



The Natural History of Neurodegenerative Disease: Can We Modify It?

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Life expectancy is rising, and with it third-age diseases are becoming an alarming problem

Life expectancy in the Future – Linear or non-linear

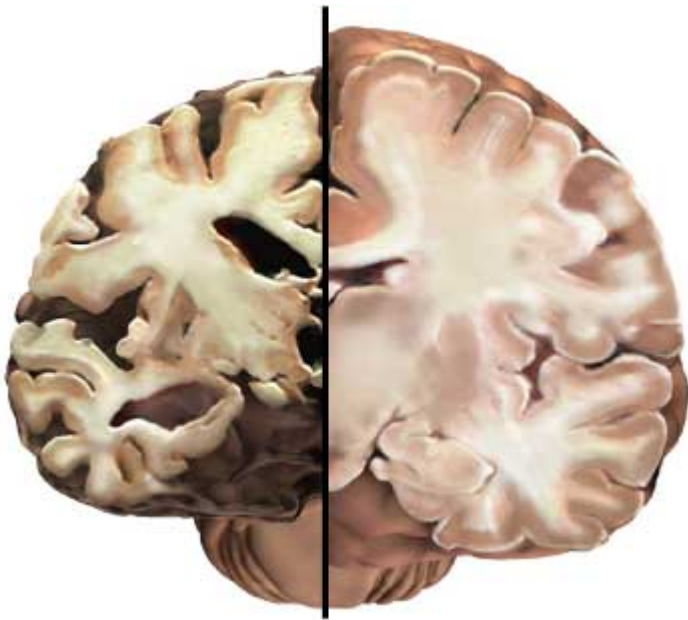


Source: National Geographic, May 26, 2013



Source: Time, Feb 23, 2015

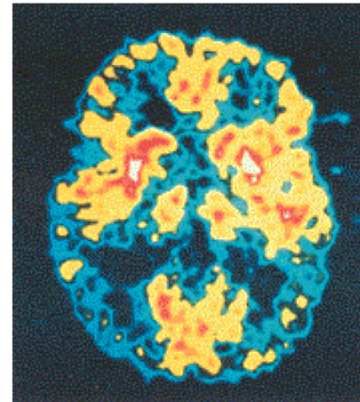
Neurodegeneration – the Modern Epidemic



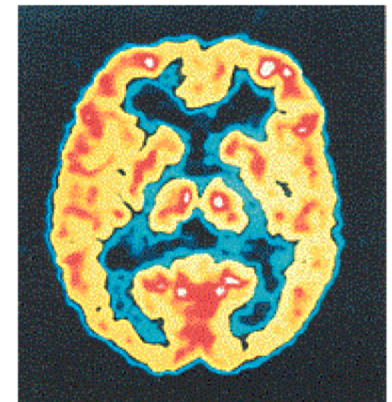
**Alzheimer's
Disease**

Normal Brain

**The difference between a normal brain
and a brain with Alzheimer's disease**



**A brain with
Alzheimer's disease**

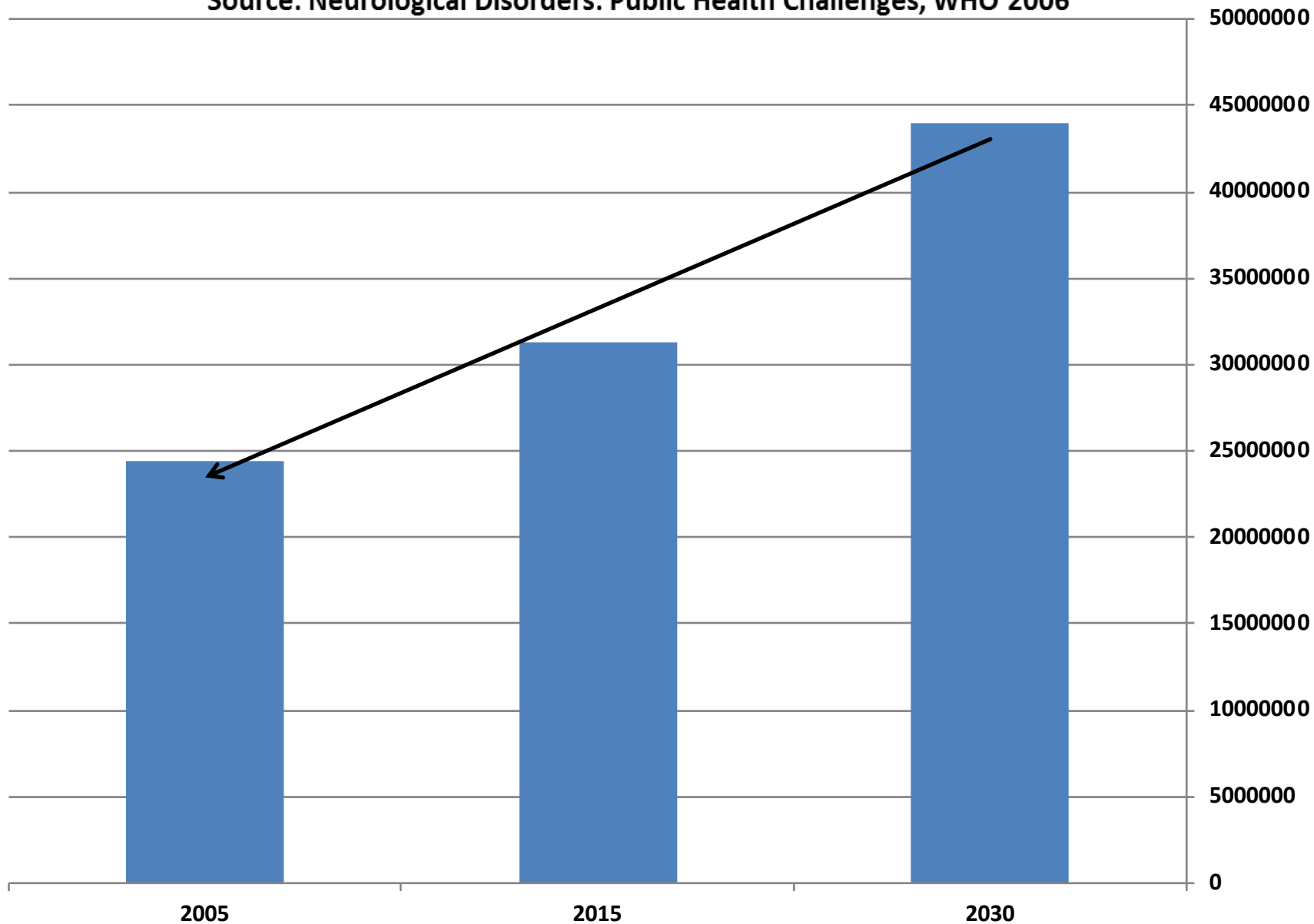


Normal brain

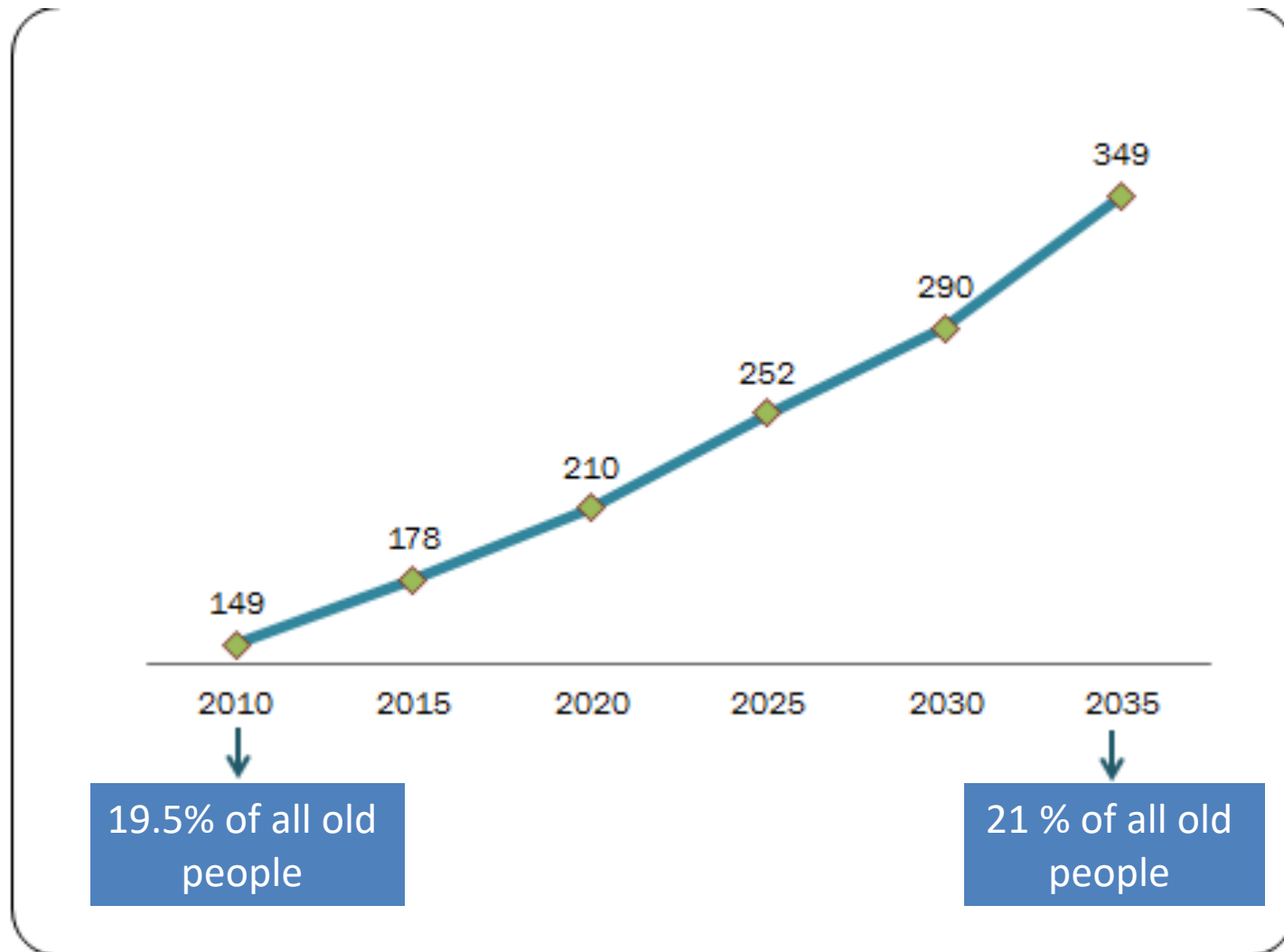
disease	Clinical features	Number of patients in Israel	% with known genetic contribution
Alzheimer's disease	Memory loss plus	120,000	1-5%
Parkinson's disease	Motor disturbances plus	20,000	5-35%
Lewy Body Disease	Cognitive disturbances + parkinsonism	20,000	5-37%
Multi-System Atrophy	Motor disturbances + autonomic disturbances	2,000	2%
ALS-FTD	Motor weakness + behavioral and cognitive decline	ALS- 700 FTD - 1500	21% ?
Huntington's disease	Motor problems + behavioral and cognitive changes	300	100%

Worldwide Prevalence of Alzheimer and other dementias Projection for 2005, 2015, 2030

Source: Neurological Disorders: Public Health Challenges, WHO 2006

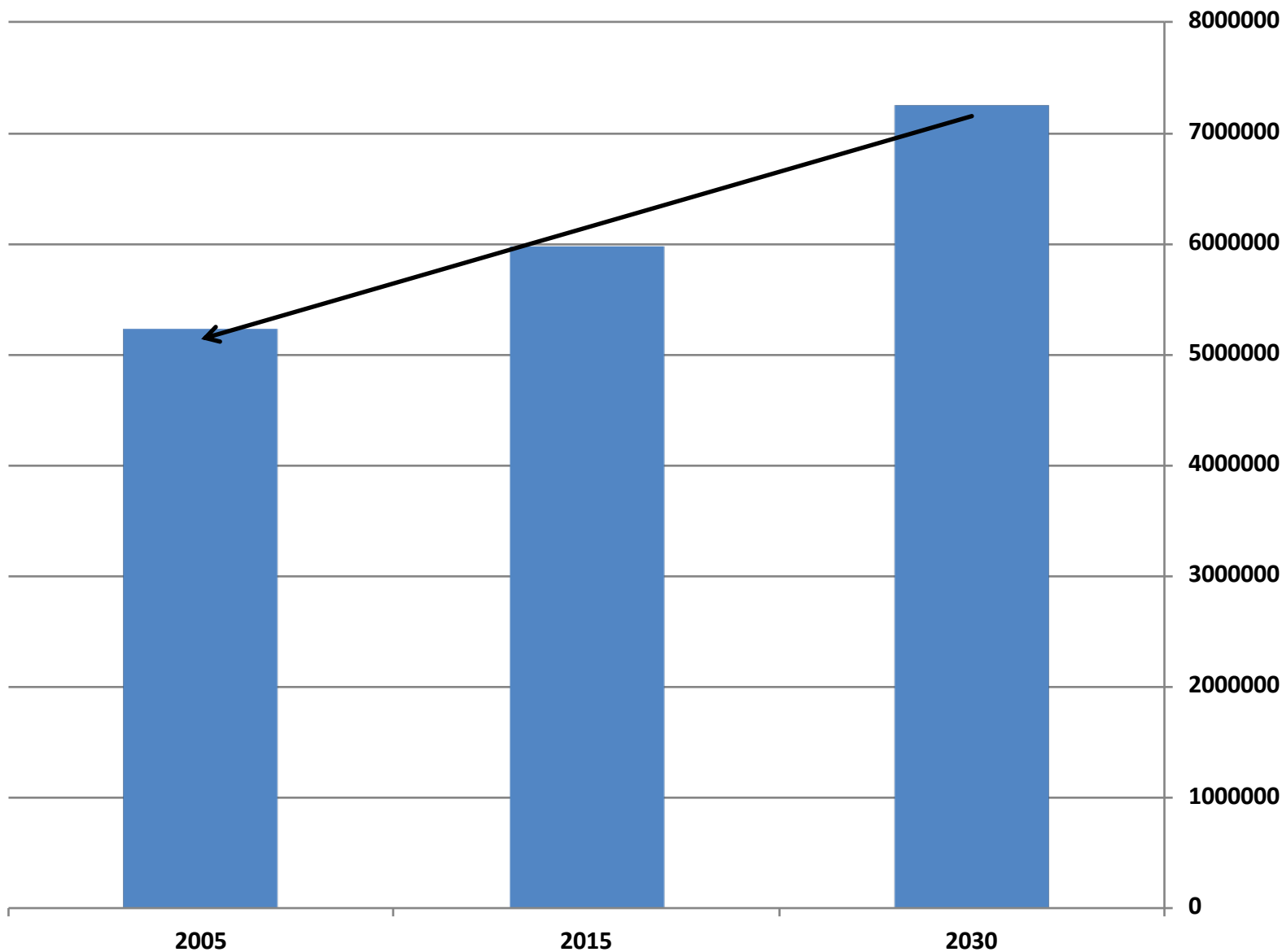


Estimate of the number of old people with substantial cognitive decline, or who are suffering from dementia, in the community and in institutions in Israel (in thousands)

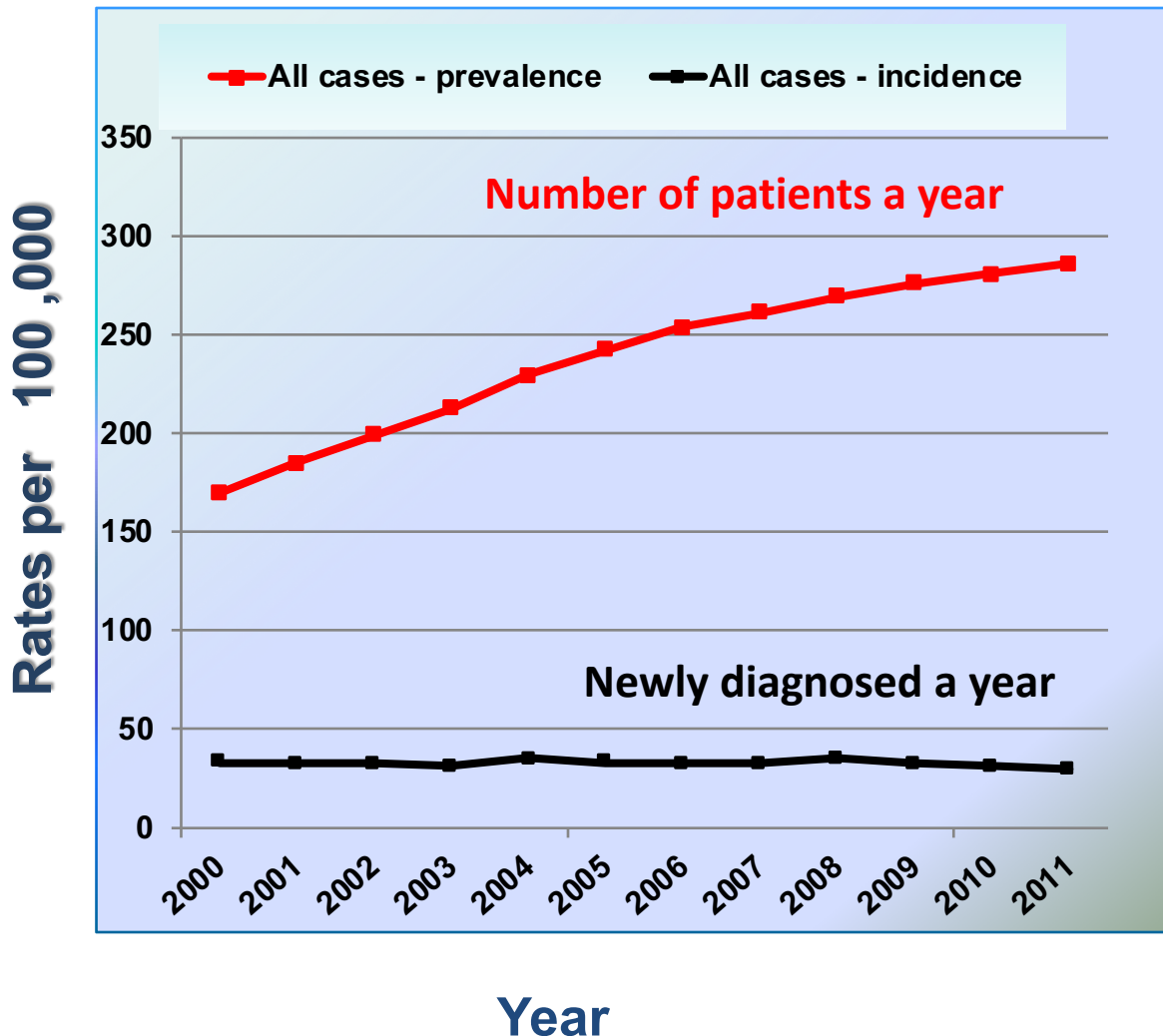


Worldwide Prevalence of Parkinson's Disease Projection for 2005, 2015, 2030

Source: Neurological Disorders: Public Health Challenges, WHO 2006



Prevalence and Incidence of Parkinson's Disease in Israel base of "Maccabi Health Services" Data



Average detection age: 65

Range: 22-95

In Israel: 25,000 Patients

2,500 New Patients a Year

Exceptionally rapid neuronal loss, even before appearance of symptoms

frontiers in
NEUROLOGY

Symptoms and Patient Complaints

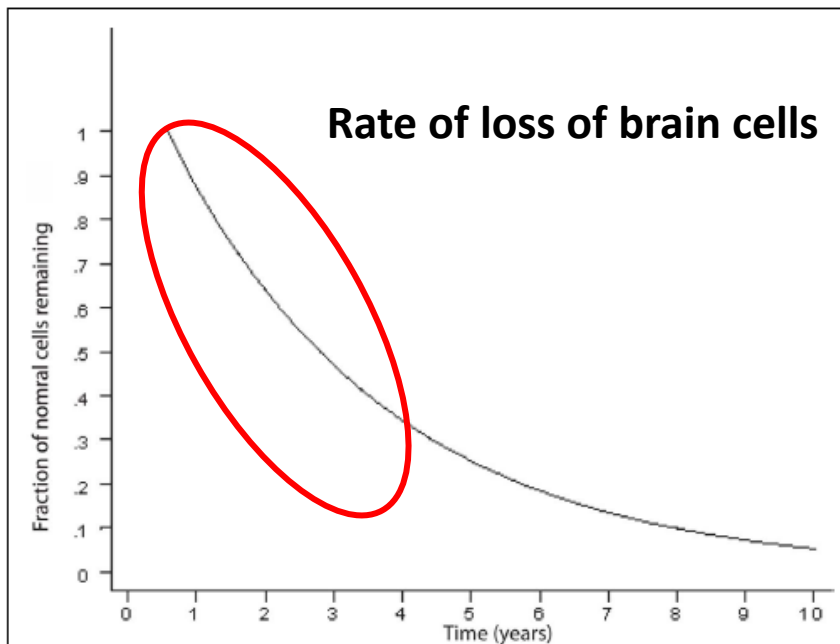


FIGURE 2 | Curve describing the kinetics of neuronal death in neurodegenerative diseases based on an animal model (adapted; Clarke et al., 2000). There is an exponential decline of neuronal number in time.

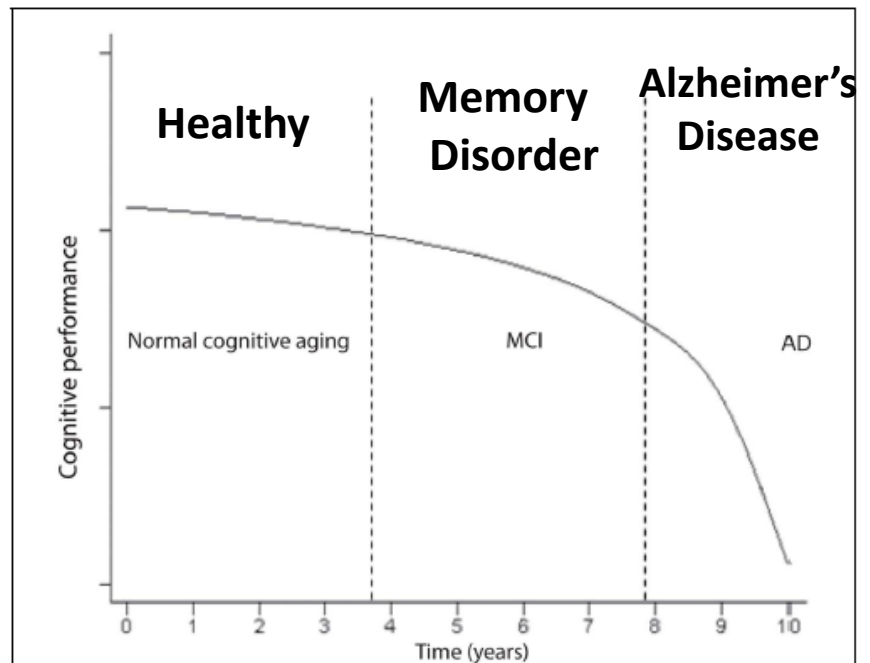
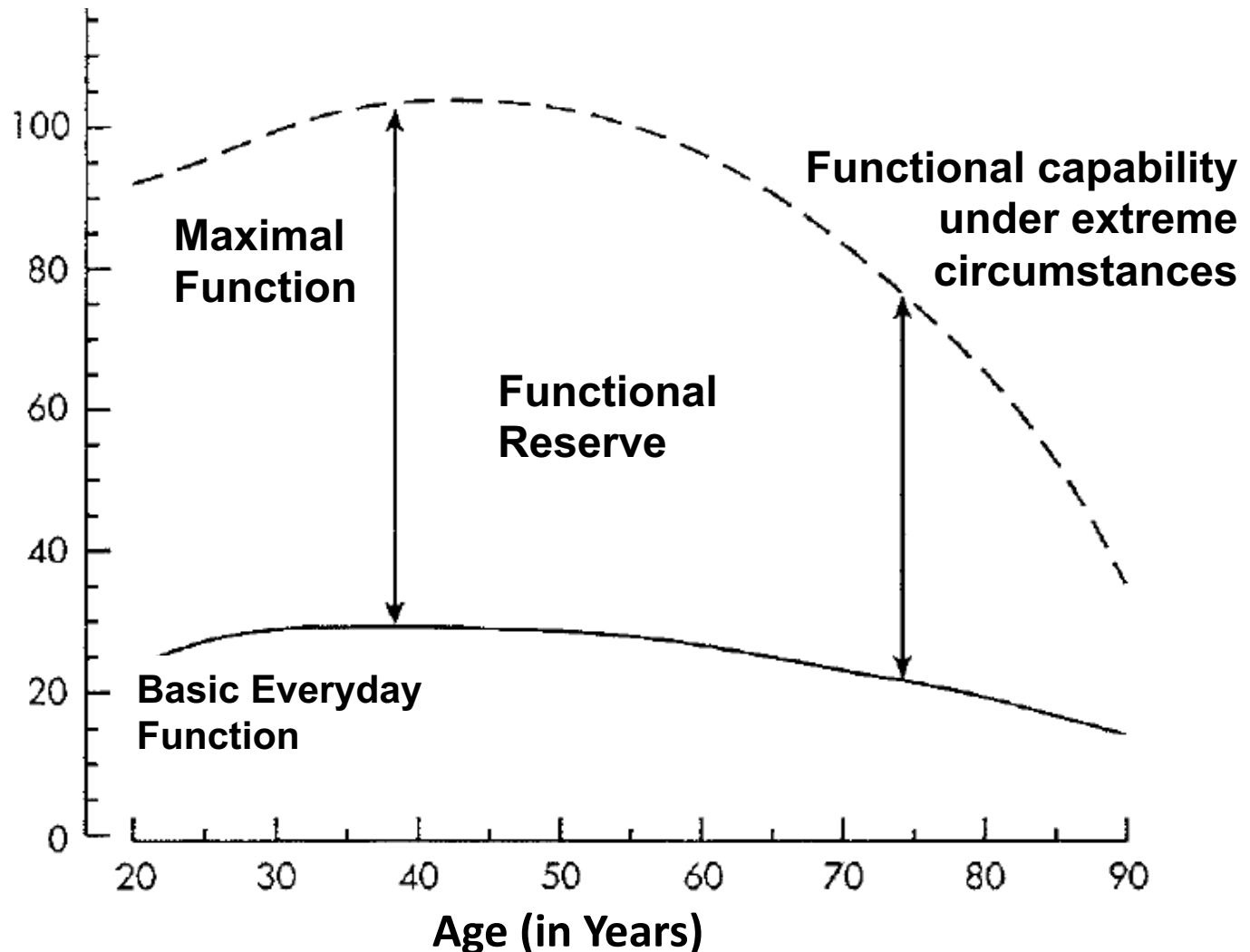


FIGURE 4 | Time course of the impairment continuum of cognition (adapted; Small et al., 2008).

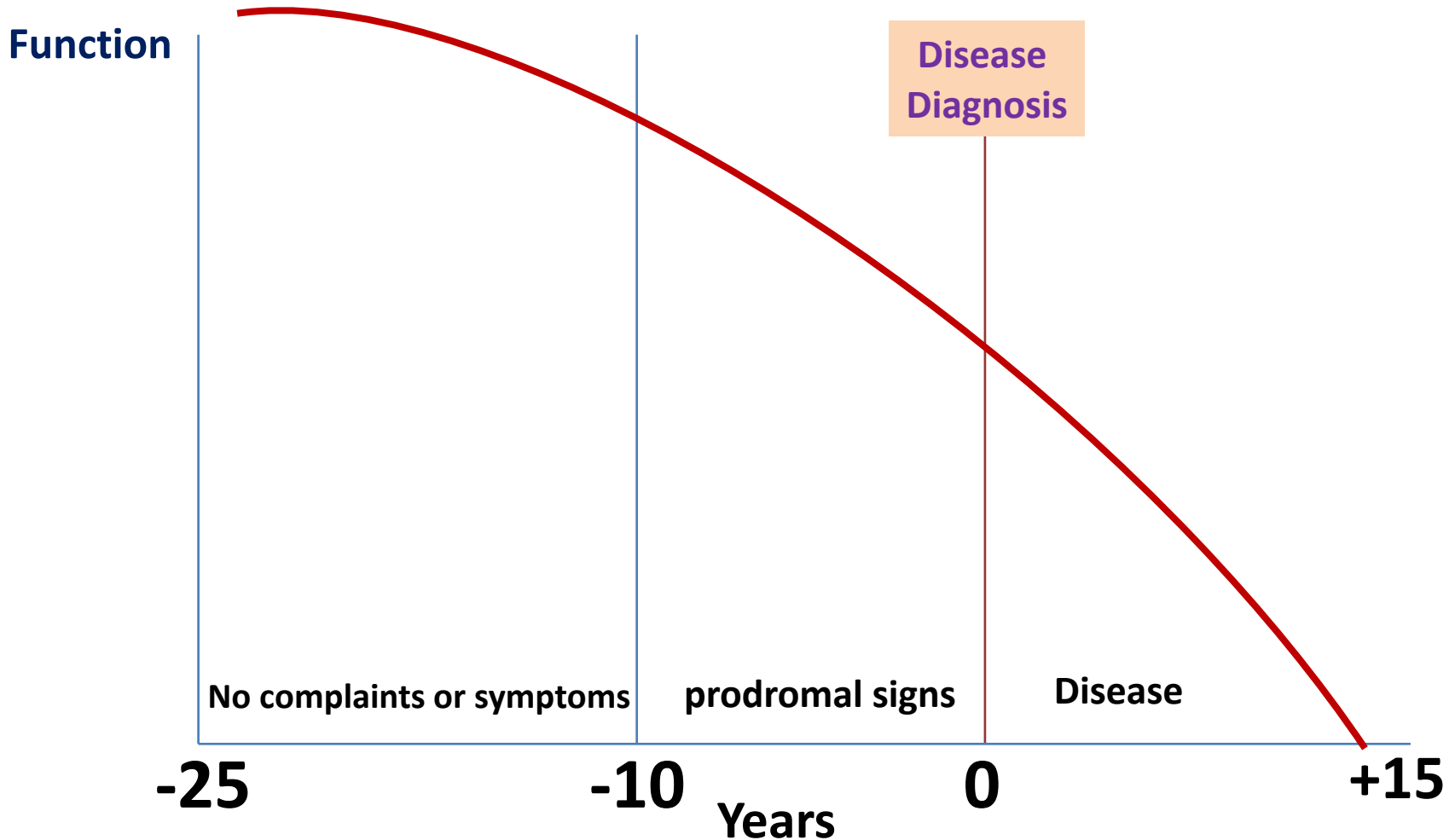
Functional Reserve – The Key to Health

Cook & Booke, 2003

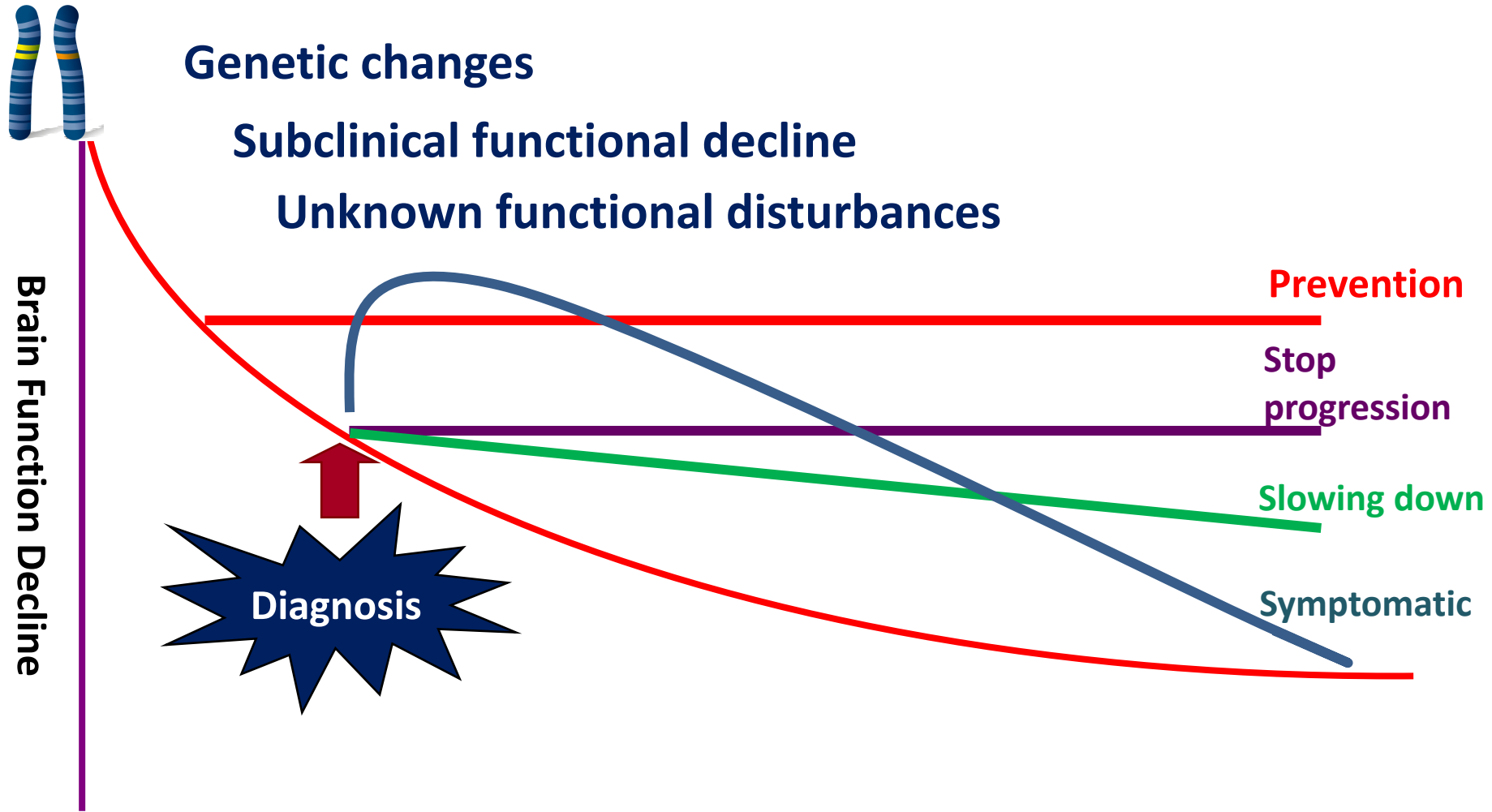
Maximal Brain
Function %



Natural History of Neurodegeneration



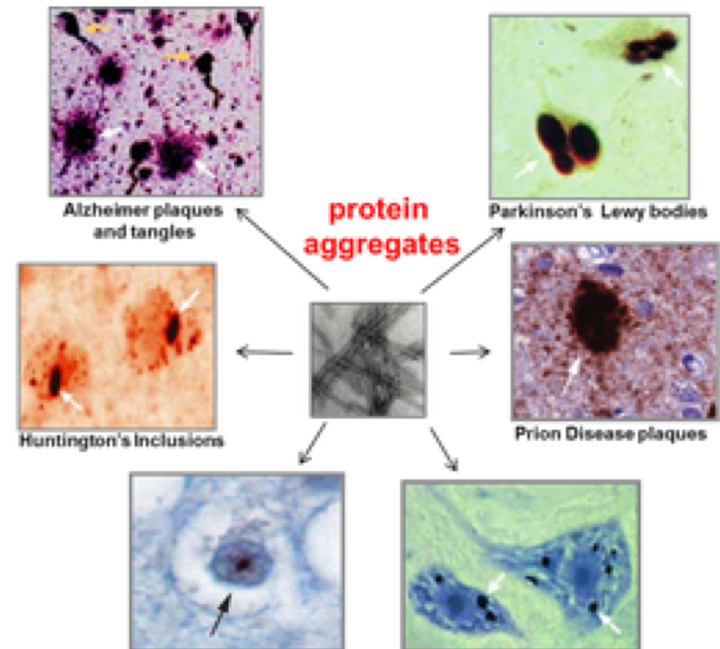
The goal - Prevention



**The basis of neuronal degeneration –
Aggregation of proteins which have
become toxic to the neurons**

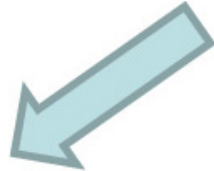
Protein aggregates - Disease

- Alzheimer's Disease – **Tau \ Amyloid β**
- Parkinson, Lewy Body dementia, MSA - **Synuclein**
- ALS, FTD – **TDP-43, Tau**
- Huntington's - **Huntingtin**
- Creutzfeld–Jakob - **PrP**



The protein (Synuclein) changes its structure and becomes toxic to the brain

The protein in its unfolded form

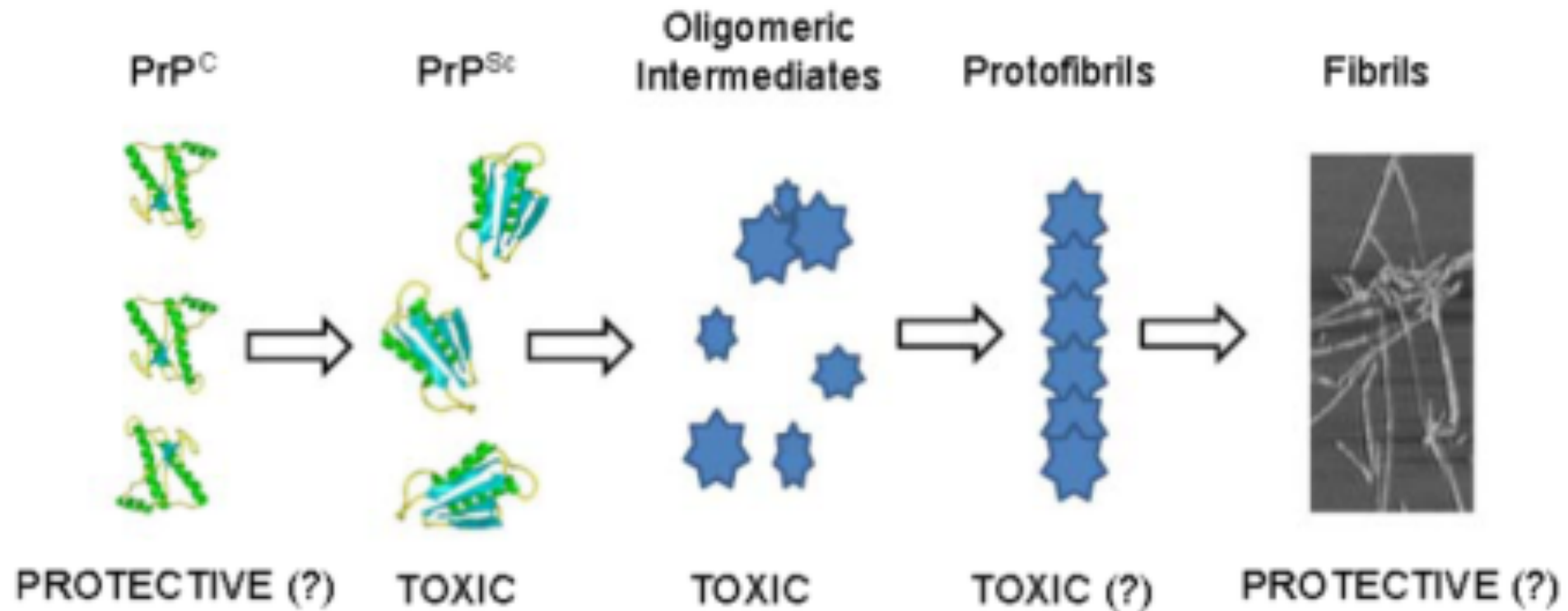


The protein in its
normal 3D form

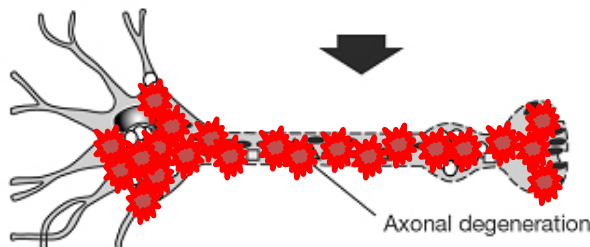
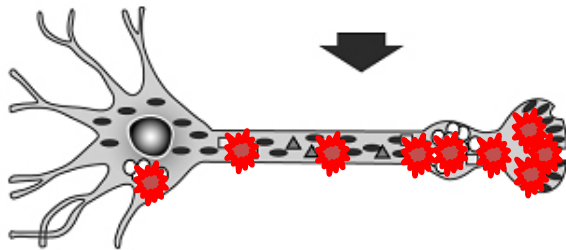
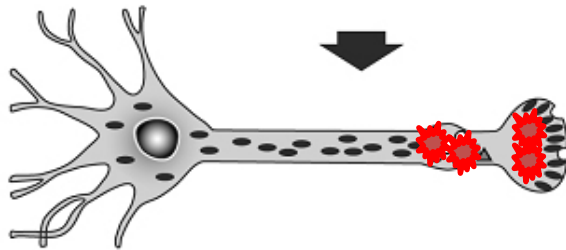
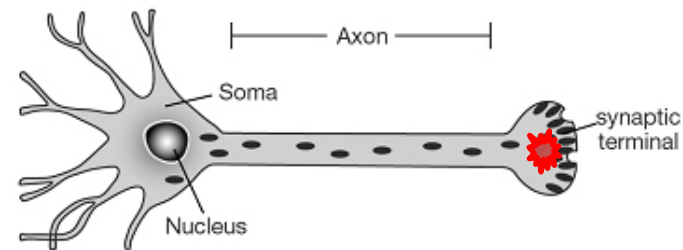


The protein in its abnormal
3D form = Toxic to the cell

Toxic protein aggregates



The basis of Parkinson's Disease – degeneration of neurons



- Normal α -synuclein
- β sheet α -synuclein
- Mitochondria/vesicles
- ▲ Neurofilaments/microtubules

**Protein aggregation
leading to
cell degeneration**

**How does the disease spread
in the brain
and in the nervous system?**

Potential mechanisms for trans-cellular propagation of protein misfolding

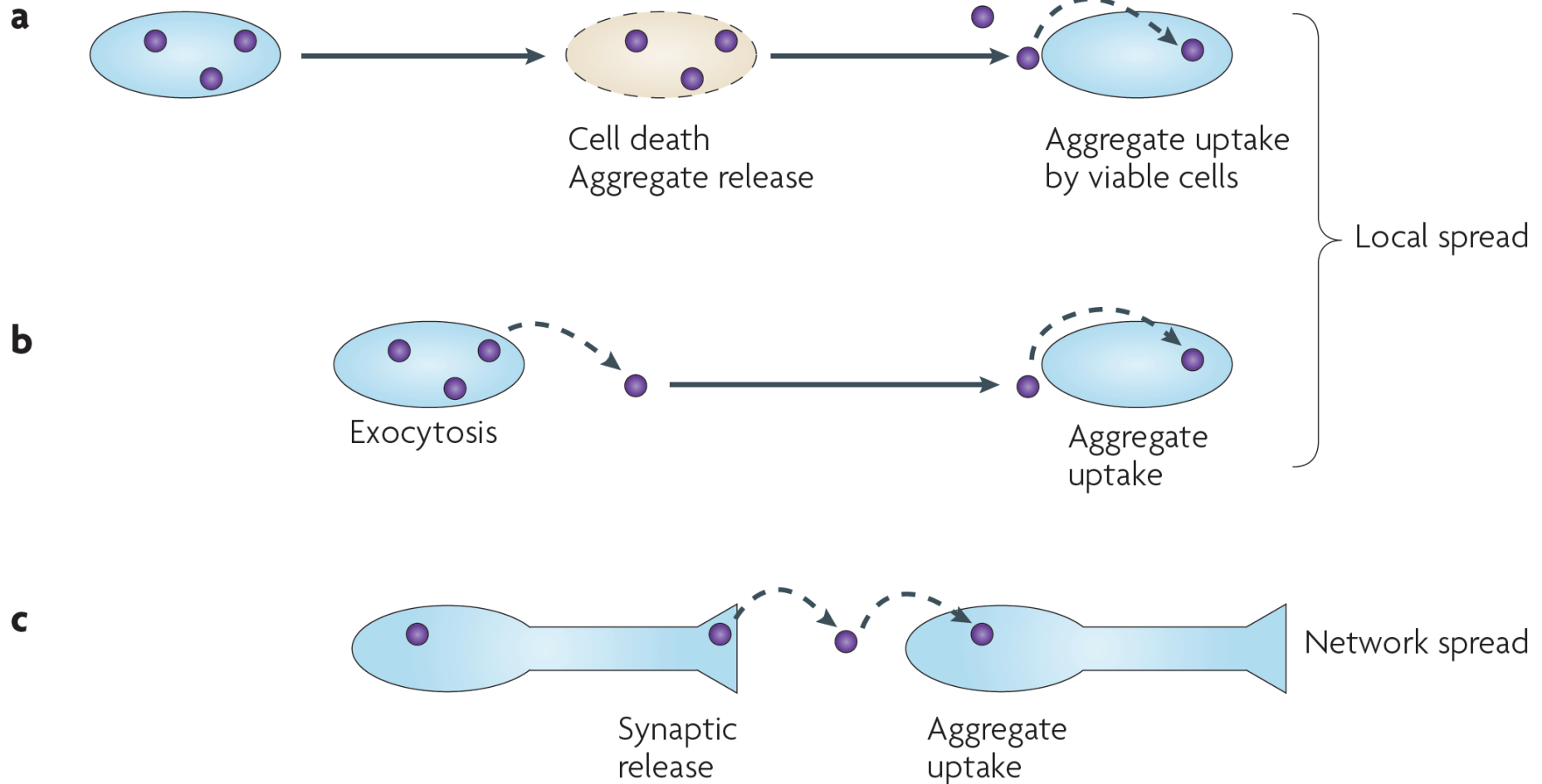
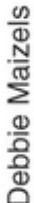


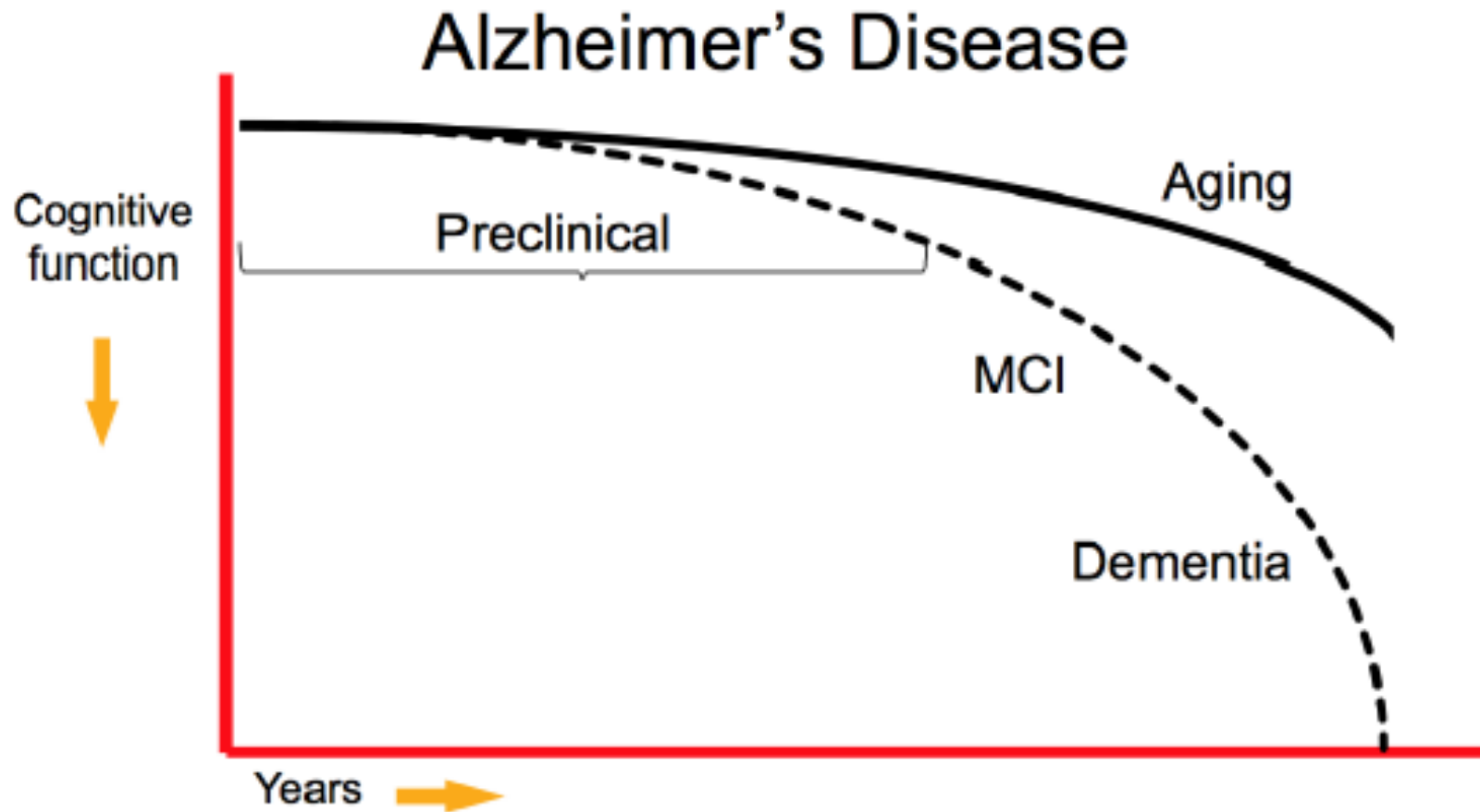
Figure 1 | **Potential mechanisms for *trans*-cellular propagation of protein misfolding.**

Trans-cellular propagation of the toxic protein



**Neuro-degeneration is not
accelerated aging,
it is a tissue specific pathology
with disease related mode of
progression**

Alzheimer's disease is NOT just accelerated aging



The spreading of the neurodegenerative process in Alzheimer's Disease

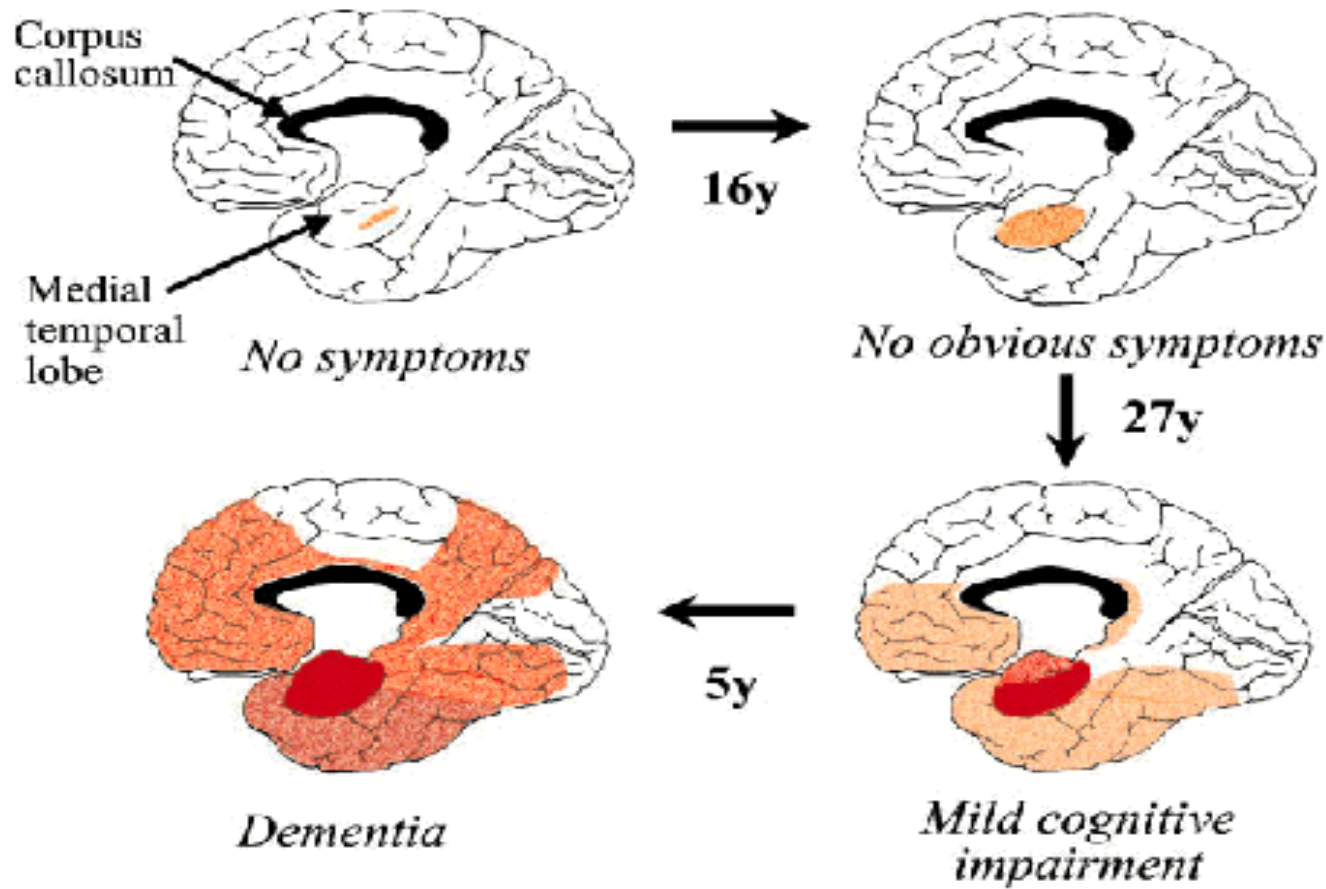
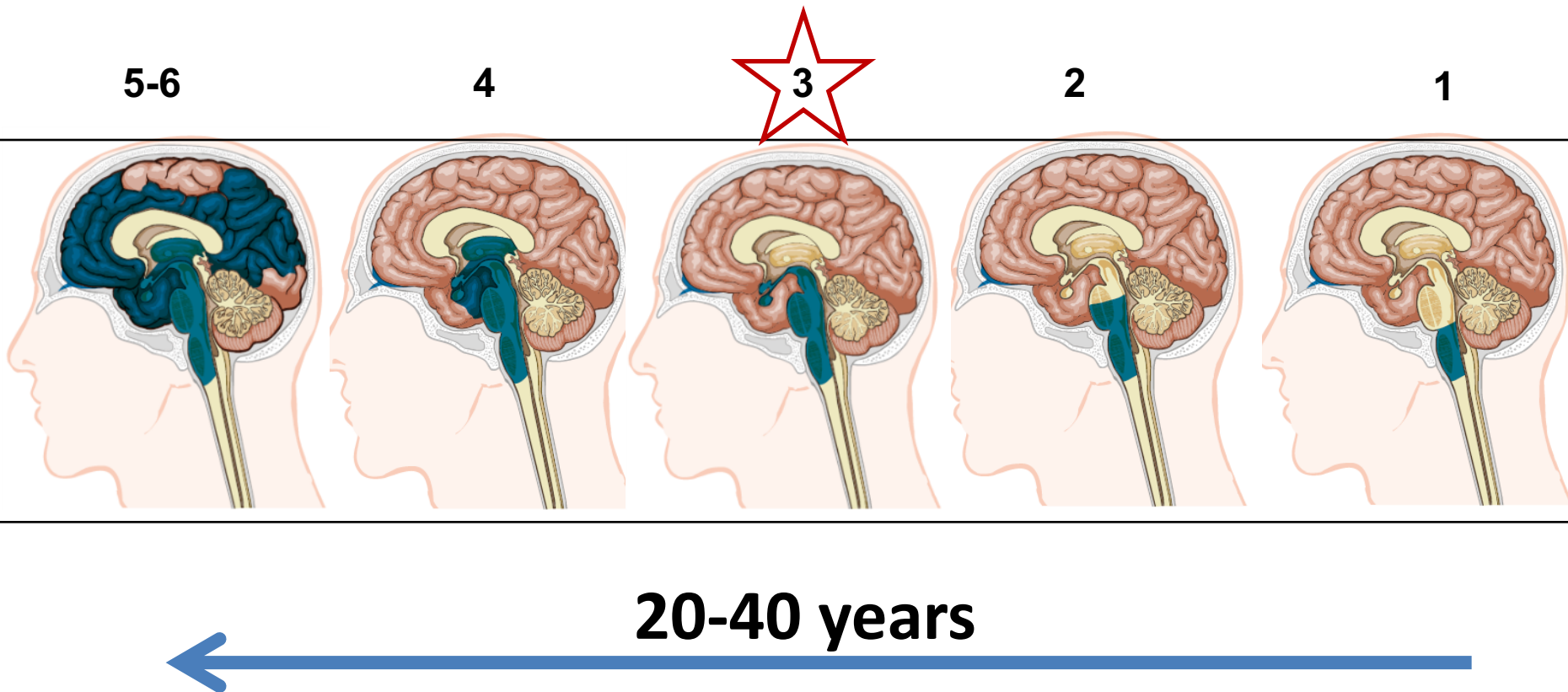


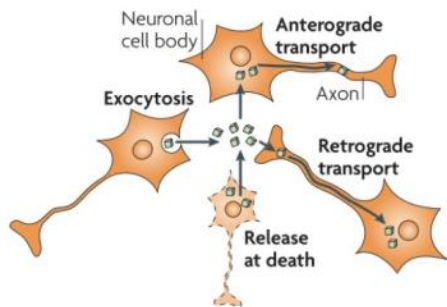
Fig. 3. Postulated sequence of spread of neurofibrillary pathology in AD, showing the medial aspect of the cerebral cortex. The depth of the red color is in proportion to the density of tangles (based on refs. 24 and 28). Several of the red areas showed atrophy in the study by Scahill et al. (6).

The spreading of Synuclein aggregates in the brain of Parkinson's disease patient

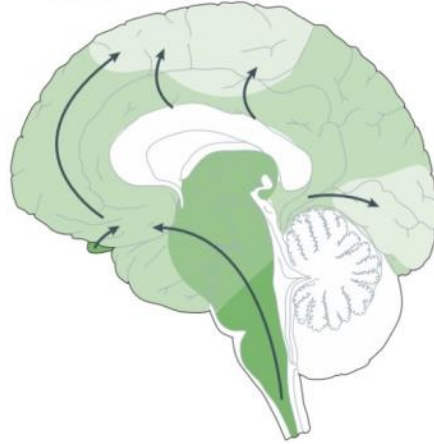


The process of neurodegeneration spreading in different diseases

a Models of spread



b Parkinson's disease



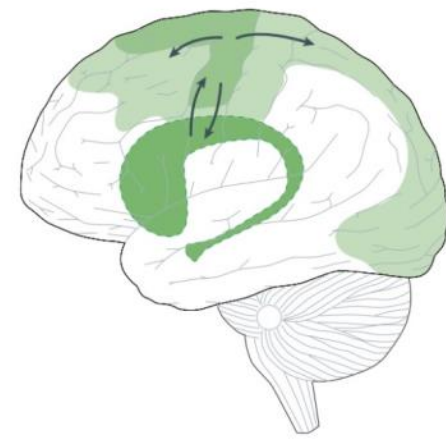
**Parkinson's
Disease**

c Alzheimer's disease



**Alzheimer's
Disease**

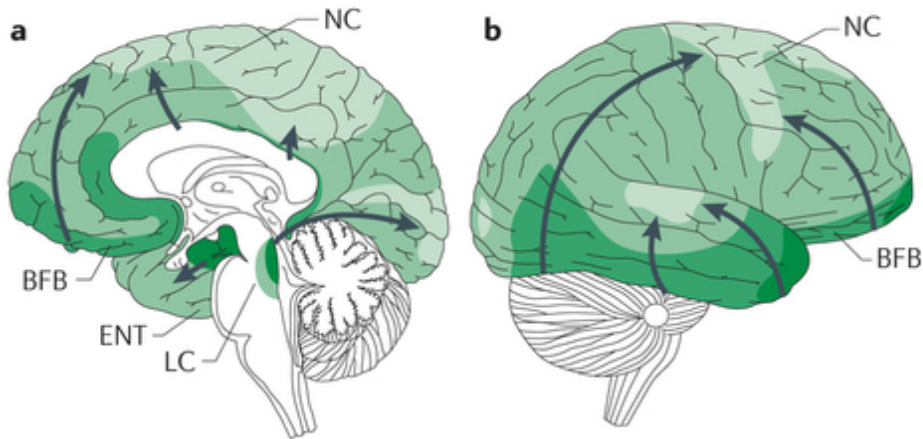
d Huntington's disease



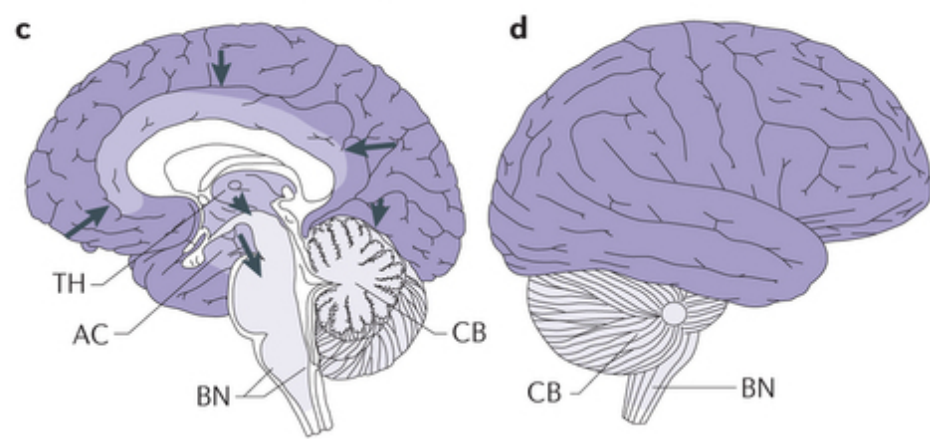
**Huntington's
Disease**

Progression of neurodegeneration

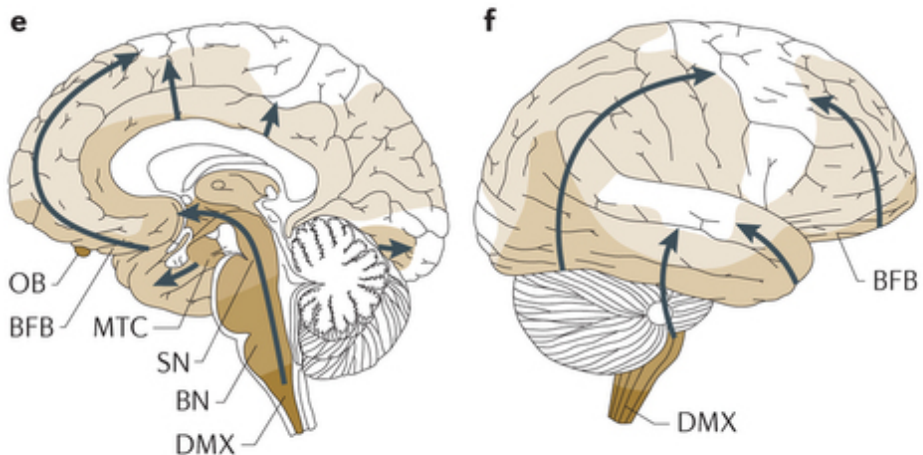
Alzheimer disease: tau



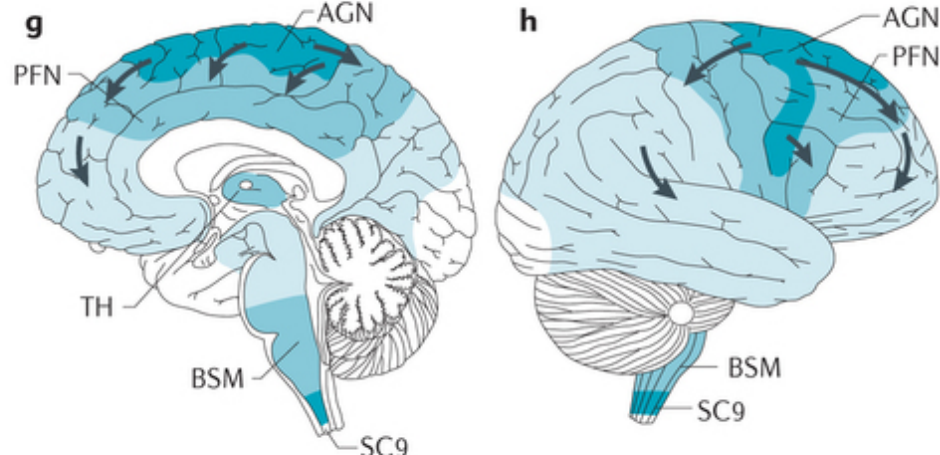
Alzheimer disease: amyloid- β



Parkinson disease: α -synuclein

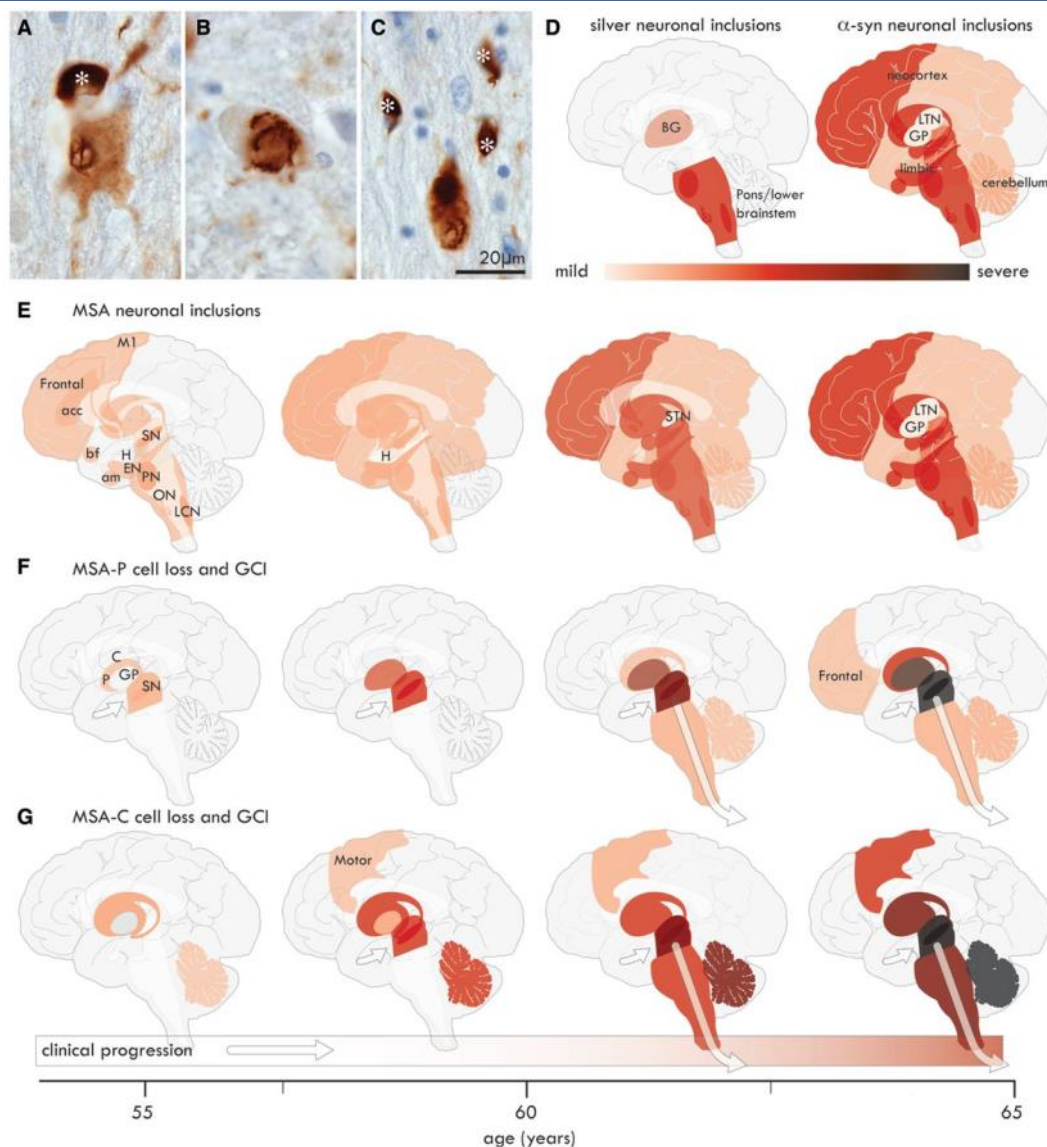


Amyotrophic lateral sclerosis: TDP43



Multiple System Atrophy:

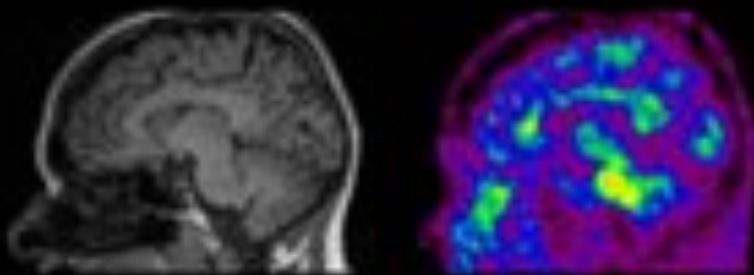
The same disease – 2 different clinical presentations



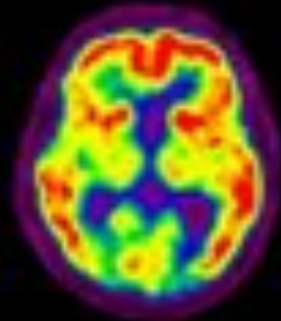
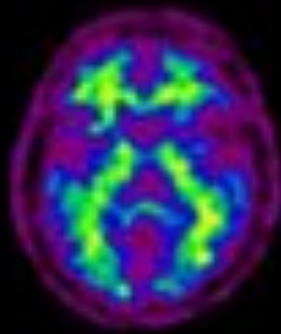
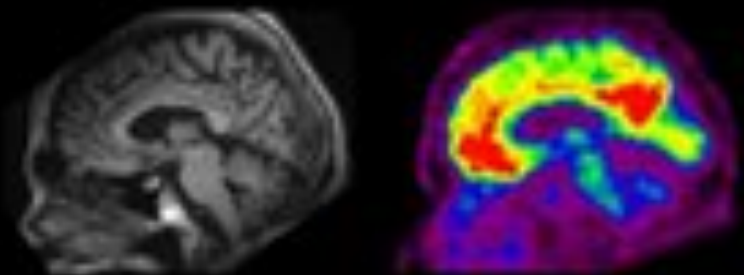
1. MSA-P: Parkinsonism
2. MSA-C: balance

Protein aggregates in AD brain

Normal



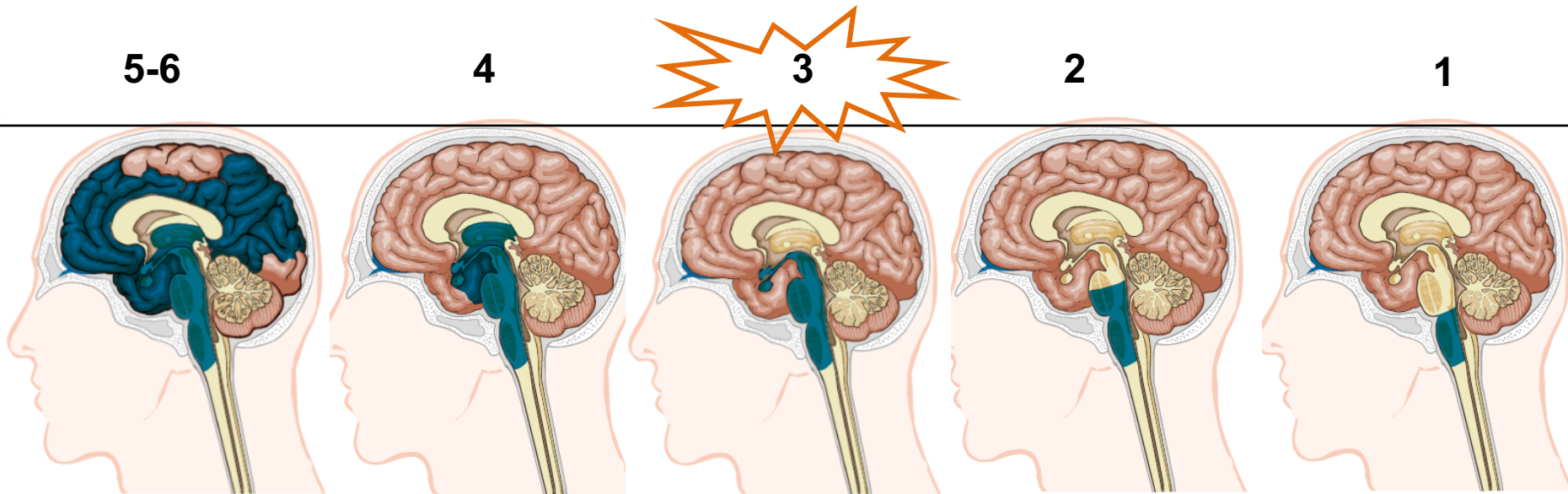
Alzheimer's Disease



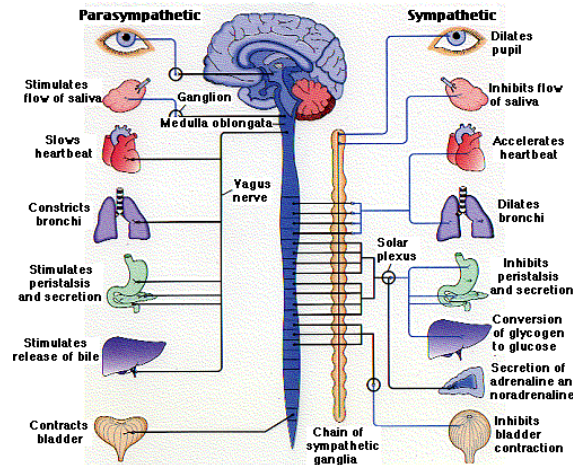
Parkinson's disease, More than brain disorder

The spreading of Synuclein aggregates in the brain and the autonomic nervous system in Parkinson's Disease

Parkinson's Disease diagnosis



Functional deterioration



Pre-diagnosis phase

Alpha synuclein deposits in the autonomic nervous system

