

ALZHEIMER'S DISEASE, SPRING 2024, DKH 2053
TU/TH 3 -4:15
DR. JANE FLINN

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

SYLLABUS

JAN 16, 18. Overview

Syllabus

History of AD. Different types of memory

AD is characterised by cognitive impairments, and the presence of amyloid and tau deposits, leading to plaques and tangles in the brain. There are different forms of memory which depend on different brain regions. Functional anatomy of the brain.

Maurer et al,1997; O'Brien, 1996. Julia vignettes in Decoding Darkness at the beginning of each chapter.

Please get Speaking our Minds for Feb 7 at the latest. .

JAN 23 LAST DAY TO ADD

JAN 23, 24. Stains and Imaging; Localization of brain damage.

How do you know what brain damage there is and where the amyloid plaques and tau tangles are? Histological studies, Imaging studies (fMRI and PET), have been used to study the AD brain. AD may begin much earlier than we thought.

Braak and Braak, 1991; Klunk et al, 2004; Cohen and Klunk, 2014; Kirby 2015; Brosch et al. 2017

JAN 30, FEB 1. Correlation of brain pathology and behavioural changes in AD.

Different impairments can be associated with damage to different regions of the brain.

Assessment of behavioural changes seen in AD.

Speaking our Minds.

The Forgetting, Film

FEB 6,8. Where does amyloid come from?

Continuation of behavioral changes.

Amyloid is produced from amyloid precursor protein (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.

Aging with Grace, pp 4-7, 34-35, 140-152

Decoding Darkness. Hardy & Selkoe, 2002.

FEB 13, 15 Other factors involved in AD

The role of tau. APOE4 is a late-onset gene and carries a risk of developing AD. The blood brain barrier may play a role and interact with APOE4.

Decoding Darkness. Aging with Grace, Chapter 8. Small and Duff, 2008; Yu et al. 2014. (Zlokovic)

FEB 20, 22. AD may begin much earlier than we thought.

The essays in Aging with Grace, chapter 7. Imaging studies. The default network is altered early in AD.

Buckner et al, 2008; Dean et al., 2014.

***FEB 20** End of unrestricted withdrawal period. (get a W on transcript, but does not affect GPA)*

FEB 27,29 Review, Animal models: Mice are useful. Transgenic mice have been used to model AD.

They can be used to assess treatments and understand factors influencing the progress of the disease. Behavioral measures of memory loss; spatial memory, passive avoidance. Memory loss is seen before plaques appear. This may be due to soluble amyloid.

Review.

Hsiao et al., 1996. (other papers)

MAR 5,7 SPRING BREAK

MAR 12, 14

(Review) Student presentation/paper/topics due,

EXAM

MAR 19,21 Animal models: Soluble versus non-soluble amyloid.

Soluble amyloid precedes tau and causes cognitive impairments in the Tg Hsiao mice. There is synaptic damage. Oligomers, LTP. Tg models, triple transgenic mice.

Billings et al., (2005); Selkow (2002). TBA.

Can Alzheimer's be stopped (Film).

JMF AWAY MAR 21

MAR 26,28 Prescription Drugs and other treatments for AD ;

AChE inhibitors, most AD drugs target acetylcholine degradation.

Memantine targets a glutamate receptor. A new drug, aducanumab (Aduhelm), has been approved for the first time in 18 years. Lecanemab (Leqembi) has also been approved.

Antibody treatment may be effective. Anti-cholesterol drugs, young blood transfusion are alternative approaches.

ALZTALK on Aducanumab

(Ballard et al., 2005); Middeldorp et al, 2016; Parsons et al., 2007; Villeda et al., 2011; Zhao et al., Y., 2020.

APR 2,4 Treatments continued. 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. Copper with cholesterol may be a risk factor. Iron may be dangerous.

Drugs acting as Metal ionophores; PBT2 is a possible remedy for AD.

Sparks & Schreurs, 2003; Bush et al, 2008; Duce et al, 2011; (Bjorklund et al. 2012; Duce et al, 2010; James 2012)

Student presentations begin.

APR 9,11 Risk Factors

Lack of education, low SES, head injury (inflammation), stroke (smoking), pollution, are risk factors for the development of AD. APOE4 status may have an interactive effect with other risk factors.

Prescription drugs can cause memory loss.

Aging with Grace. Aging with Grace, pp 38 -43, 156; Moceri et al., 2001. Snowden et al., 1997; Student presentations.

APR 16,18 Preventative factors.

The rate of AD is going down, which may be due to healthier life styles. Exercise, education, sleep, 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!

Student presentations

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

Underwood. 2013; Xie et al., 2013,. (Nedergaard is the senior author.)

PAPERS DUE April 29 ??

APR 23, 25

REVIEW, FINAL EXAM APRIL 25TH

There will be a take home quiz most weeks on one or more of the papers assigned for that week. The papers will normally be posted on Blackboard. The exams will be short answers with an essay; students may bring a one page summary to the exam.

Undergraduate and MA students can work together for the presentation, a paper based on the same subject as the presentation is also required. Papers must be written independently.

Because exercise has been shown to be the best way to reduce cognitive impairment there will be a short exercise break in the middle of each class.

OFFICE HOURS, TU/ TH 4:30-5, AND BY APPOINTMENT

PHONE, 703 362 0202, E-MAIL jflinn@gmu.edu

Learning Outcomes

Students should understand: how the brain is changed in Alzheimer's disease (AD) and how this leads to changes in behaviour; the factors (both positive and negative) influencing the possibility of getting AD, and the drugs available to treat it.

GRADING

QUIZZES, INCLUDING IN-CLASS QUESTIONS, 20%

GROUP PRESENTATION, 10%; WRITE UP 10%,

MID-TERM EXAM, 30%, FINAL EXAM, 30%

There will be an additional question on the exams for the graduate students.

89-100 A, 79-88 B, 69-78 C, 59-68 D, < 59 F

+ and - grades will be used within each grade

Late quizzes will be marked down.

Books

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

REQUIRED

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

Decoding Darkness, R. Tanzi & A. Parsons. A history of the search for genes underlying Alzheimer's disease. Required for graduate students, recommended for undergraduates.

Required Papers

Adlard P.A., Perreau V.M., Pop V. & Cotman C.W.. (2005) Voluntary exercise decreases amyloid load in a transgenic model of Alzheimer's disease, *J Neurosci* 25 , 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., McLaugh J.L. & LaFerla M. (2005) Intraneuronal A β 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, Tagliatela 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) Neuropathological staging of Alzheimer-related changes. *Acta Neuropath* 82:239-159.)

Brosch J.R. et al., (2017) Tau Imaging in Alzheimer's Disease Diagnosis and Clinical Trials.

Neurotherapeutics, 2017 Jan;14(1):62-68. doi: 10.1007/s13311-016-0490-y.

PMC full text

Bush A.I. (2008) Drug Development Based on the Metals Hypothesis of Alzheimer's Disease

Journal of Alzheimer's Disease 15 (2008) 223–240 223

IOS Press

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Buckner R.L., Andrews-Hanna J.R., Schacter 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. (2014). 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. et al. (2010) Iron-Export Ferroxidase Activity of b-Amyloid Precursor Protein Is Inhibited by Zinc in Alzheimer's Disease. *Cell* 142, 857–867, September 17, 2010

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 *Aging Brain* .

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

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

Kirby, T. (2015) William Klunk: imaging Alzheimer's disease in vivo [Lancet Neurol.](https://doi.org/10.1016/j.lanneu.2015.08.001) 14(8):791.

Klunk W.E. et al Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. *Ann Neurol.* 2004 Mar;55(3):306-19. doi: 10.1002/ana.20009.PMID: 14991808

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

- Middelcorp, 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.
- O'Brien, C. (1996) Auguste D. and Alzheimer's Disease: *Science, New Series*, Vol. 273, No. 5271 (Jul. 5, 1996), p. 28
- Parsons, C.G., Stoßfler, A., Danysz, W. Memantine: (2007) An 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.
- Scott A. Small and Karen Duff, (2008). Linking Ab and Tau in Late-Onset Alzheimer's Disease: A Dual Pathway Hypothesis. *Neuron*. 2008 Nov 26;60(4):534-42. doi:0.1016/j.neuron.2008.11.007. (PMC)
- 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. (2003) 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.* 100(19) :11065-9.
- Tergesen, A.,. (2019) What Science tells us about preventing dementia. *Wall St J.* 11/17/19
- Underwood, Sleep the Brain's Housekeeper (a commentary). 2013; *Science* 342, p 301.
- 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.
- Xie et al., 2013,. Sleep Drives Metabolite Clearance from the Adult Brain. *Science* 342, p 373 (Nedergaard is the senior author.)
- Yu, J.T., Tan, L., Hardy J. 2014. Apolipoprotein E in Alzheimer's Disease: An Update. *Annu Rev Neurosci*. 2014 Apr 21
- Zhao Y, Qian R, Zhang J, Liu F, Iqbal K, Dai C, Gong C. (2020) Young blood plasma reduces Alzheimer's disease-like brain pathologies and ameliorates cognitive impairment in 3×Tg-AD mice. *Alzheimer's Research & Therapy* 2020;12(1):70

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.

Papers, quizzes, and exams will be scanned for AI or plagiarism.

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.

Class Cancellation

If class has to be cancelled, an e mail will be sent to the class.