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Dementia

David J Brooks

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Dementia

- Syndrome of acquired global impairment of intellectual function which is usually progressive, and occurs in a setting of clear consciousness.
- Affects:

  Memory, language, abstract thinking and judgement, praxis, visospatial or perceptual skills, personality and social conduct

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Epidemiology

- Prevalence:
  - 1% at age 60
  - Doubles every five years
  - 30% by age 80
  - Prevalence curve flattens out at about age 90
- 4th leading cause of death in the elderly
- Life expectancy after diagnosis 3-15 years

Wolfson, NEJM April, 2001

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Alzheimer's disease

- Accounts for 60-70% of dementia cases
- Risk factors:
  - Aging
  - Family history - maternal
    - (Apo ε4 allele and other chromosomal defects)
    - 3x risk with 1st degree relative
    - Female gender
  - Lower education level (unable to mask)
  - Previous brain trauma or stroke?

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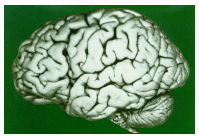
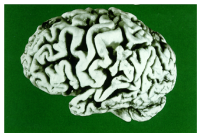
Anatomical features of AD

Gross atrophy

- shrinkage of brain
- thinning of gyri
- widened sulci



Normal brain



Alzheimer brain

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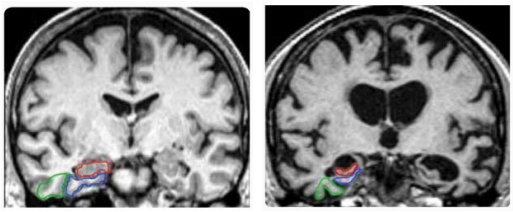
Alzheimer MRIs



Early Advanced

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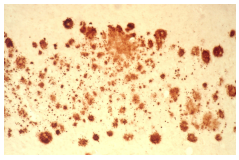
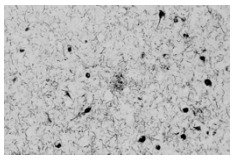
Alzheimer's disease

Cortical pathology



Extracellular β amyloid



tau neurofibrillary tangles

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Alzheimer patient

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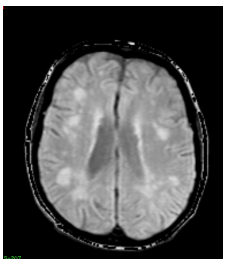
Vascular dementia

- May be progressive or stepwise
- Overlap with Alzheimer features
- Risk factors
  - Aging
  - Male > female, Black/Asian > Caucasian
  - Hypertension
  - Cigarettes, atrial fibrillation, DM, hyperlipidemia
- Ischemic stroke survivors: 9x increased dementia risk



T2-weighted MRI

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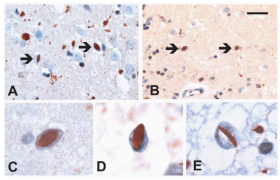
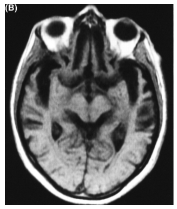
Frontotemporal dementia

Personality changes, euphoria, apathy or disinhibition. Compulsive and obsessional behaviors. Relatively preserved visuospatial function.

Pathology: Pick's or TDP43 inclusions, spongioform degeneration



Pick bodies
3 repeat tau inclusions)



MRI
Temporal atrophy

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Frontotemporal dementia

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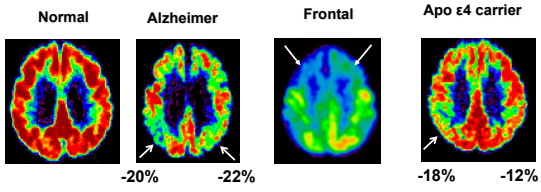
Brain glucose metabolism

^{18}F-FDG PET



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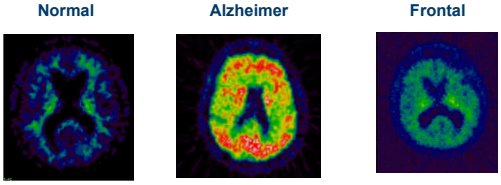
Detecting amyloid in dementia

^{11}C-PIB PET



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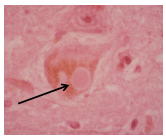
Other dementias

- Lewy body:
  - 2nd most common: male > female
  - Parkinsonism
  - visual hallucinations
  - fluctuating confusion



- Subcortical:
  - Progressive supranuclear palsy
    Parkinsonism, failure of eye movement control
  - Huntington's disease
    Chorea, depression, dementia due to a CAG repeat expansion of the htt gene

Supranuclear gaze palsy

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Diagnosis of Dementia

- Multiple cognitive deficits manifesting as impaired memory plus:
  - Impaired language or
  - Apraxia or
  - Agnosia or
  - Impaired executive function
- Deficits:
  - Significant enough to impair function
  - Interferes with work or social activities
- Normal conscious level
- Progressive syndrome

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Cognitive Impairment: other causes

- Post-anoxic
- toxic
- Hydrocephalus
- Hypoglycaemia
- B12
- Hypothyroidism
- Hypercalcemia
- Alcohol / thiamine
- Encephelopathy
  - Uremic
  - Hepatic
  - autoimmune
- Encephalitis
  - Syphilis
  - Lyme's
  - HIV
  - Prion disease

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Differential Diagnosis

- Delirium
- Depression
- Psychotic disorders
- Medication induced cognitive problems
- Sensory deficits
- Aphasia
- Developmental disability
- Low literacy or education

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Investigations

- History: onset, personality, meds, family, social supports, functioning
- Examination: Neurological / systemic
  - Labs: electrolytes, Ca, Cr, LFT, Glu, TSH, B12
  - Consider: HIV, RPR, drug / heavy metal screen, autoantibodies, LP (Aβ, tau)
- Neuroimaging: Highest yield in young, rapid onset, seizures, gait abnormality, focal exam

Patterson 1999

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Neuropsychology tests

- Helpful to quantitate cognitive deficits
- Aids differential diagnosis
- Detect mild early impairments
- Allows treatment efficacy to be monitored
- May help in competency determination
- May help with management and family recommendations

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Abbreviated mental test score

- What is your age?
- What is the time to the nearest hour?
- Give the patient a 3-line address, and ask him or her to repeat it at the end of the test
- What is the year?
- What is the name of the hospital or number of the residence where the patient is situated?
- Can the patient recognize two persons (the doctor, nurse, home help, etc.)?
- What is your date of birth?
- In which year did the xxx (eg First World War) begin (choose a world event the patient would have known during childhood)?
- What is the name of the present monarch (head of state, etc.)?
- Count backwards from 20 down to 1.

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Mini Mental State Examination

- **Orientation**
  What is the year, season, date, day and month
  (1 point for each; maximum total 5 points).
  Where are we: town, county, country, which hospital, surgery or house, and which floor (1 point for each; maximum total 5 points).
- **Registration**
  Name 3 objects (e.g., apple, table, penny) taking 1 second to say each one. Then ask the individual to repeat the names of all 3 objects.
  Give 1 point for each correct answer.
  Repeat the object names until all 3 are learned (up to 3 trials).
  Record number of trials needed (maximum total 3 points).
- **Attention and Calculation**

  Serial 7s:
  - Ask the person to take 7 away from 100. Continue until I ask you to stop
  - (i.e., 93, 86, 79, 72, 65).
  - Stop after 5 subtractions.
  - Give one point for each correct answer. If one answer is incorrect (e.g. 92) but the following answer is 7 less than the previous answer (i.e., 85), count the second answer as being correct. 1 point for each subtraction (maximum total 5 points).
  -

  Spell "world" backwards Give 1 point for each letter that is in the right place (e.g., DLROW = 5 points, DLORW = 3 points).

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- **Recall**
  Ask for the 3 objects repeated above (e.g., apple, table, penny). Give 1 point for each correct object (maximum total 3 points).
- **Language (naming and repetition)**
  Point to a pencil and ask the person to name this object (1 point).
  Do the same thing with a wrist-watch (1 point). (maximum total 2 points)

  Ask the person to repeat the following: "No ifs, ands or buts" (1 point). Allow only one trial (1 point).
- **Praxis**
  Give the person a piece of blank white paper and ask them to follow a 3-stage command: "Take a paper in your right hand, fold it in half and put it on the floor" (1 point for each part that is correctly followed). (maximum total 3 points)
- Write "CLOSE YOUR EYES" in large letters and show it to the patient. Ask him or her to read the message and do what it says (give 1 point if they actually close their eyes).
- Ask the individual to write a sentence of their choice on a blank piece of paper. The sentence must contain a subject and a verb, and must make sense. Spelling, punctuation and grammar are not important (1 point).

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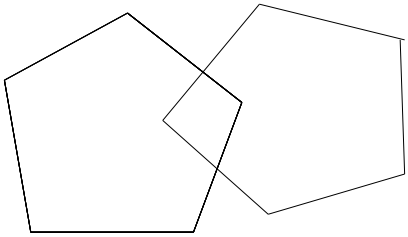
Intersecting pentagons

- Show the person a drawing of 2 pentagons which intersect to form a quadrangle. Each side should be about 1.5 cm. Ask them to copy the design exactly as it is (1 point). All 10 angles need to be present and the two shapes must intersect to score 1 point. Tremor and rotation are ignored.



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Copying shapes

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CLOCK DRAWING

The person undergoing testing is asked to;
Draw a clock
Put in all the numbers
Set the hands at ten past eleven.

- **Scoring system for Clock Drawing test (CDT)**
  There are a number of scoring systems for this test. The Alzheimer's disease cooperative scoring system is based on a score of five points.
  1 point for the clock circle
  1 point for all the numbers being in the correct order
  1 point for the numbers being in the proper special order
  1 point for the two hands of the clock
  1 point for the correct time.
- A normal score is four or five points.

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Neuropsychometric testing

Mental Status: **Recognition memory:**	Mini Mental State Examination (Folstein) Warrington recognition memory test
Verbal Memory:	1- Alzheimer's Disease Assessment Scale Word 2- List Learning test & 30-minute delayed recall (Rose et al., 1984)
Visual Memory:	Immediate & delayed recall of modified complex figure (Becker et al., 1987)
Attention:	1- Digit Span forwards (WAIS-R; Wechsler,1981), 2- Trail Making Part A (Reitan,1958)
Executive/ Working	1. Trail Making Part B (Reitan, 1958); 2. Clock drawing (Freedman, 1994)
Visuoconstruction:	Copy of modified complex figure (Becker et al., 1987)
Language:	1. 30-item Boston Naming Test (Saxton et al., 2000); 2. Letter fluency (F,A S)(Benton, 1968), 3. Category fluency (animals, birds and dogs).

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Famous people

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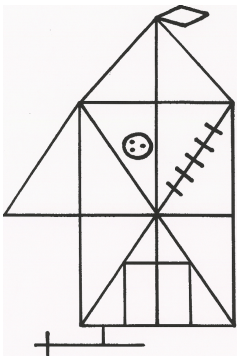
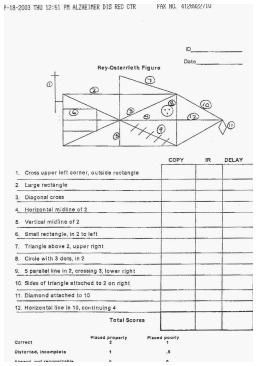
Complex figure





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ADAS Word List Learning Test

- Butter
  Arm
  Shore
  Letter
  Queen
  Cabin
  Pole
  Ticket
  Grass
  Engine

3 attempts

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Digit Span Forward

- 5-8-2
- 6-9-4
- 6-4-3-9
- 7-2-8-6
- 4-2-7-3-1
- 7-5-8-3-6
- 6-1-9-4-7-3
- 3-9-2-4-8-7
- 5-9-1-7-4-2-8
- 4-1-7-9-3-8-6
- 5-8-1-9-2-6-4-7
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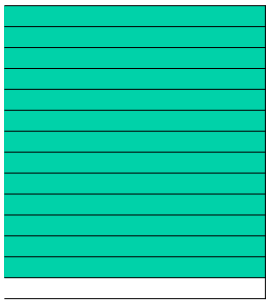
- 2-7-5-8-6-2-5-8-4
- 7-1-3-9-4-2-5-6-8



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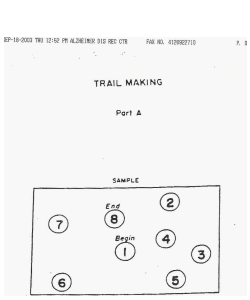
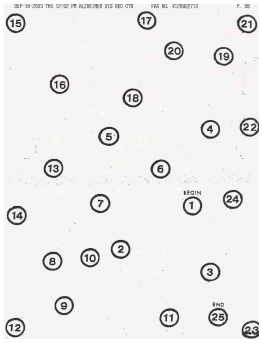
Trail Making A





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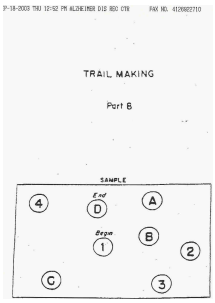
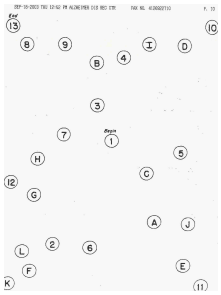
Trail making B





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30-item Boston Naming Test

Tree	Knocker	Snail
Pencil	Stethoscope	Dart
Scissors	Unicorn	Globe
Comb	Funnel	Wreath
Flower	Compass	Beaver
Toothbrush	Tripod	Acorn
Broom	Scroll	Stilts
Mushroom	Trellis	Dominoes
Camel	Palette	Cactus
Bench	Abacus	Harp

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Naming test

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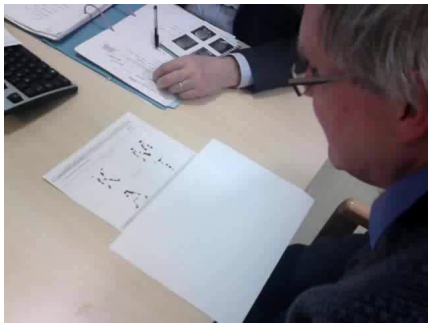
Degraded letters



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CATEGORY FLUENCY

- **CATEGORY FLUENCY INSTRUCTIONS**
  The categories are: Animals, Birds, and Dogs
- "Tell me all the animals you can think of. You have one minute. Tell me as many animals as you can. Start now."
- "Now tell me as many different birds as you can. Start now."
- "Now tell me as many dogs as you can – *breeds* of dogs. Start now."

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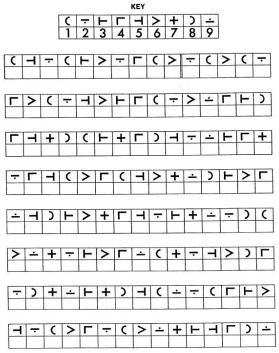
KEY

1	2	3	4	5	6	7	8	9



Digit Symbol test

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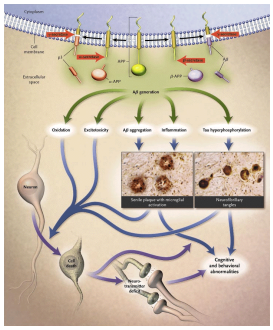
Anti-amyloid strategies

- Secretase blockers
- Anti-aggregants
- Metal chelators
- Immunotherapy
  - Vaccines
  - Antibody infusions
- Anti-inflammatories



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Subacute meningoencephalitis in a subset of patients with AD after Aβ42 immunization

J.-M. Orgogozo, MD; S. Gilman, MD, FRCP; J.-F. Dartigues, MD, PhD; B. Laurent, MD; M. Puel, MD; L.C. Kirby, MD; P. Jouanny, MD, PhD; B. Dubois, MD; L. Eisner, MD; S. Flitman, MD; B.F. Michel, MD; M. Boada, MD; A. Frank, MD, PhD; and C. Hock, MD

Abstract—*Background:* AD is characterized by cerebral deposition of β-amyloid plaques with amyloid β-peptide (Aβ) 42 as the major peptide constituent, along with neurofibrillary tangles and neuronal loss. In transgenic mice, active immunization against Aβ42 removes these plaques and improves cognitive function. A Phase I study in AD patients demonstrated good safety and tolerability of multiple injections of aggregated Aβ42 (AN1792) with QS-21 as adjuvant. *Methods:* Three hundred seventy-two patients with mild to moderate AD were randomized to receive IM injections of AN1792 or placebo (4:1) at baseline and at months 1, 3, 6, 9, and 12 in a multicenter Phase II safety, tolerability, and pilot efficacy study. Dosing was terminated after four early reports of meningoencephalitis, but follow-up continued. The study remains blinded, and further results will be reported after its termination. *Results:* Symptoms and laboratory findings consistent with meningoencephalitis occurred in 18 of 298 (6%) patients treated with AN1792 compared with 0 of 74 on placebo ($p = 0.020$). Sixteen of the 18 had received two doses, one had received one dose, and one had received three doses of the study drug before symptoms occurred. The median latency from the first and last injections to symptoms was 75 and 40 days. No case occurred later than 6 months after the first immunization. Anti-Aβ42 antibody titers were not correlated with the occurrence or severity of symptoms or relapses. Twelve patients recovered to or close to baseline within weeks, whereas six remain with disabling cognitive or neurologic sequelae. All 18 patients remain alive to date (December 31, 2002), 6 months to >1 year after symptom onset. *Conclusions:* Postvaccination meningoencephalitis occurred without clear relation to serum anti-Aβ42 antibody titers. Potential mechanisms such as T-cell and microglial activation may be responsible and are under consideration to develop a safer anti-Aβ immunotherapy for AD.

NEUROLOGY 2003;61:46–54

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^{11}C-PiB PET assessment of change in fibrillar amyloid-β load in patients with Alzheimer's disease treated with bapineuzumab: a phase 2, double-blind, placebo-controlled, ascending-dose study

Juha O Rinne, David J Brooks, Martin N Rossor, Nick C Fox, Roger Bullock, William E Klunk, Chester A Mathis, Kaj Blennow, Jerome Barakos, Aren A Okello, Sofia Rodriguez Martinez de Liano, Enchi Liu, Martin Koller, Keith M Gregg, Dale Schenk, Ronald Black, Michael Grundman

Summary

Background Carbon-11-labelled Pittsburgh compound B (^{11}C-PiB) PET is a marker of cortical fibrillar amyloid-β load in vivo. We used ^{11}C-PiB PET to investigate whether bapineuzumab, a humanised anti-amyloid-β monoclonal antibody, would reduce cortical fibrillar amyloid-β load in patients with Alzheimer's disease.

Methods Patients with mild-to-moderate Alzheimer's disease were randomly assigned to receive intravenous bapineuzumab or placebo in a ratio of seven to three in three ascending dose groups (0·5, 1·0, or 2·0 mg/kg). Each dose group was enrolled after safety review of the previous group. Randomisation was by interactive voice response system; masking was achieved with numbered kit allocation. Patients, investigators, study site personnel, sponsor staff, and carers were masked to treatment. Patients received up to six infusions, 13 weeks apart, and had ^{11}C-PiB PET scans at baseline and at weeks 20, 45, and 78. The primary outcome was the difference between the pooled bapineuzumab group and the pooled placebo group in mean change from screening to week 78 in ^{11}C-PiB cortical to cerebellar retention ratio averaged across six cortical regions of interest. Analysis was by modified intention to treat. This study is registered with EudraCT, number 2004-004120-12; ISRCTN17517446.

Findings 28 patients were assigned to bapineuzumab (n=20) or placebo (n=8). 19 patients in the bapineuzumab group and seven in the placebo group were included in the modified intention-to-treat analysis. Estimated mean ^{11}C-PiB retention ratio change from baseline to week 78 was −0·09 (95% CI −0·16 to −0·02; p=0·014) in the bapineuzumab group and 0·15 (95% CI 0·02 to 0·28; p=0·022) in the placebo group. Estimated mean difference in ^{11}C-PiB retention ratio change from baseline to week 78 between the bapineuzumab group and the placebo group was −0·24 (95% CI −0·39 to −0·09; p=0·003). Differences between the bapineuzumab group and the placebo group in the individual regions of interest were similar to the overall mean difference. Adverse events were typically mild to moderate in severity and transient. Two patients in the 2·0 mg/kg bapineuzumab group had transient cerebral vasogenic oedema.

Interpretation Treatment with bapineuzumab for 78 weeks reduced cortical ^{11}C-PiB retention compared with both baseline and placebo. ^{11}C-PiB PET seems to be useful in assessing the effects of potential Alzheimer's disease treatments on cortical fibrillar amyloid-β load in vivo.

Lancet Neurol 2010; 9: 363–72
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See Reflection and Reaction page 333

Turku PET Centre and Clinical Research Services Turku, University of Turku and Turku University Hospital, Turku, Finland (J O Rinne MD); Division of Neuroscience and Medical Research Council Clinical Sciences Centre, Faculty of Medicine, Imperial College London, London, UK (D J Brooks MD, A A Okello MRCP, S Rodriguez Martinez de Liano MD); Institute of Neurology, University College London, London, UK (M N Rossor FRCP, N C Fox FRCP); Kingshill Research Centre, Swindon, UK (R Bullock MRCPsych); University of Pittsburgh Medical Center, Pittsburgh, PA, USA (W E Klunk MD, C A Mathis PhD); University of Göteborg, Sahlgrenska University Hospital, Mölndal, Sweden (K Blennow MD); California Pacific Medical Center, San

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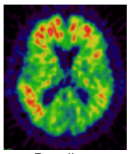
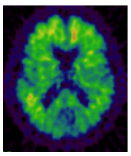
Bapineuzimab in Alzheimer's disease

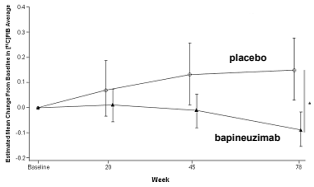
^{11}C-PIB PET



Baseline

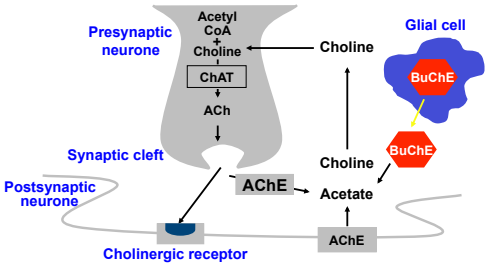


After immunotherapy



Rinne at al. 2009

Normal cholinergic function



ACh = acetylcholine; AChE = acetylcholinesterase; BuChE = butyrylcholinesterase; ChAT = choline acetyltransferase; CoA = coenzyme A.

Adem, 1992

Imperial College London

Cholinergic dysfunction in AD

Reduced:

- Choline acetyltransferase
- Choline uptake
- Acetylcholine release
- Cholinergic neurons
- Nicotinic receptors

= progressively impaired memory and cognition

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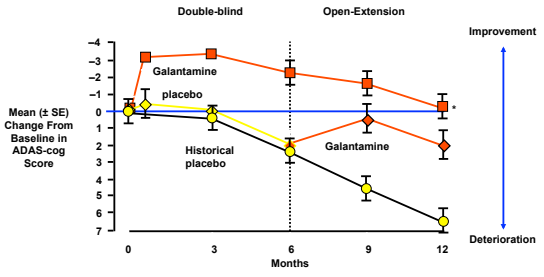
Anti-cholinesterase treatment



****P* < .05 vs placebo/galantamine**

Raskind MA et al, *Neurology*. 2000; 54: 2261-2268.

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Summary

- No cure or proven neuroprotection
- Symptomatic drugs mildly effective – acetylcholinesterase and glutamate inhibitors
- Anti-amyloid strategies – experimental and may cause inflammation
- Supportive care still mainstay of treatment