. The default network is altered early in AD.

Can Alzheimer's be stopped (Film).
Buckner et al, 2008; Dean et al., 2014
MAR 10/12 SPRING BREAK

MAR 17/19 review, Student presentation/paper topics due **,** E**XAM**

MAR 24/26 Animal models: Mice are useful. Soluble versus non-soluble amyloid.
Transgenic mice have been used to model AD. They can be used to assess treatments and understand factors influencing the progress of the disease. Memory loss is seen before plaques appear. This may be due to soluble amyloid. Soluble amyloid precedes tau and causes cognitive impairments in Tg Hsiao, mice. There is synaptic damage. ADDLS, oligomers, etc.
Behavioral measures of memory loss; spatial memory, passive avoidance. LTP. Tg models, 2576, J20 and triple transgenic mice.
Hsiao et al., 1996; Billings et al., (2005); Selkow (2002).

MAR 30/APR 2 Prescription Drugs and other treatments for AD ; AChE inhibitors, most AD drugs target acetylcholine degradation. Memantine targets a glutamate receptor. Antibody treatment may be effective. Anti-cholesterol drugs. Blood transfusion.
Ballard et al., 2005; Parsons et al., 2007. Villeda et al., 2011. Middeldorp et al, 2016. Herandez et al., 2020

APR 7/9 Role of metals in AD.
Possible role of the metals in AD. The plaques are high in iron, copper, zinc, and (?) aluminium. Zinc can cause memory loss, but this may be due to an induced copper deficit. Behavioral and histological data in normal and Tg mice. Zinc is prescribed for age-related macular degeneration, but could impact circadian rhythms. Cholesterol with copper may be a risk factor. Iron may be dangerous.
Drugs acting as Metal ionophores; PBT2 is a possible remedy for AD.
Sparks & Schreurs, 2003; Duce et al, 2011; Bjorklund et al. 2012. Lippi et al., (2020) (Bush et al, 2008, Duce et al, 2010, James 2012.)
Student presentations begin.

APR 14/ 16 Risk factors
Lack of education, low SES, head injury (inflammation), stroke (smoking) are risk factors.
APOE status may have an interactive effect with other risk factors. .
Prescription drugs can cause memory loss.
Aging with Grace. Snowden et al., 1997; Moceri et al., 2001.
Student presentations.

APR 21/23/ Preventative factors.
Exercise, education, and music, etc. are helpful.
Diet can include foods with folic acid, caffeine and those that act as anti oxidants: dark chocolate, spinach, blueberries, curcumin, pomegranates. Brushing your teeth is important! The rate of dementia might be going down.

Student presentations
Adlard et al., 2005; Mathews et al., 2013; Drew, 2014. Tergesen, 2019. Ide, 2016.

APR 28/30/ Summary
Student presentations.

PAPERS DUE MAY 3
FINAL EXAM DUE MAY10TH (take home)
There will be a take home quiz most weeks on an assigned paper. The exams will be essay exams. Graduate student presentations should be ~ 20 mins (- points for going over!)

OFFICE HOURS, TU/ TH 4:30-5 DKH
AND BY APPOINTMENT
PHONE, 993-4107, E-MAIL jflinn@gmu.edu

GRADING
QUIZZES, UNDERGRADUATE, INCLUDING IN-CLASS QUESTIONS, 20%
QUIZZES, GRADUATE, INCLUDING IN-CLASS QUESTIONS, 15%
UNDERGRADUATE, 10 MIN GROUP PRESENTATION, 7%; WRITE UP 8%, (15%)
GRADUATE, 15 MIN INDIVIDUAL PRESENTATIONS 10%; WRITE UP 10%, (20%)
MID-TERM EXAM, 30%
FINAL EXAM, 30% (take home)

Since the total is 95 points for both the undergraduates the total score will be divided by 95 and multiplied by 100 to give the % grade. There will be an additional; question on the exams for the graduate students.

Books
Aging With Grace, D. Snowden. Describes the School Sisters of Notre Dame study in which risk factors for Alzheimer's disease are studied.

Speaking Our Minds L. Snyder. Personal reflections from individuals with Alzheimer's disease.

Decoding Darkness, R. Tanzi & A. Parsons. A history of the search for genes underlying Alzheimer's disease.
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Required Papers
Adlard P.A., Perreau V.M., Pop V. & Cotman C.W.. Voluntary exercise decreases amyloid load in a transgenic model of Alzheimer's disease, *J Neurosci* **25** (2005), 4217-4221.

Ballard C.G., Greig N.H., Guillozet-Bongaarts A.L., Enz A. & Darvesh S. (2005) Cholinesterases: roles in the

brain during health and disease. Curr. Alzheimer res. 2(3):307-18

Billings L.M., Oddo S., Green K.N., McGaugh J.L. & LaFerla M. (2005) Intraneuronal Aβ Causes the onset of early Alzheimer's disease-related cognitive deficits in transgenic mice. Neuron. Mar 3;45(5):675-88

Bjorklund NL, Reese LC, Sadagoparamanujam VM, Ghirardi V, Woltjer RL, Taglialatela G. (2012) Absence of amyloid β oligomers at the postsynapse and regulated synaptic Zn2+ in cognitively intact aged individuals with Alzheimer's disease neuropathology. Mol Neurodegener. 7:23 (Find on google)

Braak H. & Braak E. (1991) Neuropathalogical staging of Alzheimer-related changes. Acta Neuropath 82:239-159.)

Buckner R.L., Andrewa-Hanna J.R., Schatcter D.L. (2008) The Brain's Default Network, Anatomy, Function, and Relevance to Disease. Ann. N.Y. Acad. Sci. 1124: 1–38 (2008).

Cohen A.D., Klunk W.E. (2015). Early detection of Alzheimer's disease using PiB and FDG PET. Neurobiol Dis. 2014 Dec;72 Pt A:117-22.

Dean et al. 2014. Brain differences in infants at differential genetic risk for late-onset Alzheimer disease: a cross-sectional imaging study. *JAMA Neurol.* 71:11–22.

Drew L. (2014) Down with Dementia. New Scientist, Jan 11.

Duce J.A., Bush, A.I. Adlard P.A. (2011) Role of amyloid-β- metal interactions in Alzheimer's disease. (2011). Future Neurology, 6(5):641.

Hardy J. and Selkow D. (2002). The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science 297(5580): 353-356.

Hernandez et al., submitted to J. Alz Dis.

Hsiao K. Chapman P., Nilsen S., Eckman C., Harigaya Y., Younkin S., Yang F., and Cole G. (1996) Correlative memory deficits, Abeta elevation, and amyloid plaques in transgenic mice. Science 274:99-102.

Ide M., Periodontitis and Cognitive Decline in Alzheimer's Disease Ide. PLoS One. 2016; 11(3): e0151081.Published online 2016 Mar 10. doi: 10.1371/journal.pone.0151081

Kirby, T. (2015) William Klunk: imaging Alzheimer's disease in vivo Lancet Neurol. 14(8):791.

Lippi et al., submitted to Frontiers in Neuroscience.

Marquie et al, (2015) Validating novel tau positron emission tomography tracer [F-18]-AV-1451 (T807) on postmortem brain tissue. Ann Neurol. 2015 Nov;78(5):787-800

Maurer, K., Volk S., Gerbaldo H. (1997). Auguste D. and Alzheimer's disease. Lancet, 349:1546-49.

Mathews, F.E., Arthur, A., Barnes, L.E., Bond, J., Jagger, C., Robinson, L., Brayne, C. (2013). A two-decade comparison of prevalence of dementia .... Lancet 382: 1405-1411

Middeldorp, J., Lehallier, B., Villeda, S.A., Miedema, S.S.M., Evans, E., Czirr, E. (2016). Preclinical Assessment of Young Blood Plasma for Alzheimer Disease. *JAMA Neurology. 73*(11):1325-1333 doi:10.1001/jamaneurol.2016.3185

Moceri VM, et al. (2001) Using census data and birth certificates to reconstruct the early-life socioeconomic environment and the relation to the development of Alzheimer's disease. Epidemiology. 12(4):383-9.

Parsons, C.G., Sto¨ffler, A., Danysz, W. Memantine: a NMDA receptor antagonist that improves memory by restoration of homeostasis in the glutamatergic system - too little activation is bad, too much is even worse. Neuropharmacology 53 (2007) 699e723

Selkoe D.J. Alzheimer's disease is a synaptic failure. (2002) Science 298:789-791.

Snowden et al. Brain Infarction and the clinical expression of Alzheimer Disease. The Nun Study. (1997) JAMA 277:813-817.

Sparks D.L. & Schreurs B.G. Trace amounts of copper in water induce beta-amyloid plaques and learning deficits in a rabbit model of Alzheimer's disease. P.N.A.S. (2003) 100(19) :11065-9.

Tergesen, A.,. What Science tells us about preventing dementia. Wall St J. 11/17/19

Villeda, S. A., Luo, J., Mosher, K. I., Zou, B., Britschgi, M., Bieri, G., … Wyss-Coray, T. (2011). The ageing systemic milieu negatively regulates neurogenesis and cognitive function. *Nature*,*477*(7362), 90–94.

Yu, J.T., Tan, L., Hardy J. Apolipoprotein E in Alzheimer's Disease: An Update. Annu Rev Neurosci. 2014 Apr 21

Reference papers

Bero AW, Yan P, Roh JH, Cirrito JR, Stewart FR, Raichle ME, Lee JM, Holtzman DM (2011) Neuronal activity regulates the regional vulnerability to amyloid-β deposition. Nature Neurosci. Jun;14(6):750-6.

Bishop G.M., Robinson S.R., Liu Q., Perry G., Atwood C.S., & Smith M.A.. (2002). Iron: A pathological marker of Alzheimer Disease? Developmental Neuroscience, 24:184-187.

Bjorklund NL, Sadagoparamanujam VM, Taglialatela G. (2012) Selective, quantitative measurement of releasable synaptic zinc in human autopsy hippocampal brain tissue from Alzheimer's disease patients. J. Neurosci Methods. 203(1):146-51.

Duce et al. (2010) Iron-export ferroxidase activity of β-amyloid precursor protein is inhibited by zinc in Alzheimer's disease. Cell. 142(6):857-67.

House E., Collingwood J., Khan A., Korchazkina O., Berthon G., and Exley C. (2004) Aluminum, iron, zinc and copper influence the *in vitro* formation of amyloid fibrils of $A\beta_{42}$ in a manner which may have consequences for metal chelation therapy in Alzheimer's disease. J. Alz. Dis. 6:291-301.

James SA, Volitakis I, Adlard PA, Duce JA, Masters CL, Cherny RA, Bush AI. (2012) Elevated labile Cu is associated with oxidative pathology in Alzheimer disease. Free Radic Biol Med. 2(2):298-302

Linkous, D. H.. Adlard P.A., Wanschura P.B., Conko K.M., Flinn J.M. (2009) The effects of enhanced zinc on spatial memory and plaque formation in transgenic mice. J. Alzheimer's Disease. 18(3) 541-551.

Ognibene E., Middei S., Daniele S., Adriani W., Ghirardi O., et al. (2005) Aspects of spatial memory and behavioral disinhibition in Tg2576 transgenic mice as a model of Alzheimer's disease. Behav. Brain Res. 2005:225-232.

Roberts BR, Ryan TM, Bush AI, Masters CL, Duce JA. (2012) The role of metallobiology and amyloid-β peptides in Alzheimer's disease. Neurochem. 2012 Jan;120 Suppl 1:149-66. *

Tanzi R. (2005) The synaptic Aβ hypothesis of Alzheimer disease. Nature Neuroscience 8: 977-979. (2005)

If you are a student with a disability and you need academic accommodations, please see me and contact the Disability Resource Center (DRC) at 703-993-2474. All academic accommodations must be arranged through that office.

Honor Code

George Mason University has an Honor Code, which requires all members of this community to maintain the highest standards of academic honesty and integrity. Cheating, plagiarism, lying, and stealing are all prohibited. It is every student's responsibility to familiarize himself or herself with the Honor Code. The Honor Code is available at: http://oai.gmu.edu/the-mason-honor-code-2/ All violations of the Honor Code will be reported to the Honor Committee.

Communications via GMU E-mail:

Mason uses electronic mail to provide official information to students. Examples include communications from course instructors, notices from the library, notices about academic standing, financial aid information, class materials, assignments, questions, and instructor feedback. Students are responsible for the content of university communication sent to their Mason e-mail account and are required to activate that account and check it regularly.

Technology

Quizzes will be posted on Blackboard. Dr Flinn and the TA will also communicate with students in the class via e mail.

Cell phones may not be used in class. Students may use computers to take class notes but for no other purpose. I may ask to see your notes at the end of class, those using the computer for other reasons than note taking can get a zero on the next quiz.

Class Cancellation

If class has to be cancelled, e.g. for weather, an e mail will be sent to the class. In such cases the class will be rescheduled during the snow day.

Add/Drop deadlines

2/5 last day to add/drop with no tuition penalty, 2/24 last day to drop.