

MEMORY, METALS AND ALZHEIMER'S DISEASE, SPRING 2006

DR. JANE FLINN

THE GOAL OF THIS COURSE IS TO UNDERSTAND THE FACTORS UNDERLYING ALZHEIMER'S DISEASE

SYLLABUS

JAN 26. Overview

AD is characterised by cognitive impairments and the presence of amyloid deposits, including plaques and CAA, and tangles in the brain. Anatomy of the brain. There are different forms of memory which depend on different brain regions. Correlates of brain damage in AD and behavioural changes.

Aging with Grace pp 145; Speaking our Minds.

FEB 2. Stains and Imaging.

How do you know what brain damage there is and where the amyloid is? Plaques are made of amyloid; there are different types of plaques and different forms of amyloid. Amyloid deposits are also found around blood vessels, cerebral amyloid angiopathy (CAA). Imaging studies.

Dickerson. & Sperling; Braak and Braak.

FEB 7 Last day to add classes

FEB 9. The Forgetting. (Film)

Presentations of people with Alzheimer's disease.

FEB 16 Where does this amyloid come from?

Amyloid is produced from APP. There are 2 forms of AD, early onset and late onset.

The search for the genes underlying AD.

Decoding Darkness.

FEB 23 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. LTP. Hsiao, Westaway and triple transgenic mice (LaFerla)

Hsiao et al. Sparks & Schreurs.

FRIDAY FEB 24, LAST DAY TO DROP WITHOUT PENALTY OF "F"

MAR 2 Soluble versus non-soluble amyloid.

Soluble amyloid may be as dangerous as the aggregated form in plaques, and could be intraneuronal.

Soluble amyloid precedes τ and causes cognitive impairments in Tg mice. There is synaptic damage. ADDLS, oligomers etc.
Billings et al.; Hardy & Selkoe. Selkoe

MAR 13-19 SPRING BREAK

MAR 23 EXAM

MAR 30 Risk factors.

Possible role of the metals in AD. The plaques are high in iron, copper, zinc, and (?) aluminium. Behavioral and histological data. Zinc can cause memory loss in normal rats and mice and has been prescribed for age-related macular degeneration.
Cholesterol, head injury (inflammation), stroke (smoking) are all risk factors.
Lack of education, low SES are also risk factors.
Aging with Grace; Bush & Tanzi.

APR 6 Potential Cures.

Metal chelators, AChE inhibitors. Anti-cholesterol drugs. Antibodies. : Some AD drugs target glutamate receptors, others target acetylcholine degradation. Antibody treatment may be effective.
Guest speaker.
Ballard et al.

APR 13 Prevention.

Exercise and education are helpful. Diet can include foods that act as anti oxidants: blueberries, curcumin, pomegranates and folic acid.
Aging with Grace

APR 20 Wrap -up

APR 27 Student presentations

MAY 4 Student presentations

MAY 11 FINAL EXAM DUE (takehome)

There will be an in class quiz most weeks on an assigned paper. The exams will be essay exams. Graduate student presentations should be 20-30 mins (- points for going over!) Undergraduates should be 10-15 minutes.

GRADING

QUIZZES, 10%
IN CLASS PRESENTATIONS 10%
WRITE UP 10%
MID-TERM EXAM, 30%
FINAL EXAM 30%

OFFICE HOURS
TH 4:30-5:30
AND BY APPOINTMENT.

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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.

Required Papers

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.

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

Bush A.I. & Tanzi R. (2002). The galvanization of β -amyloid in Alzheimer's disease. *PNAS.* 99:7317-7319.

Dickerson B.C. & Sperling R.A. (2005) Neuroimaging biomarkers for clinical trials of disease-modifying therapies in Alzheimer's disease. *NeuroRx.* 2:348-360.

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

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

Selkoe D.J. Alzheimer's disease is a synaptic failure. (2003?) *Science* 298:789-791.

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

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.*

Reference papers

Barnes P. & Good M. (2005) Impaired Pavlovian cued fear conditioning in Tg 2576 mice expressing a human mutant amyloid precursor protein gene. Behav. Brain Res. 157(1) 107-117.

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.

Brendza R.P., Bacskai B.J., Cirrito J.R., Simmons K.A., Skoch J.M., Klunk W.E., Mathis C.A., Bales K.R., Paul S.M., Hyman B.T., and Holtzman D.M. 2005. Anti-A β antibody treatment promotes the rapid recovery of amyloid-associated neuritic dystrophy in PDAPP transgenic mice. J.Clin. Invest. 115(2):428-433.

*Bush A.I. Masters C.L. & Tanzi R.E. (2003) Copper, beta -amyloid, and Alzheimer's disease: tapping a sensitive connection. P.N.A.S. 100(20):11816 Comment on Sparks and Schreurs.

Flinn, J.M., Hunter, D., Linkous, D.H., Lanzirrotti, A., Smith, L., Brightwell, J.J. and Jones B.F..(2005) Enhanced zinc consumption causes memory deficits and increased brain levels of zinc. Physiology and Behavior. 83 (5) 793-803.

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 β_{42} in a manner which may have consequences for metal chelation therapy in Alzheimer's disease. J. Alz. Dis. 6:291-301.

Klunk W.E., Engler H., Nordberg A., Wang Y/Daniele S., Blomquist G. et al. (2004) Imaging brain amyloid in Alzheimer's disease with Pittsburgh compound-B. Ann. Neurol. 55:306-319.

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.

Sparks L.D. (2004) Cholesterol, copper, and accumulation of thioflavine S-reactive Alzheimer's like amyloid beta in rabbit brain. J. Mol. Neurosci. 24 (1): 97-104

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.

Undergraduate students can enroll in Psyc 328 and earn an extra hour of course credit.