Neurodegenerative Diseases
En Route to Early Detection and Prevention

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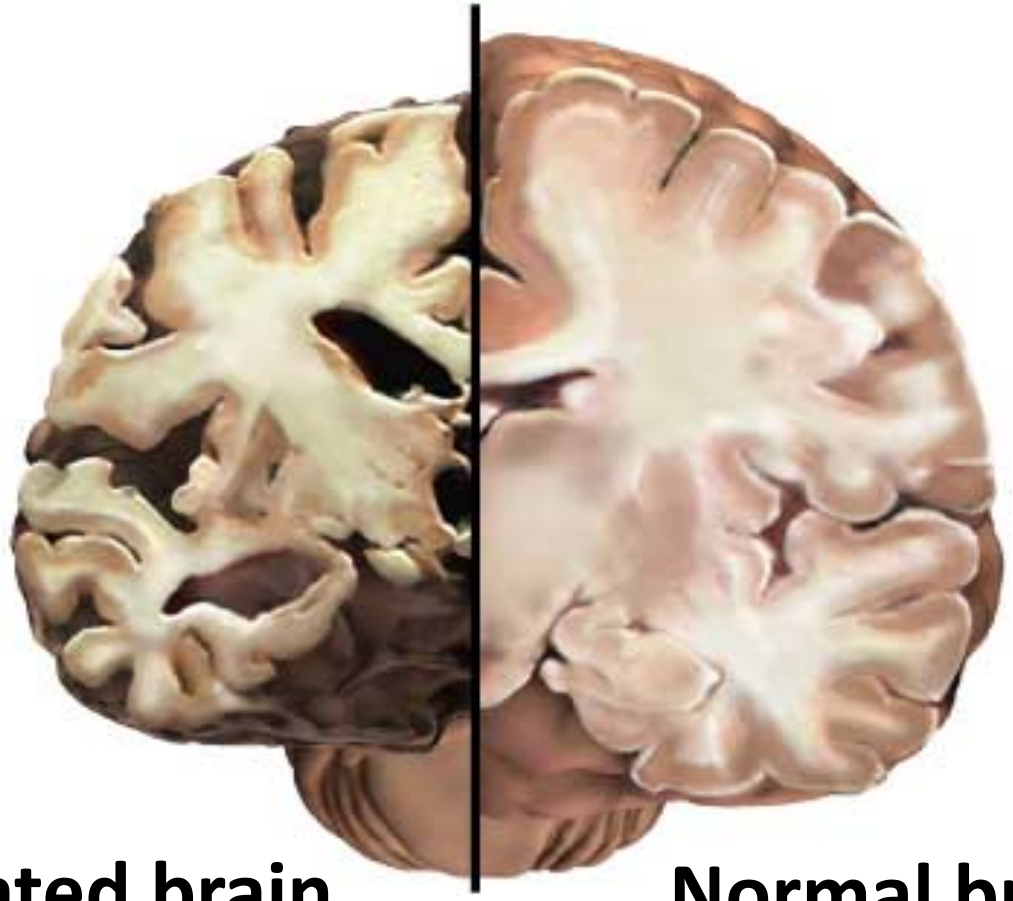
Life expectancy is rising and with it third-age diseases are becoming an alarming problem

Life expectancy in the Future – Linear or non-linear ….

Source: National Geographic, May 26, 2013

Source: Time, Feb 23, 2015

Neurodegeneration – the modern epidemic



Degenerated brain

Normal brain

Decreased brain metabolism (FDG uptake) prior to neuronal loss

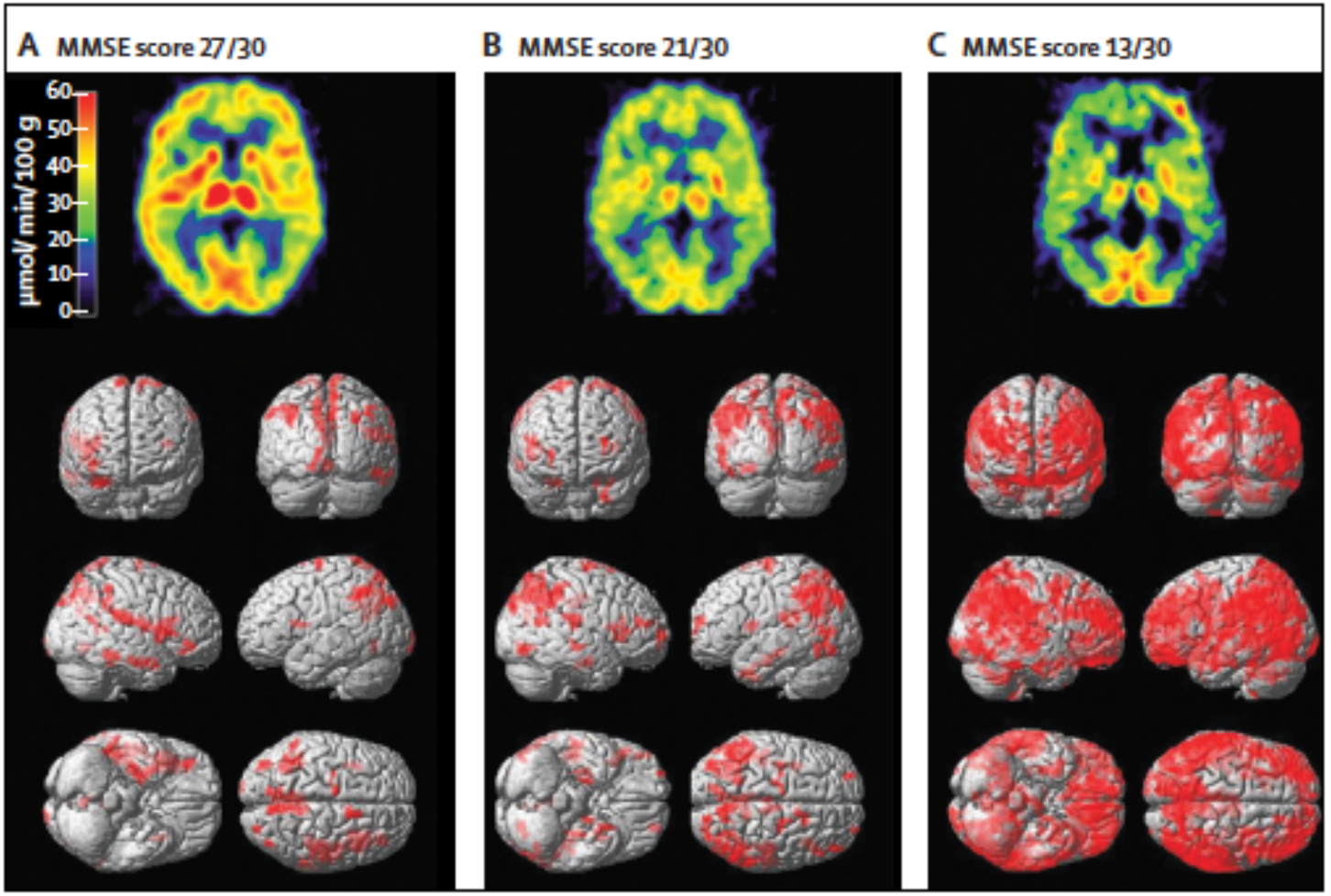
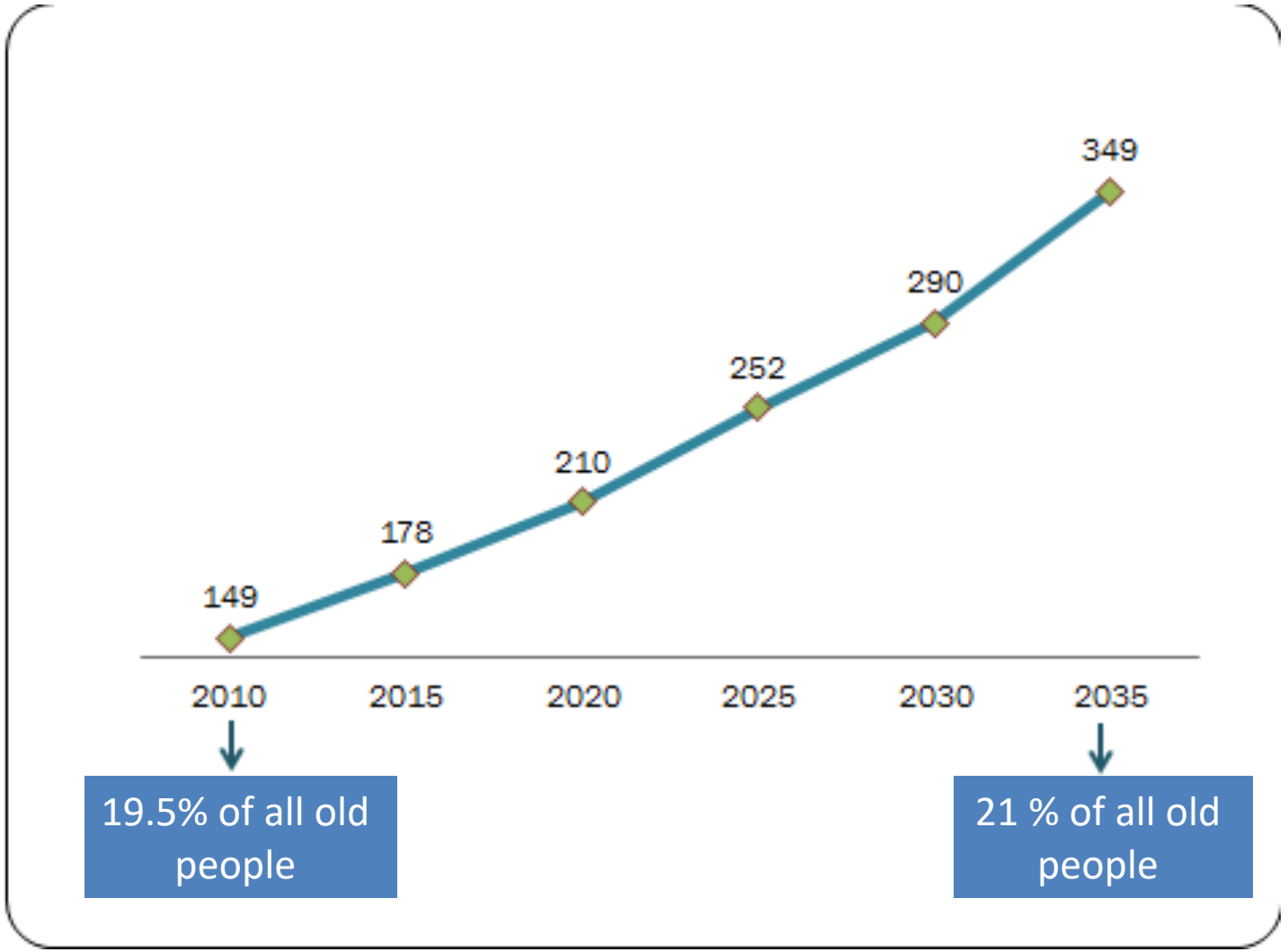


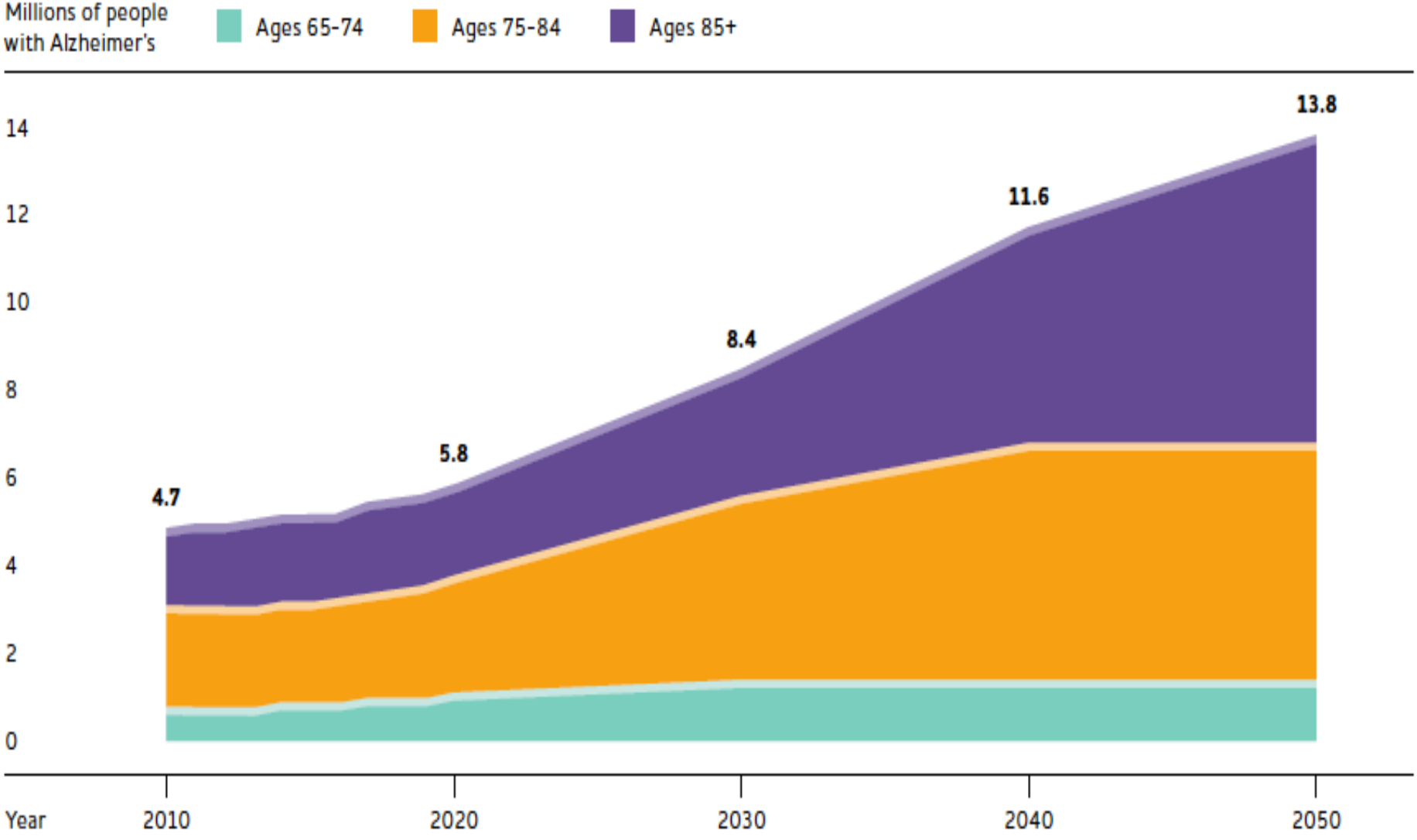
Figure 9: Progressive reduction in regional cerebral glucose metabolism in a patient with Alzheimer's disease

Disease	Clinical features	Prevalence in Israel 	% with known genetic contribution
Alzheimer's disease	Memory loss plus	120,000	10%
Parkinson's disease	Motor disturbances plus	25,000 *	5-35%
Lewy Body Disease	Cognitive disturbances + parkinsonism	20,000 ?	5-37%
Multi-System Disease	Motor + autonomic disturbances	2,000	2%
ALS-FTD	Motor weakness + behavioral and cognitive decline	ALS- 700 FTD - ???	20%
Huntington's disease	Motor problems + behavioral and cognitive changes	300	100%

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)



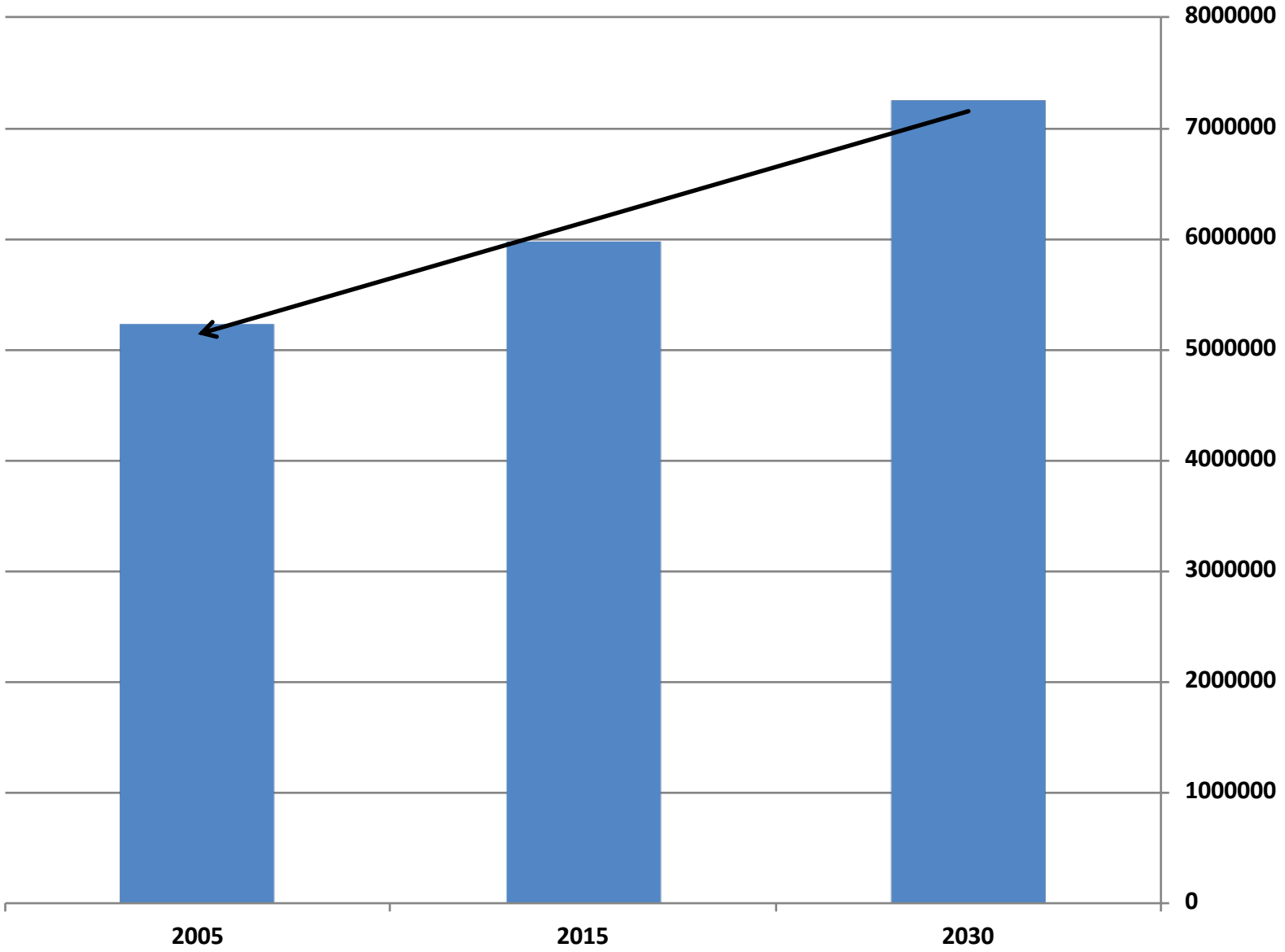
Projected Number of People Age 65 and Older (Total and by Age Group) in the U.S. Population with Alzheimer's Dementia, 2010 to 2050



Created from data from Hebert et al.[A12.31]

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

Source: Neurological Disorders: Public Health Challenges, WHO 2006



Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030

E.R. Dorsey, MD, MBA; R. Constantinescu, MD; J.P. Thompson, BA; K.M. Biglan, MD, MPH; R.G. Holloway, MD, MPH; K. Kieburtz, MD, MPH; F.J. Marshall, MD; B.M. Ravina, MD, MSCE; G. Schifitto, MD; A. Siderowf, MD, MSCE; and C.M. Tanner, MD, PhD

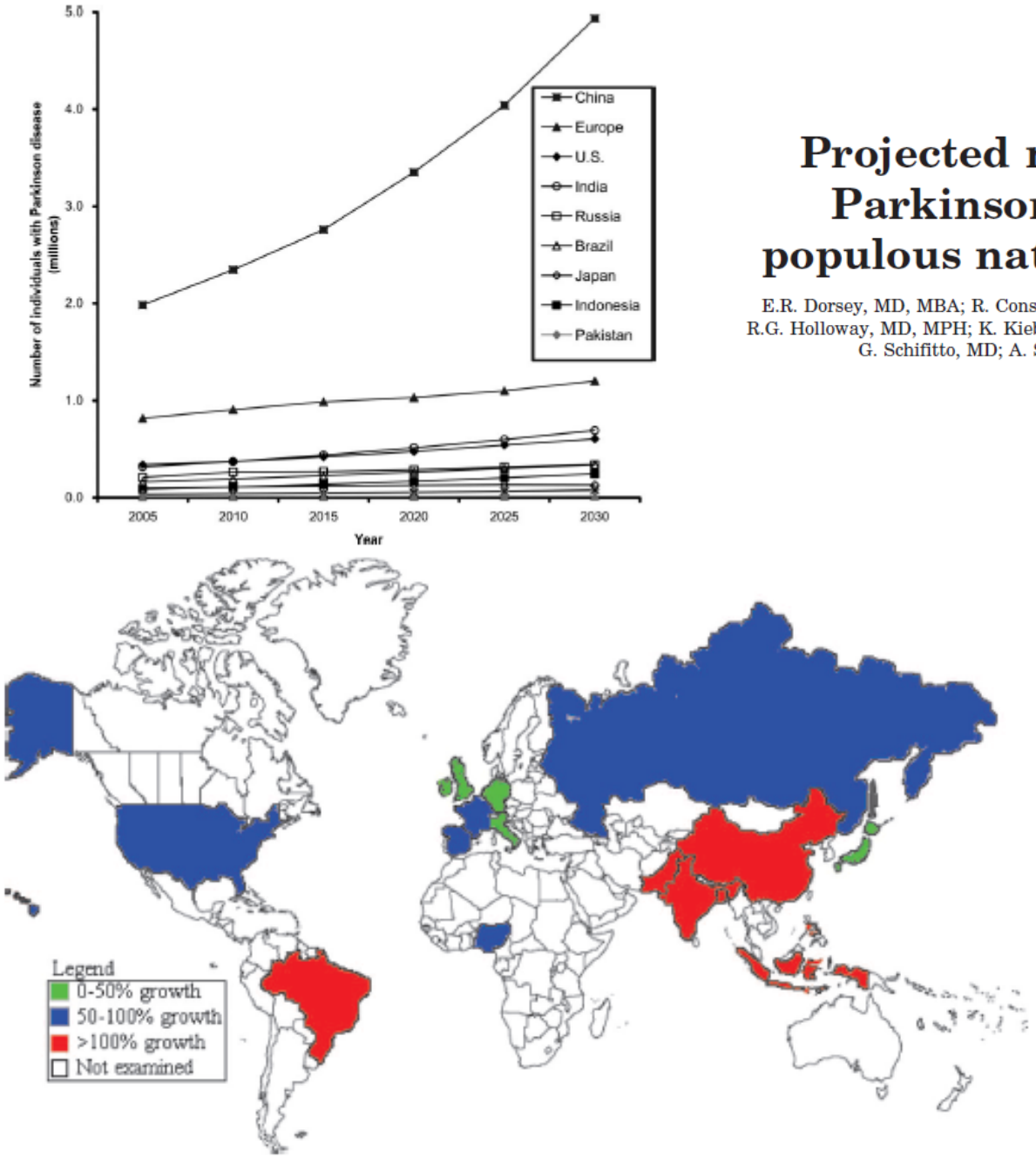
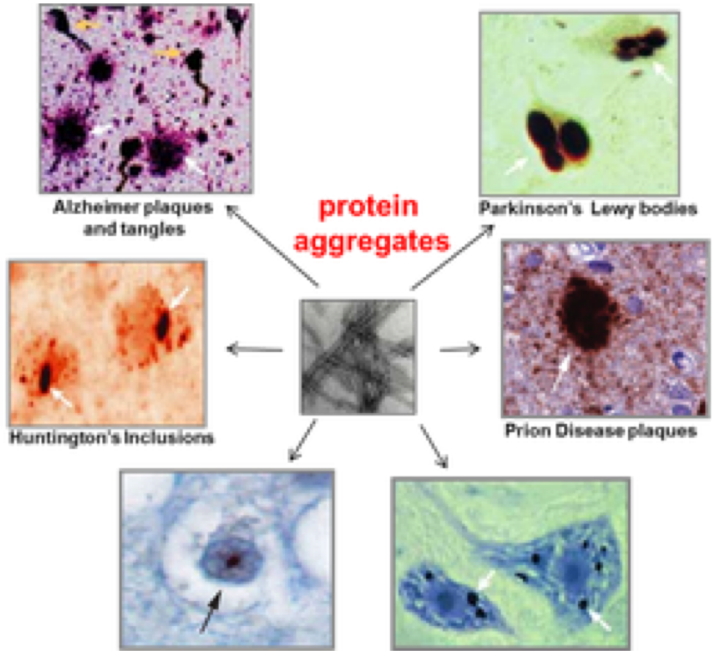


Figure 2. Projected growth rates in number of individuals over 50 with Parkinson disease in the most populous nations in Western Europe and the world from 2005 to 2030.

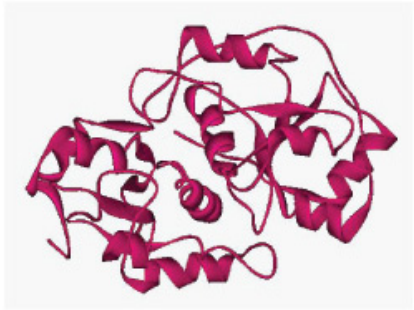
Proteinopathies

- Alzheimer's Disease - tau
- Parkinson's disease - Synuclein
- ALS – TDP-43
- Huntington's - Huntingtine
- Creutzfeldt–Jakob - PrP



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

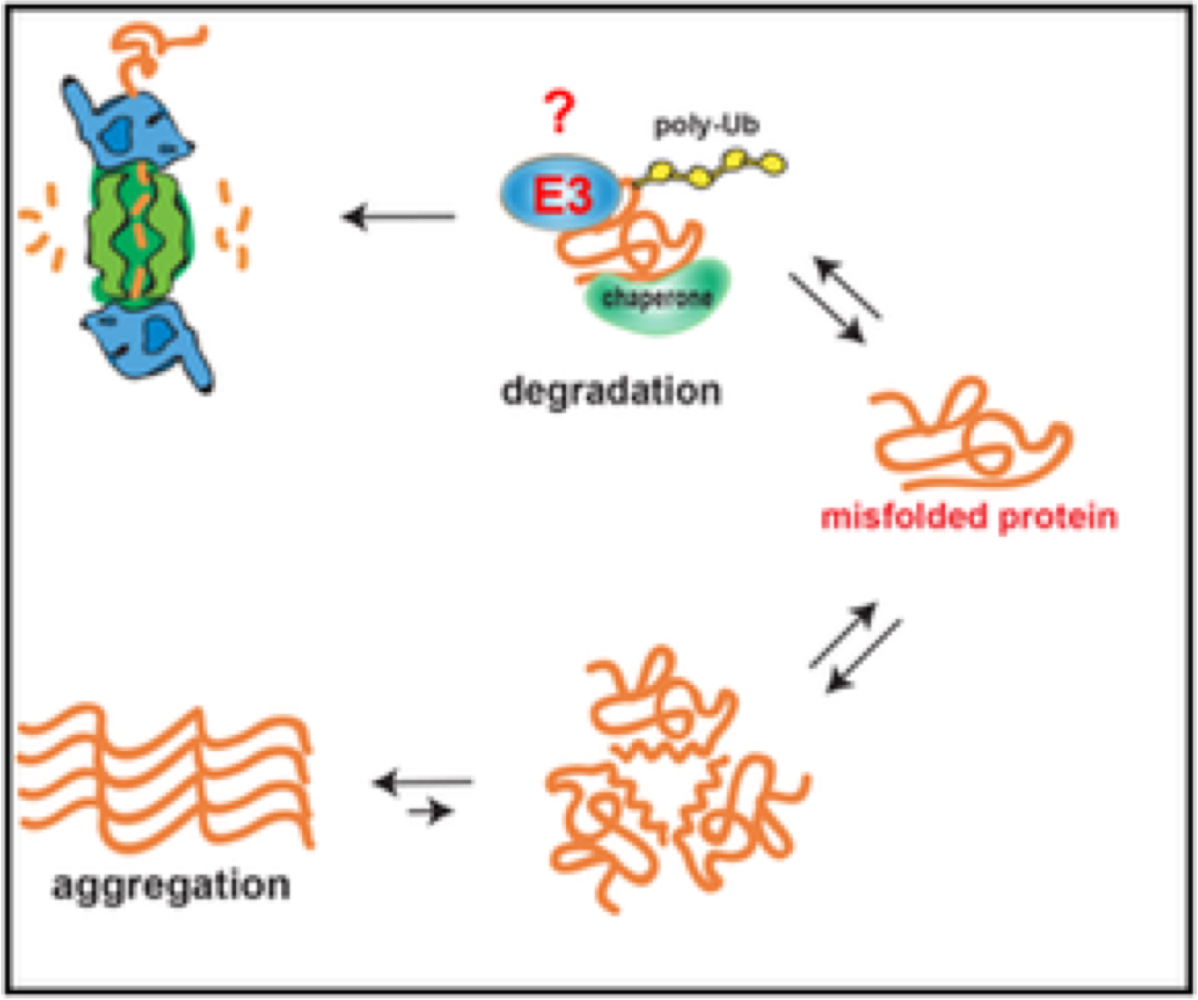
The protein in its unfolded form



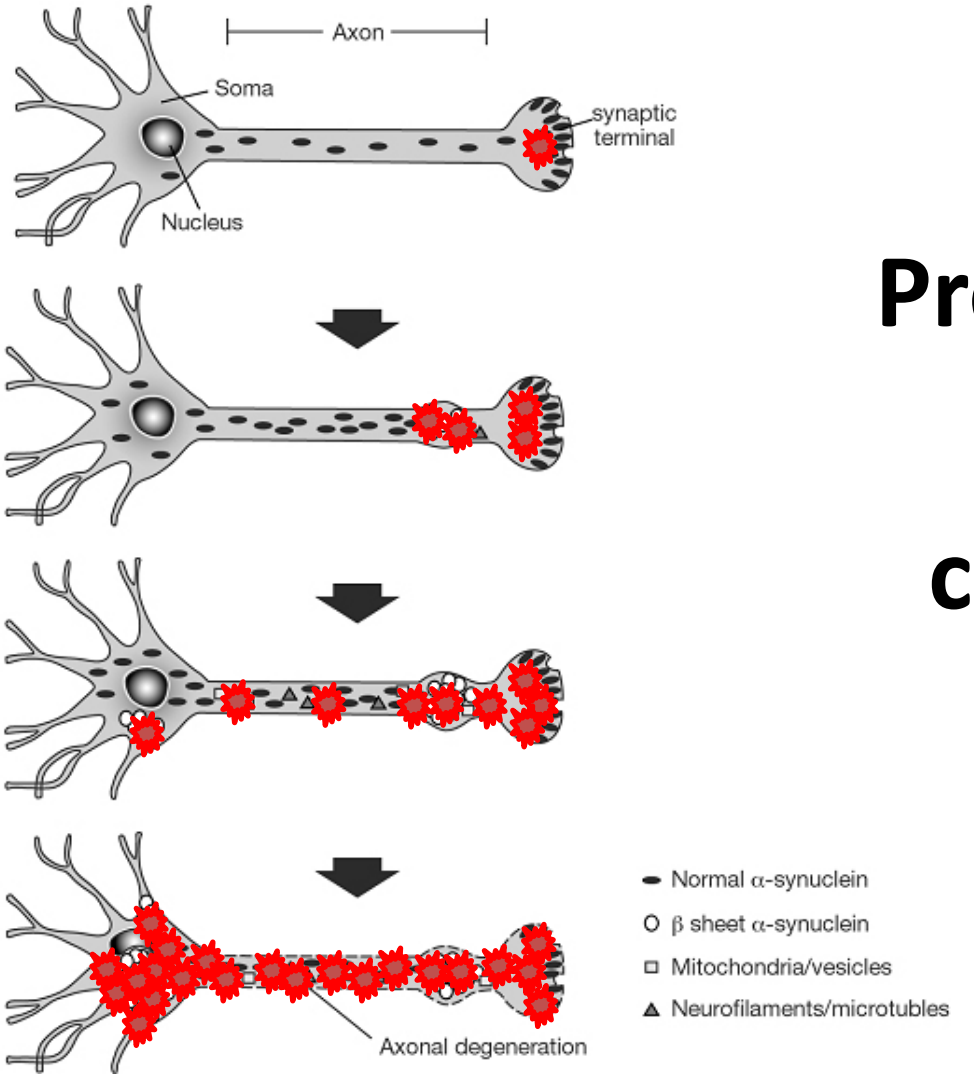
The protein in its normal 3D form

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

Mis-folded protein leads to aggregation

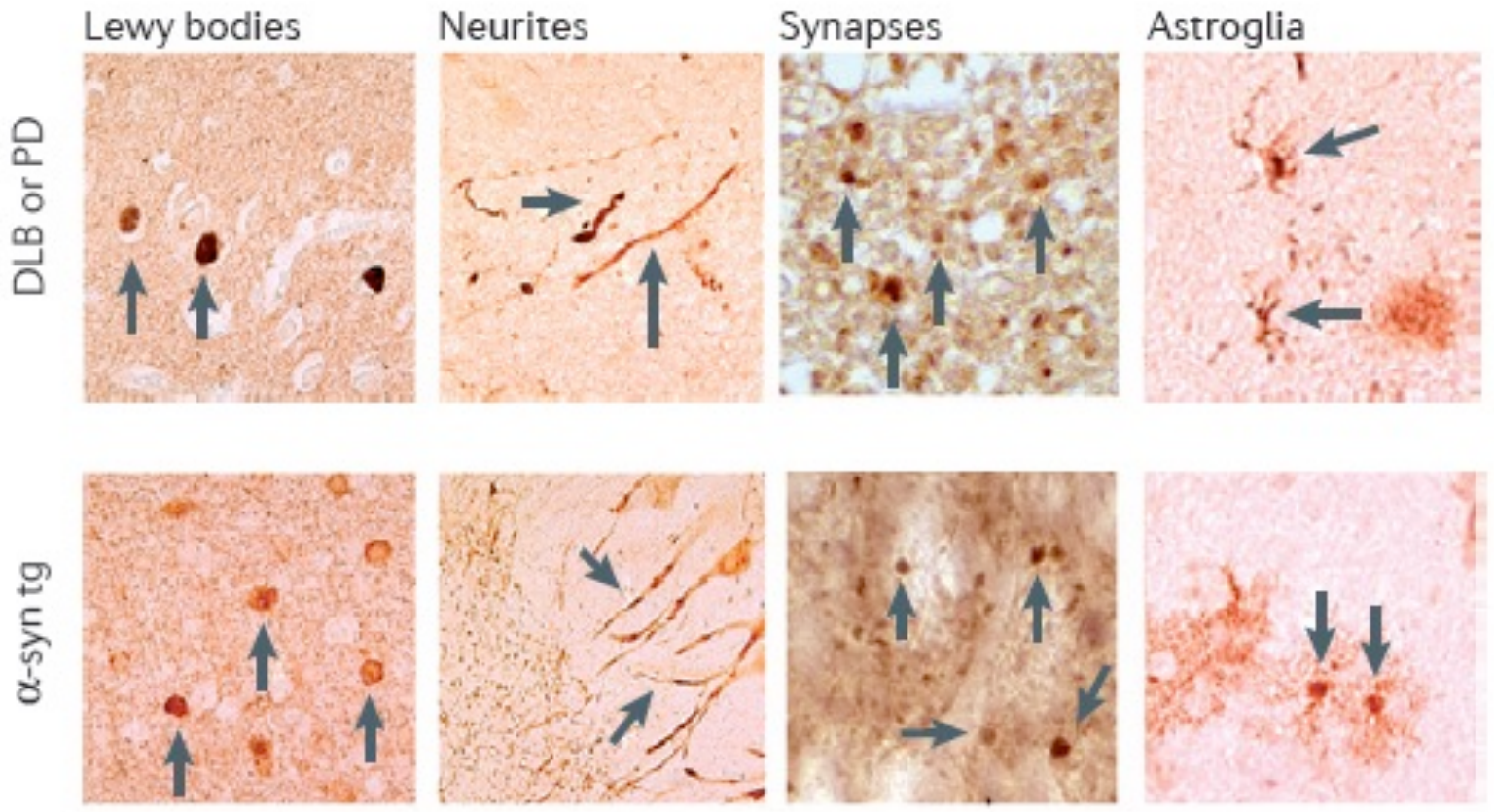


Aggregation of synuclein oligomers initially at the synapses and later throughout the neuron in Parkinson's Disease



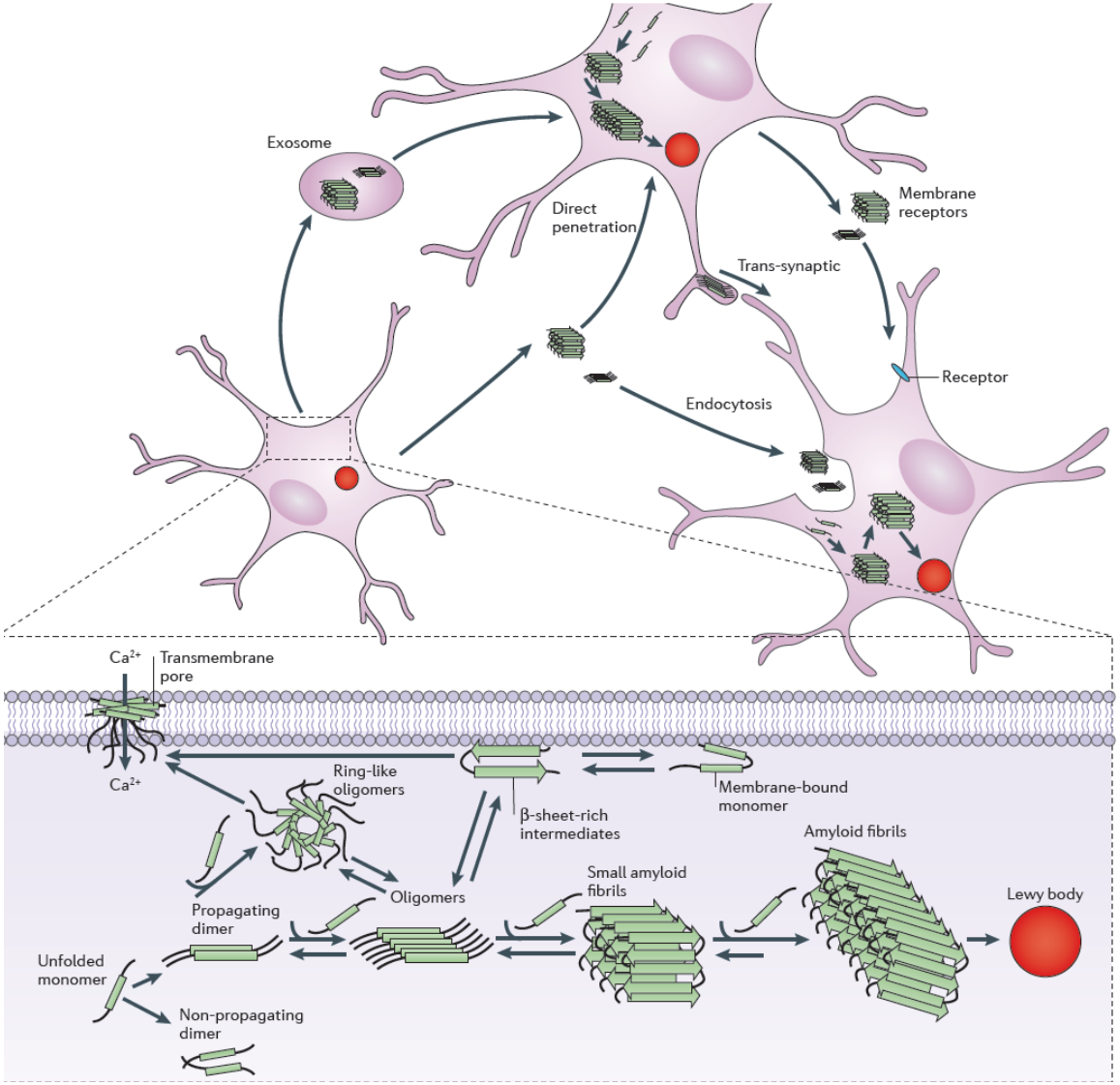
Protein aggregation leading to cell degeneration

Different pathological forms of synuclein

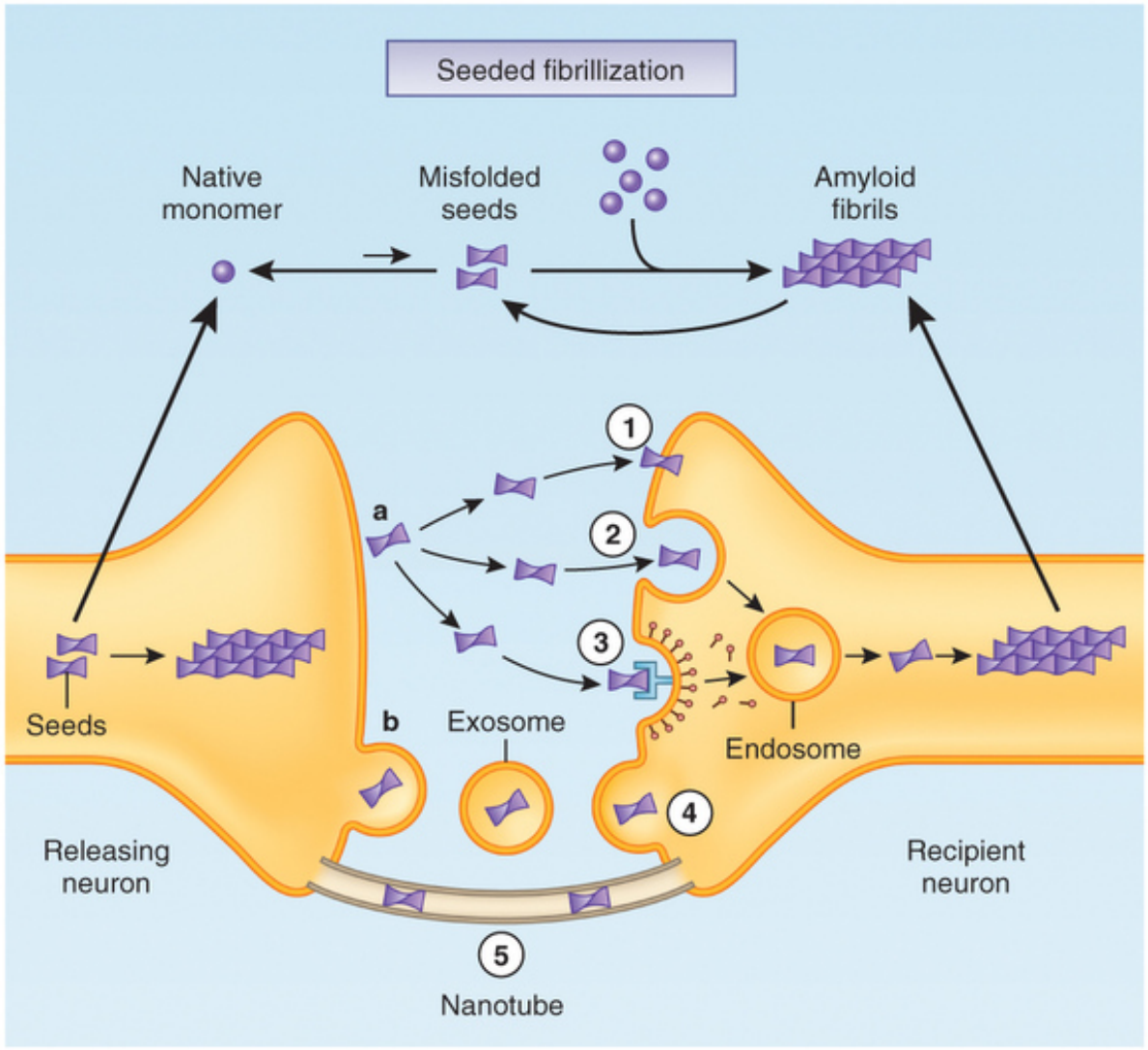


Lashuel et al, Nature Rev. Neurosc. 2013

Mechanism of α-synuclein aggregation and propagation



Trans-cellular propagation of the toxic protein



Spreading of the neurodegenerative process in Alzheimer's Disease

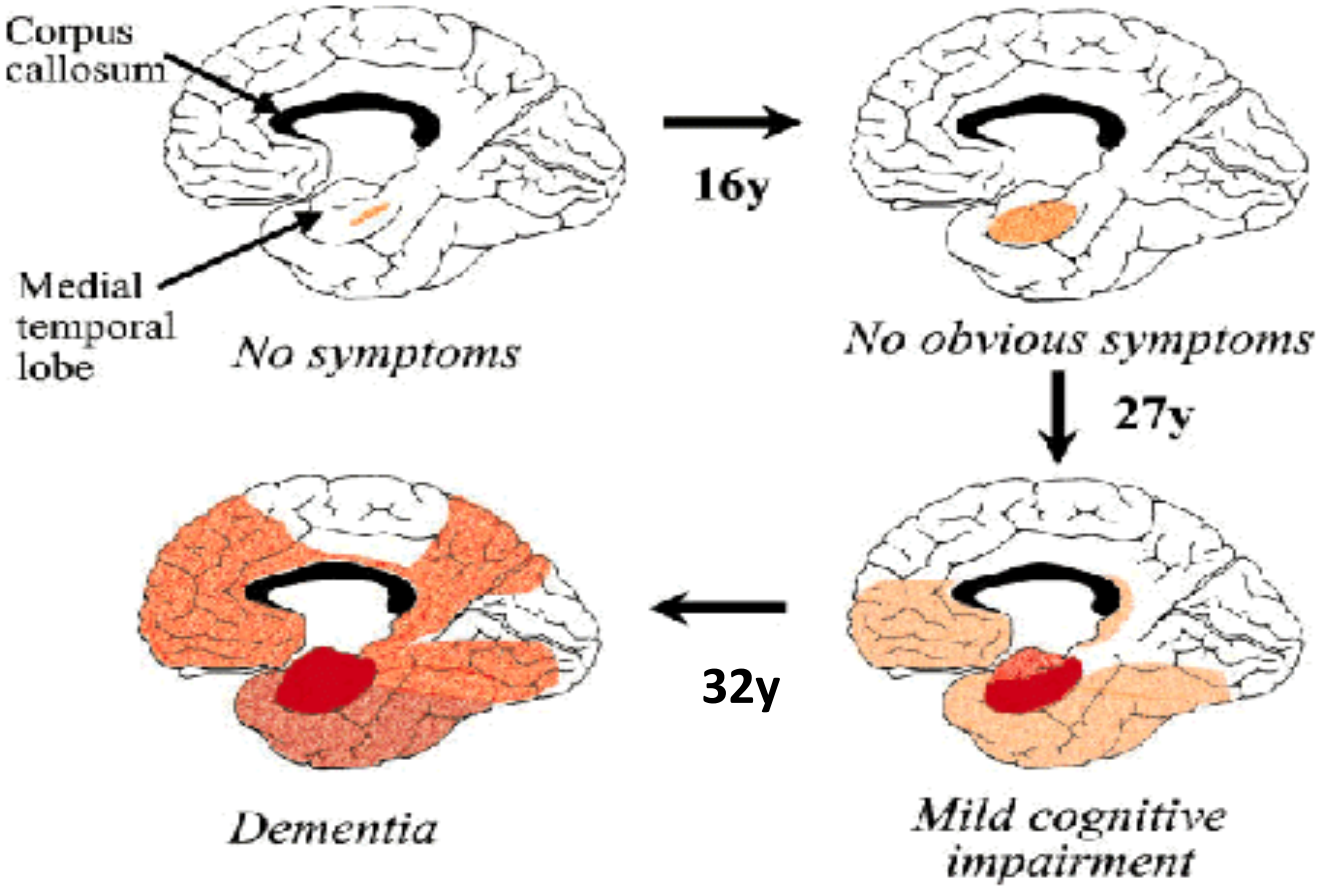
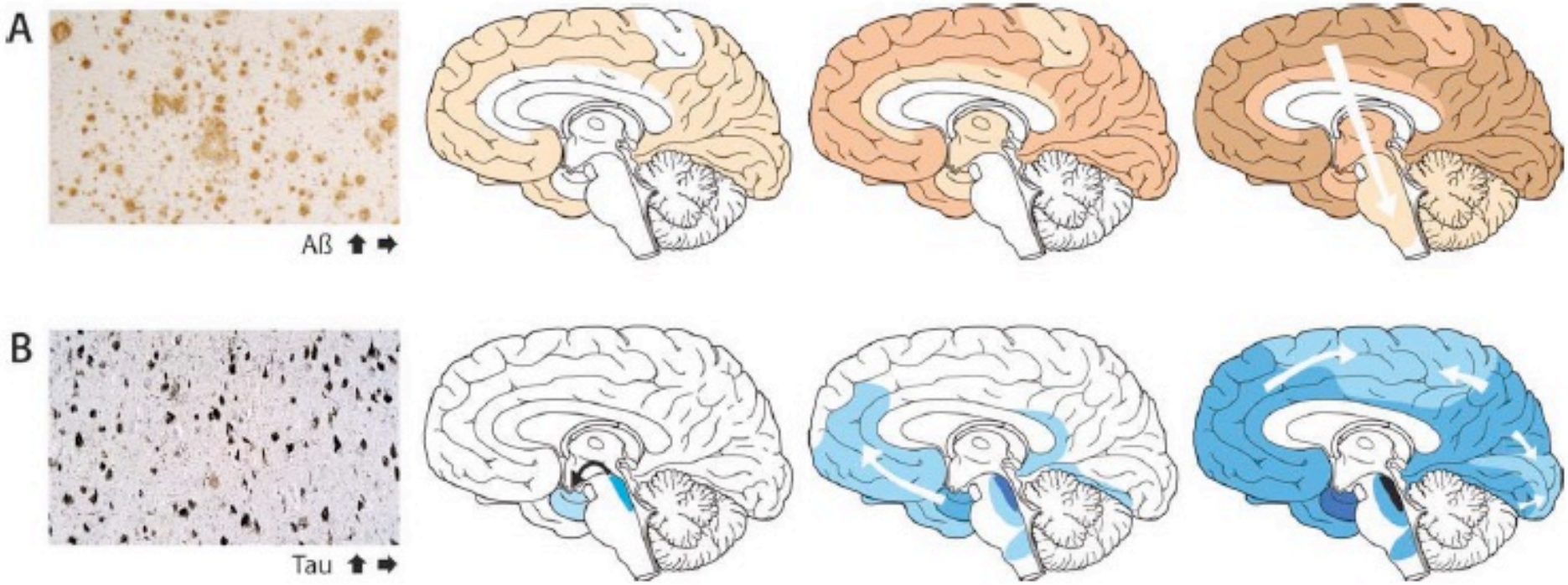


Fig. 3. Postulated sequence of spread of neurofibrillary pathology in AD, showing the medial aspect of the cerebral cortex. The depth of the red color is in proportion to the density of tangles (based on refs. 24 and 28). Several of the red areas showed atrophy in the study by Scahill *et al.* (6).

Pathogenic protein seeding in Alzheimer's disease

Jucker and Walker: Protein Seeding

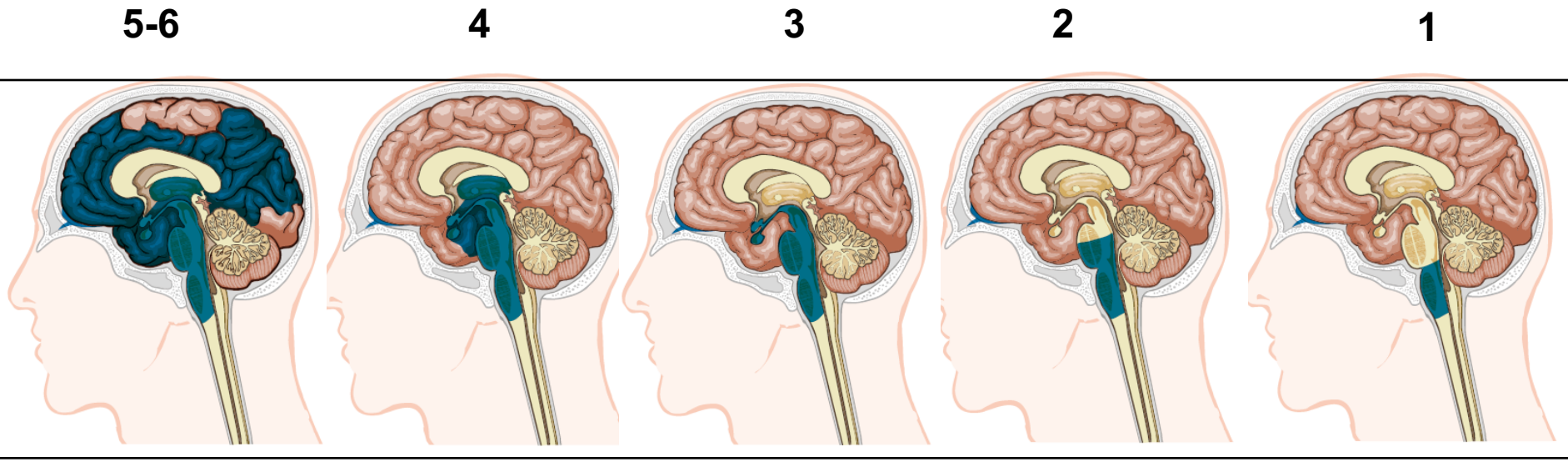
β-amyloid



Neurofibrilary tangles

ANN NEUROL 2011;70:532–540

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

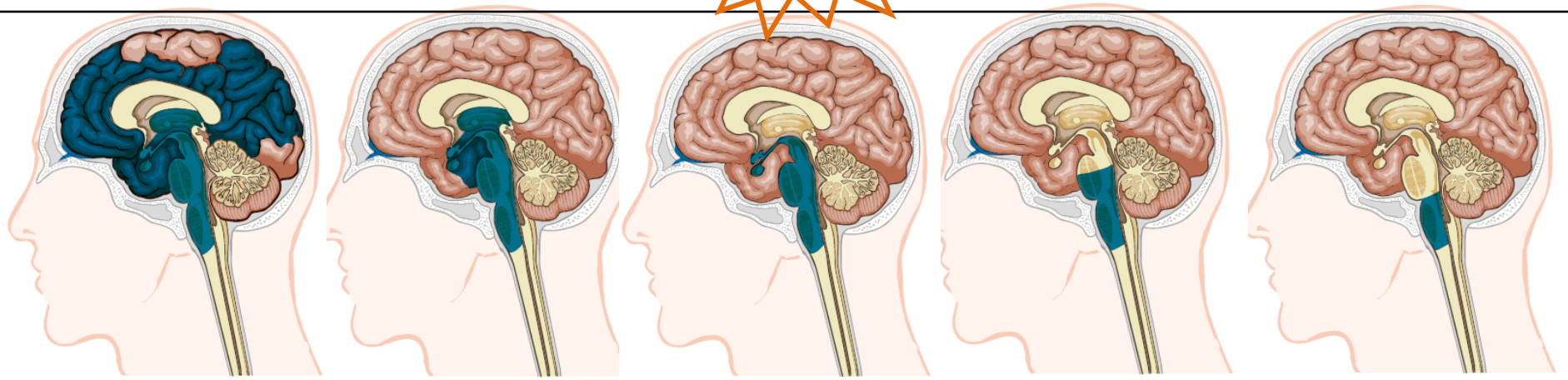


20-40 years

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

Parkinson's Disease diagnosis

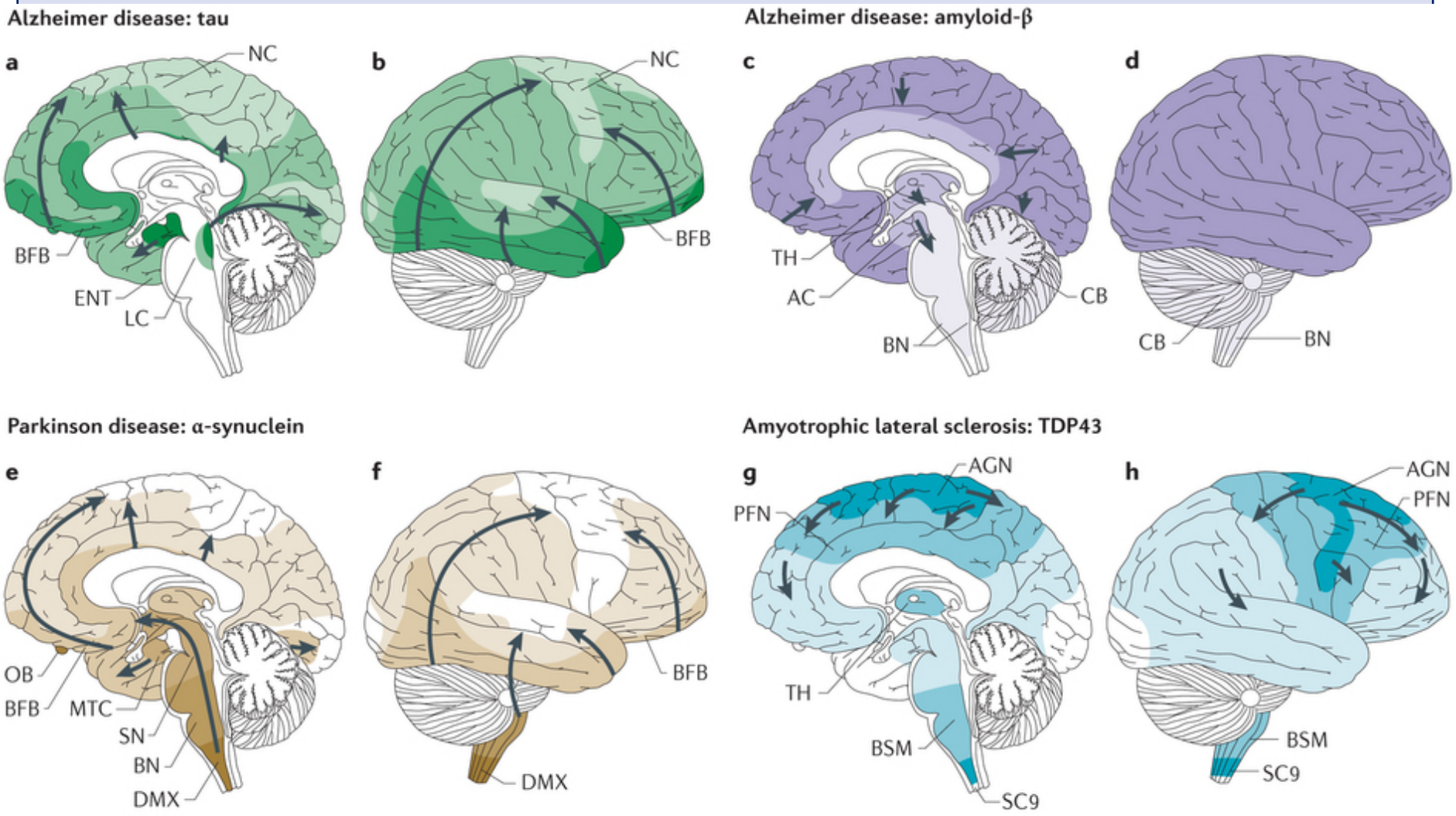
5-6 4 3 2 1



Functional deterioration

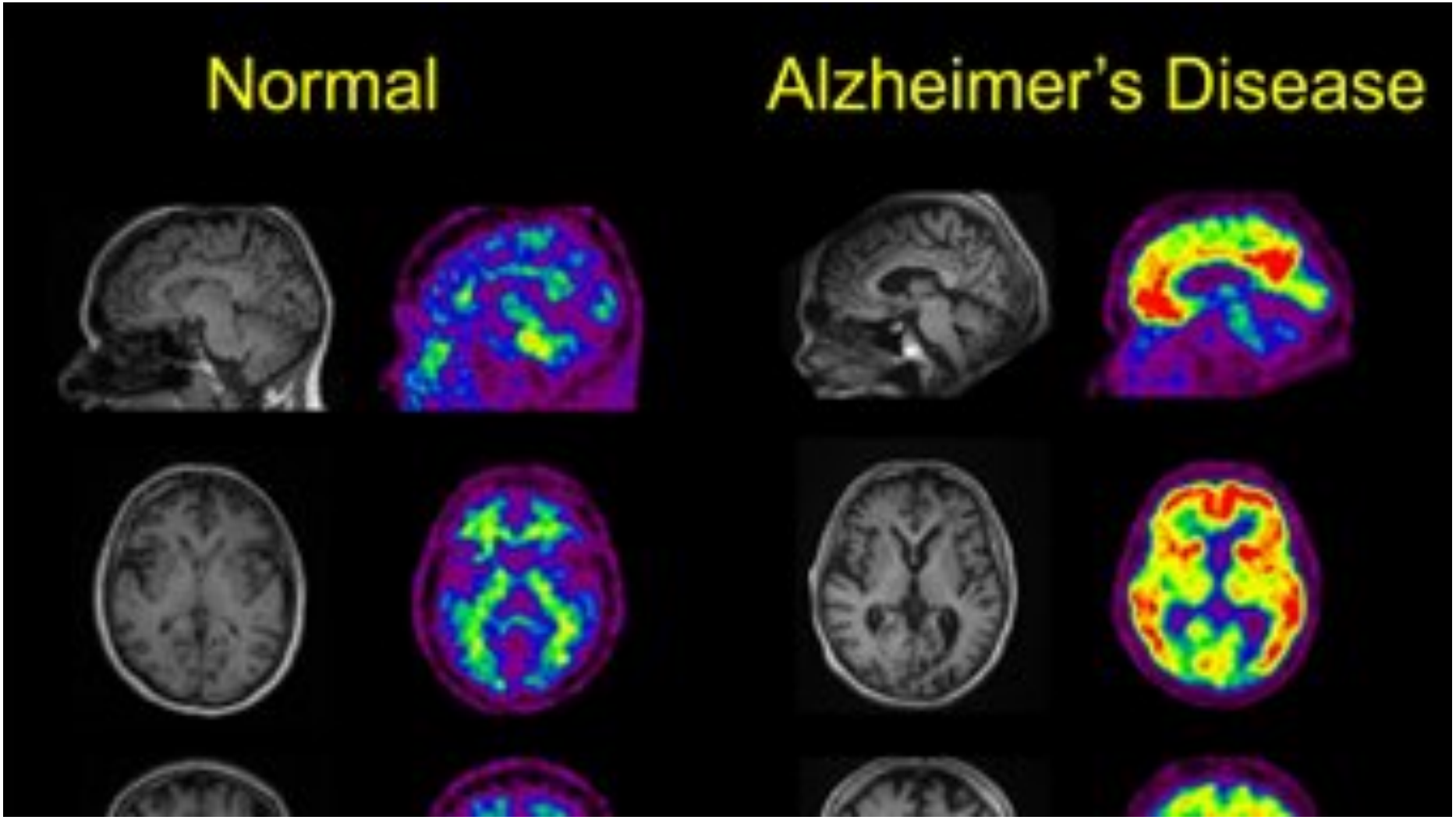
Pre-diagnosis phase

Progression of neurodegeneration

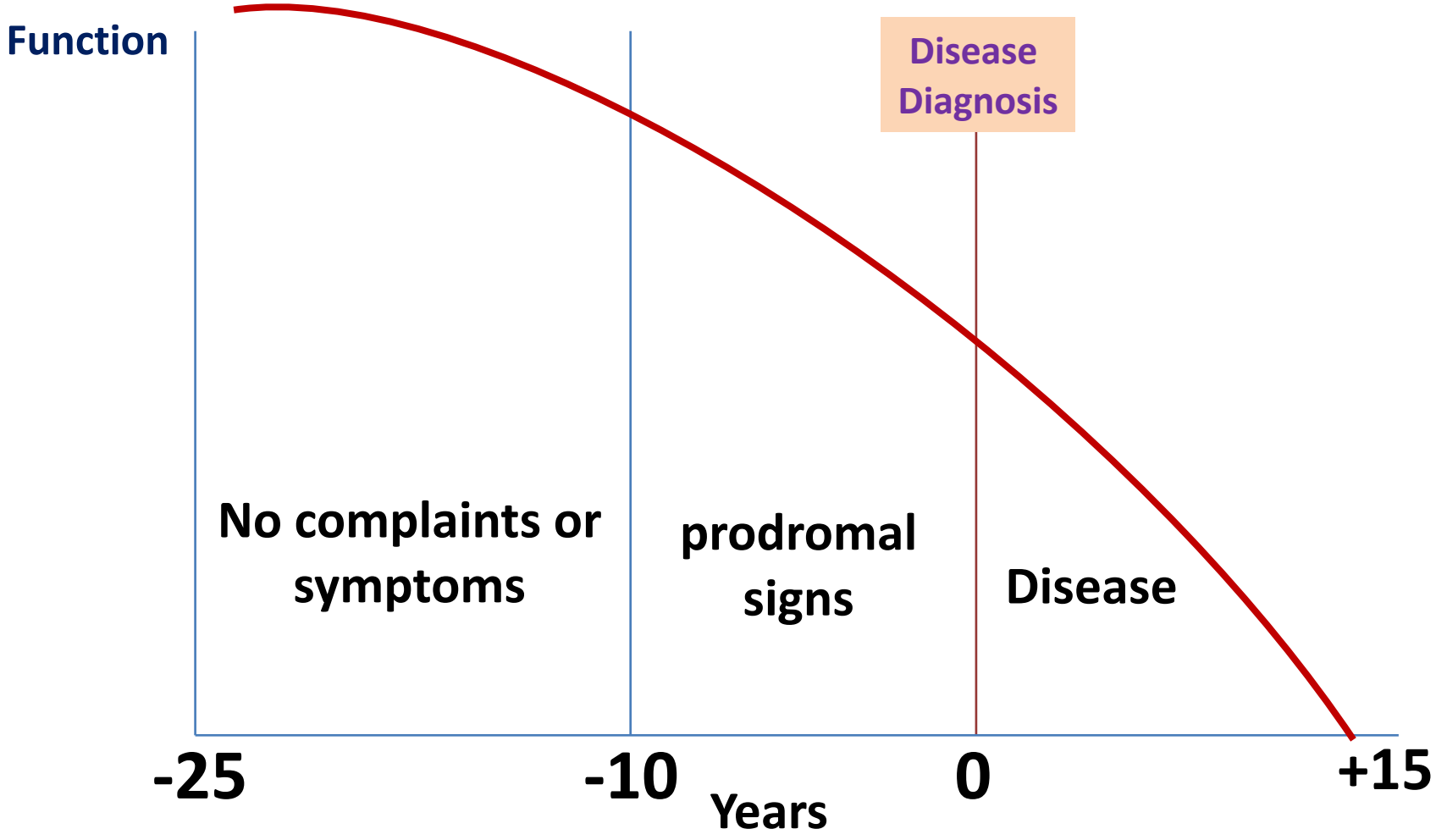


Nature Reviews | Neuroscience

Protein aggregates in AD brain



Natural History of Neurodegeneration



Exceptionally rapid neuronal loss, even before appearance of symptoms

frontiers in NEUROLOGY

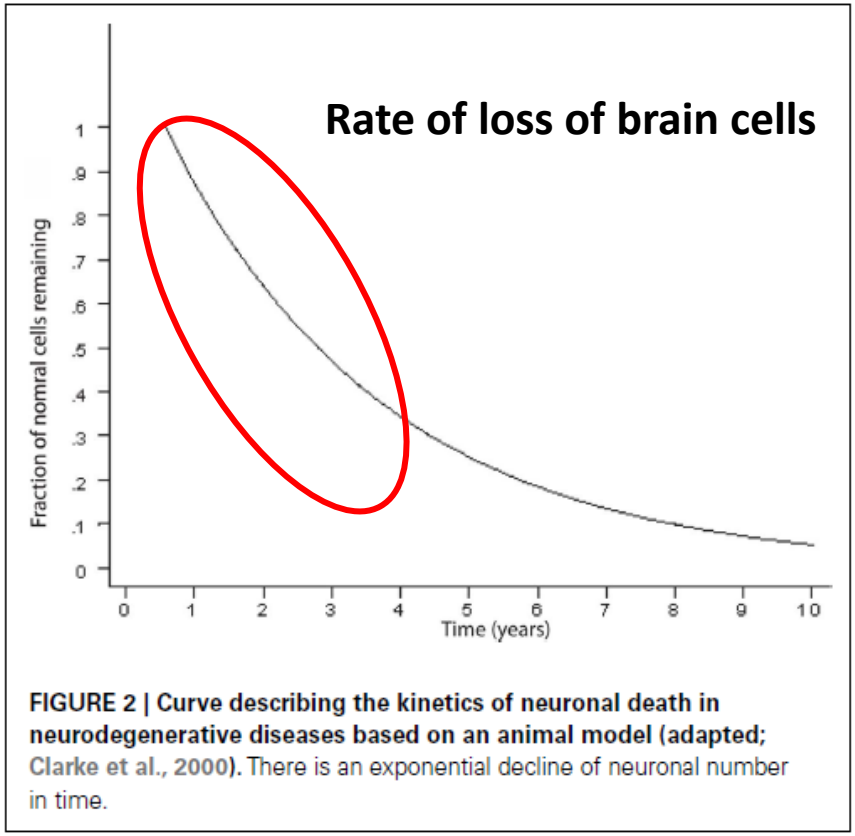


FIGURE 2 | Curve describing the kinetics of neuronal death in neurodegenerative diseases based on an animal model (adapted; Clarke et al., 2000). There is an exponential decline of neuronal number in time.

Symptoms and Patient Complaints

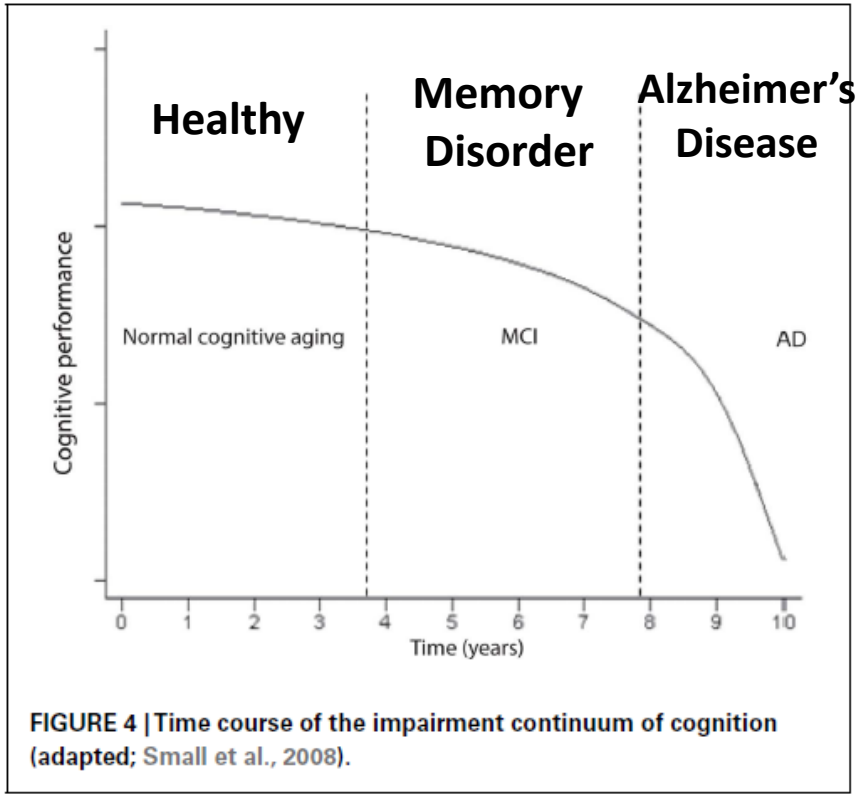
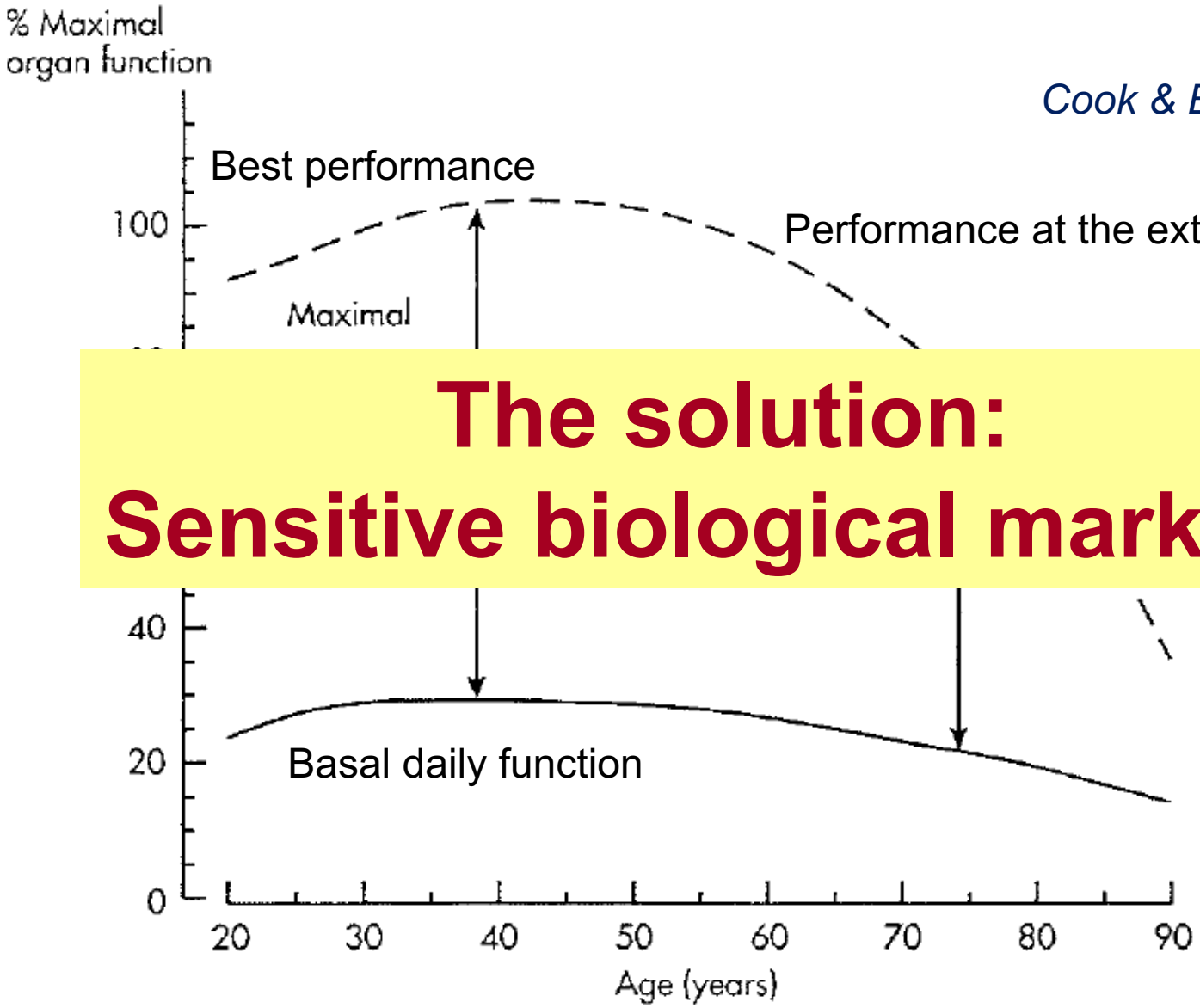


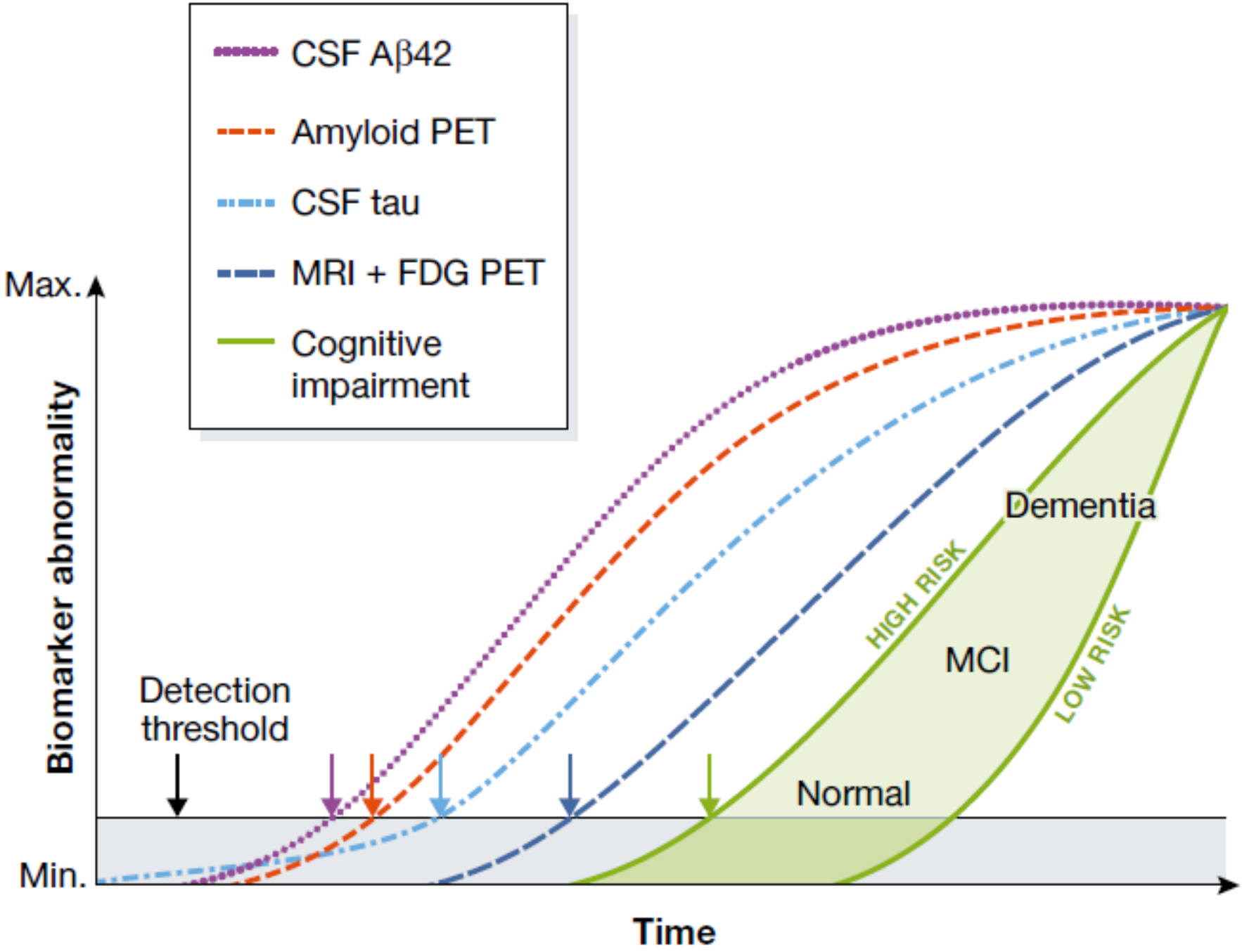
FIGURE 4 | Time course of the impairment continuum of cognition (adapted; Small et al., 2008).

Functional reserve:
A measure we need but we do not have

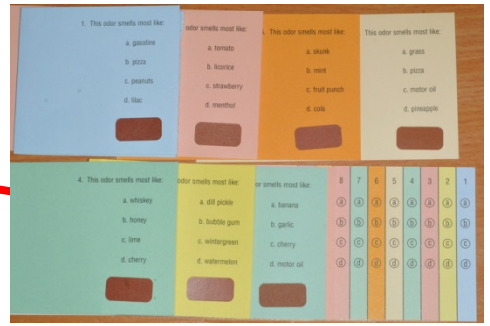


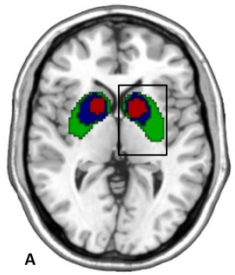
Cook & Booke, 2003

The solution:
Sensitive biological markers


CSF Aβ42
Amyloid PET
CSF tau
MRI + FDG PET
Cognitive impairment
Max.
Min.
Biomarker abnormality
Detection threshold
Normal
MCI
Dementia
HIGH RISK
LOW RISK
Time

Biological markers of disease state





Function

Insensitive to disease state

Moderate predictor of disease state

Sensitive predictor of disease state

No complaints or symptoms

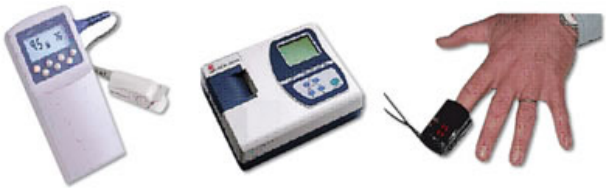
Prodromal signs

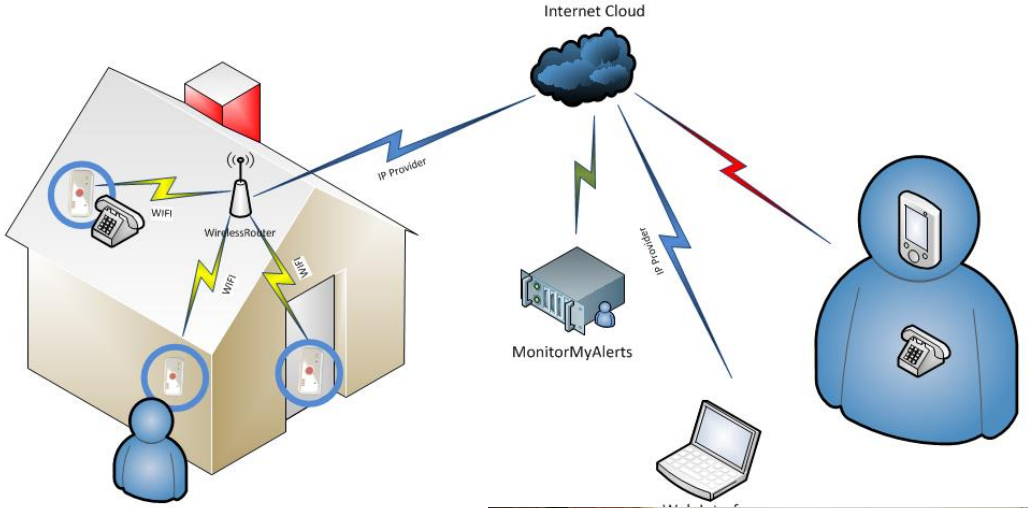
Disease

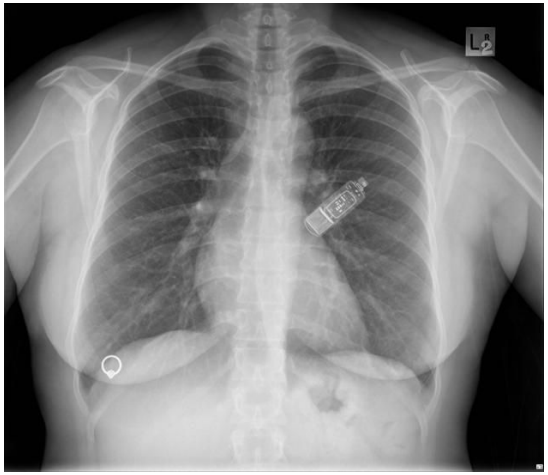
Years

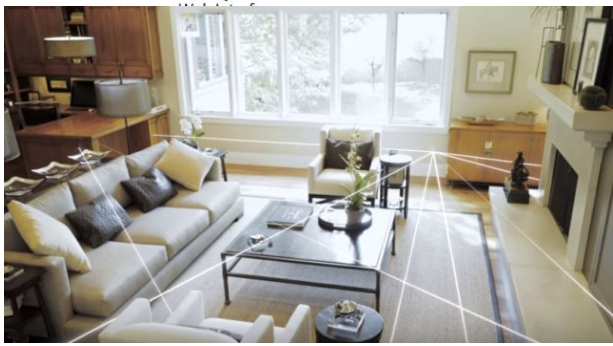
Disease Diagnosis

Continuous, home based monitoring









The significance of biomarkers

- Collecting bio-markers of health and disease is relatively easy with current and future technology
- **The challenge:**
  - Understanding the significance of those bio-markers at the spectrum of the disease's natural history, progression and response to intervention
  - Using the bio-markers at the level of the individual

Neurodegeneration – a multifactorial process

Genetics
Epigenetics

Age

Co-morbidities:

Atherosclerosis
Diabetes
Obesity
Depression
Sleep disturb.

Exposure to pesticides

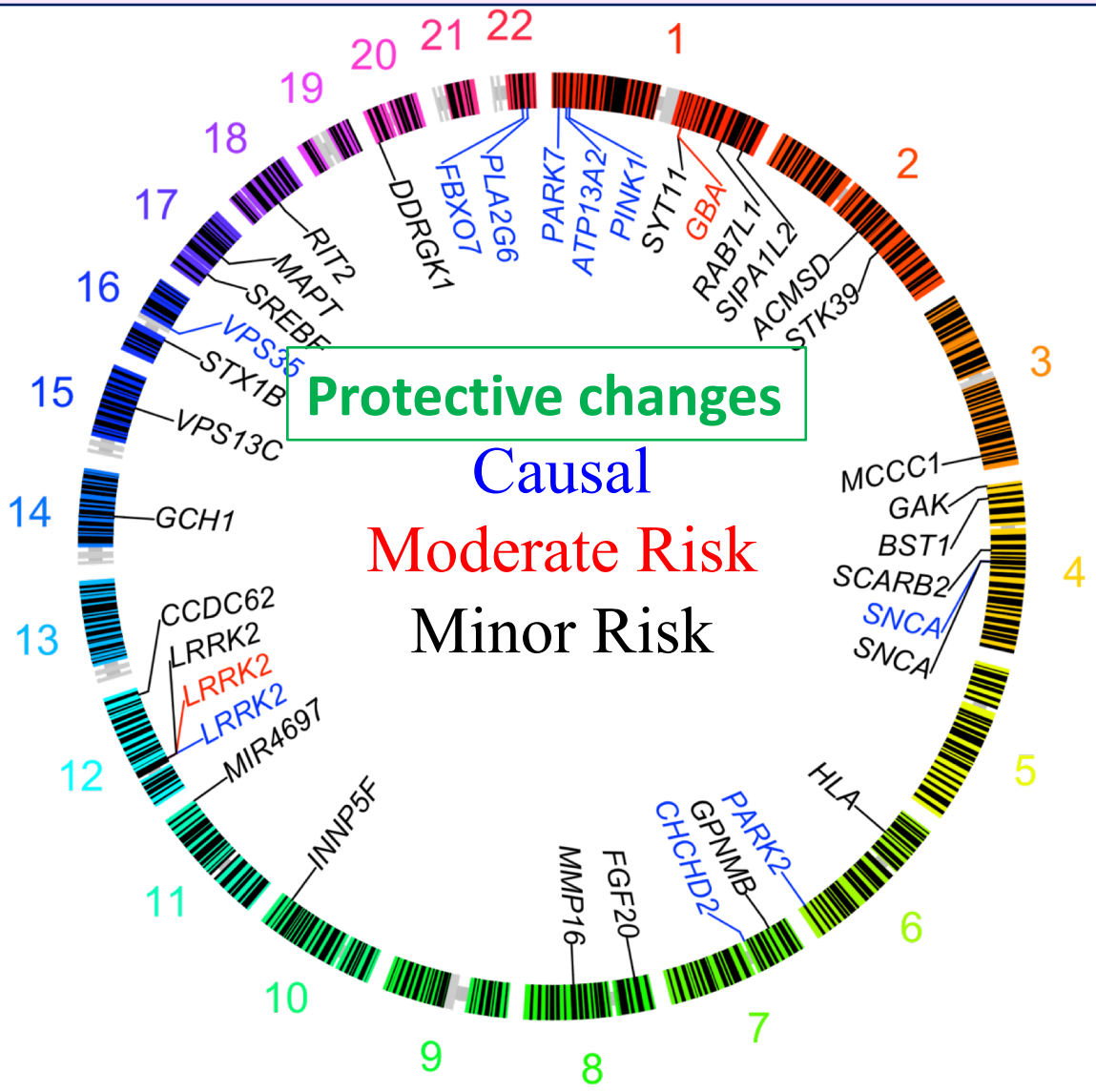
Head injuries

Environment

Education

Lifestyle

Mutations in 70 genes have been associated with Parkinson



Environmental and behavioral risk *and* protective factors for PD

- **Increasing the risk**
  - Pesticides
  - Metals
  - Industrial solvents
  - Head injury
  - Vibration ?
  - Obesity
  - Depression
- **Decreasing the risk**
  - Cigarette smoking
  - Caffeine
  - Estrogen?
  - Anti-inflammatory medications
  - Exercise
  - Urate enriched diet
  - Mediterranean diet
  - Longer use of oral contraceptives

Factors contributing to the development of neurodegenerative diseases

Genetics and aging

Environment and lifestyle

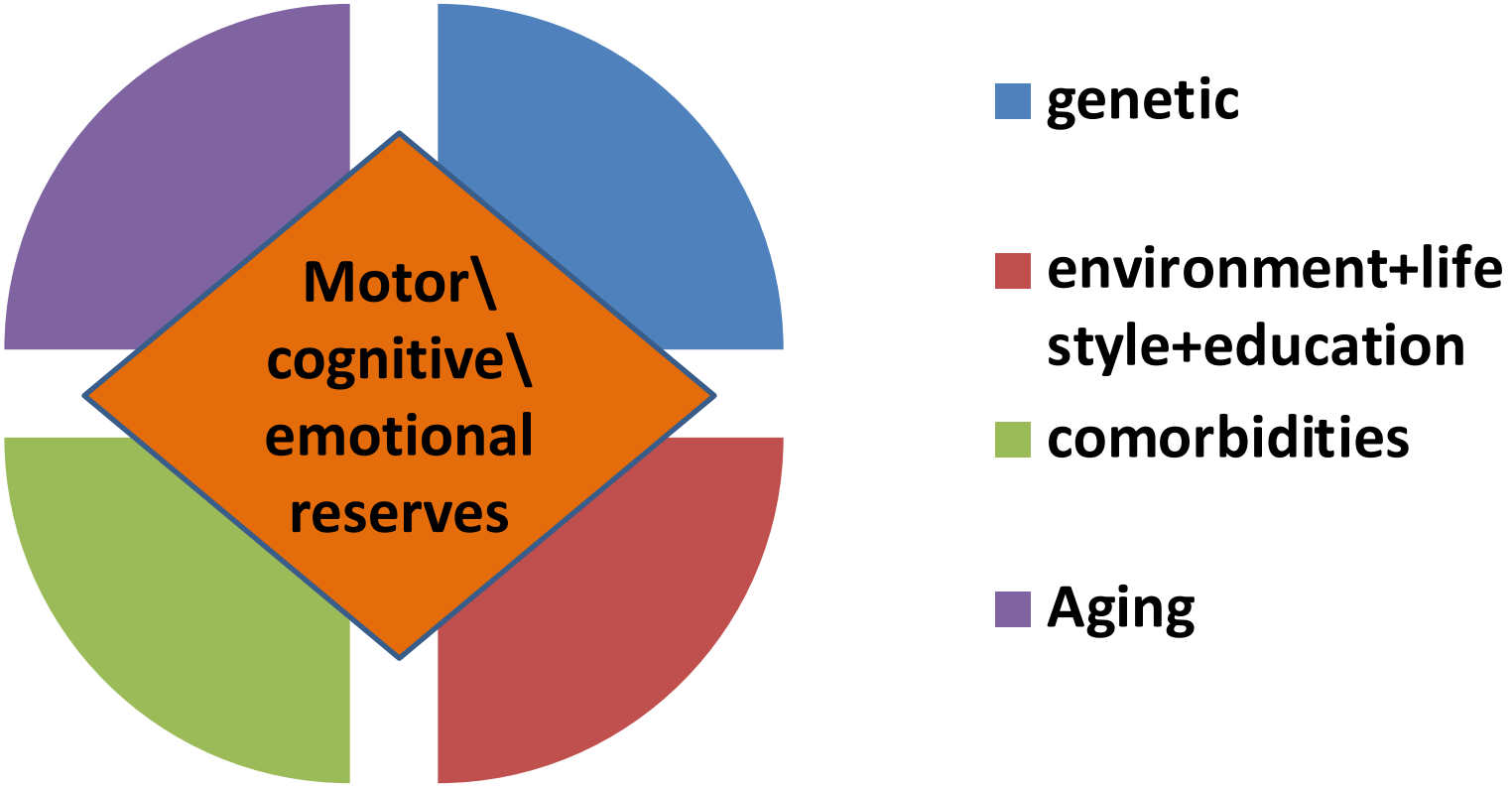
Genetic and environmental modifiers

- **Genetics & epigenetic features that can:**
  - Increase or decrease the risk for disease to appear
  - Effect time of symptoms onset
  - Influence disease phenotypic characteristics

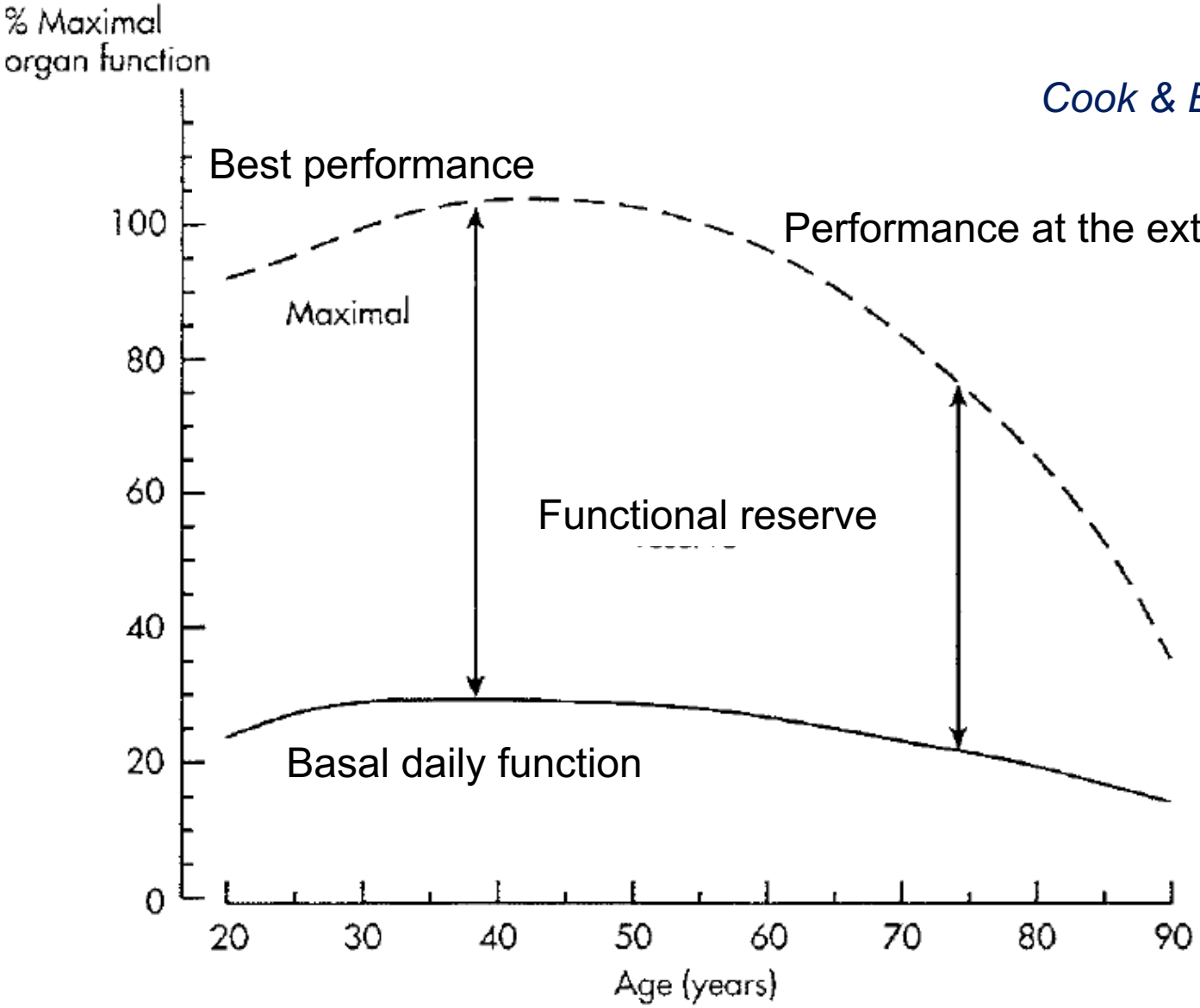
- **Environmental and life style features that can:**
  - Increase or decrease the risk for disease to appear
  - Effect time of symptoms onset
  - Influence disease phenotypic characteristics

Individual contribution

Contributing factors to the clinical syndrome



Motor, cognitive or emotional reserves influence the clinical syndrome



Cook & Booke, 2003

Intensive physical activity as disease modifying therapy

Prescription

5/7/2017

Name: Israel Israeli
Age: 45

Medication: Aerobic physical activity

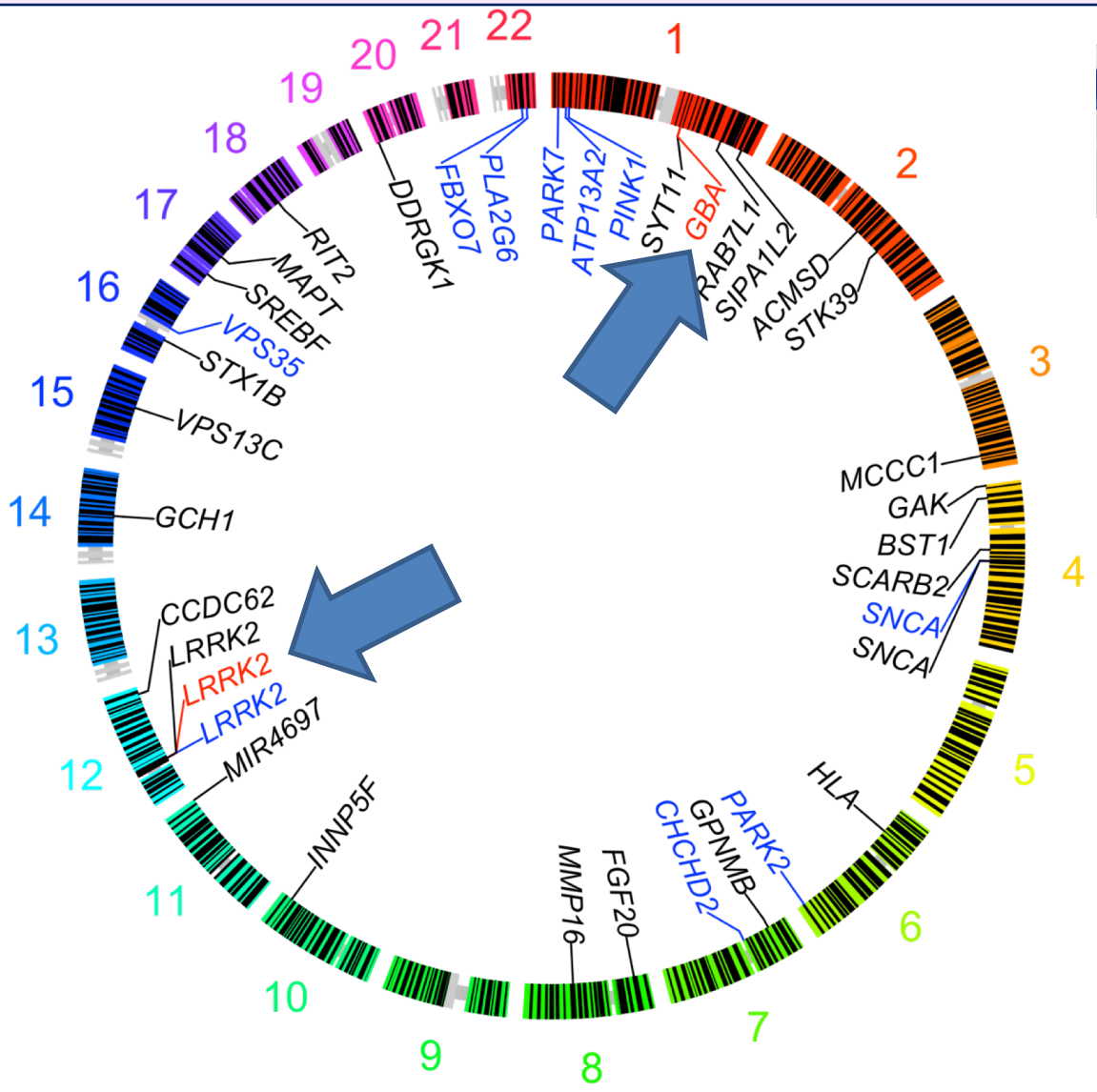
Dosage: 5 times a week - 60 minutes (200-300 minutes a week)

Notes: 50% aerobic activity, 25% resistance, 25% flexibility

Dr. Nir Giladi, License No. 12345

Tel-Aviv Sourasky Medical Center

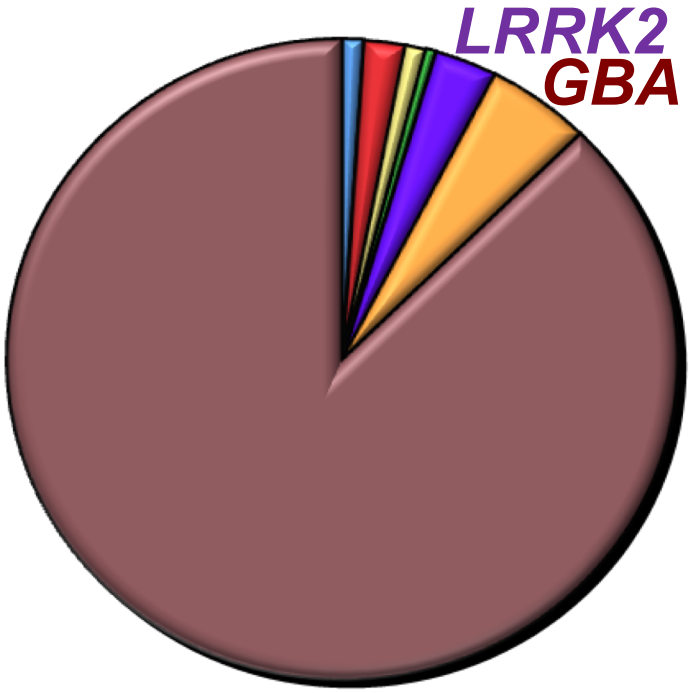
LRRK2 G2019S and 7 mutations in the *GBA* gene are present in 8.7% of Ashkenazi Jews in Israel



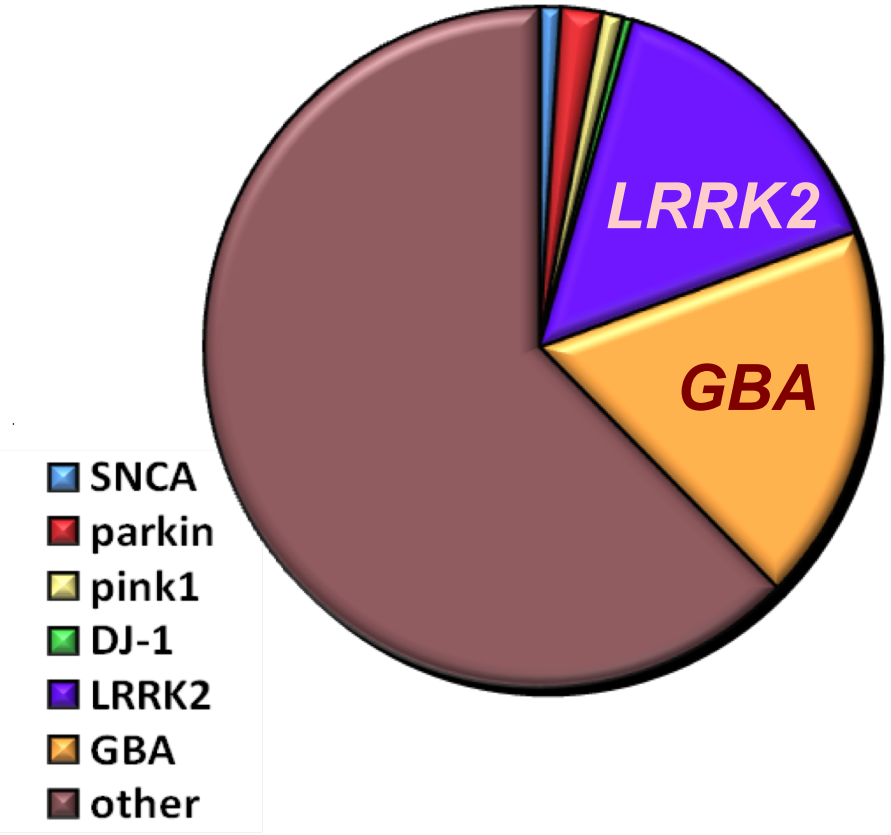
The Israeli story with Parkinson's disease:

Increased prevalence – 2% at 60 y.o.

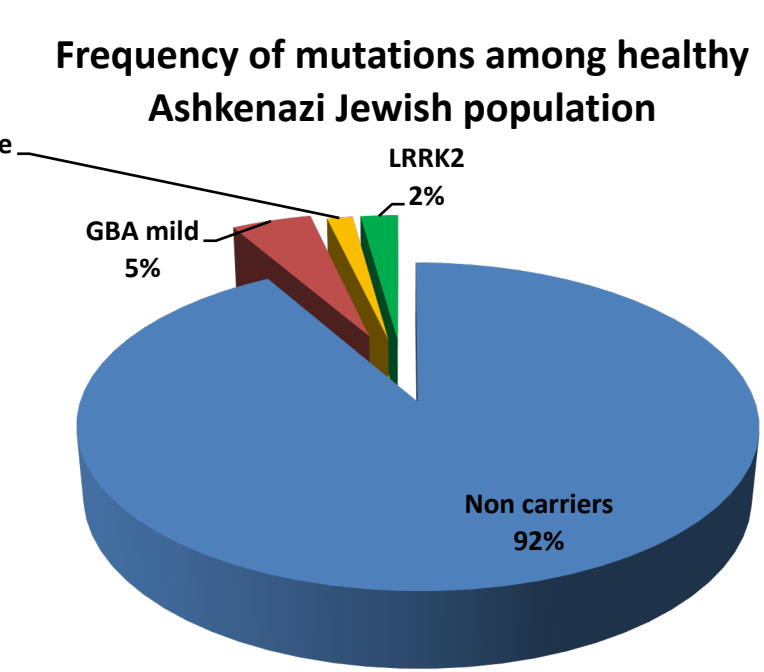
Worldwide

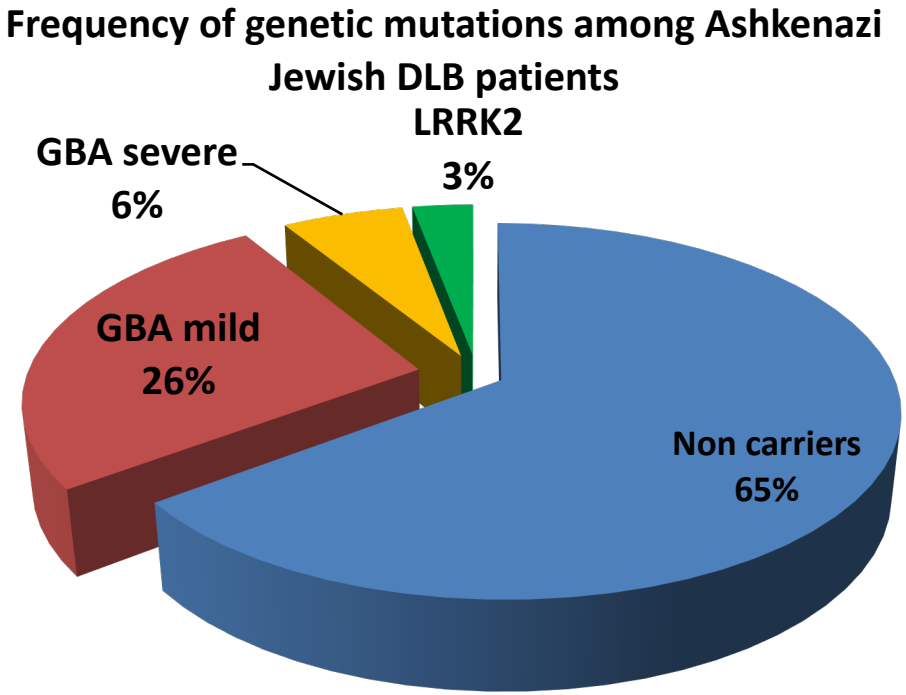


In Ashkenazi Jews



Dementia with Lewy Bodies, the second most common neurodegenerative dementia among Ashkenazi Jews

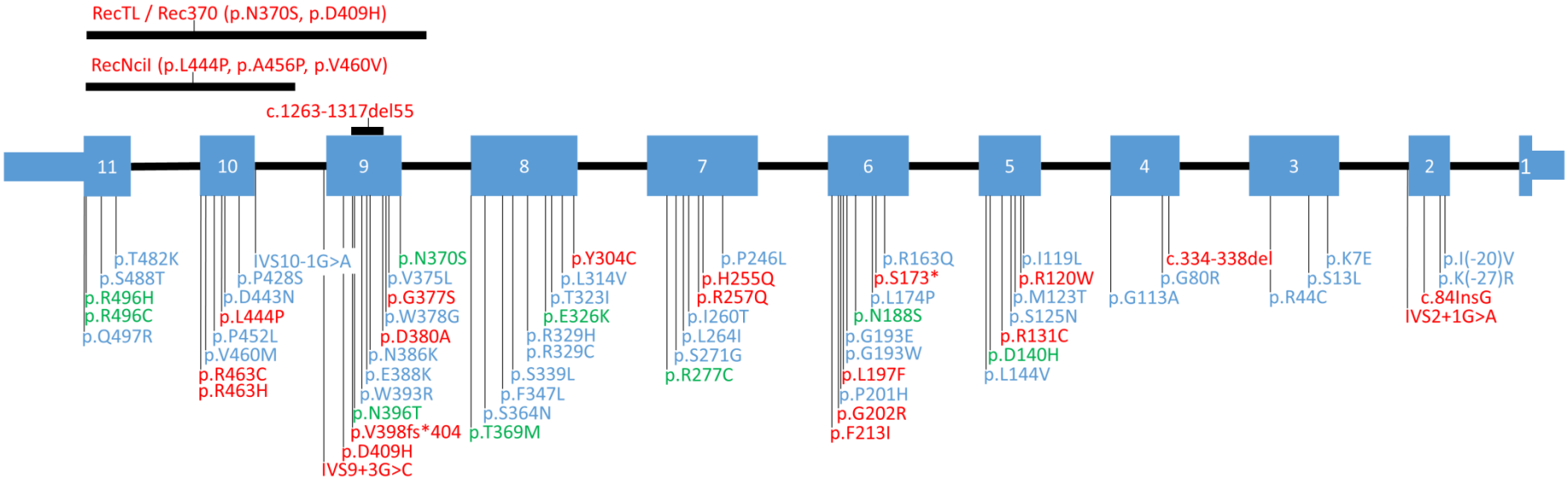




Sheiner et al, JAMA Neurology 2016

GBA gene - mutations

Recombinant alleles / large deletions

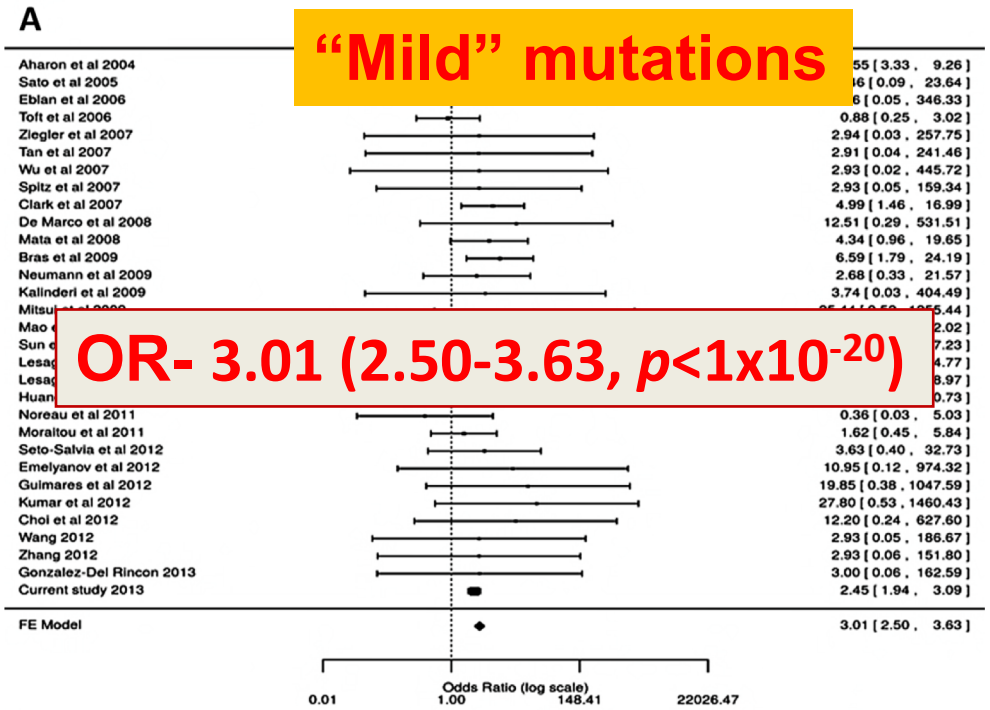


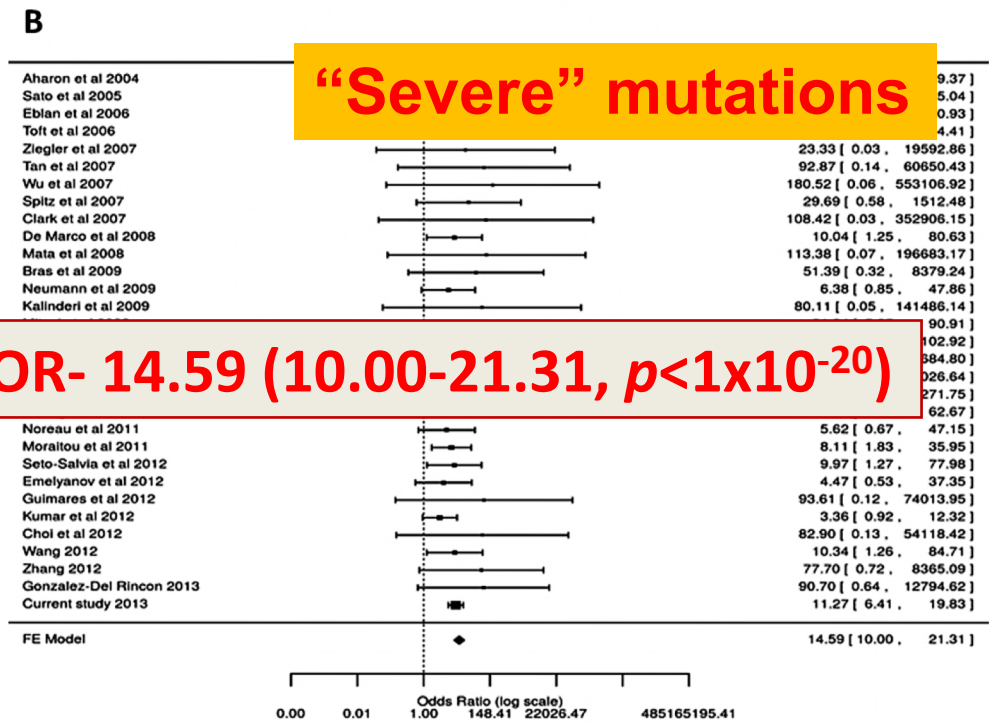
Mutations

Severe

Mild

Undetermined





Risk to develop PD according to mutation in the GBA gene

"Mild" mutations:

N370S

R496H

"Severe" mutations:

84GG

L444P

IVS2+1

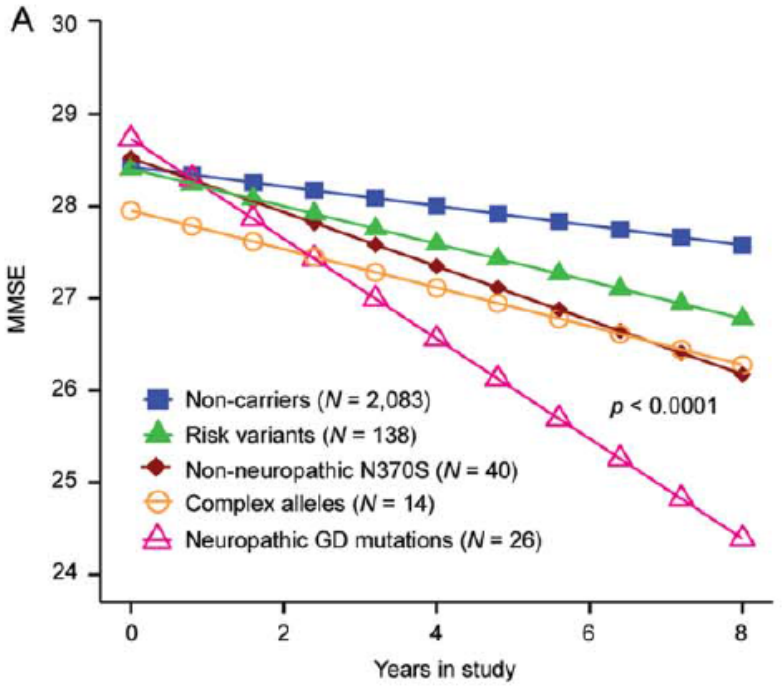
V394L

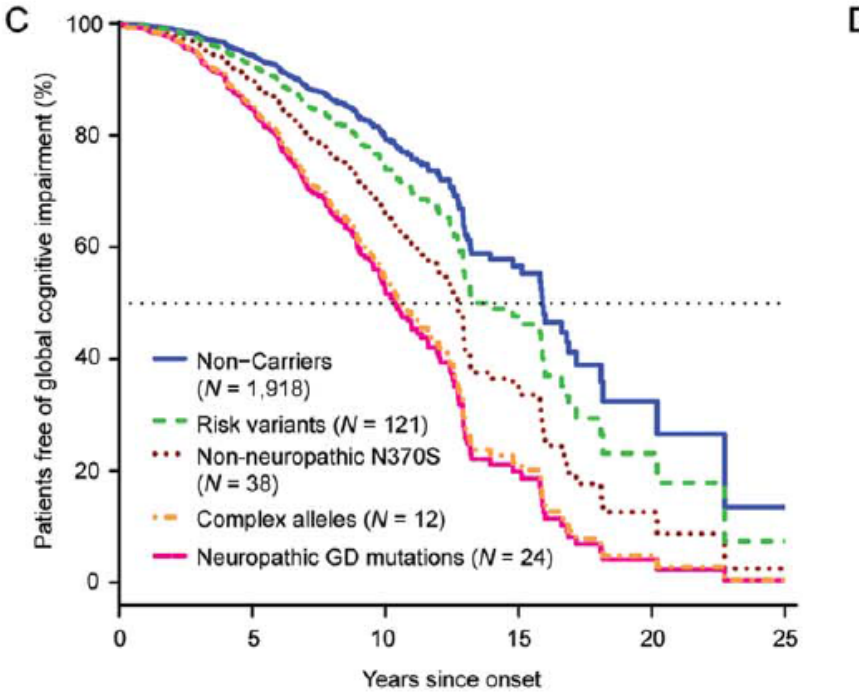
RecTL

Gan-Or et al. 2015

GBA mutations effect rate of Parkinson's disease progression:

Earlier falls
Earlier cognitive decline
Earlier death





Jesus et al, PLOS one 2016
Liu et al, Ann Neurol 2017
Cilia et al, Ann Neurol 2016

BIN1 is a modifier of age of onset among *GBA* mutation carriers

Gan Or et al, J Neurol November 2015

BIN1 **(Bridging Integrator 1) locus previously associated with Alzheimer disease is involved in synaptic vesicle endocytosis, interacts with transport & synaptic proteins (dynamin, clathrin)**

Carrying the *B1N1* rs13403026 minor allele among the GBA–PD (n=153), was associated with later age of onset:

Later age of motor symptoms onset by 12.4 years (p=0.0001)

GBA – mild mutation –later AAO of 10.5 years

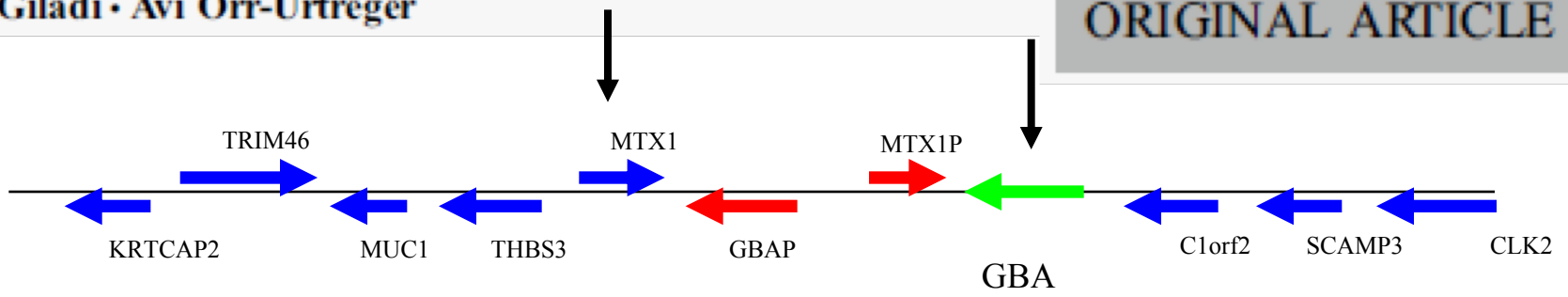
GBA – severe mutation – later AAO of 17 years

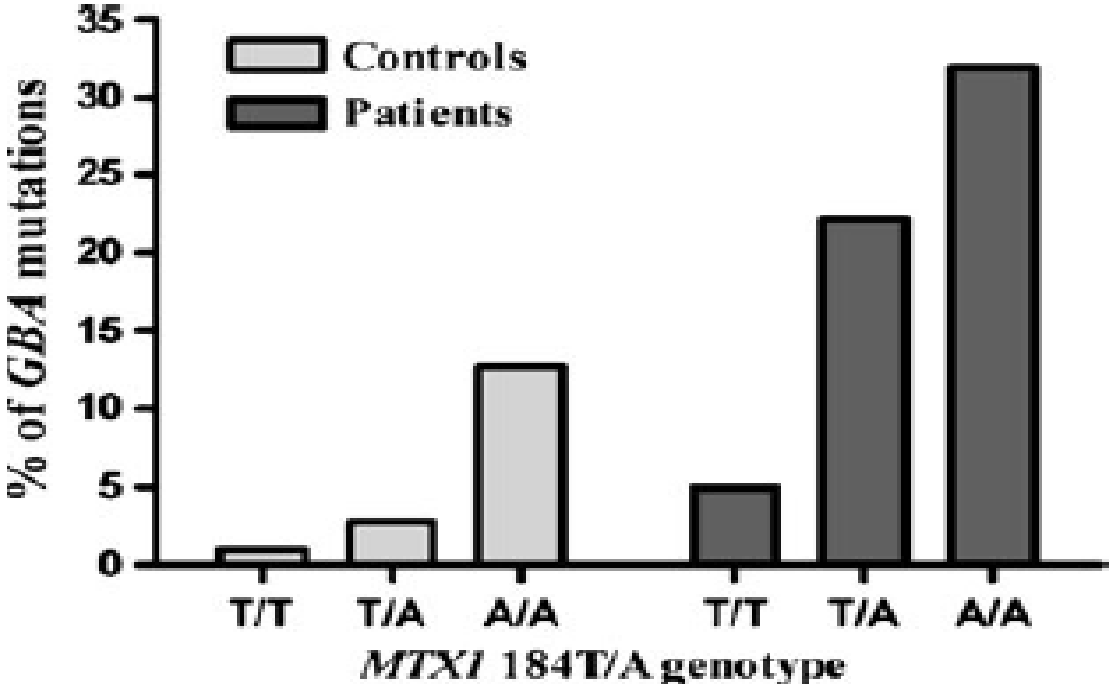
Homozygosity for the *MTX1* c.184T>A (p.S63T) alteration modifies the age of onset in *GBA*-associated Parkinson's disease

Neurogenetics
DOI 10.1007/s10048-011-0293-6

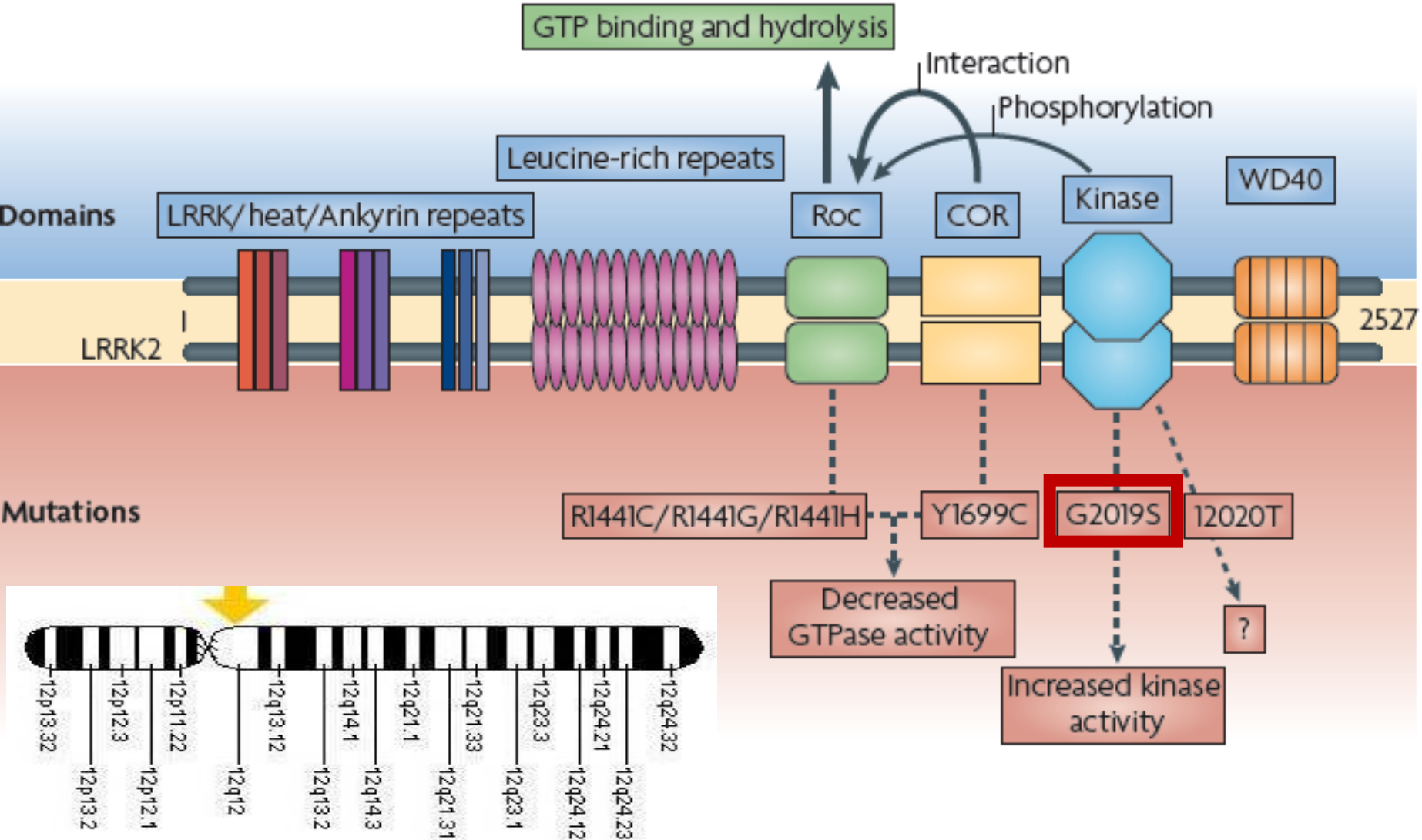
Ziv Gan-Or · Anat Bar-Shira · Tanya Gurevich · Nir Giladi · Avi Orr-Urtreger

ORIGINAL ARTICLE





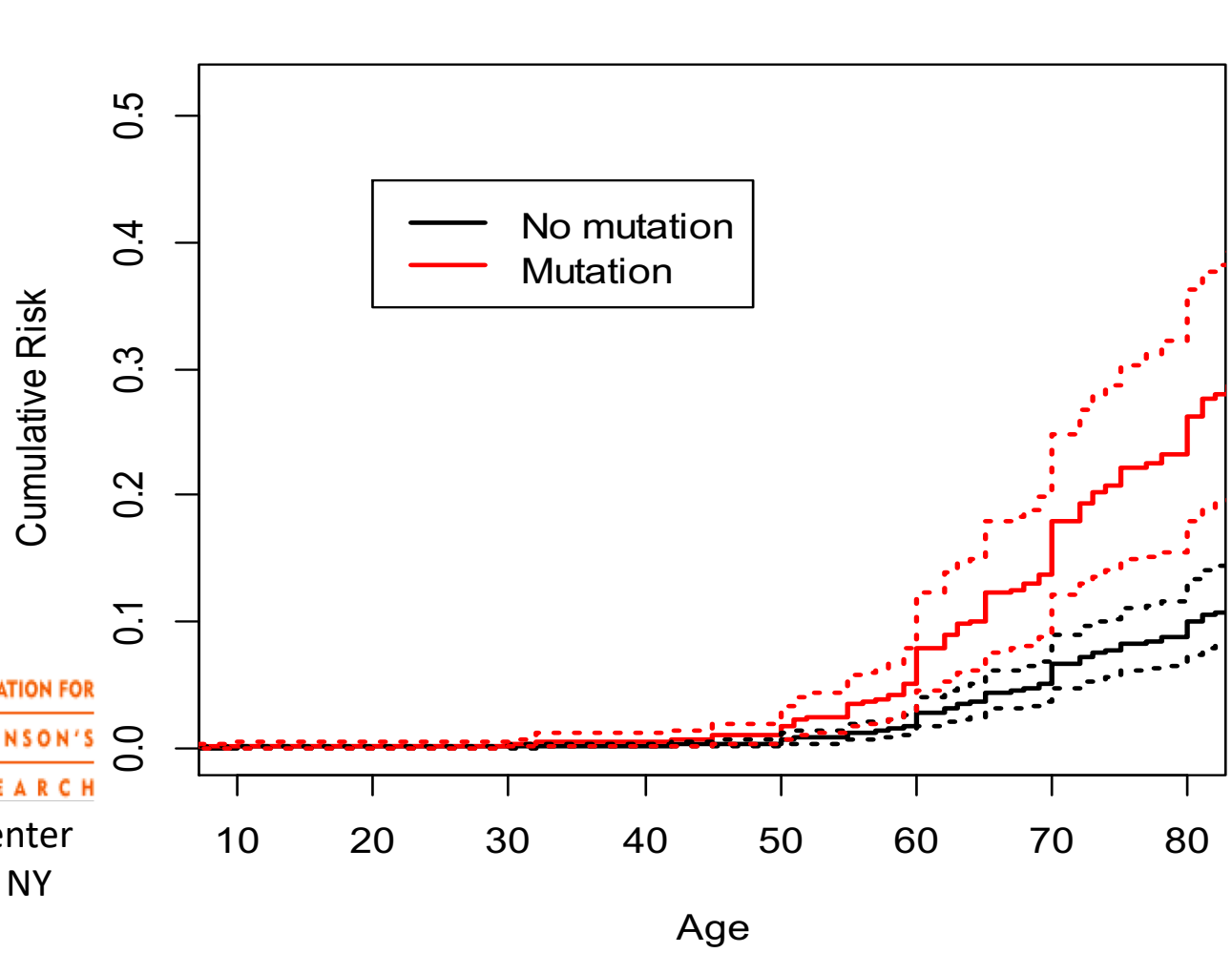
LRRK2-Leucine rich kinase 2



Age Specific Penetrance of the LRRK2 G2019S Mutation in the Michael J. Fox Ashkenazi Jewish (AJ) LRRK2 Consortium

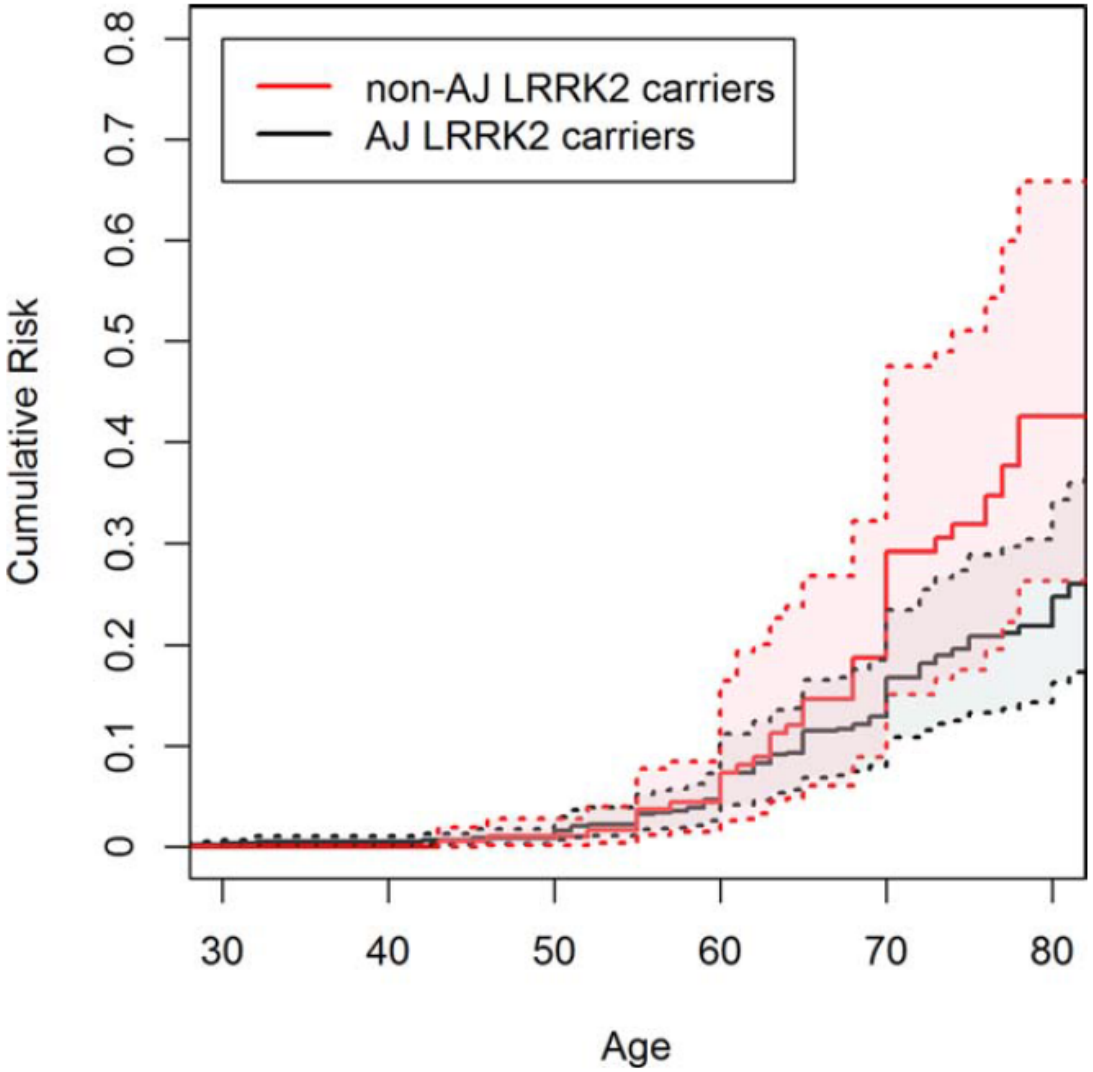
Karen Marder MD MPH, Yuanjia Wang PhD, Roy Alcalay MD, MSc, Helen Mejia-Santana MS, Ming-Xin Tang PhD, Annie Lee MS, Deborah Raymond MS, Anat Mirelman PhD, Rachel Saunders-Pullman MD MPH, Lorraine Clark PhD, Laurie Ozelius PhD, Avi Orr Urtreger MD PhD, Nir Giladi MD, Susan Bressman MD for the LRRK2 Ashkenazi Jewish Consortium

Neurology
June 2015



Tel Aviv Sourasky Medical Center
Beth Israel Medical Center, NY
Columbia University, NY

Age specific risk of PD among carriers of G2019S mutation in the *LRRK2* gene, comparing non-Jews and Ashkenazi Jews



Mov Dis J 2017

Gender specific risk to develop PD till age 80 among G2019S-*LRRK2* mutation carriers

Relatives	G20109S mutation carrier status	Cumulative risk in non-Ashkenazi Jewish[a] relatives to age 80, %	Cumulative risk in Ashkenazi Jewish[b] relatives to age 80, %[9]	Cumulative risk in non-Ashkenazi Jewish relatives to age 80 compared to Ashkenazi Jewish relatives to age 80
All	Carriers	42.5 (26.3-65.8)	25.0 (16.7-34.2)	$P = .106$
	Noncarriers	2.7 (0.1-10.7)	11.0 (8.0-14.7)	$P = .013$
Male	Carriers	35.2 (17.8-58.4)	21.5 (9.0-35.6)	$P = .268$
	Noncarriers	2.1 (0.1-7.8)	15.2 (10.5-20.6)	$P < .001$
Female	Carriers	49.3 (30.3-74.3)	28.5 (18.8-39.4)	$P = .098$
	Noncarriers	3.2 (0.1-13.4)	6.6 (4.0-9.7)	$P = .394$

Mov Dis 2017

ORIGINAL CONTRIBUTION

Association of Sequence Alterations in the Putative Promoter of *RAB7L1* With a Reduced Parkinson Disease Risk

Arch Neurol. 2012;69(1):105-110

Ziv Gan-Or, BMedSci; Anat Bar-Shira, PhD; Dvir Dahary, MSc; Anat Mirelman, PhD; Merav Kedmi, PhD; Tanya Gurevich, MD; Nir Giladi, MD; Avi Orr-Urtreger, MD, PhD

Subjects: Five single-nucleotide polymorphisms (SNPs) located between *RAB7L1* and *SLC41A1* were analyzed in 720 patients with PD and 642 controls, all of Ashkenazi Jewish origin.

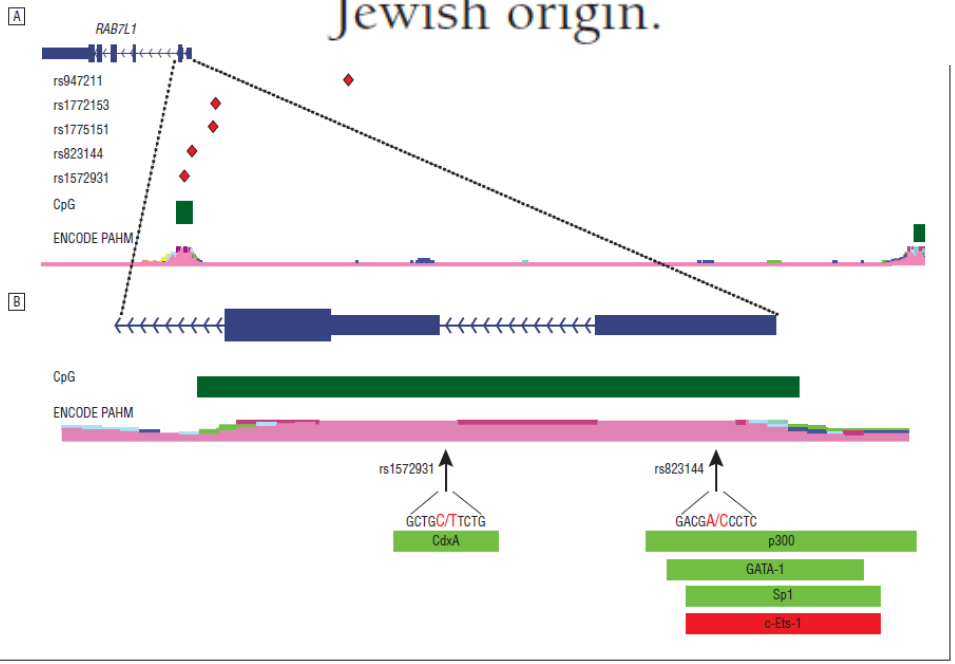


Figure. The *RAB7L1* putative promoter region and single-nucleotide polymorphisms and their effects on transcription factor binding sites. A, Scheme of part of the *PARK16* locus (between 204 003 500-204 049 000 according to genome assembly GCRh37) depicting the structure of the *RAB7L1* and *SLC41A1* genes (exons

Specific SNPs variations and haplotype in the PARK16 locus are associated with significant reduced (1\10) risk to develop PD among Ashkenazi Jews.

J Mol Neurosci (2016) 59:343–350
DOI 10.1007/s12031-016-0738-3

SEPT14 Is Associated with a Reduced Risk for Parkinson's Disease and Expressed in Human Brain

Liron Rozenkrantz[1,2] · Ziv Gan-Or[1,2] · Mali Gana-Weisz[1] · Anat Mirelman[3] · Nir Giladi[2,3] · Anat Bar-Shira[1] · Avi Orr-Urtreger[1,2]

Received: 14 February 2016 / Accepted: 22 March 2016 / Published online: 26 April 2016

Abstract Genes involved in cytoskeletal stability and trafficking, such as *MAPT* and *SNCA*, are important risk factors for Parkinson's disease (PD). Two members of the cytoskeletal Septin family, SEPT4 and SEPT5, were implicated in PD pathobiology. We aimed to determine whether *Septin* genes are associated with Parkinson's disease. To this end, six SNPs located in four different *Septin* loci were analyzed in 720 PD patients and 740 controls, all of Ashkenazi–Jewish origin. In addition, *SEPT14* was sequenced and its expression was determined in different fold ($p = 0.002$). *SEPT14* was found to be expressed in the brain and in the Substantia Nigra. These results suggest that *SEPT14* may have a protective role in Parkinson's disease pathogenesis, yet more studies are necessary to validate these results.

Keywords Parkinson's disease · Septin 14 · SEPT14 · Genetics

Orr-Urtreger et al.

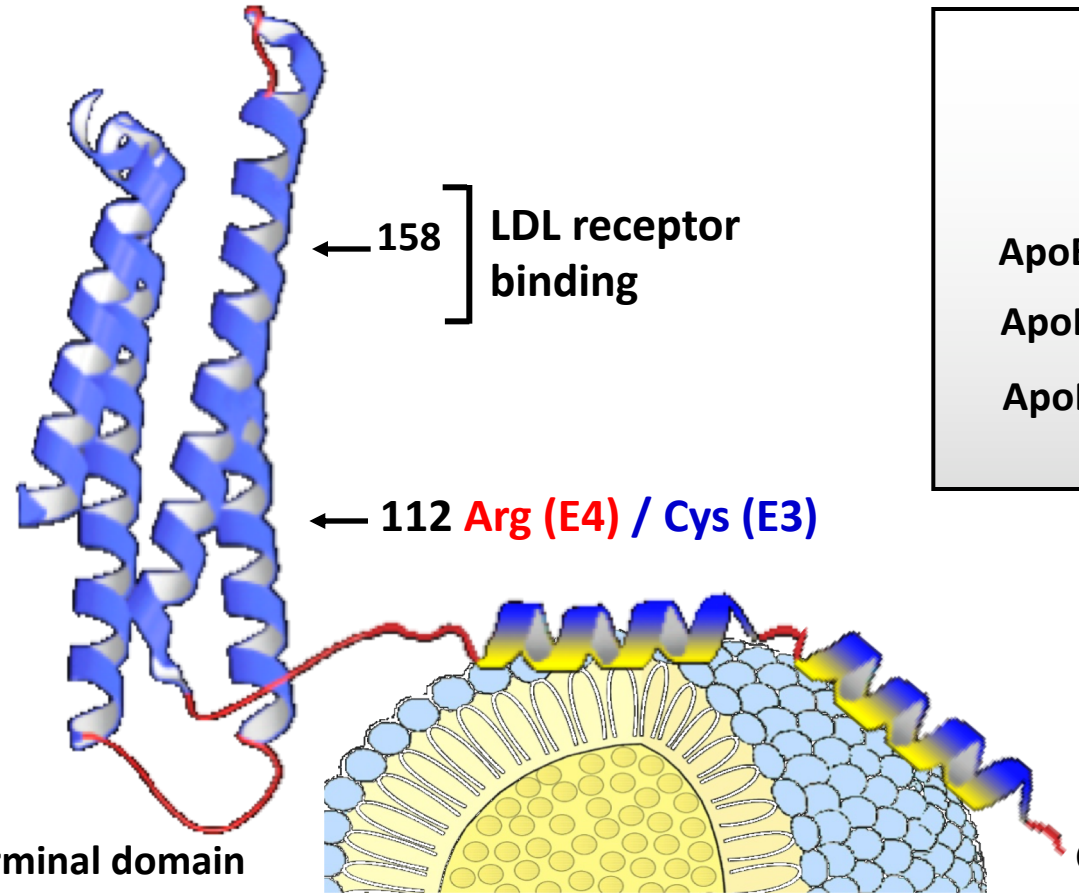
Modifier genes for risk or severity of Parkinson's disease among AJ

MTX1
BIN1
MAPT (TAU)
SEPT14
PARK16

Red – increased risk or severity
Blue – decreased risk or severity

Orr-Urtreger et al.

Apolipoprotein E (ApoE)



	Position	
	112	158
ApoE2	Cys	Cys
ApoE3	Cys	Arg
ApoE4	Arg	Arg

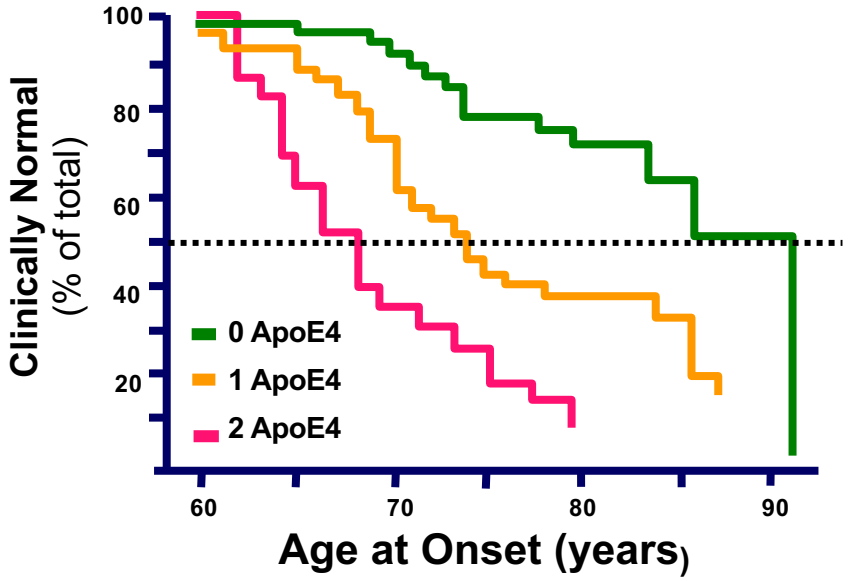
ApoE4 as modifier of the risk and age of onset of Alzheimer's Disease

The Genetics of ApoE4 and AD

APOE genotype	Control	AD
ε2/ε2	<1%	<1%
ε2/ε3	15%	5%
ε3/ε3	58%	33%
ε2/ε4	2%	3%
ε3/ε4	22%	42%
ε4/ε4	2%	16%

26% (ε2/ε4, ε3/ε4, ε4/ε4) 61%

Age of Onset of AD

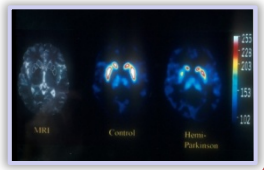


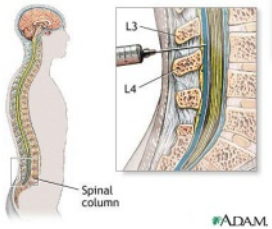
Corder et.al (1993)

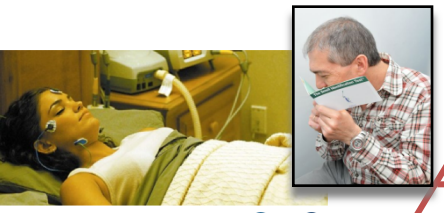
Adapted from Rebeck & Hyman (1999) in Alzheimer's Disease (Terry et al eds.), p340.

The pyramid of Parkinson's disease

From population at risk to diagnosed disease







25-100%

Parkinson's

Prodromal stage

Biological markers

Non-motor symptoms

Population at risk\

Genetic & behavioral modifiers

Modifiers effecting penetrance

All mutation carriers will develop the disease
100% penetrance

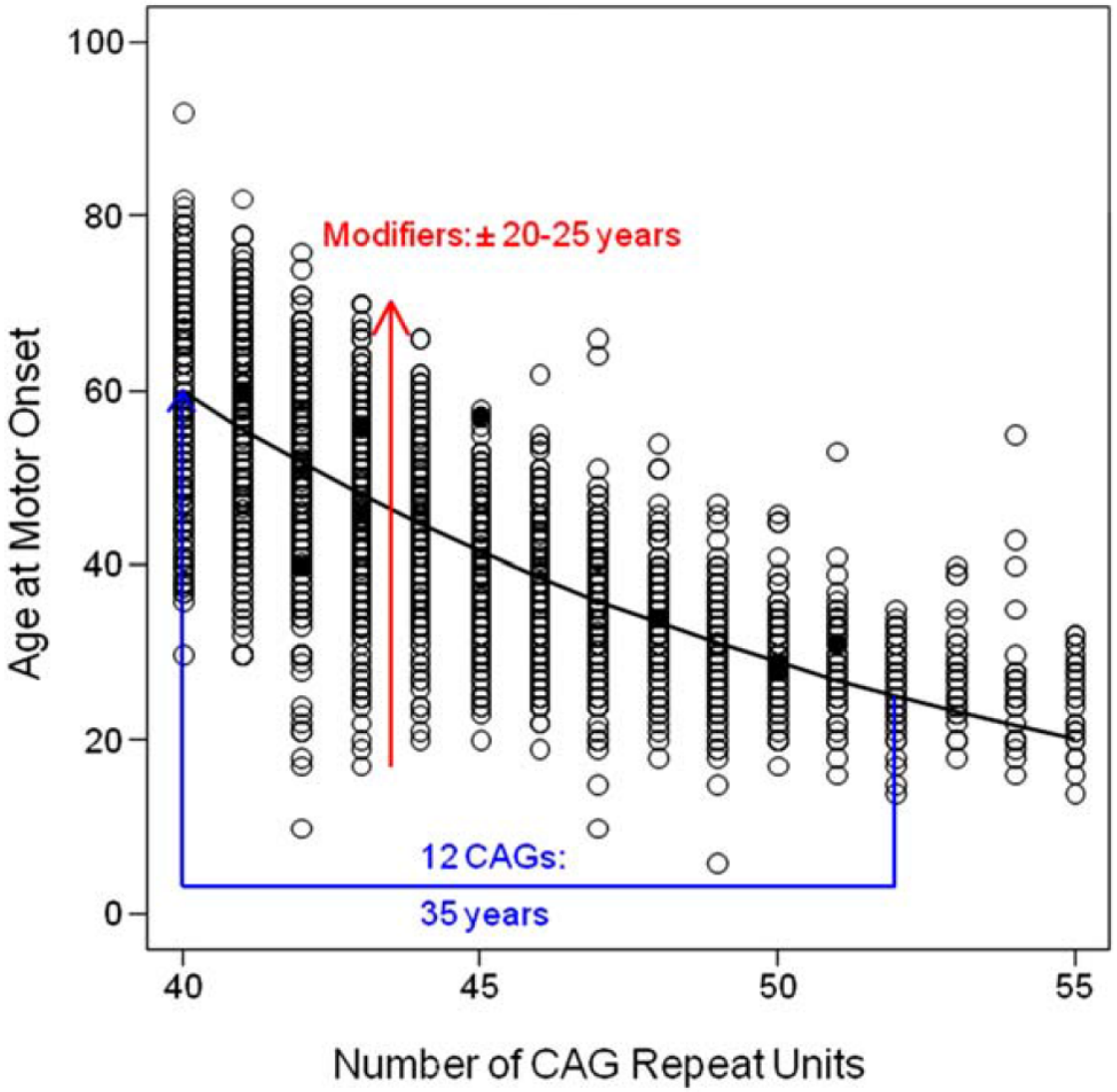
Modifiers effecting age of onset and the natural history

Huntington's disease\ CJD
Prodromal stage
Biological markers
Non-specific symptoms
Population at risk Genetic & behavioral modifiers

Genetic Modifiers of Huntington's Disease

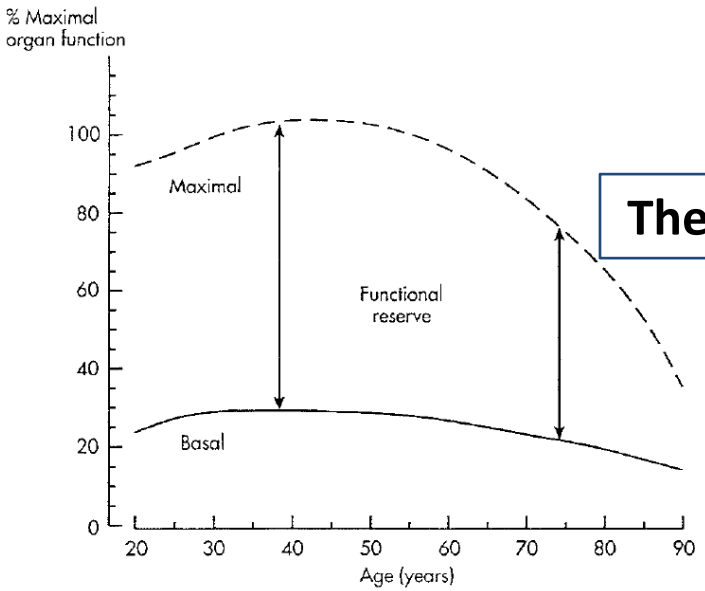
James F. Gusella, PhD,* Marcy E. MacDonald, PhD, and Jong-Min Lee, PhD

REVIEW

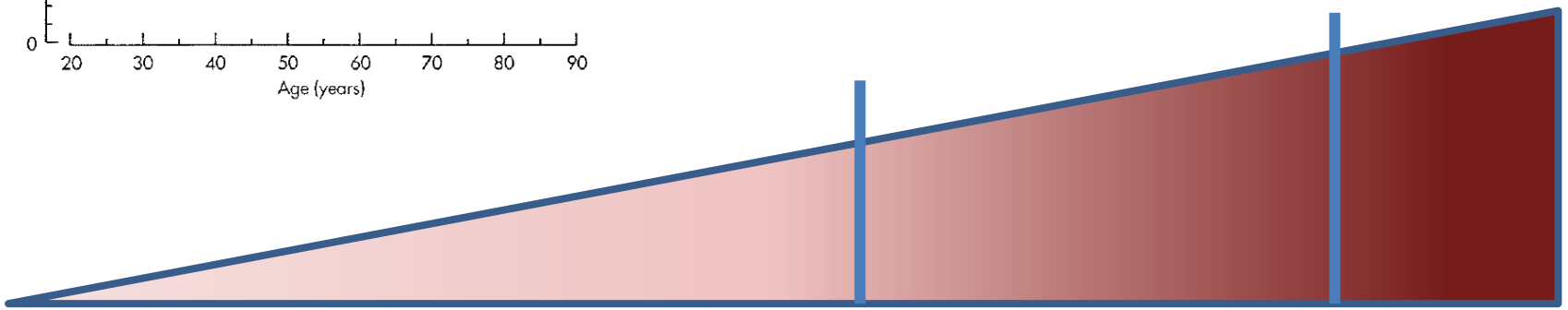


A Challenge:

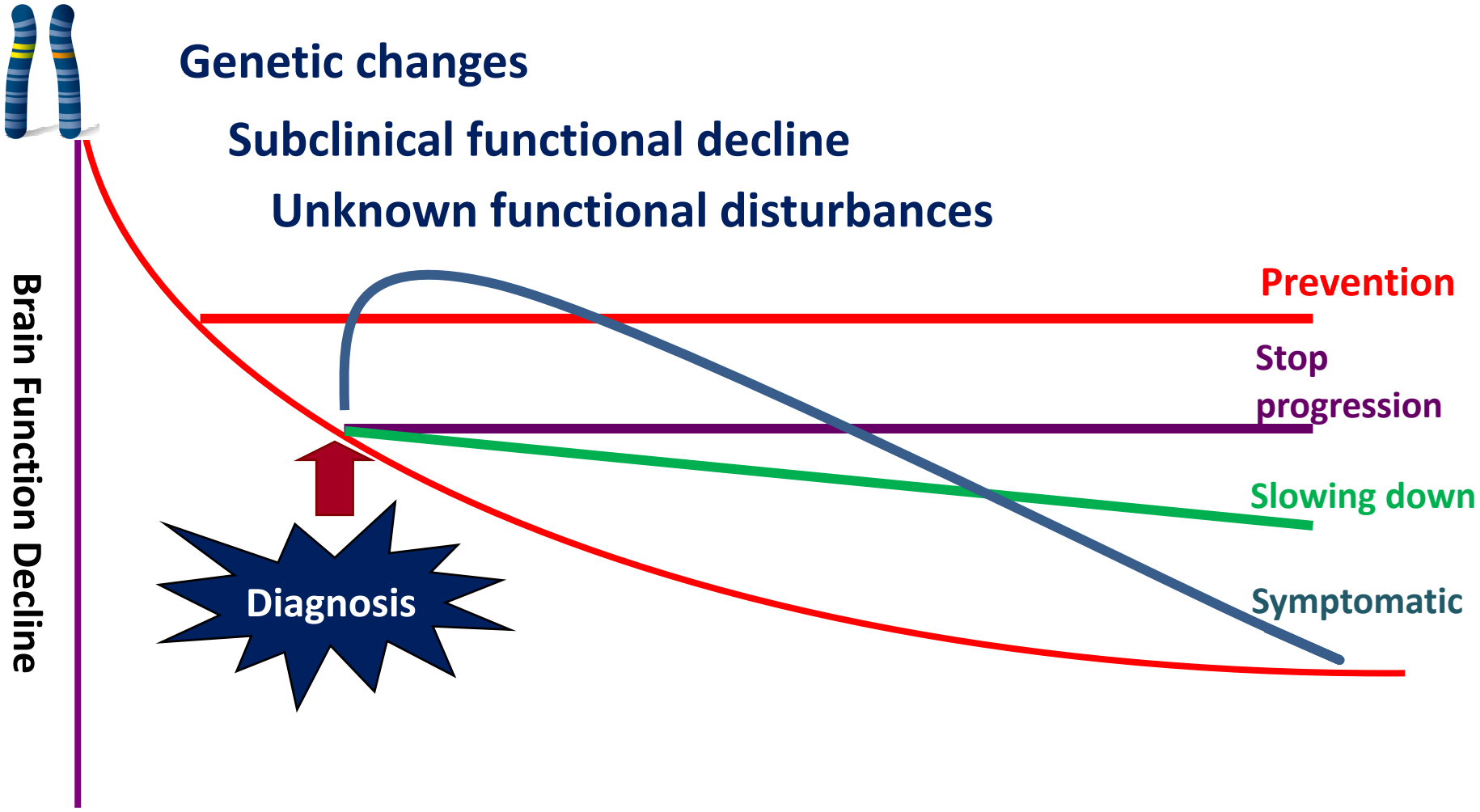
When does a person convert from asymptomatic subject at risk to prodromal stage to a patient?



The role of motor-cognitive reserve



The goal - Prevention



Novel therapeutic approaches for stopping neurodegeneration

- Vaccines
- Gene silencing\ RNA silencing
- Manipulating enzymatic activity
- Stem cell therapy – trophic factors

ARTICLE

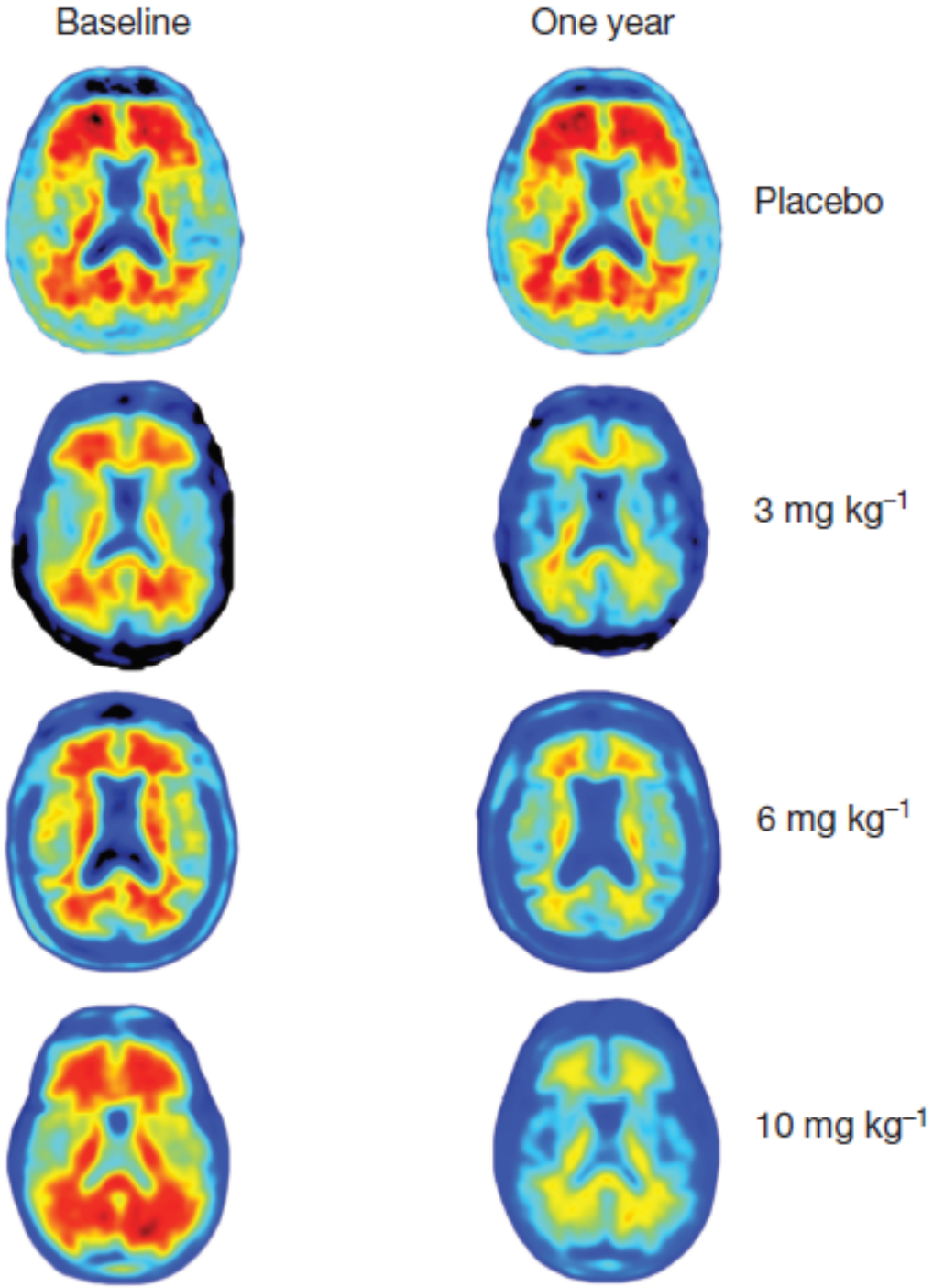
Nature 2016

doi:10.1038/nature19323

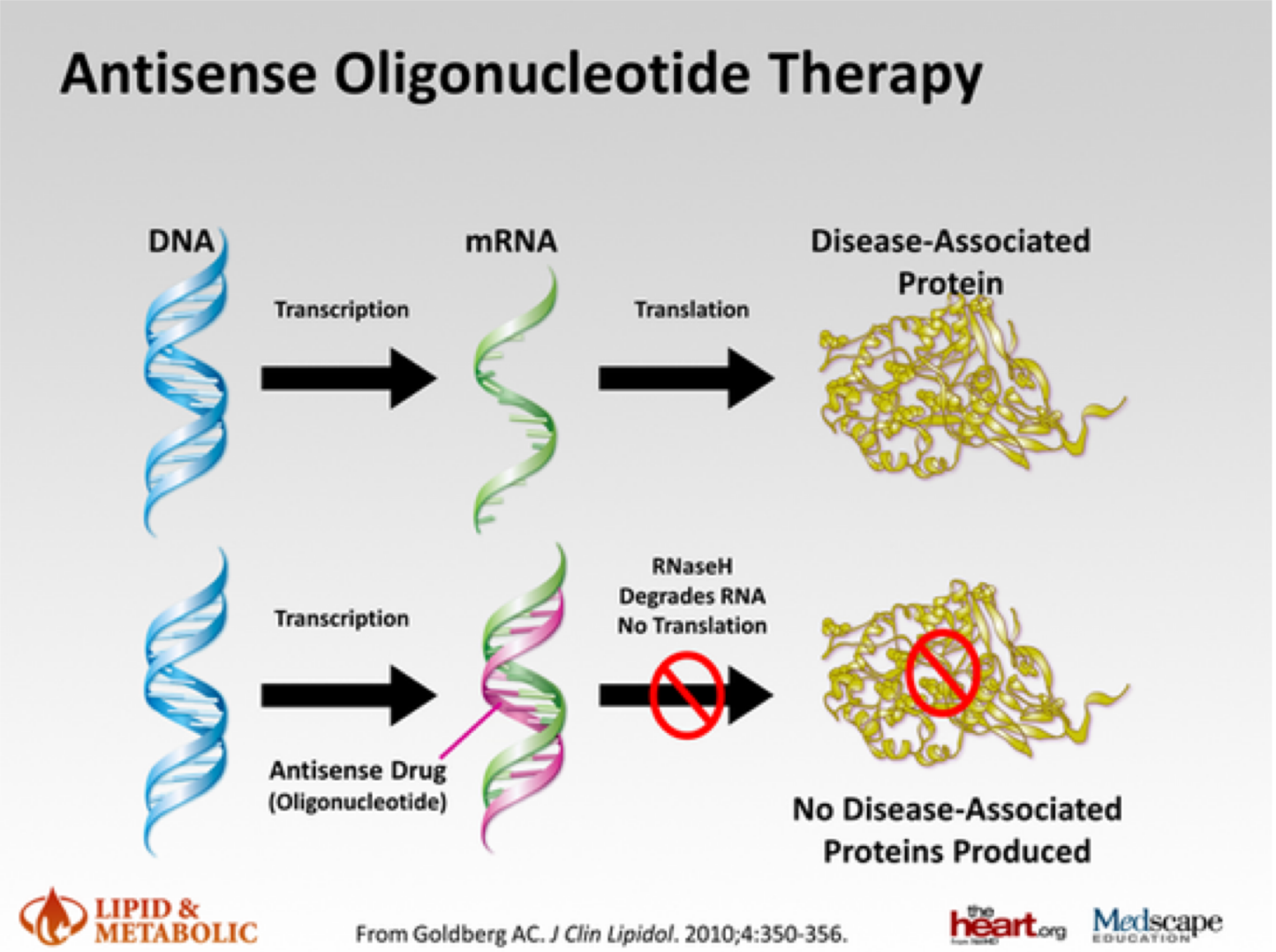
The antibody aducanumab reduces Aβ plaques in Alzheimer's disease

Jeff Sevigny[1]*, Ping Chiao[1]*, Thierry Bussière[1]*, Paul H. Weinreb[1]*, Leslie Williams[1], Marcel Maier[2], Robert Dunstan[1], Stephen Salloway[3], Tianle Chen[1], Yan Ling[1], John O'Gorman[1], Fang Qian[1], Mahin Arastu[1], Mingwei Li[1], Sowmya Chollate[1], Melanie S. Brennan[1], Omar Quintero-Monzon[1], Robert H. Scannevin[1], H. Moore Arnold[1], Thomas Engber[1], Kenneth Rhodes[1], James Ferrero[1], Yaming Hang[1], Alvydas Mikulskis[1], Jan Grimm[2], Christoph Hock[2,4], Roger M. Nitsch[2,4]§ & Alfred Sandrock[1]§

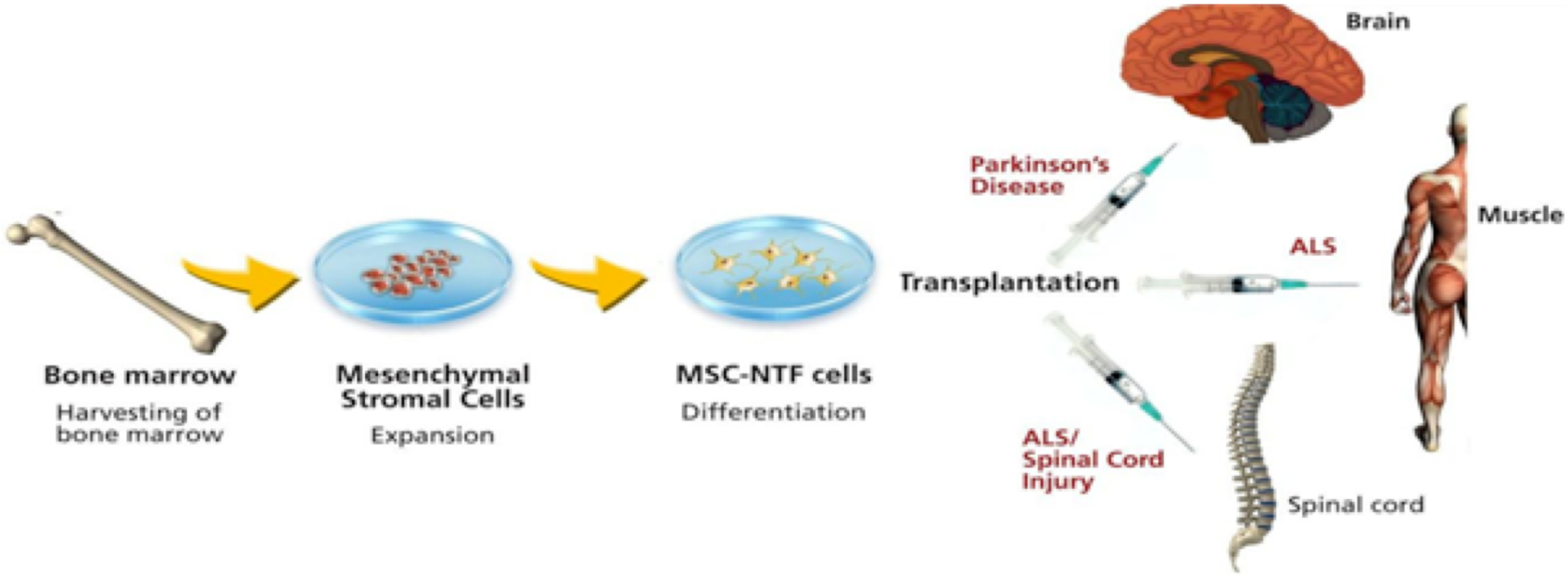
Alzheimer's disease (AD) is characterized by deposition of amyloid-β (Aβ) plaques and neurofibrillary tangles in the brain, accompanied by synaptic dysfunction and neurodegeneration. Antibody-based immunotherapy against Aβ to trigger its clearance or mitigate its neurotoxicity has so far been unsuccessful. Here we report the generation of aducanumab, a human monoclonal antibody that selectively targets aggregated Aβ. In a transgenic mouse model of AD, aducanumab is shown to enter the brain, bind parenchymal Aβ, and reduce soluble and insoluble Aβ in a dose-dependent manner. In patients with prodromal or mild AD, one year of monthly intravenous infusions of aducanumab reduces brain Aβ in a dose- and time-dependent manner. This is accompanied by a slowing of clinical decline measured by Clinical Dementia Rating—Sum of Boxes and Mini Mental State Examination scores. The main safety and tolerability findings are amyloid-related imaging abnormalities. These results justify further development of aducanumab for the treatment of AD. Should the slowing of clinical decline be confirmed in ongoing phase 3 clinical trials, it would provide compelling support for the amyloid hypothesis.


Baseline
One year
Placebo
3 mg kg−1
6 mg kg−1
10 mg kg−1

Gene silencing – prevention of toxic protein production



Stem cells therapy in ALS



Patients and relatives are waiting…

Thank you!