

# Alzheimer's disease and the neurotrophins BDNF/NGF

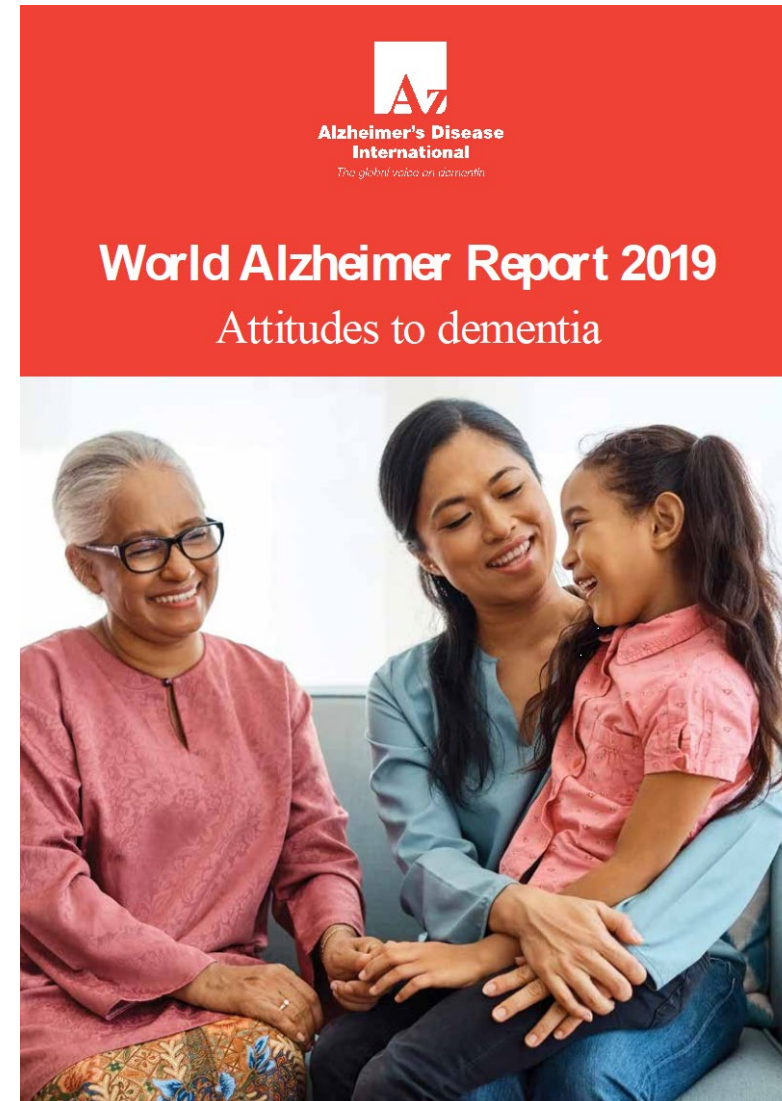
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# Dementia disorders-

## Alzheimer's disease most common

- 47 million worldwide-increasing to 150 million by 2050! (*World Alzheimer's report*)
- New dementia case every 3 seconds!
- Studies indicate that the incidence of dementia may have begun to decline (*Qui, Fratiglioni et al 2013 et al*).
- Why? - Increased awareness of the importance of lifestyle-related risk factors. Prevention successful!





Population	10 000 000
Proportion $\geq 65$ y	20 %
Estimated number with dementia	140-160 000
Estimated new cases per year	20-25 000

**COST: 63 bn SEK**

cost of cancer: 30bn SEK

cardiovascular disease

61,5 bn SEK



## 100 000 unika personer i SveDem!

Nu har SveDem fått sin hundratusende unika person registrerad i registret. SveDem är ett av världens största register för personer med kognitiva sjukdomar/demenssjukdomar. Tack vare att ni användare flitigt registrerar in i SveDem kan vi tillsammans förbättra kvaliteten vad gäller utredning, diagnos, behandling och omvårdnad av personer med kognitiva sjukdomar/demenssjukdomar i Sverige.



### SveDems utbildningar

Aktuella utbildningar och konferenser...

### Utbildningsmiljö

Till SveDems utbildningsmiljö

### Problem med inloggning SveDem

Läs mer om inloggningsproblem

### Resultat av förbättringsarbete i SveDem

Läs mer om förbättringsarbete i SveDem

### Information till dig med demenssjukdom

### Senaste nytt

Tack till er alla som deltog på vår invigning av den nya plattformen!

Nyheter i SveDem

Ny Styrgruppsmedlem

Ny artikel som vägleder kliniker i utredning och uppföljning av personer med mild cognitive impairment, MCI.

### Publika rapporter SveDem

Välkommen till SveDems publika rapporter

Välkommen till SveDem!  
Här hittar du all information om SveDem och dess verksamhet.



Till SveDems publika rapporter

## ❑ **SveDem** ([www.svedem.se](http://www.svedem.se)): National quality registry on dementia

- ✓ Established in 2007
- ✓ Internet based
- ✓ Includes patients at the time of the dementia diagnosis
- ✓ Annual follow-up
- ✓ Main purpose: following national dementia guidelines by quality indicators
- ✓ Covering 35-40% of the entire expected annually incident dementia cases in all Sweden –but ca 50% of expected cases are undetected

*Religa, Eriksdotter et al. PLoS One. 2015;10(2):e0116538.*

# Through SveDem we have much information on the demography, diagnostics, treatment and care of persons with dementia

- At the time when the dementia diagnosis is established:
- The mean age is 79.5 years
  - 28% > 85 years old
  - 4% < 65 years old
- 94% live in their own home, of which 44% live alone
- The majority is women (58%)
- Cognitive level: mild dementia (MMSE scores 22/30)
- 32% have home care at diagnosis
- 70% are on medication for cardiovascular disorders

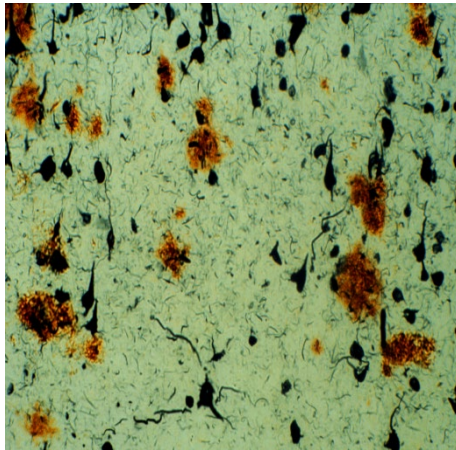


Fotograf: Yanan Li

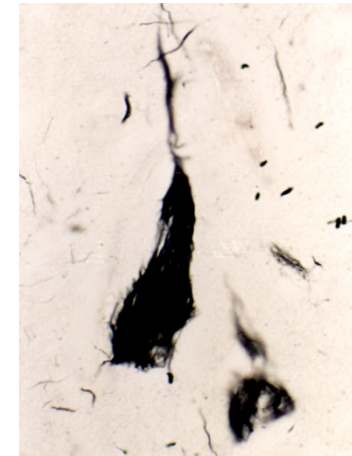
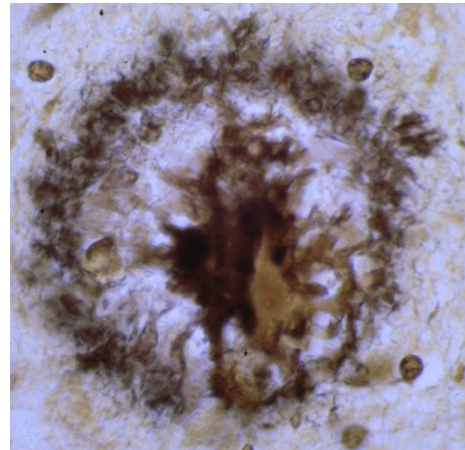


# Hallmarks of brain pathology in Alzheimer's disease

Beta-amyloid plaques in brain



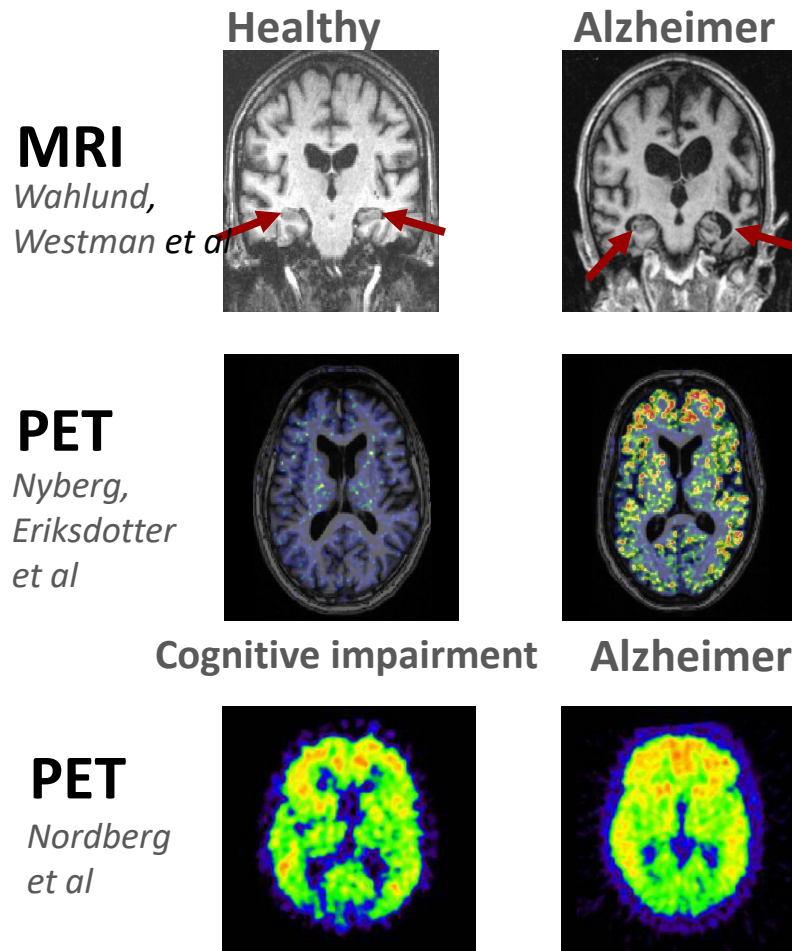
Fibrillary tangles with tau



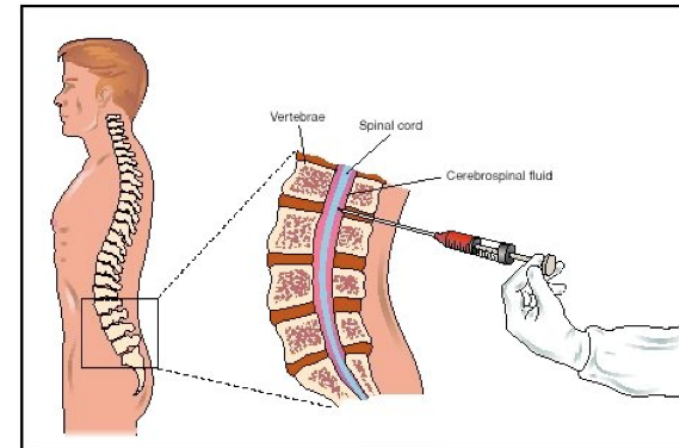
- Neuronal loss
- Inflammation
- Vascular damage

*Bogdanovic, Winblad, Huddinge Hjärnbank*

# Biomarker research has shown that changes in brain develop many years before Alzheimer dementia onset



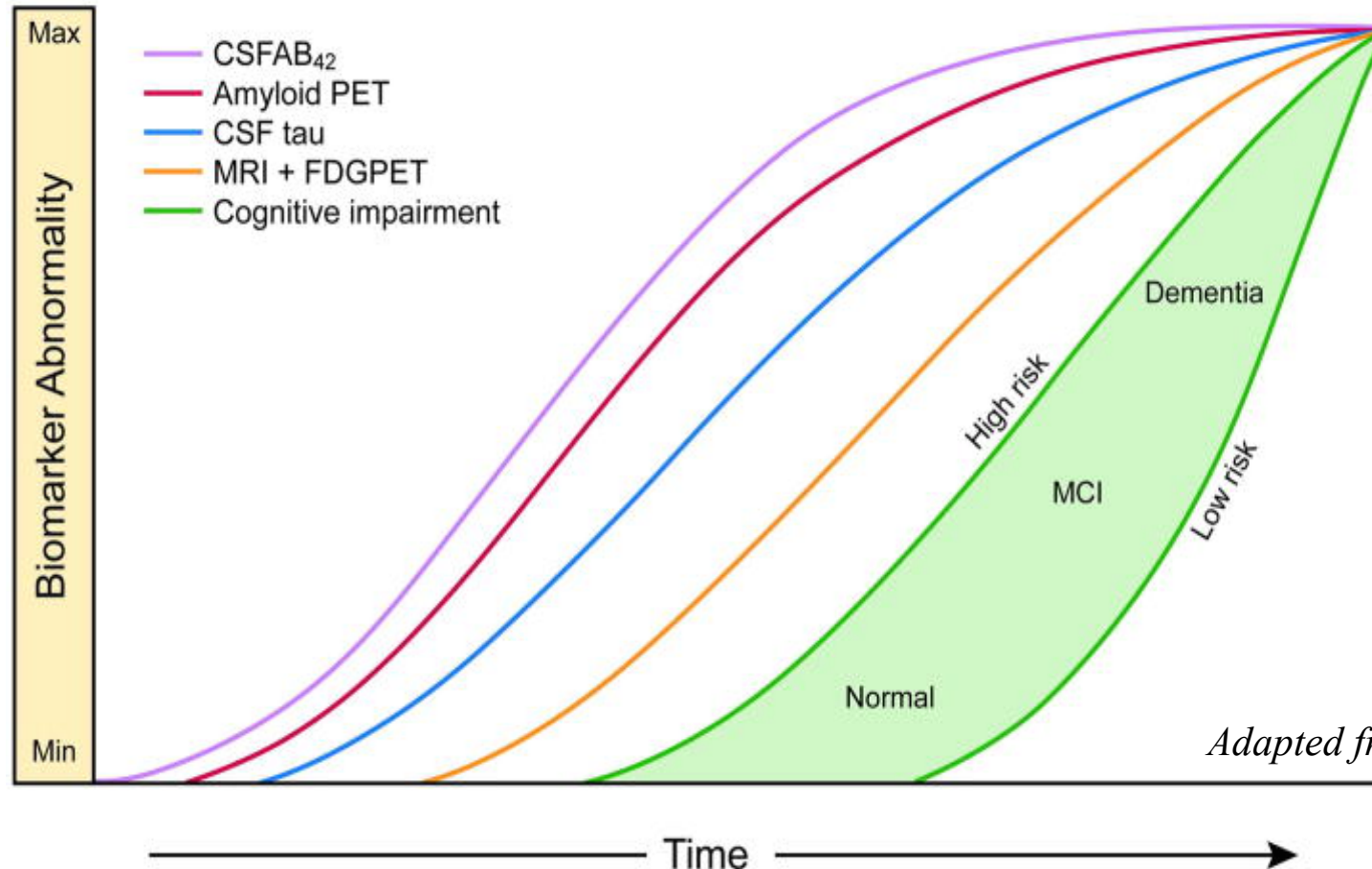
## Spinal fluid (CSF) analysis



**Beta-amyloid** ↓ **tau** ↑

*Andreasen, Blennow, Zetterberg et al*

# Changes in brain or CSF develop many years before dementia onset

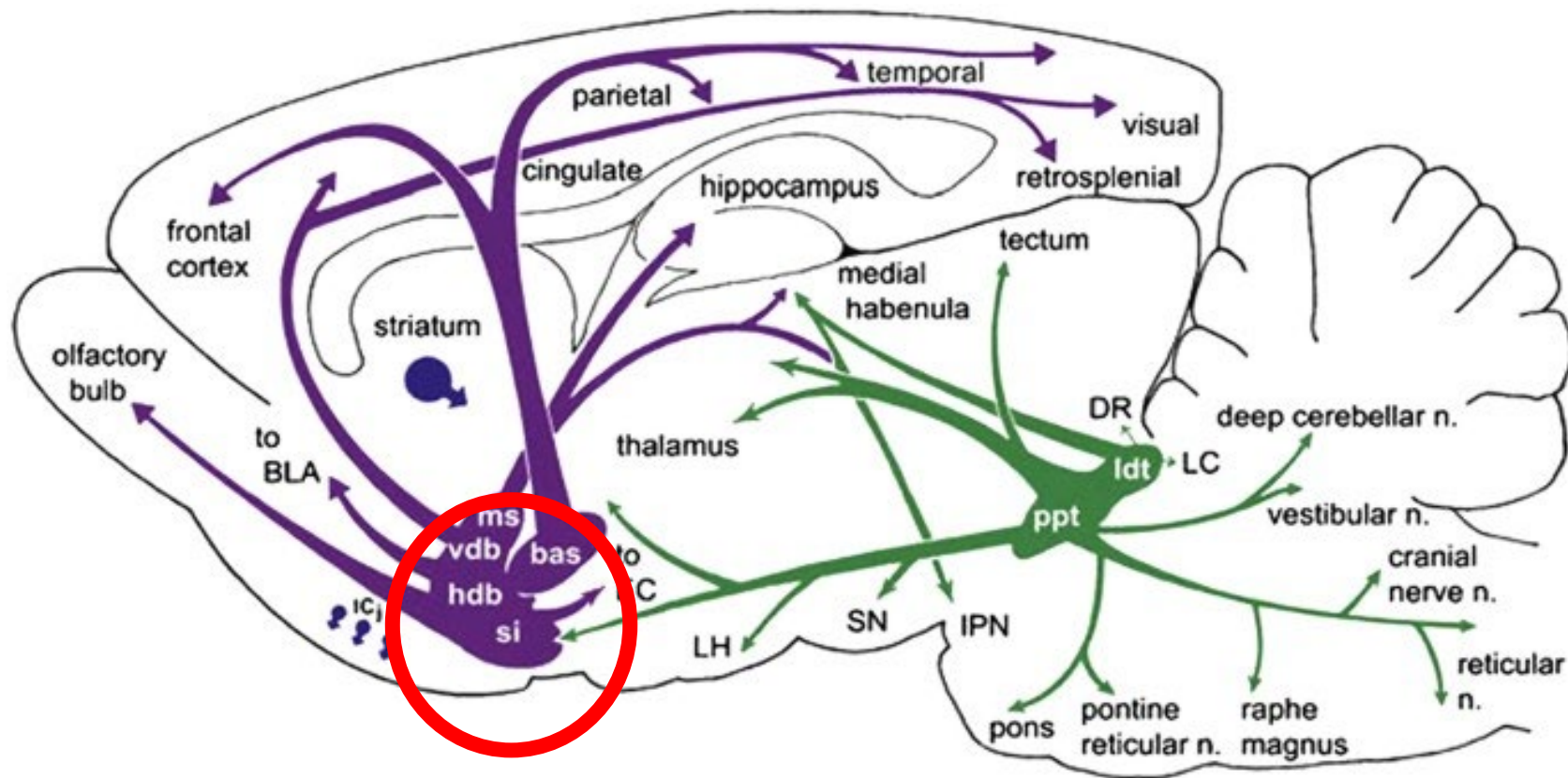


*Adapted from Jack et al, Lancet Neurology 2013*

No cognitive symptoms-Mild Cognitive Impairment (MCI)-dementia



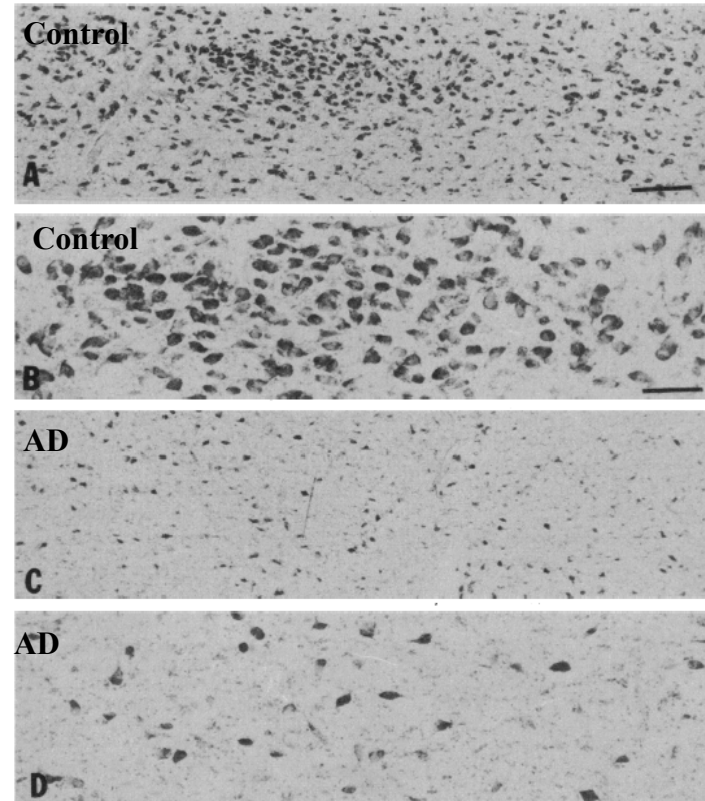
# Cholinergic signaling and cognition



Woolf and Butcher, 2011. Behav. Brain. Res., 221(2)

Basal forebrain cholinergic neurons (BFCN's) are crucial for maintaining normal cognition

# Loss of Cholinergic neurons in AD



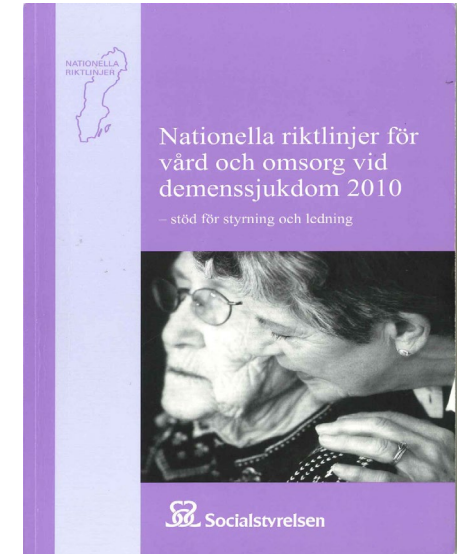
Whitehouse et al., 1982. Science. 215(4537)

Loss of cholinergic neurons in the basal forebrain and hippocampal atrophy & synaptic loss are early hallmarks of AD and correlates with cognitive decline (*Bartus et al 1982, Whitehouse et al 1982. Mesulam, 2004; Turnbull et al., 2018*)

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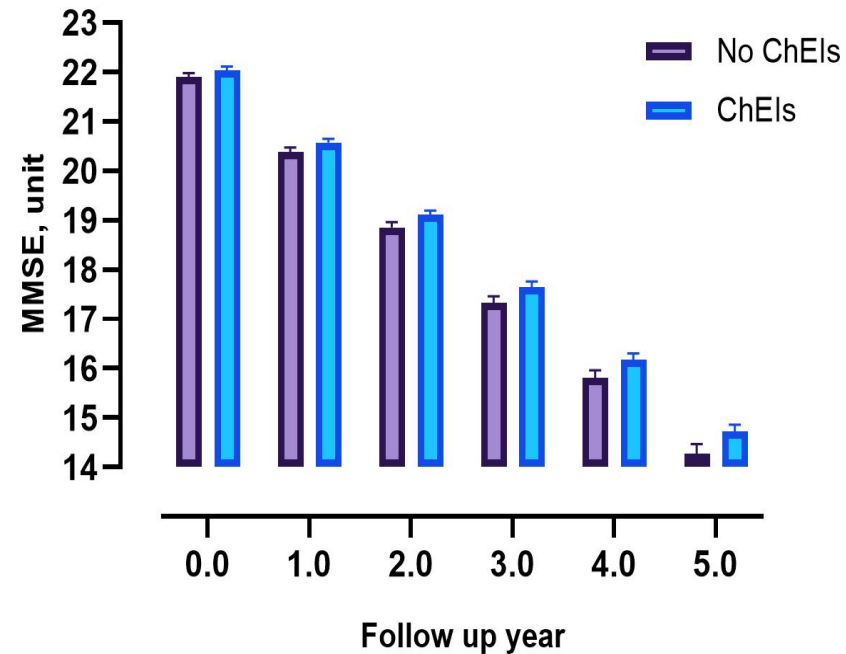
# Pharmacological treatment in Alzheimer's disease

- Guidelines by the Swedish National Board of Health and Welfare recommends when a patient is diagnosed with AD:
  - ✓ treatment with Cholinesterase-inhibitors (ChEIs) in mild to moderate AD
  - ✓ treatment with Memantine in moderate AD
- The ChEIs currently in use: donepezil, galantamine and rivastigmine



# Drugs affecting the cholinergic system

## Cholinesterase-inhibitors, ChEIs, are the current standard treatment for Alzheimer's disease



Small but persistent benefits  
with ChEIs over five years

27% reduction in mortality!

Data from SveDem:  
11652 patients with ChEI  
5826 not treated  
Propensity scored matched

*Xu ...Eriksson et al Neurology 2021*

# Why has it been so difficult to find a cure for Alzheimer's disease?

- Alzheimer's disease has not been well-defined – development of novel biomarkers & diagnostics are underway
  - Complex symptoms which vary over time
  - Several different neuronal systems are affected
  - Treatment has probably been given too late in the course of the disease
  - Lack of robust outcomes – improved endpoints being developed
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- *There is a need for well validated targets beyond  $A\beta$  for the development of novel disease modifiers*
  - *There will be a continued need for effective cognitive enhancers*
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# Drug target strategies

- Immunotherapies targeting beta – amyloid
- Immunotherapies targeting tau
- Antiinflammatory substances
- Growth factors eg NGF; BDNF
- Cocktail of substances?



# Neurotrophins - important growth factors for cognition

- Nerve growth factor (NGF)
  - Brain-derived neurotrophic factor (BDNF)
  - Neurotrophin-3 (NT-3)
  - Neurotrophin-4/5 (NT 4/5)
  - NT-6, NT-7
-

# NGF and BDNF

The neurotrophins BDNF and NGF are vital for the function and survival of the cholinergic neurons in the hippocampus and basal forebrain, and their role in memory and learning is well documented.

- Nerve growth factor – NGF
    - Development of the neuronal system.
    - Maintenance of neuronal proliferation, differentiation and survival.
  - Brain-derived neurotrophic factor – BDNF
    - Neuronal function, differentiation and cognition.
-

# Nerve Growth factor (NGF)

- NGF (*Levi-Montalcini and Hamburger 1951*) stimulates survival and function of the cholinergic nerve cells (*Thoenen et al 1987, Eriksdotter et al 1989*)
- Nobel Prize 1986
- NGF is produced in cortex and hippocampus and retrogradely transported to the basal forebrain (*Schwab et al 1979*)
- NGF is a large molecule that does not pass the blood-brain barrier



# Brain-derived neurotrophic factor

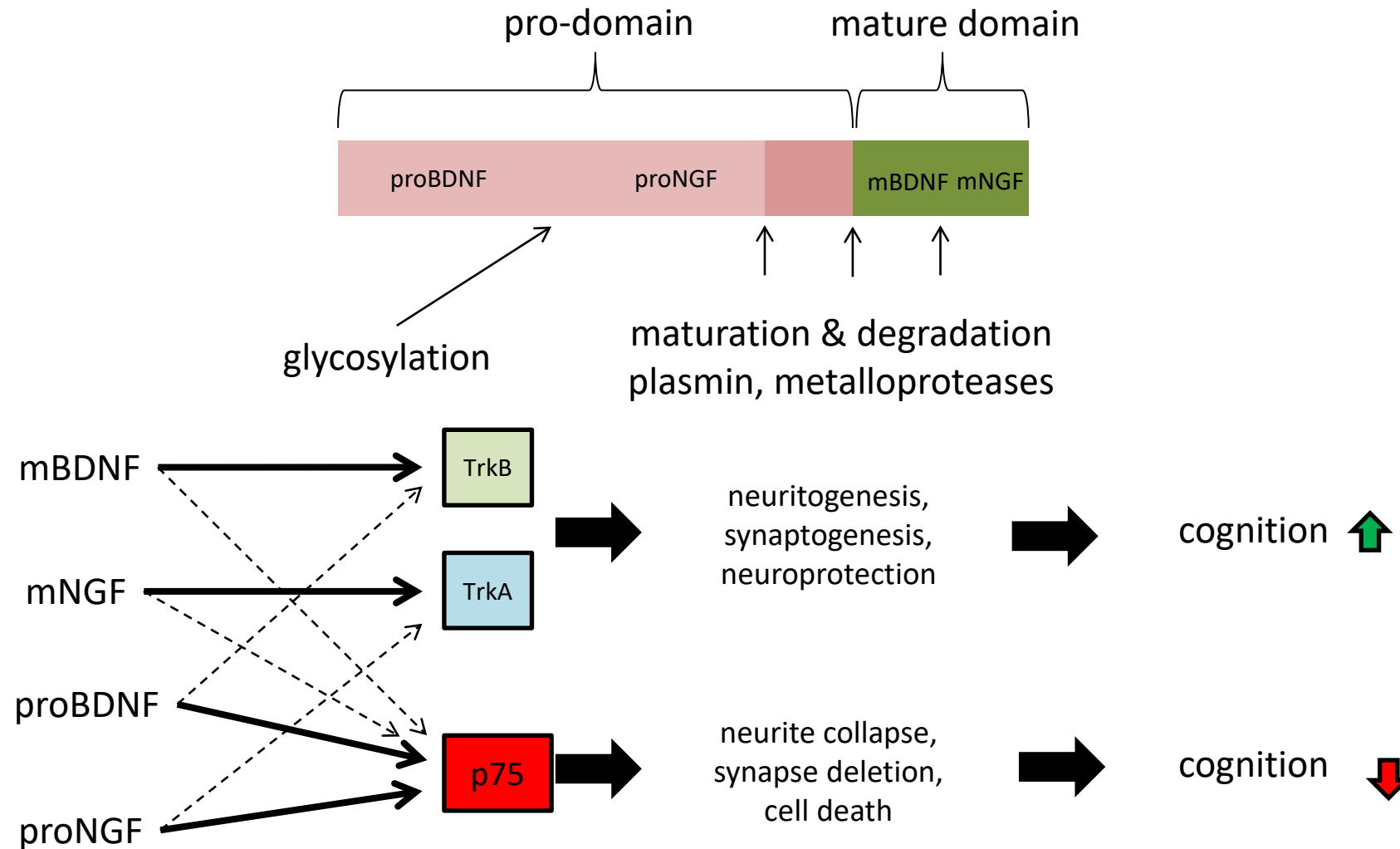
- BDNF is widely expressed in the brain especially in hippocampus and cerebral cortex
  - Important for survival of hippocampal, cortical, cholinergic and dopaminergic neurons
  - Important for synaptic plasticity and cognition
  - Implicated in AD, depression, schizophrenia, stress
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# Relevance of NGF and BDNF signaling in Alzheimer's Disease

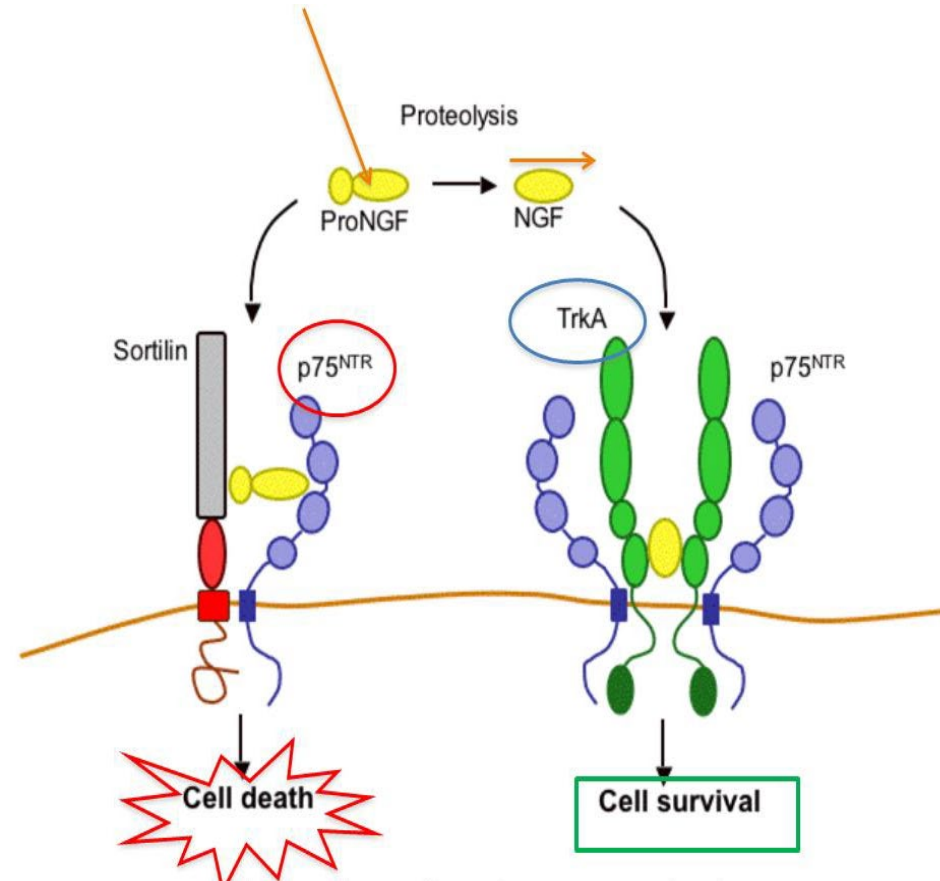
- Loss of cholinergic neurons in the basal forebrain and hippocampal atrophy & synaptic loss are early hallmarks of AD and correlates with cognitive decline (*Bartus et al 1982, Mesulam, 2004; Turnbull et al., 2018*)
  - NGF and BDNF signaling are strongly implicated in cholinergic function, hippocampal neurogenesis and plasticity, learning and memory; i.e. key neuronal structures and functions impaired in AD (*Connor et al 1997, Nagahara and Tuszynski 2011*)
  - In Alzheimer's disease levels of NGF in the basal forebrain and BDNF in the hippocampus are reduced
  - Human carriers of the BDNF Val66Met polymorphism, resulting in decreased levels of secreted BDNF, have shown memory decline and hippocampal atrophy in early AD (*Boots et al 2017*).
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# Pro- and mature forms of neurotrophins – opposite effects!



# In AD - imbalance NGF/Pro-NGF

- NGF is produced by the precursor Pro-NGF
- In Alzheimer brains pro-NGF is increased (*Fahnestock et al 2001*)
- High concentration of pro-NGF activates p75 and other receptors, leading to cell death
- NGF activating TrkA-receptors leads to cell survival
- AD - imbalance NGF/Pro-NGF? (*Cuello 2012, Mufson et al 2019*)



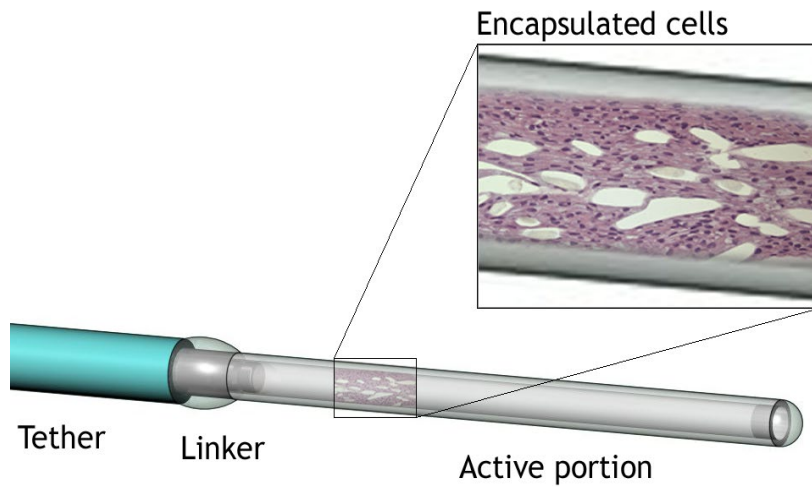
(Cuello et al 2008, Mufson et al 2008, Cattaneo et al 2009)

# How to reach the target?

## The delivery challenge

- ICV?
- Gene therapy?
- **Encapsulated cell biodelivery?**
- Intranasal?
- Eyedrops?
- Development of new small NGF-like molecules that pass the BBB?

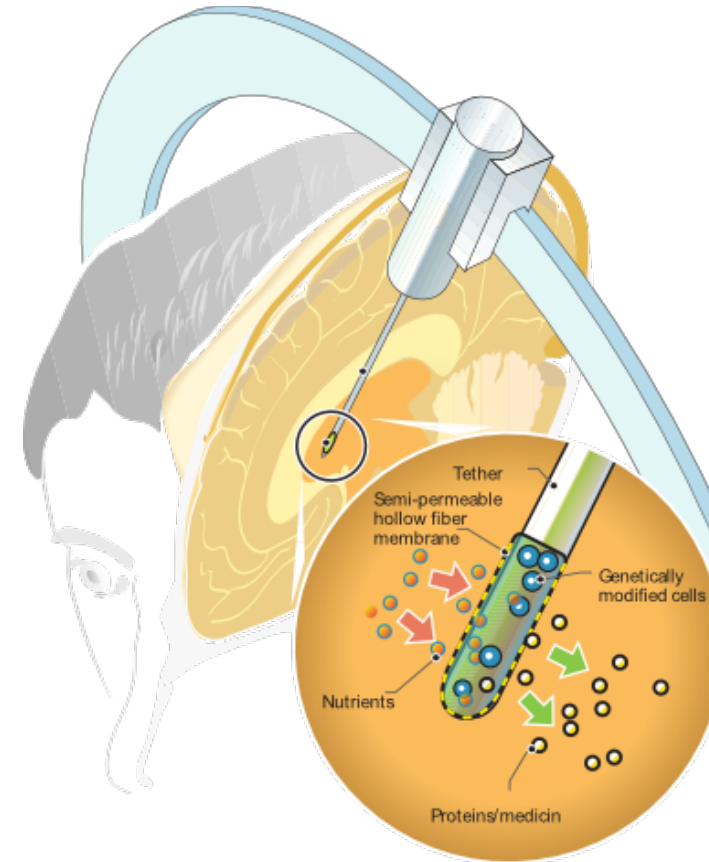
# Encapsulated cell biodelivery of NGF to the basal forebrain



- Combination product from NsGene A/S
  - Medical device
  - Drug substance (human retinal pigment epithelial cells from a commercial cell line transfected with the NGF gene expressing human NGF)

*Wahlberg et al, J Neurosurg 2012*

*Eriksdotter et al Dem Cogn Disord 2012*

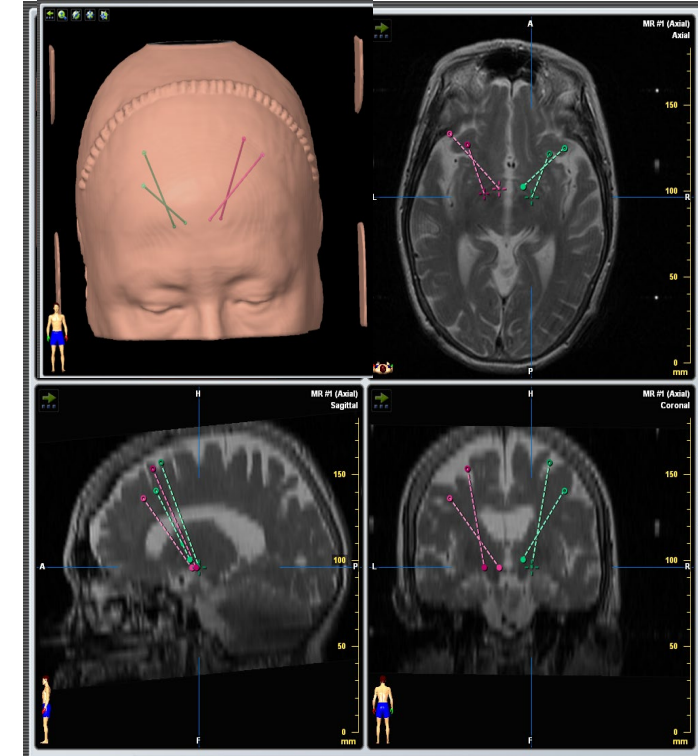
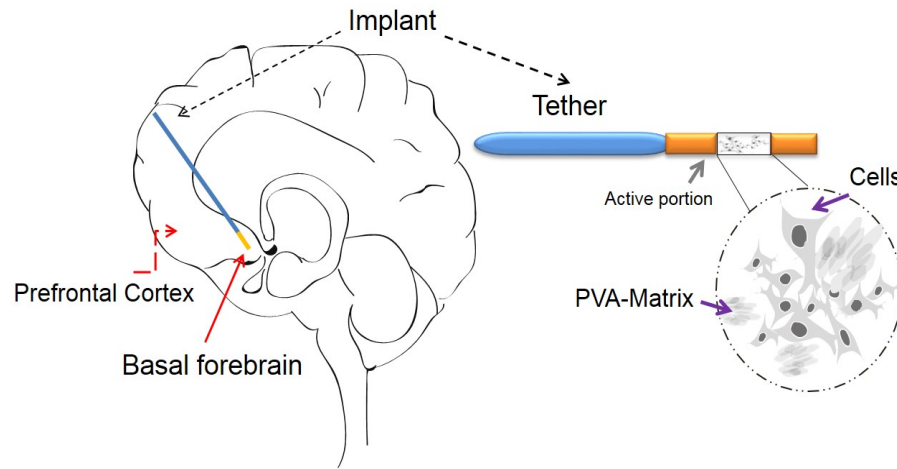
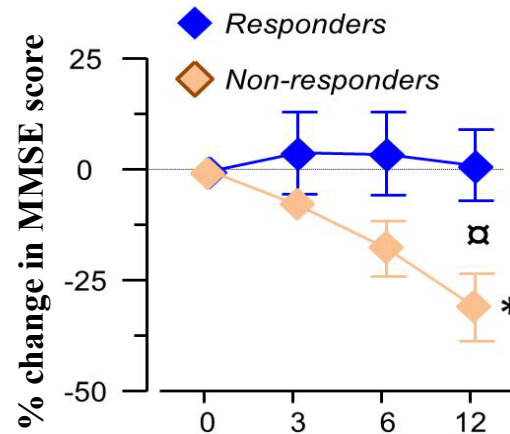


## *Hypothesis:*

Biodelivery of NGF to the cholinergic basal forebrain will provide neurotrophic support



# Cell therapy treatment with NGF in 10 patients with Alzheimer's disease



Eriksdotter et al 2012, Wahlberg et al 2012, Karami, Eyjolfssdottir et al 2015, Ferreira et al 2015, Eyjolfssdottir et al 2016, Machado et al 2020, Mitra et al 2021

## Next step?

### Small molecule modulators targeting neurotrophin receptors - Project NeuroRestore®

*The aim is to develop novel small molecule positive modulators of TrkA and TrkB for the treatment of AD.*

- Molecules that act as positive modulators of TrkA- and TrkB-signaling have been identified
  - The leading compound is ACD-856, which is a potent enhancer of TrkA and TrkB signaling, improves memory in preclinical models and is currently in clinical development
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Thank you

The Neo building at KI Campus Flemingsberg  
photo Marie Franzén