Klinisk neuropsykologi: epilepsi och neurodegenerativa sjukdomar—del II

Thomas Karlsson

Syfte

- Presentera de viktigaste ND sjukdomarna
  - Inklusive möjliga orsaker
- Titta på vad man bör titta på
- Förstå att ”demens” är ett otillräckligt, föråldrat och felaktigt begrepp för att vara av värde för neuropsykologer
- Plus lite nytt (?)

Two unique human phenomena

- Prolonged adolescence (11—18 years): 200000 years ago?
- Late-life survival: <100 years old?

Att överväga…

- Det har funnits ca. 5000 generationer
- I de flesta av dessa (4900?) har få blivit äldre än 35 år och ingen äldre än 50
- Det är under tre generationer som människan levt mer än 50 år igenomsnitt
- Endast under den senaste generationen har människan levt längre än 80 år

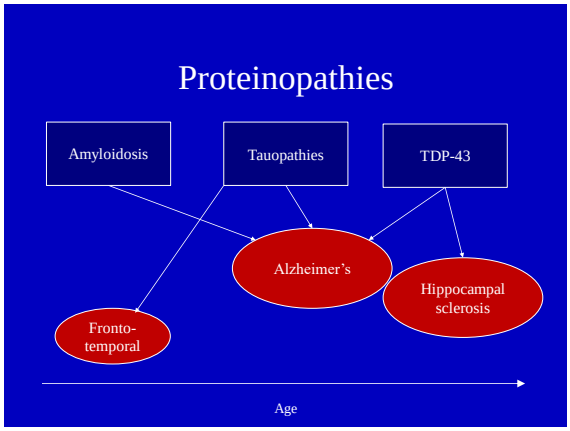
Schirrmacher, F. (2004). *Das Methusalem-Komplott*. Berlin: Blessing Verlag

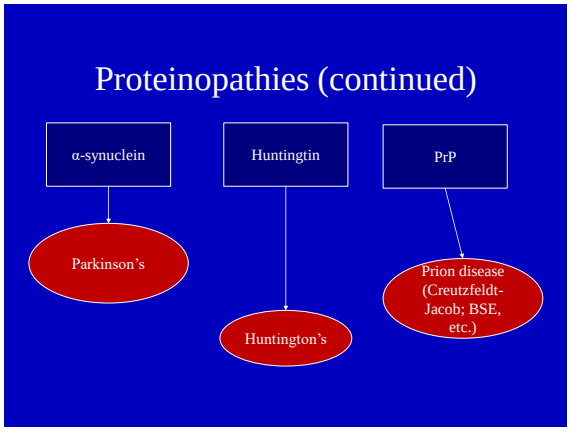
Slutsats?

- Vår generation är den första där åldrandet är ett massfenomen
- Det mesta vi behöver veta om åldrandet (inklusive dess sjukdomar) återstår att lära…

Overview: proteinopathies

- Work in recent years have demonstrated that neurodegenerative disorders all have occurrence and abundance of protein misfolding and abnormal intraneuronal inclusions in common – *proteinopathies*
- Give rise to distinct, but overlapping, disruption of localized brain networks
- Localization, not pathology (or illness), produces different phenotypes

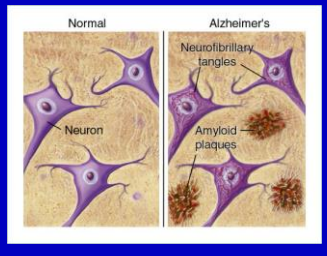


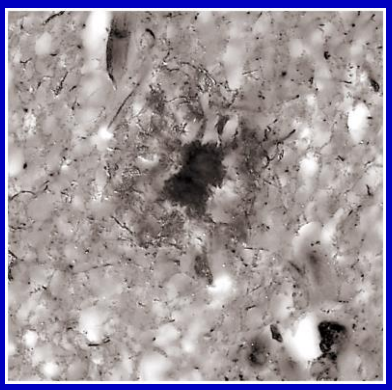


Native Protein	Aggregated Protein or Peptide	Main Associated Diseases in humans	Acquired by Infection in Humans	Subcellular Localization	
				Native	Aggregates
PrP^{C}	PrP^{Sc}	(variant, introgenic) Creutzfeldt-Jacob, Kuru	yes	plasma membrane anchored	mostly extracellular
		(sporadic, familial) Creutzfeldt-Jacob, Fatal familial insomnia, Gerstmann-Straussler Scheinker	no		
Tau	Tau	frontotemporal lobar dementia, Alzheimer	no	cytoplasmic	cytoplasmic
α-synuclein	α-synuclein	Parkinson, lewy body dementia	no	nuclear and synaptic	cytoplasmic
APP	β-amyloid	Alzheimer	no	transmembrane	mostly extracellular
Huntingtin	PolyQ	Huntington	no	nuclear	nuclear
Ataxins		spinocerebellar ataxias	no		
SOD1	SOD1	amyotrophic lateral sclerosis	no	cytoplasmic	cytoplasmic
TDP-43	TDP-43	amyotrophic lateral sclerosis, frontotemporal lobar degeneration	no	nuclear	mostly cytoplasmic
FUS/TLS	FUS/TLS	amyotrophic lateral sclerosis, frontotemporal lobar degeneration	no	nuclear	mostly cytoplasmic

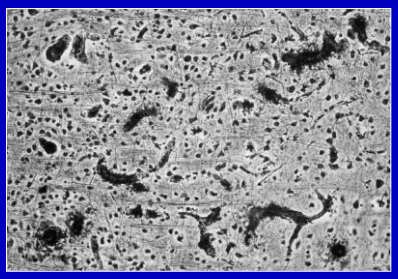
Inclusion	Association	Main constituents
Neurofibrillary tangles	Aging, Alzheimer disease, progressive supranuclear palsy, post-encephalitic parkinsonism, Guam parkinsonism–dementia, myotonic dystrophy, subacute sclerosing panencephalitis, Niemann–Pick disease type C, other rare disorders	Phosphorylated tau protein (3R, 4R), ubiquitin
Lewy bodies	Aging, Parkinson's disease, dementia with Lewy bodies	α-synuclein, neurofilament protein, and ubiquitin
Pick bodies	Pick's disease	Neurofilament protein, phosphorylated tau protein (3R), ubiquitin
MND inclusions	Motor neuron disease/amyotrophic lateral sclerosis	TAR DNA-binding protein 43 (sporadic cases) or superoxide dismutase 1 (some familial cases) or fused-in-sarcoma protein (other familial cases) ubiquitin, p62

Alzheimers sjukdom





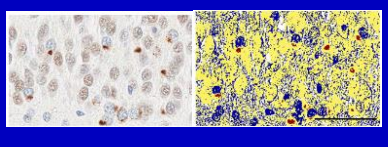
Neurofibrillary tangles that are typically observed in Alzheimer's disease



Source: CNRI/SPL/Photo Researchers, Inc.

A New Player

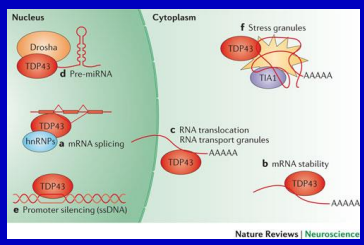
- TDP-43 (Tar DNA-binding protein of 43 kDa); an rNA-binding protein that functions in exon skipping and is identified in an abnormal phosphorylated state in cellular inclusions



Why?

- Plaque and NFT burden does not sufficiently account for cognitive, psychiatric, and functional impairment
- Normal elderly persons can have a high load without impairment
- Scavenging plaques has no clear effect in humans

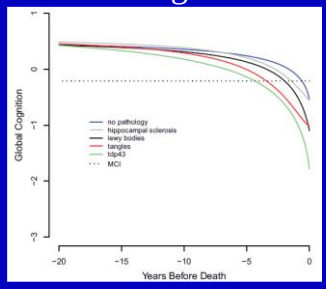
Functions



TDP depositions

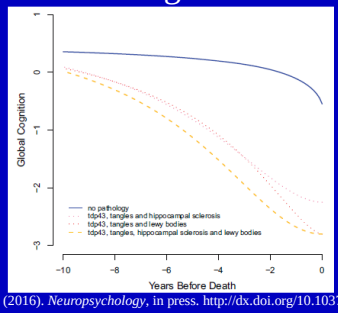
- Alzheimer's disease
- Frontotemporal dementia
- ALS
- Supranuclear palsy
- Repeated head trauma (CTE)

TDP-43 may affect the early stages



Wilson, et al. (2016). *Neuropsychology*, in press. http://dx.doi.org/10.1037/neu0000282

TDP-43 may affect the early stages

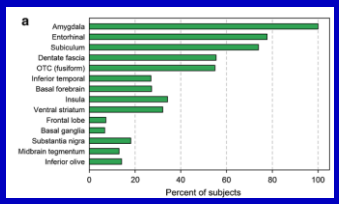


Wilson, et al. (2016). *Neuropsychology*, in press. http://dx.doi.org/10.1037/neu0000282

Outcome variable	Regression estimate (95 % CI)		Adjusted *p* value*		
	Regression β[a]	Logistic odds ratio[b]	Age adjusted	Age and Braak adjusted	Fully adjusted[c]
Demographics					
APOE ε4 carrier		1.0 (0.9, 1.1)	0.85	0.92	0.29
Clinical features					
Cognitively impaired		2.3 (1.2, 7.7)	0.07	0.14	0.06
Mini-mental state examination	−0.4 (−0.7, −0.1)		0.02	0.02	0.08
Clinical Dementia Rating scale	0.4 (0.2, 0.7)		<0.001	<0.001	0.007
Boston naming test	−0.6 (−1.2, 0.0)		0.05	0.05	0.03
Dementia Rating scale—memory	−0.4 (−0.6, −0.2)		<0.001	<0.001	0.001
Neuropsychiatric inventory—Q	0.0 (0.0, 0.1)		0.35	0.34	0.44

Josephs, K. A. *et al.* (2014). TDP-43 is a key player in the clinical features associated with Alzheimer's disease. *Acta Neuropathol* (in press), DOI 10.1007/s00401-014-1269-z

Where?



- That is, medial temporal lobe

Mechanism(s)?

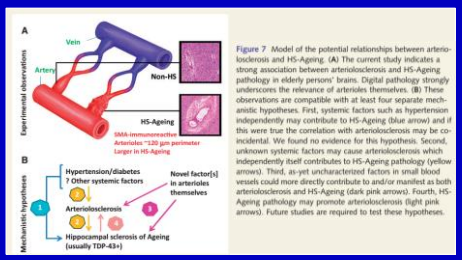


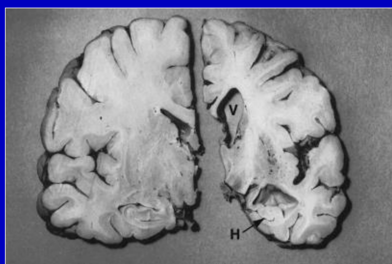
Figure 7 Model of the potential relationships between arteriolosclerosis and HS-Ageing. (**A**) The current study indicates a strong association between arteriolosclerosis and HS-Ageing pathology in elderly persons' brains. Digital pathology strongly underscores the relevance of arterioles themselves. (**B**) These observations are compatible with at least four separate mechanistic hypotheses. First, systemic factors such as hypertension independently may contribute to HS-Ageing (blue arrow) and if this were true the correlation with arteriolosclerosis may be coincidental. We found no evidence for this hypothesis. Second, unknown systemic factors may cause arteriolosclerosis which independently itself contributes to HS-Ageing pathology (yellow arrow). Third, as-yet uncharacterized factors in small blood vessels could more directly contribute to and/or manifest as both arteriolosclerosis and HS-Ageing (dark pink arrows). Fourth, HS-Ageing pathology may promote arteriolosclerosis (light pink arrow). Future studies are required to test these hypotheses.

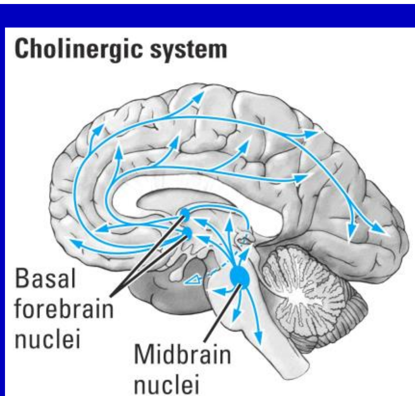
Table 4 HS-Ageing versus presence of regional arteriolosclerosis in UK-ADC participants

Area	HS-Ageing n, % of group	n	No HS-Ageing n, % of group	n	P	Significant
Frontal cortex (BA 8)	17 (68.0)	25	36 (25.0)	144	0.0001	Yes
Temporal cortex (BA 21/22)	14 (56.0)	25	35 (24.3)	144	0.0032	No
Parietal cortex (BA 39/40)	12 (52.2)	23	38 (26.0)	146	0.022	No
Occipital cortex (BA 17/18)	14 (60.9)	23	36 (25.2)	143	0.0018	Yes
Amygdala	14 (60.9)	23	29 (19.9)	146	0.0002	Yes
Entorhinal cortex (BA 28)	12 (52.2)	23	18 (12.7)	142	<0.0001	Yes
Hippocampus CA1	8 (34.8)	23	18 (12.5)	144	0.0094	No
Subiculum	3 (13.0)	23	14 (9.7)	144	0.59	No
Posterior cingulate (BA 23)	14 (66.7)	21	21 (25.3)	83	0.0014	Yes
Anterior cingulate (BA 24)	15 (65.2)	23	26 (26.0)	100	0.0016	Yes
Thalamus	13 (56.5)	23	28 (21.4)	131	0.0023	Yes
Caudate	15 (65.2)	23	23 (16.7)	138	<0.0001	Yes
Putamen	15 (65.2)	23	25 (17.9)	140	<0.0001	Yes
Insular cortex (BA 13)	14 (60.9)	23	28 (20.7)	135	0.0005	Yes
Internal capsule	4 (17.4)	23	9 (6.5)	138	0.0767	No
Globus pallidus	14 (63.6)	22	17 (63.6)	135	<0.0001	Yes

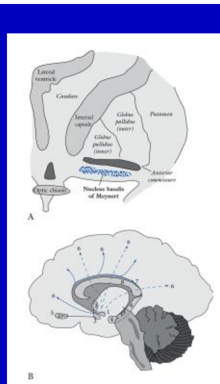
BA = Brodmann area; *P*-value determined by logistic regression controlling for age at death by covariate adjustment; the Bonferroni-Holm method was used to correct for multiple comparisons.

Cell loss due to Alzheimer's disease





The nucleus basalis of Meynert and cholinergic projections, which are affected by Alzheimer's disease.



AMYLOID PLAQUES

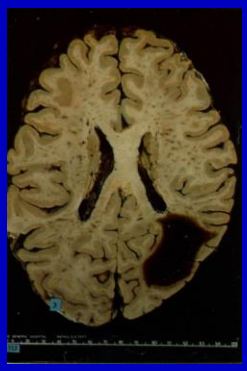
One of the hallmarks of Alzheimer's disease is the accumulation of amyloid plaques between nerve cells (neurons) in the brain. Amyloid is a general term for protein fragments that the body produces normally. Beta-amyloid is a fragment of a protein that is snipped from another protein called amyloid precursor protein (APP). In a healthy brain, these protein fragments would be broken down and eliminated. In Alzheimer's disease, the fragments accumulate to form hard, insoluble plaques.

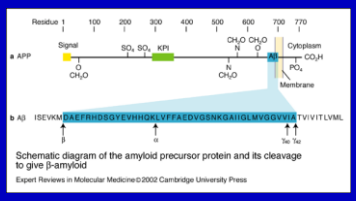
NEUROFIBRILLARY TANGLES

Neurofibrillary tangles consist of insoluble twisted fibers that are found inside of the brain's cells. They primarily consist of a protein called tau, which forms part of a structure called a microtubule. The microtubule helps transport nutrients and other important substances from one part of the nerve cell to another. In Alzheimer's disease, however, the tau protein is abnormal and the microtubule structures collapse.

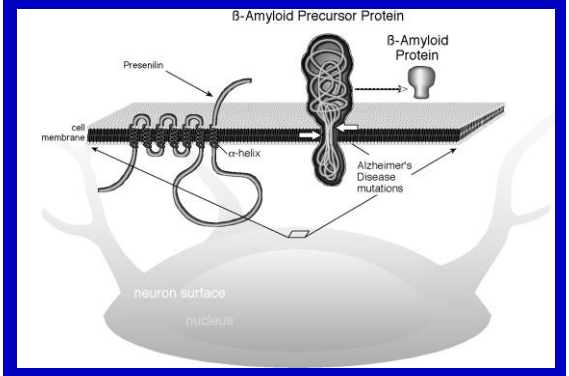
Cerebral Amyloid Angiopathy

This is a section of the brain at autopsy in a patient who died after a CAA-related bleeding stroke. The dark area in the lower right has been destroyed by leakage of blood into the brain.



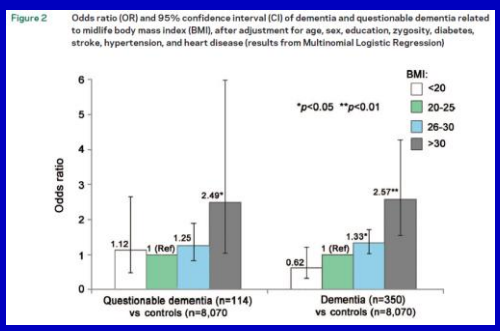


Schematic diagram of the amyloid precursor protein and its cleavage to give b-amyloid. (a) Amyloid precursor protein (APP) is an integral membrane, proteoglycan-like molecule of approximately 700 amino acids; sulphation (SO4), phosphorylation (PO4) and carbohydrate attachment (CH2O) sites, the Kunitz-type protease inhibitor domain (KPI) and the secretory signal sequence ('Signal') are shown. (b) The protein is proteolytically processed by secretases in several different pathways. Cleavage of APP at the beta and gamma sites, which define the b-amyloid (Ab) peptide, generates Ab sequences of 40 or 42/43 residues (amino acids in single-letter code). The most common cleavage by a-secretase precludes Ab formation



Etiology

- Genetics
  - Apolipoprotein E (ApoE; chr. 19)
    - 40 to 80% of AD possess at least one apo ε4 allele
  - The chromosome 21 connection: APP gene
  - Presenilin 1 and 2 (Chr. 14 and 1)
- Metabolism
  - Adipose tissue
  - Leptin, insulin…
- 'Wear-and-tear'
  - Head trauma
  - Drug abuse

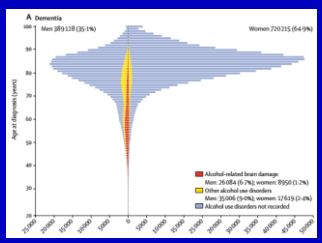


Xu, *et al.*, Neurology 2011;76:1568–1574

Contribution of alcohol use disorders to the burden of dementia in France 2008–13: a nationwide retrospective cohort study

*Michaël Schwarzinger, Bruce G Pollock, Omer S M Hasan, Carole Dufouil, Jürgen Rehm, for the QalyDays Study Group**

Lancet (2018). http://dx.doi.org/10.1016/S2468-2667(18)30022-7



Lancet (2018). http://dx.doi.org/10.1016/S2468-2667(18)30022-7

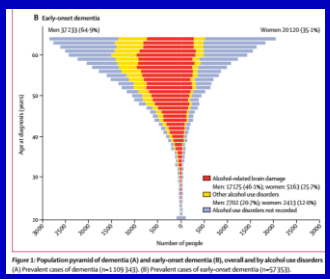


Figure 1: Population pyramid of dementia (A) and early-onset dementia (B), overall and by alcohol use disorders
(A) Prevalent cases of dementia (n=1 109 343). (B) Prevalent cases of early-onset dementia (n=57 353).

Lancet (2018). http://dx.doi.org/10.1016/S2468-2667(18)30022-7

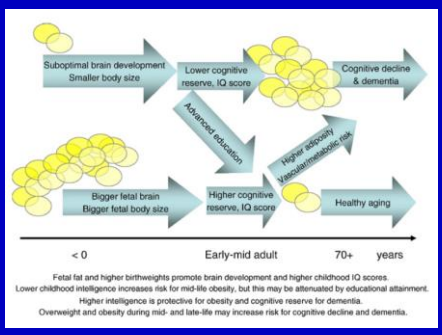
Table 2 Adjusted odds ratio (OR) and 95% confidence interval (CI) of dementia, Alzheimer disease, and vascular dementia related to midlife BMI (results from generalized estimating equation models)

Midlife BMI	No. of twins	All dementia			Alzheimer disease			Vascular dementia		
		No.	OR (95% CI)[a]	OR (95% CI)[b]	No.	OR (95% CI)[a]	OR (95% CI)[b]	No.	OR (95% CI)[a]	OR (95% CI)[b]
Continuous	8,534	464	1.09 (1.06–1.12)	1.06 (1.03–1.10)	232	1.09 (1.04–1.13)	1.06 (1.01–1.10)	74	1.14 (1.08–1.21)	1.11 (1.04–1.19)
Categorical										
<20	627	17	0.74 (0.44–1.25)	0.79 (0.45–1.38)	8	0.89 (0.64–1.23)	0.66 (0.31–1.41)	0	—	—
20–25	5,366	240	1 (Reference)	1 (Reference)	120	1 (Reference)	1 (Reference)	36	1 (Reference)	1 (Reference)
>25	2,541	207	1.50 (1.22–1.84)	1.80 (1.37–2.35)	104	1.52 (1.15–2.02)	1.98 (1.36–2.88)	38	1.62 (1.01–2.59)	1.35 (0.81–2.24)
25–30	2,297	177	1.37 (1.11–1.70)	1.71 (1.30–2.25)	90	1.41 (1.05–1.89)	1.91 (1.30–2.80)	31	1.39 (0.85–2.29)	1.17 (0.69–2.00)
>30	244	30	3.01 (1.95–4.64)	3.88 (2.12–7.11)	14	2.87 (1.57–5.26)	3.43 (1.49–7.90)	7	4.38 (1.89–10.14)	3.50 (1.36–8.99)

Abbreviations: BMI = body mass index; CI = confidence interval; OR = odds ratio.
[a] Adjusted for age, sex, and education.
[b] Adjusted for age, sex, education, diabetes, hypertension, stroke, and heart disease.

Xu, *et al.*, Neurology 2011;76:1568–1574

Life-time involvement?



Gustafsson, European Journal of Pharmacology 585 (2008) 163–175

Life-time involvement?

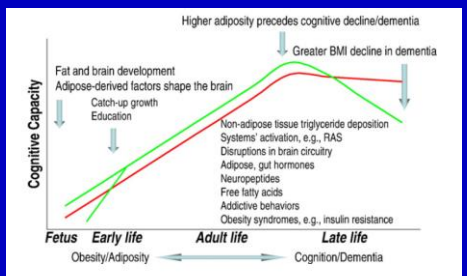
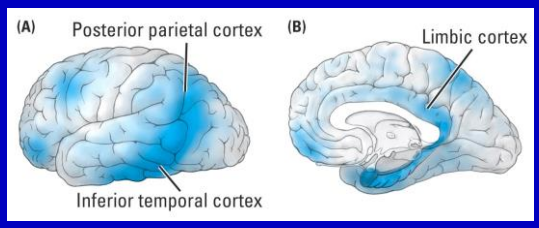
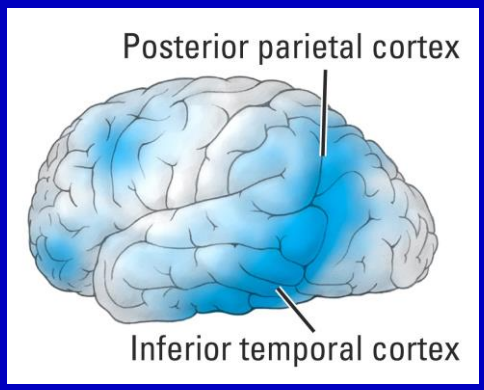


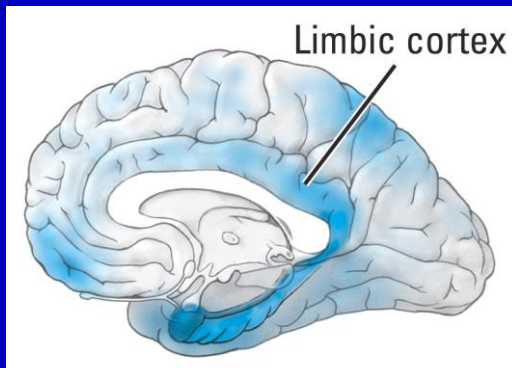
Fig. 3. Mechanisms whereby adiposity may influence cognition and dementia over the life course.

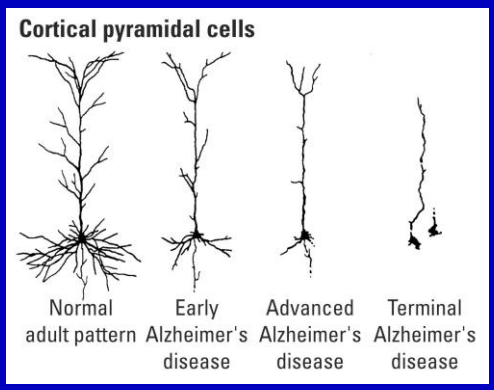
Gustafsson, European Journal of Pharmacology 585 (2008) 163–175

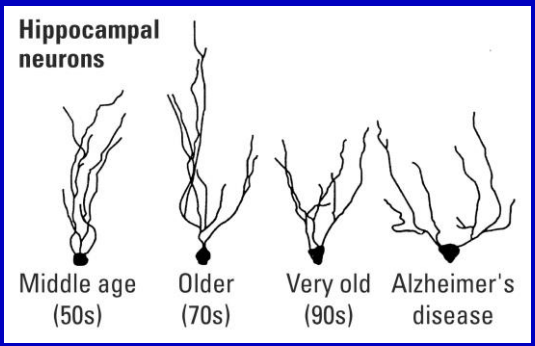
Lesion Localization in AD











Tidig Alzheimers sjukdom

- De flesta studier pekar på en utdragen prodromalfas
  - Skador ackumuleras under lång tid
  - Kognitiva förändringar uppträder sent i processen
  - 10 till 50 år…

Studier från universitetscentra visar excellenta resultat...

'Mild' Alzheimers sjukdom; MMSE<25; N=84...

	Sensitivity	Specificity	Classification
Ten-min Battery	97.6	97.6	97.6

Storandt, *et al*. (1984). *Arch Neurol*, *41*, 497-9

Studier från universitetscentra visar excellenta resultat...

…och 'mycket mild' Alzheimers sjukdom; MMSE>24; N= 196

	Sensitivity	Specificity	Classification
Delayed Vis Mem +Fluency	96.1	93.0	89.1

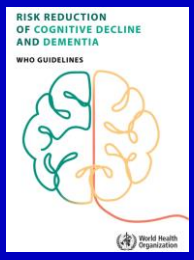
Salmon, *et al*. (2002). *Neurology*, *59*, 1022-8

…att ställas mot:

- Mellan 3 % till 12 % av patienter i primärvård över 65 år har demens.
- 79 % av patienter med mild Alz och 71 % med moderat Alz saknar notering om sjukdomen i journal (Valcour et al., 2000).

Begränsningar

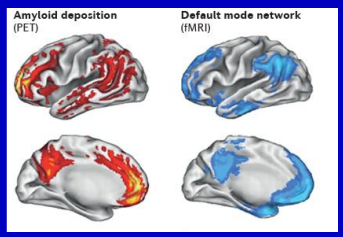
- Svårare att skilja mellan lätt och moderat
- Mindre tydliga resultat i studier utförda i primärvård
- Svårt att differentiera mellan olika demenssjukdomar
- Detektion av patienter på primärvårdsnivå skulle fördubbla antalet kända fall (Boustani et al., 2003)



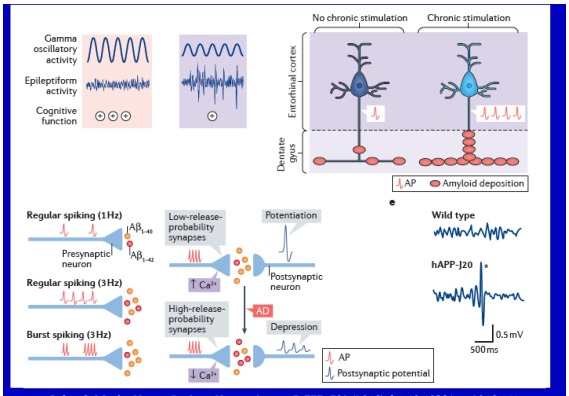
https://apps.who.int/iris/bitstream/handle/10665/312180/9789241550543-eng.pdf?ua=1

Physical activity interventions	**Physical activity should be recommended to adults with normal cognition to reduce the risk of cognitive decline.** *Quality of evidence:* ***moderate*** *Strength of the recommendation:* ***strong***
	Physical activity may be recommended to adults with mild cognitive impairment to reduce the risk of cognitive decline. *Quality of evidence:* ***low*** *Strength of the recommendation:* ***conditional***
Nutritional interventions	**The Mediterranean-like diet may be recommended to adults with normal cognition and mild cognitive impairment to reduce the risk of cognitive decline and/or dementia.** *Quality of evidence:* ***moderate*** *Strength of the recommendation:* ***conditional***
	A healthy, balanced diet should be recommended to all adults based on WHO recommendations on healthy diet. *Quality of evidence:* ***low to high (for different dietary components)*** *Strength of the recommendation:* ***conditional***
	Vitamins B and E, polyunsaturated fatty acids and multi-complex supplementation should not be recommended to reduce the risk of cognitive decline and/or dementia. *Quality of evidence:* ***moderate*** *Strength of the recommendation:* ***strong***

Cognitive interventions	Cognitive training may be offered to older adults with normal cognition and with mild cognitive impairment to reduce the risk of cognitive decline and/or dementia. *Quality of evidence:* ***very low to low*** *Strength of the recommendation:* ***conditional***
Interventions for alcohol use disorders	Interventions aimed at reducing or ceasing hazardous and harmful drinking should be offered to adults with normal cognition and mild cognitive impairment to reduce the risk of cognitive decline and/or dementia in addition to other health benefits.
Weight management	Interventions for mid-life overweight and/or obesity may be offered to reduce the risk of cognitive decline and/or dementia. *Quality of evidence:* ***low to moderate*** *Strength of the recommendation:* ***conditional***
Management of depression	There is currently insufficient evidence to recommend the use of antidepressant medicines for reducing the risk of cognitive decline and/or dementia. The management of depression in the form of antidepressants and/or psychological interventions should be provided to adults with depression according to existing WHO mhGAP guidelines.

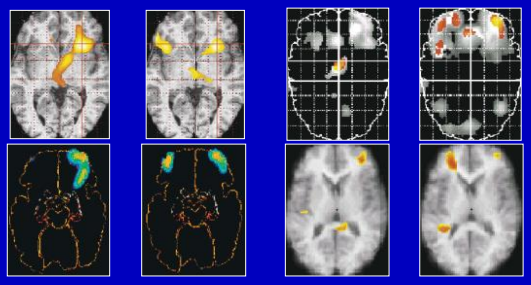


Palop & Mucke *Nature Reviews Neuroscience 17*, 777–792 (2016) doi:10.1038/nm.2016.141



Palop & Mucke *Nature Reviews Neuroscience 17*, 777–792 (2016) doi:10.1038/nm.2016.141

Changes in the brain activation associated with aging



Source: From Cabeza, 2002 .

MCI--Mild Cognitive Impairment

- Smith, et al. (1996)
  - Minne < 1,5 SD
  - Klagomål från patient, anhörig eller kliniker
  - Ingen demens (GDS=0,5)
- 10-15% konverterar till Alzheimers sjukdom per år

Kardinalsymtom

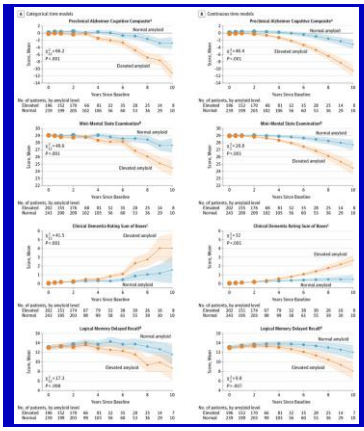
- Episodiskt minne
- Kan ha ytterligare kognitiva symtom
  - Spatial kognition
  - Språk
  - Exekutiva funktioner
  - Uppmärksamhet

Utredningsmall

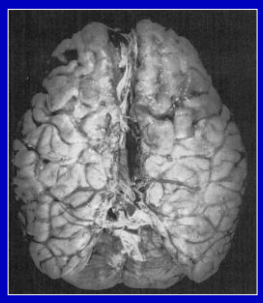
- Dokumentera förändringar avseende fördröjd återgivning
- Utesluta/konfirmera global kognitiv reduktion (demens)
- Påvisa eventuella andra, mer avgränsade störningar vad gäller kognition och/eller personlighet

Table 8: Age-related, MCI, and DAT effects on memory, general cognitive and executive functions.

	Memory	General Cognitive Functions: Learning, attention and concentration, thinking, and use of language	Executive functions: Problems abstracting, organizing, planning or sequencing information	Daily life: Work and social functioning
"Normal" Aging	Loss Comp-laints	Declined but within age and education norms	Preserved	Preserved
MCI	Impaired	Declined but within age and education norms	Preserved	"Preserved"
DAT	Impaired	Impaired: aphasia (problems using language) ***or*** apraxia (trouble carrying out organized gestures, despite intact motor functioning) ***and/or*** agnosia (despite intact sensory functioning, the patient fails to recognize or identify objects presented)	Impaired	Deteriorated



Donohue MC, Sperling RA, Petersen R, Sun C, Weiner MW, Aisen PS, for the Alzheimer's Disease Neuroimaging Initiative. Association Between Elevated Brain Amyloid and Subsequent Cognitive Decline Among Cognitively Normal Persons. *JAMA*. 2017;317(22):2305-2316. doi:10.1001/jama.2017.6669



Frontotemporal demens

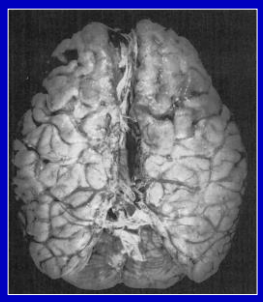
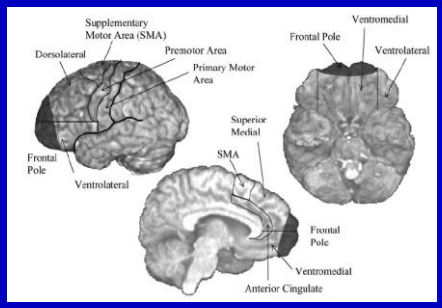


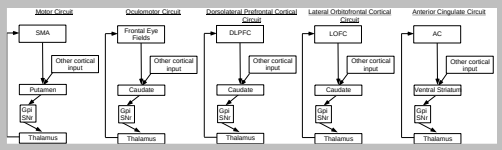
Table. Selected Features Shown to Predict Underlying Pathology in Cases of Semantic Dementia

Feature	Pathology[a] TDP-43	Tau	AD
Approximate prevalence,[1] %	74	14	12
Clinical feature			
Secondary behavioral syndrome[2,12]	++	++	–
Secondary corticobasal or marked amnestic syndrome[12]	–	+/–	+
Early dyscalculia[4]	–	+	–
Early phonologic errors[1,2]	+/–	+	+/–
Mutism at any time in disease course[5]	–	–	+
Signs of motor neuron disease at any time in disease course[1,3]	++	–	–
Imaging finding			
Knife-edge atrophy[6,10]	+	++	+/–
Very asymmetrical atrophy[6]	+	++	+/–
Anterior > posterior temporal atrophy[1,3]	+	+	–

Abbreviations: AD, Alzheimer disease; TDP-43, TAR DNA-binding protein 43; ++, highly supportive; +, supportive; +/–, indeterminate; –, not supportive.

[a] Many of the pathologically confirmed series did not differentiate between 3-repeat and 4-repeat tau or subtypes of TDP-43. However, it is accepted that most TDP-43 cases were type C and most tau cases had changes consistent with modern definitions of Pick disease.





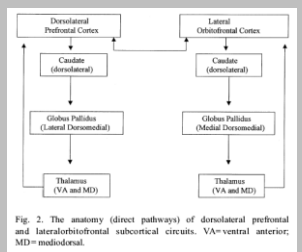


Fig. 2. The anatomy (direct pathways) of dorsolateral prefrontal and lateralorbitofrontal subcortical circuits. VA= ventral anterior; MD= mediodorsal.

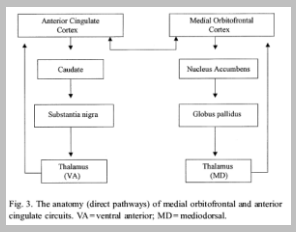


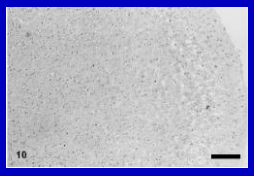
Fig. 3. The anatomy (direct pathways) of medial orbitofrontal and anterior cingulate circuits. VA = ventral anterior; MD = mediodorsal.

Allmänna fynd

- Står för ca 20% av demenser före 65 år
- Vanl debut mellan 45—65 år (knappt 80% av fallen); dock sporadiskt före 30
- Flera ärftliga former, fr kromosom 17 (tau)
- Ca. 15% nedgång/år

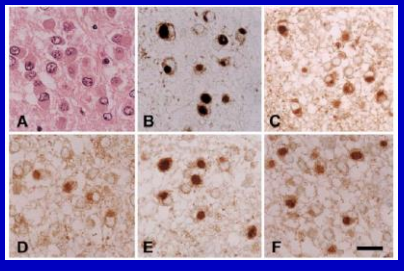
Neuropatologi

I. Cellförlust (60%)
   Temporallob relativt bevarad
   Mikrovakuolära förändringar
   Glios
II. Pick-celler (’balooned cells’) (25%)
   Medial temporallob mer påverkad
III. ALS (15%)

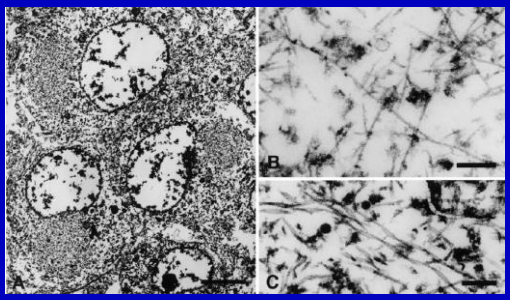


Mikrovakuolära förändringar i temporalloben (Jackson & Lowe, 1996).

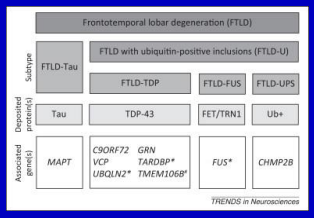
Glios i frontalloben (Jackson & Lowe, 1996).



Pick bodies in Pick's disease; various staining methods (Mori et al., 2002)



Pick bodies in Pick's disease. B and C shows straight and twisted filaments at higher levels of magnification (Mori et al., 2002).



A summary of the subtypes of frontotemporal lobar degeneration (FTLD) and their respective underlying pathologies and genetics. *TARDBP (encoding trans-activating response element with an approximate molecular weight of 43 kDa, TDP-43), UBQLN2 (ubiquilin 2), and FUS (fused in sarcoma) are common causes of familial amyotrophic lateral sclerosis (ALS) and only rarely cause FTLD. #TMEM106B (encoding transmembrane protein 106B) is a genetic risk factor for FTLD that works indirectly by affecting progranulin levels. Box sizes do not reflect the relative frequency of the different pathologies or genetic mutations.

Terri L. Petkau , Blair R. Leavitt **Progranulin in neurodegenerative disease**. Trends in Neurosciences, 2014, http://dx.doi.org/10.1016/j.tins.2014.04.003

APPENDIX

Behavioural features of frontotemporal dementia specified in diagnostic criteria

Core features

Insidious onset and gradual progression
Early decline in social interpersonal conduct
Early impairment in regulation of personal conduct
Early emotional blunting
Early loss of insight

Supportive features

(a) ***Behavioural disorder***
Decline in personal hygiene and grooming
Mental rigidity and inflexibility
Distractibility and impersistence
Hyperorality and dietary changes
Perseverative and stereotyped behaviour
Utilisation behaviour

(b) ***Speech and language***
Altered speech output:
(i) aspontaneity and economy of speech
(ii) press of speech
Stereotypy of speech
Echolalia
Perseveration
Mutism

(c) ***Physical signs***
Primitive reflexes
Incontinence
Akinesia, rigidity and tremor
Low and labile blood pressure

(d) ***Investigations***
Neuropsychology: significant impairment on frontal lobe tests in the absence of severe amnesia, aphasia or perceptuospatial disorder
Electroencephalography: normal on conventional electroencephalography despite clinically evident dementia
Brain imaging (structural and/or functional): predominant frontal and/or temporal abnormality

Neuropsykologi

Flera fenotyper…

- Semantisk demens
- Progressiv afasi av ”icke-flytande” typ
- Beteendestörningar och dysexekutiva förändringar
- Anterograd amnesi

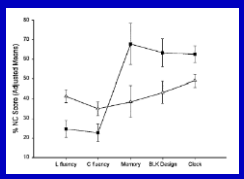
Flera fenotyper…

- Semantisk demens
  - Enda formen med tydlig koppling kognition-neuropatologi
  - En majoritet TDP43 typ C
- Progressiv afasi av ”icke-flytande” typ
- Beteendestörningar och dysexekutiva förändringar
- Anterograd amnesi

Cognitive profiles differ in autopsy-confirmed frontotemporal dementia and AD

K. Rascovsky, MA; D.P. Salmon, PhD; G.J. Ho, MD; D. Galasko, MD; G.M. Peavy, PhD; L.A. Hansen, MD; and L.J. Thal, MD

NEUROLOGY 2002;58:1801–1808



Journal of the International Neuropsychological Society (2002), 8, 561–572.
Copyright © 2002 INS. Published by Cambridge University Press. Printed in the USA.
DOI: 10.1017.S1355617702810173

Increased variability accompanies frontal lobe damage in dementia

SUSAN MURTHA,[1,2] ROXANNA CISMARU,[1] RANDALL WAECHTER,[1] AND HOWARD CHERTKOW[1,2,3]

Table 1b. Neuropsychological test performance ($M \pm SEM$) on tasks that measure frontal lobe impairment for ENC, DAT, and FLD

	Frontal Behavioral Inventory	Modified Card Sort Task: Perseverations	Modified Card Sort Task: Total categories	Animal fluency	Shape fluency	Shape perseverations
ENC	—	11.5 ± 2.4	2.6 ± 0.3	21.0 ± 1.7*	18.5 ± 2.3*	3.2 ± 1.2
Range		(8–20)	(2–4)	(12–30)	(8–36)	(1–6)
DAT	10.2 ± 3.4	18.5 ± 2.5	2.0 ± 0.3	8.3 ± 1.9	8.5 ± 2.6	3.2 ± 1.3
Range	(1–19)	(6–32)	(0–4)	(3–12)	(3–13)	(1–13)
FLD	29.4 ± 4.3**	22.4 ± 3.1#	1.6 ± 0.4	12.8 ± 2.4	6.6 ± 3.3	8 ± 1.7
Range	(8–40)	(13–29)	(0–3)	(5–22)	(8–40)	(2–17)

*ENC significantly different from DAT and Frontal, $p < .05$.
**FLD significantly different from DAT, $p < .05$.
#FLD significantly different from ENC, $p < .05$.
ENC–elderly normal control, DAT–dementia of the Alzheimer's type, FLD–frontal lobe dementia.

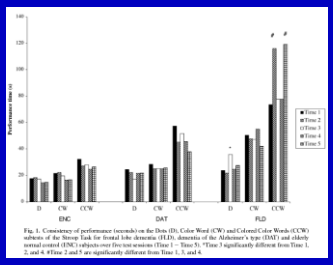
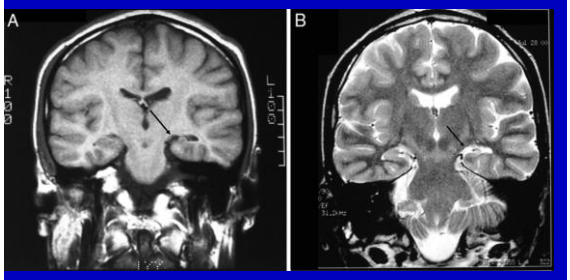


Fig. 1. Consistency of performance (seconds) on the Dots (D), Color Word (CW) and Colored Color Words (CCW) subtests of the Stroop Task for frontal lobe dementia (FLD), dementia of the Alzheimer's type (DAT) and elderly normal control (ENC) subjects over five test sessions (Time 1 – Time 5). *Time 3 significantly different from Time 1, 2, and 4. #Time 2 and 5 are significantly different from Time 1, 3, and 4.

Slutsatser

- Olika profiler på np test (FTD vs. Alz)
- Ökad variabilitet vid FTD
- Ökat antal ej genomförbara uppgifter vid FTD
- Minne: ökad känslighet för interaktioner inkodning—framplockning vid FTD

Hippocampal Sclerosis



Hippocampal sclerosis--aging

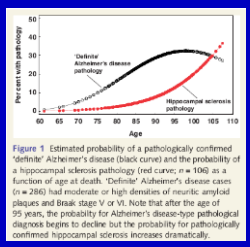


Figure 1 Estimated probability of a pathologically confirmed 'definite' Alzheimer's disease (black curve) and the probability of a hippocampal sclerosis pathology (red curve; $n = 106$) as a function of age at death. 'Definite' Alzheimer's disease cases ($n = 286$) had moderate or high densities of neuritic amyloid plaques and Braak stage V or VI. Note that after the age of 95 years, the probability for Alzheimer's disease-type pathological diagnosis begins to decline but the probability for pathologically confirmed hippocampal sclerosis increases dramatically.

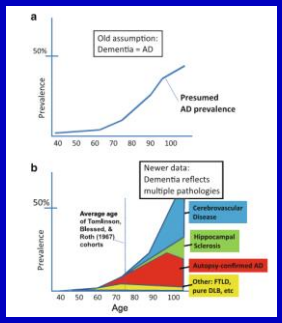


Table 5 **Cases from the UK-Alzheimer's Disease Centre and Nun Study matched for age, gender, APOE allele frequencies and education level: comparison on neuropsychological test scores by pathological diagnosis**

	HS-Ageing negative				HS-Ageing positive			
	Alzheimer's disease negative	*n*	Alzheimer's disease positive	*n*	Alzheimer's disease negative	*n*	Alzheimer's disease positive	*n*
At intake								
Test scores (average ± SEM)								
MMSE	27.8 ± 0.3	52	27.5 ± 0.4	23	27.6 ± 0.4	30	26.2 ± 0.6	13
Verbal fluency	16.7 ± 0.6	52	15.1 ± 0.9	23	16.3 ± 0.8	30	14.5 ± 1.2	13
Word list delay	5.9 ± 0.4	52	5.7 ± 0.5	23	5.1 ± 0.5	30	3.7 ± 0.7	13
Word list delay/verbal fluency	0.36 ± 0.02	52	0.39 ± 0.04	23	0.32 ± 0.03	30	0.26 ± 0.05	13
5.5–6.5 years prior to death								
Test scores (average ± SEM)								
MMSE	27.6 ± 0.9	37	25.0 ± 1.6	12	25.4 ± 1.1	25	18.7 ± 2.7	4
Verbal fluency	16.5 ± 0.9	37	12.9 ± 1.6	12	13.9 ± 1.1	25	12.0 ± 2.7	4
Word list delay	6.8 ± 0.4	37	5.7 ± 0.8	11	4.2 ± 0.5	25	2.1 ± 1.3	4
Word list delay/verbal fluency	0.42 ± 0.03	37	0.43 ± 0.05	10	0.30 ± 0.04	24	0.20 ± 0.10	3

"Det är för nonchalant av läkare"

Nytt forskarlarm – hjärnskakningar kan ta över fyra månader att läka: 'Alla måste skärpa till sig'

Idrottsrelaterade hjärnskakningar har ökat dramatiskt på senare år.

Nu visar ny forskning att de läker långsammare än man tidigare trott.

– Både idrottare och läkare har varit alldeles för nonchalanta, säger Luleå Hockeys läkare Yelverton Tegner.

7–10 dagar. Det är den normala frånvaroperioden när en hockeyspelare drabbats av hjärnskakning.

Men ny forskning – som Sahlgrenska akademin presenterar i dag men som Sportbladet redan tagit del av – visar att hjärnskakningar läker betydligt långsammare än man tidigare trott.

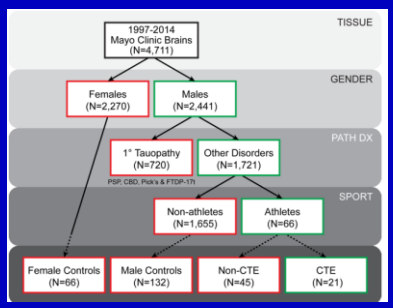
Genom att analysera ryggmärgsvätska på idrottare som drabbats av hjärnskakning har forskaren Sanna Nieselius kunnat konstatera att

Chronic traumatic encephalopathy

- Described in 2002 (??)
  - The definition of chronic traumatic encephalopathy (CTE) has changed from the original 'classic' description seen in boxers
- Risk factors
  - Contact sports
  - Military service
  - *I.e.*: frequently repeated concussions of varying severity, but typically of mild or moderate severity

Chronic traumatic encephalopathy

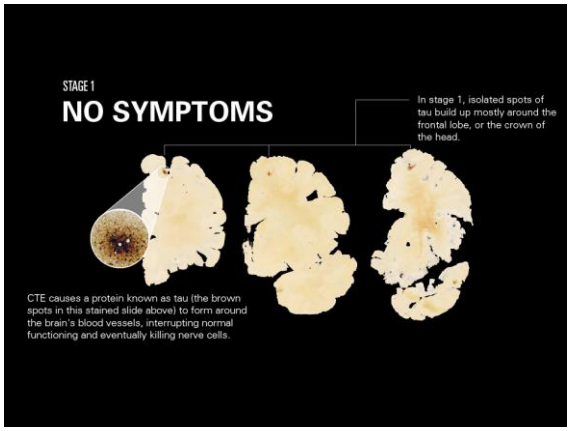
- Prevalence unknown (?)

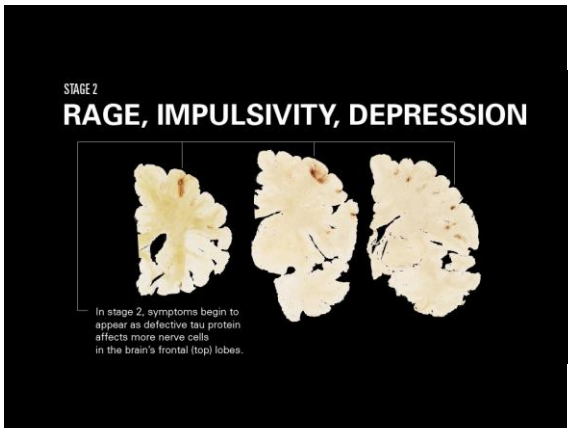


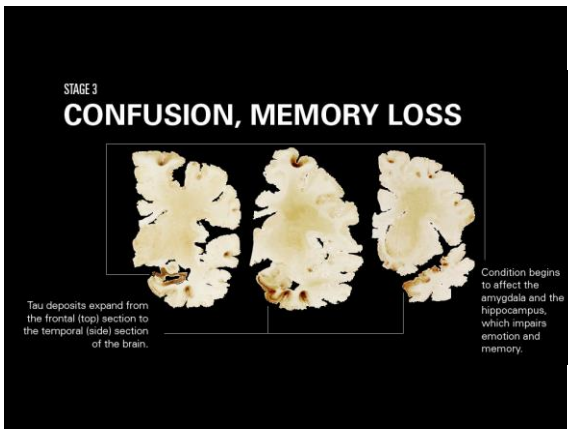
Bienek *et al.* (2015) *Acta Neuropathol 130*:877–889. DOI 10.1007/s00401-015-1502-4

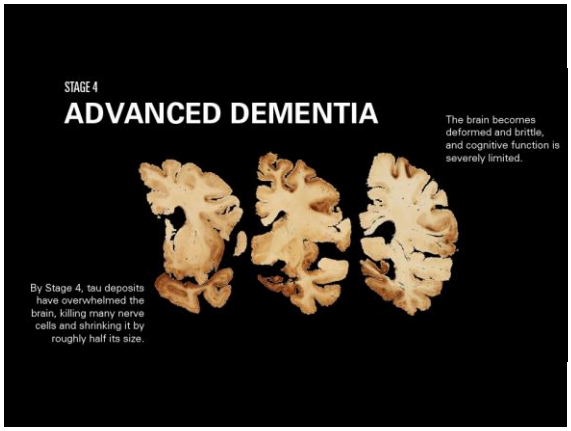
Chronic traumatic encephalopathy

- Prevalence unknown (?)
- Four stages in terms of histopathology


STAGE 1
NO SYMPTOMS
In stage 1, isolated spots of tau build up mostly around the frontal lobe, or the crown of the head.
CTE causes a protein known as tau (the brown spots in this stained slide above) to form around the brain's blood vessels, interrupting normal functioning and eventually killing nerve cells.


STAGE 2
RAGE, IMPULSIVITY, DEPRESSION
In stage 2, symptoms begin to appear as defective tau protein affects more nerve cells in the brain's frontal (top) lobes.


STAGE 3
CONFUSION, MEMORY LOSS
Tau deposits expand from the frontal (top) section to the temporal (side) section of the brain.
Condition begins to affect the amygdala and the hippocampus, which impairs emotion and memory.



Clinical features of CBT

Table 5. Clinical symptoms of CTE and other neurodegenerative conditions.

Symptoms	CTE (stages)				Presence in other neurodegenerative conditions			
	I	II	III	IV	PCS	AD	PD	FTLD
Asymptomatic	x	x	x					
Headache	x	x	x	x	x			
Attention/Concentration loss	x	x	x	x	x	x	x	x
Short-term Memory loss	x	x	x	x	x	x	x	x
Mood Disorder	x	x	x	x	x	x	x	x
Behavioral Problem	x	x	x	x		x	x	x
Executive Dysfunction	x	x	x	x		x	x	x
Language Difficulties	x	x	x	x		x	x	x
Visuospatial Difficulties			x	x			x	
Cognitive Impairments	x	x	x			x	x	
Suicidality		x	x	x		x		
Dementia			x	x		x	x	x
Motor Impairments		x	x	x		x	x	x

doi:10.1371/journal.pone.0117338.t005

Maroon JC, Winkelman R, Bost J, Amos A, Mathyssek C, et al. (2015) Chronic Traumatic Encephalopathy in Contact Sports: A Systematic Review of All Reported Pathological Cases. PLoS ONE 10(2): e0117338. doi:10.1371/journal.pone.0117338 http://127.0.0.1:8081/plosone/article?id=info:doi/10.1371/journal.pone.0117338

PLOS | ONE

Table 5. Clinical symptoms of CTE and other neurodegenerative conditions.

Symptoms	CTE (stages)				Presence in other neurodegenerative conditions			
	I	II	III	IV	PCS	AD	PD	FTLD
Asymptomatic	x	x	x					
Headache	x	x	x	x	x			
Attention/Concentration loss	x	x	x	x	x	x	x	x
Short-term Memory loss	x	x	x	x	x	x	x	x
Mood Disorder	x	x	x	x	x	x	x	x
Behavioral Problem	x	x	x	x		x	x	x
Executive Dysfunction	x	x	x	x		x	x	x
Language Difficulties	x	x	x	x		x	x	x
Visuospatial Difficulties			x	x			x	
Cognitive Impairments	x	x	x			x	x	
Suicidality		x	x	x		x		
Dementia			x	x		x	x	x
Motor Impairments		x	x	x		x	x	x

doi:10.1371/journal.pone.0117338.t005

Maroon JC, Winkelman R, Bost J, Amos A, Mathyssek C, et al. (2015) Chronic Traumatic Encephalopathy in Contact Sports: A Systematic Review of All Reported Pathological Cases. PLoS ONE 10(2): e0117338. doi:10.1371/journal.pone.0117338
http://127.0.0.1:8081/plosone/article?id=info:doi/10.1371/journal.pone.0117338

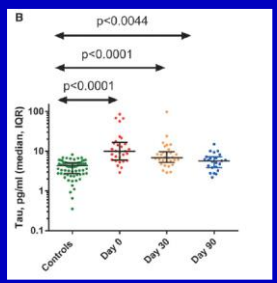
Table 1. Age group distribution in CTE diagnosed subjects.

Age range	Overall cases n (%)		Football cases n (%)	
10–19	3	(2.0%)	3	(4.8%)
20–29	16	(10.7%)	5	(7.9%)
30–39	9	(6.0%)	6	(9.5%)
40–49	21	(14.0%)	11	(17.5%)
50–59	21	(14.0%)	6	(9.5%)
60–69	39	(26.0%)	13	(20.6%)
70–79	26	(17.3%)	10	(15.9%)
80–89	12	(8.0%)	8	(12.7%)
90–99	3	(2.0%)	1	(1.6%)
Total	150		63	

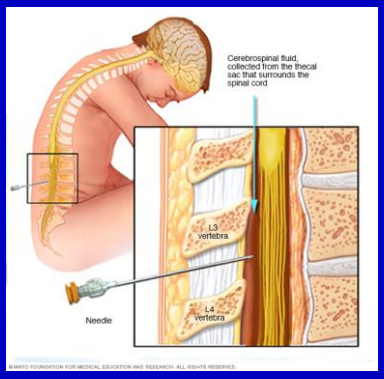
doi:10.1371/journal.pone.0117338.t001

Maroon JC, Winkelman R, Bost J, Amos A, Mathyssek C, et al. (2015) Chronic Traumatic Encephalopathy in Contact Sports: A Systematic Review of All Reported Pathological Cases. PLoS ONE 10(2): e0117338. doi:10.1371/journal.pone.0117338
http://127.0.0.1:8081/plosone/article?id=info:doi/10.1371/journal.pone.0117338

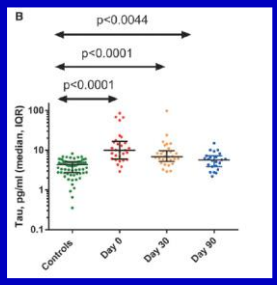
Biochemical marker: Tau



Bogolovsky, *et al*. (2017) *J Neurotrauma*, *34*, 66–73 DOI: 10.1089/neu.2015.4333



Biochemical marker: Tau

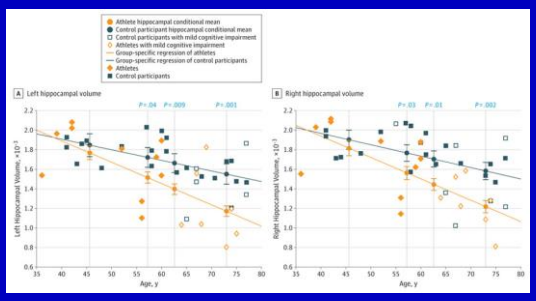


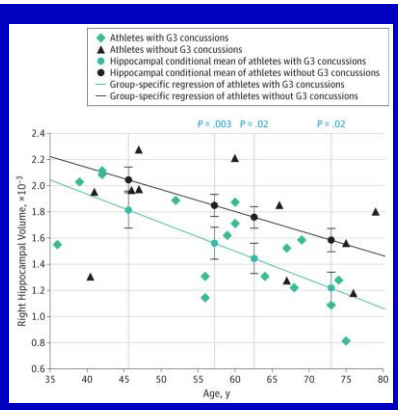
Bogolovsky, *et al.* (2017) *J Neurotrauma*, *34*, 66–73 DOI: 10.1089/neu.2015.4333

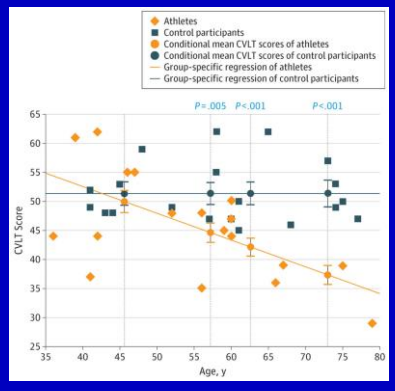
Elevated Tau: Processing speed

TEST	ELEVATED NFL(B) N = 12 Mean (range) SD	NORMAL NFL(B) N = 14 Mean (range) SD	P-value Elevated vs. normal
ROCF[1]			
Copy (max 36)	32.1 (8–36) 9.1	35.5 (4–32) 1.1	0.80
Delay (max 36)	18.0 (3.5–31) 9.5	171 (1–31) 7.7	0.67
VOCABULARY[2] **(max 70)**	28.4 (16–47) 11.5	34.3 (17–60) 11.4	0.16
COWAT[3]	32.2 (18–48) 11.2	39.3 (19–54) 11.4	0.09
DIGIT SPAN[4] **(max 14)**	6.8 (4–10) 2.1	7.3 (3–11) 2.0	0.40
LISTENING SPAN[5] **(max 38)**	12.8 (1–21) 6.1	15.4 (6–33) 8.3	0.56
TRAIL MAKING[6]			
Part A, (s)	35.8 (20–75) 15.7	26.2 (15–55) 9.9	**0.04**
Part B, (s)	98.7 (43–240) 54.7	69.0 (45–100) 18.1	0.18
REACTION TIME[7]			
Simple (msec)	371.1 (259.6–956.8) 191.3	285.1 (242.0–361.6)	**0.04**
Difference (complex-simple, msec)	126.2 (−248.0–388.0) 161.7	349.6 (92.7–3087.9) 733.3	0.84

Neselius, *et al.* (2014) *PLoS ONE*, *9*, e99870. doi:10.1371/journal.pone.0099870


Athlete hippocampal conditional mean
Control participant hippocampal conditional mean
Control participants with mild cognitive impairment
Athletes with mild cognitive impairment
Group-specific regression of athletes
Group-specific regression of control participants
Athletes
Control participants
A Left hippocampal volume
B Right hippocampal volume
P = .04 P = .009 P = .001
P = .03 P = .01 P = .002
Left Hippocampal Volume, ×10⁻³
Right Hippocampal Volume, ×10⁻³
Age, y


Athletes with G3 concussions
Athletes without G3 concussions
Hippocampal conditional mean of athletes with G3 concussions
Hippocampal conditional mean of athletes without G3 concussions
Group-specific regression of athletes with G3 concussions
Group-specific regression of athletes without G3 concussions
P = .003 P = .02 P = .02
Right Hippocampal Volume, ×10⁻³
Age, y


Athletes
Control participants
Conditional mean CVLT scores of athletes
Conditional mean CVLT scores of control participants
Group-specific regression of athletes
Group-specific regression of control participants
P = .005 P < .001 P < .001
CVLT Score
Age, y

Diffus ’Lewy-body’ sjukdom

Allmänna fynd

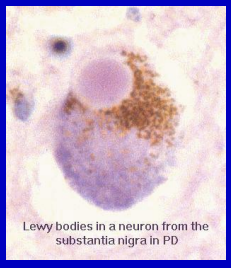
- **Utgör 15—20% av patienter som kommer till obduktion**
- **Debut mellan 50—85 år**
- **Vanligen sporadisk**
- **10% nedgång/år både betr kognition och neuropatologi**

Neuropatologi

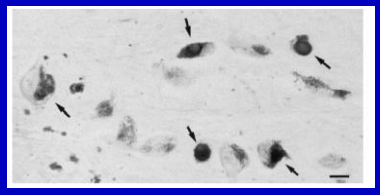
- Lewy-inklusioner
- Lewy-neuriter

Lewy-inklusioner

- Neurofilament-protein, aggregerade med ubiquitin och α-synuklein
- Förekomst i SN/hjärnstam, samt paralimbiska och kortikala områden
- Uttalad påverkan i nucleus basalis Meynerti
- Orsakar dramatisk kolinerg svikt (mer uttalad än vid Alzheimers sjukdom?)



Lewy bodies in a neuron from the substantia nigra in PD

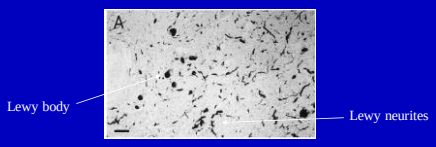


α-Synuclein staining of Lewy bodies in Parkinson's disease. Substantia nigra from a Parkinson's disease patient was stained using anti-α-synuclein antibody PER 2. Arrows indicate Lewy bodies in pigmented cells. Scale bar, 31 mm.

Cortical Lewy bodies in diffuse Lewy body dementia

Lewy-neuriter

- SN
- Hippocampus
- Dorsala Vaguskärnan
- NbM
- Entorhinal kortex
- Vanligare än LB:s
- Centrala för kognitiva och neuropsykiatriska symtom



Kliniska fynd

	Dementia with Lewy bodies		Alzheimer's disease	
	At presentation (%)	Ever (%)	At presentation (%)	Ever (%)
Dementia	82 (40–100)	100	100	100
Fluctuation	58 (8–85)	75 (45–90)	6 (3–11)	12 (5–19)
Visual hallucinations	33 (11–64)	46 (13–80)	13 (3–19)	20 (11–28)
Auditory hallucinations	19 (13–30)	19 (0–45)	1 (0–3)	4 (0–13)
Depression	29 (7–75)	38 (12–89)	16 (9–38)	16 (12–21)
Parkinsonism	43 (10–78)	77 (50–100)	12 (5–30)	23 (19–30)
Falls	28 (10–38)	37 (22–50)	9 (5–14)	18 (11–24)
Neuroleptic sensitivity	61 (0–100)		15 (0–29)	

Figures show mean (range). Based upon 261 cases of Alzheimer's disease and 190 cases of dementia with Lewy bodies, with autopsy confirmation of diagnosis.

Investigation	Alzheimer's disease	Dementia with Lewy bodies
CT/MRI	Generalised atrophy, particularly in medial temporal lobes	Relative sparing of medial temporal lobes in majority
Deep white-matter lesions on MRI	Moderate increase compared with 'normals'	Moderate increase compared with 'normals'
Periventricular lucencies on MRI	Frequent compared with 'normals'	Frequent compared with 'normals'
SPECT HMPAO scan (blood flow)	Global reduction, especially posterior parietal-temporal	Global reduction, especially occipital. Medial temporal lobes relatively preserved
SPECT FP-CIT scan (presynaptic dopamine transporter)	Normal for age	Reduced in putamen, similar to appearance in Parkinson's disease
ApoE genotype	ε4 allele increased compared with 'normals'	ε4 allele increased compared with 'normals'

Konsensuskriteria

- Progressiv kognitiv nedgång
  Minnesstörningar behöver ej förekomma initialt; svårigheter m.a.p. visuospatiala förmågor, uppmärksamhet och exekution uttalade
- Två av följande:
  -- Fluktuerande förlopp, med variation i uppmärksamhet och vakenhet
  -- Återkommande, detaljerade visuella hallucinationer
  -- Motoriska fynd som vid Parkinson

  Två kriterier = sannolik DLBD, ett kriterium = möjlig DLBD

Konsensuskriteria (forts)

- Stödjande fynd:
  - Upprepade fall
  - Synkop
  - Övergående medvetandeförlust
  - Överkänslighet för neuroleptika
  - Vanföreställningar
  - Hallucinationer i andra modaliteter
- DLBD osannolik om:
  - CVS
  - Annan neurologisk eller systemisk sjukdom kan förklara den kliniska bilden

Behandling

- AChE-hämmare effektiva (muskarinreceptor intakt till skillnad från Alzheimers sjukdom)
- 30-50% förbättras efter behandling, jämfört med placebo
- Dramatisk lättnad för anhöriga, då hallucinos och synkop är utomordentligt krävande