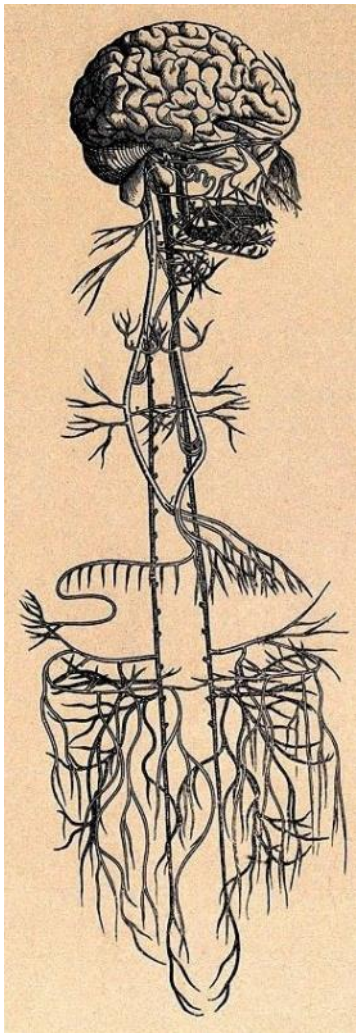
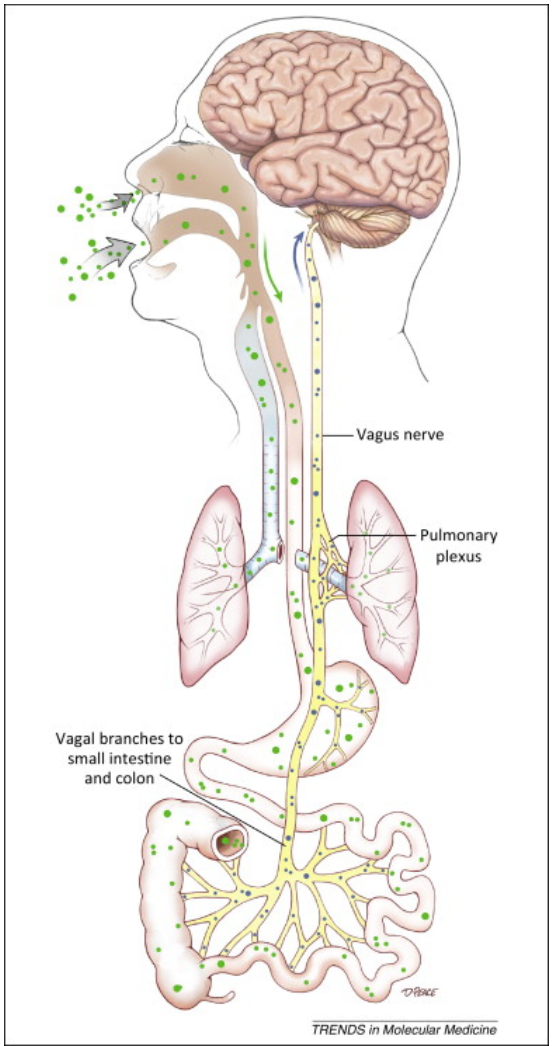
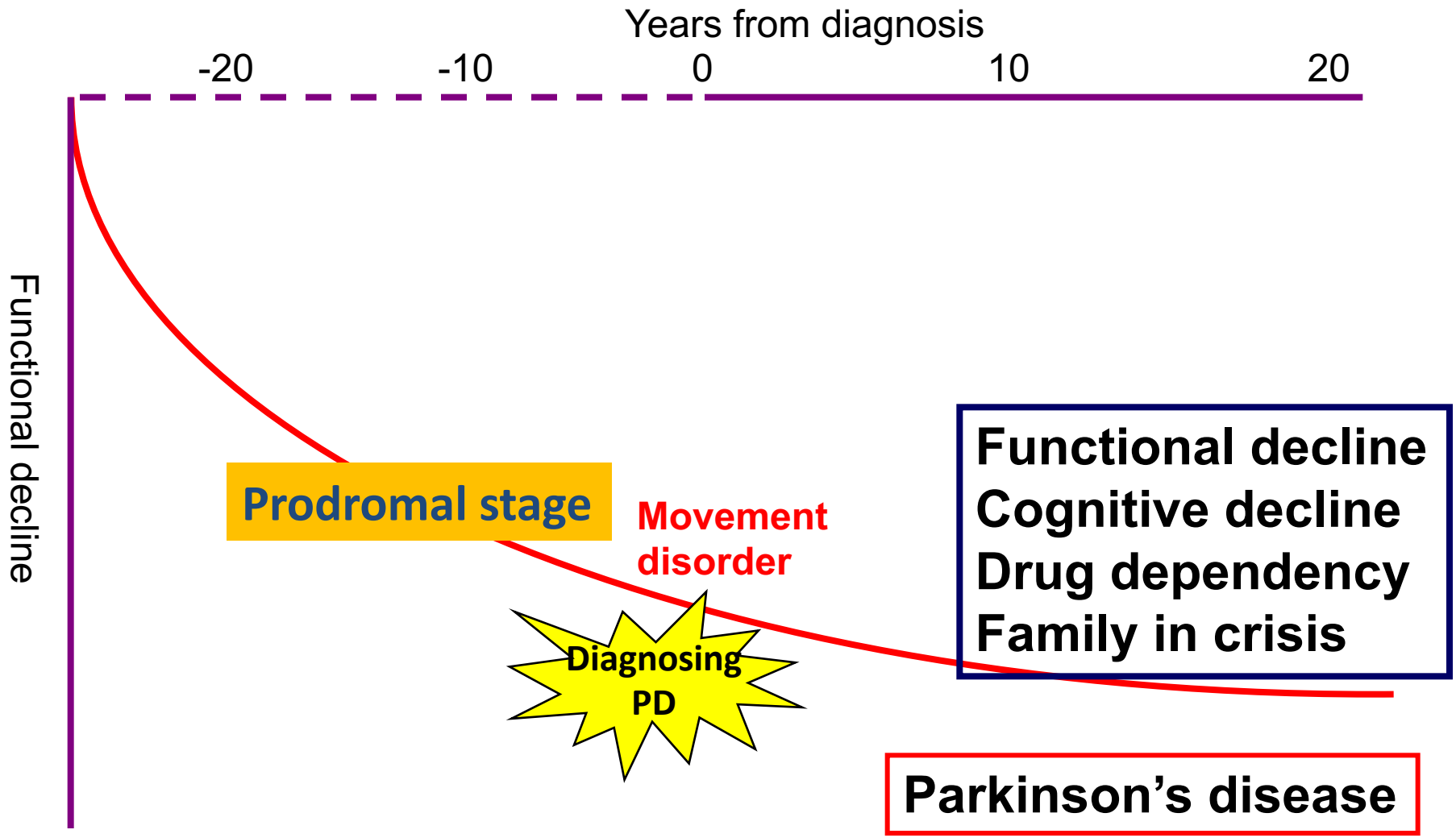
Parkinson's disease: Synuclein aggregates travel from the gut to the brain through the vagus nerve



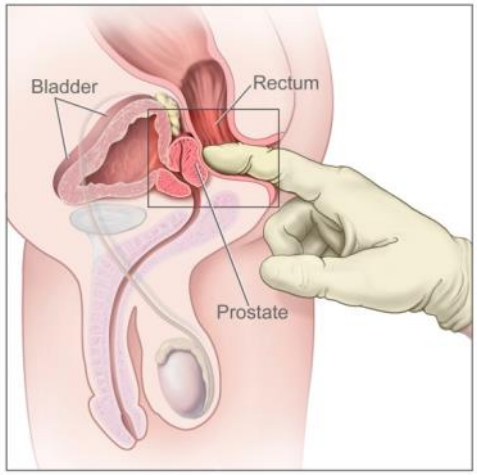


The natural history of PD



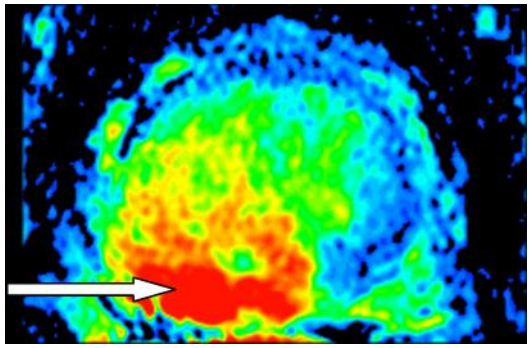
We are diagnosing PD very late in the course of the disease

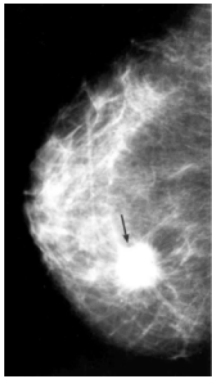
Diagnosing carcinoma based on clinical signs and symptoms



biological makers for early stages of the disease

Ga68-PSMA


MRI of the prostate


Mammography

Parkinson's disease has a long "incubation period" with non-specific signs

Years from diagnosis

-20 -10 0

Deterioration in brain function

Behavior during dream state

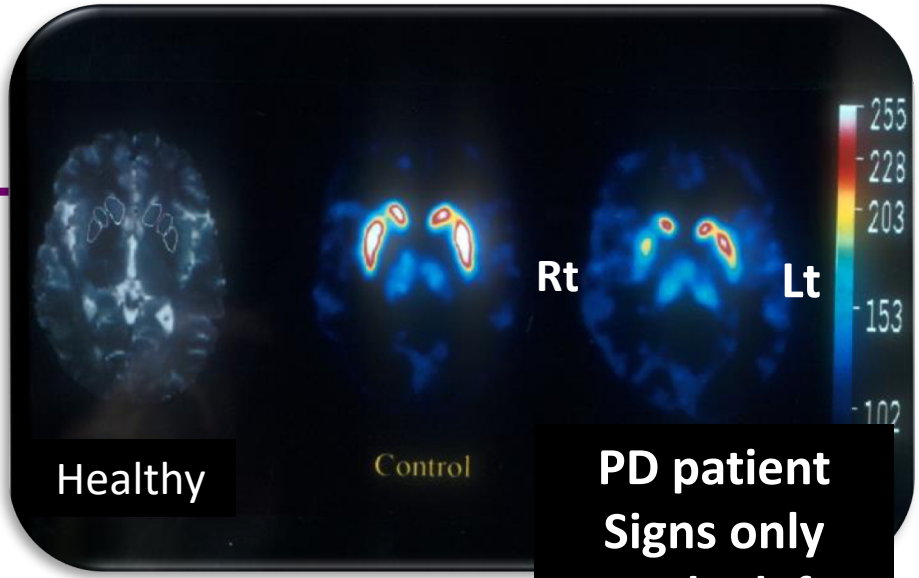
constipation

Decrease in olfactory perception

impotence

Depression

pain



PD patient Signs only on the left

Parkinson's disease

Movement Disorders

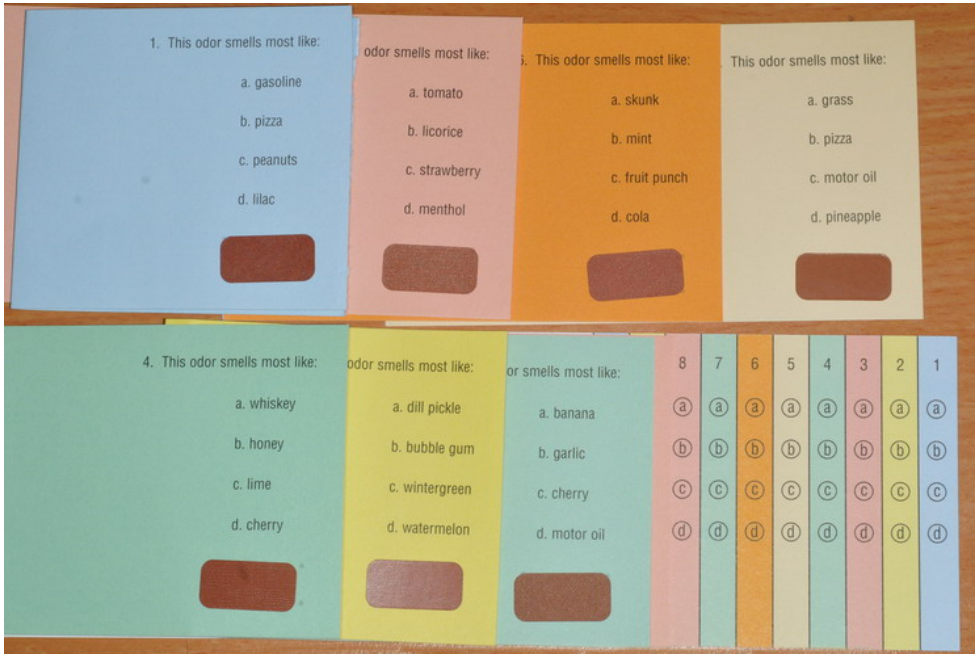
PD Diagnosis

Biological Markers

“Living the dream”

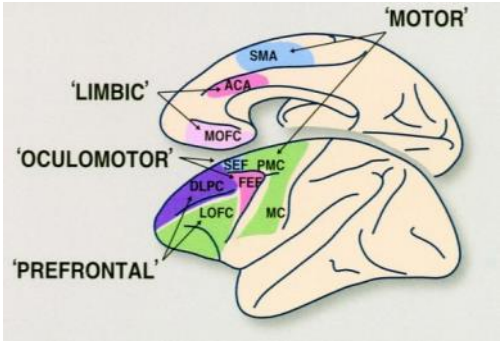
Smell Test

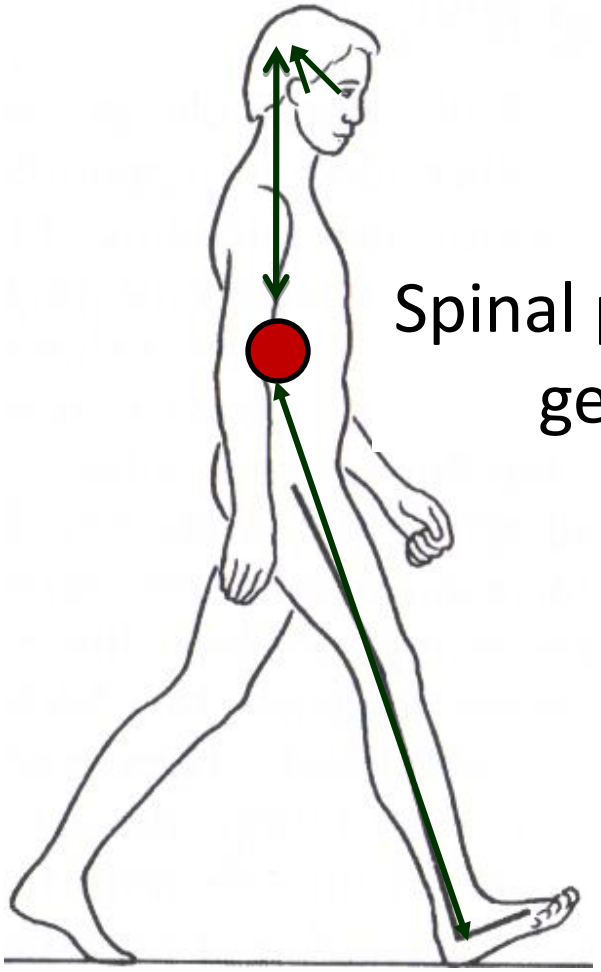
UPSIT- University of Pittsburg Smell Identification Test



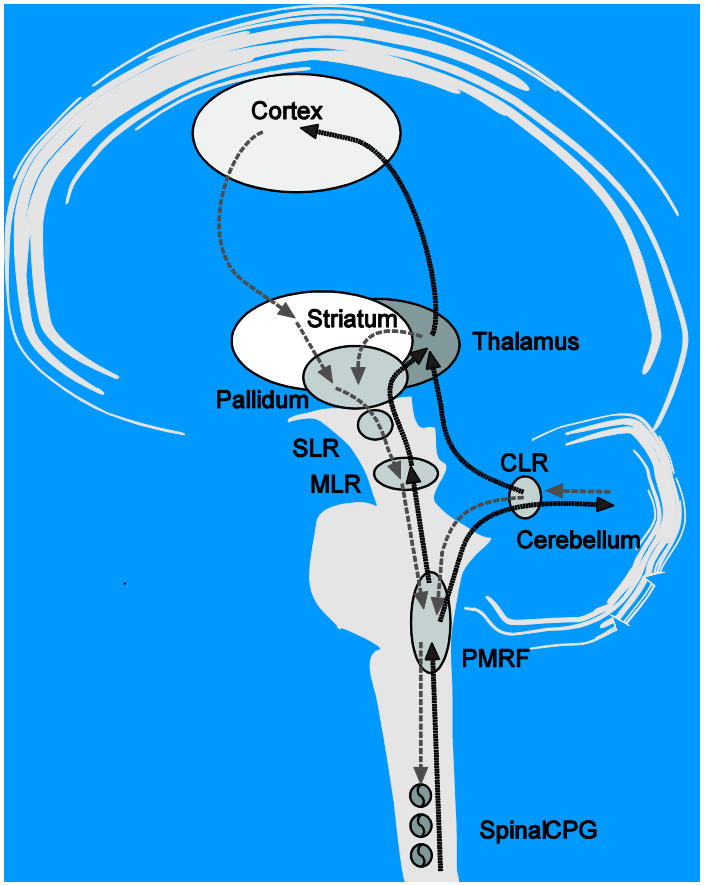
Walking as a marker for central and peripheral nervous system function

Supraspinal control of walking





Spinal pattern generator



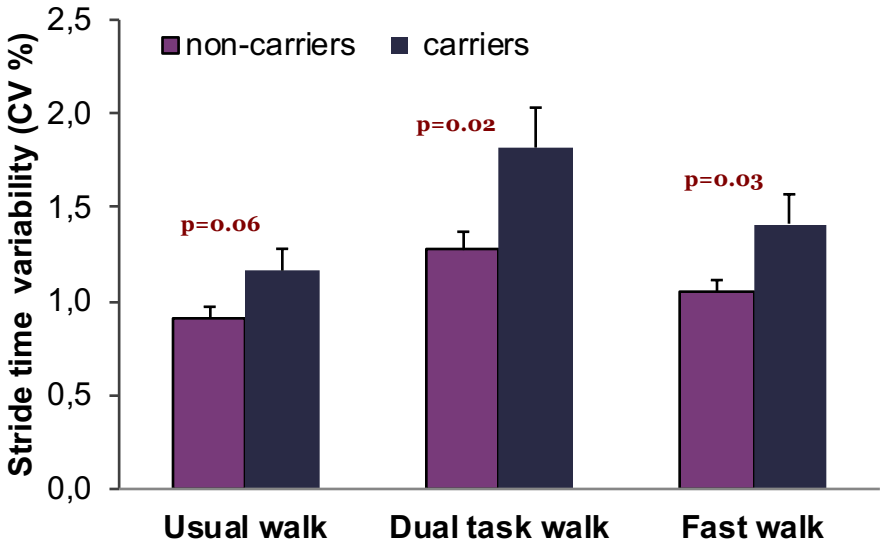
Sensory feedback

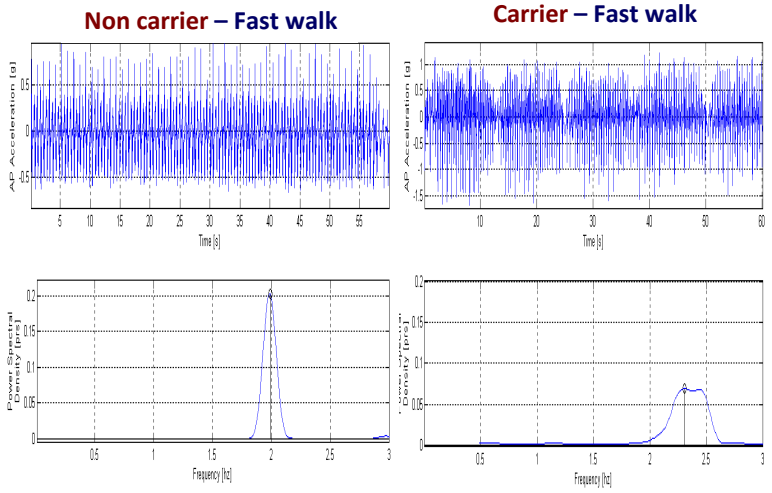
ANNALS of Neurology
THE OFFICIAL JOURNAL OF THE AMERICAN NEUROLOGICAL ASSOCIATION AND THE CHILD NEUROLOGY SOCIETY

January 2011

Gait Alterations in Healthy Carriers of the LRRK2 G2019S Mutation

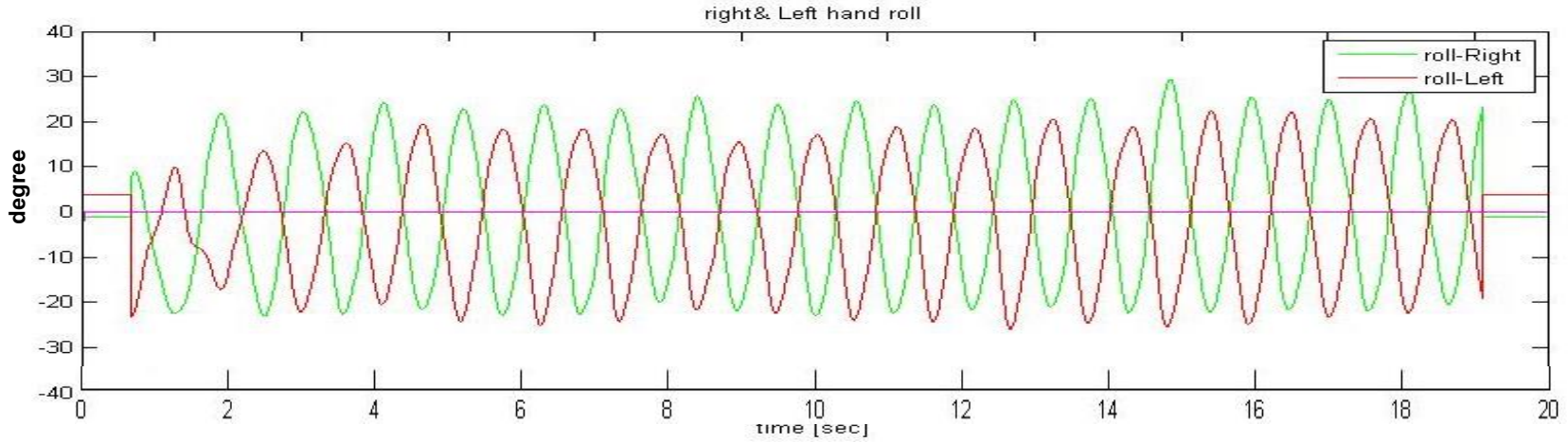
Mirelman A, Gurevich T, Giladi N, Bar-Shira A, Orr Urtreger A, Hausdorff J



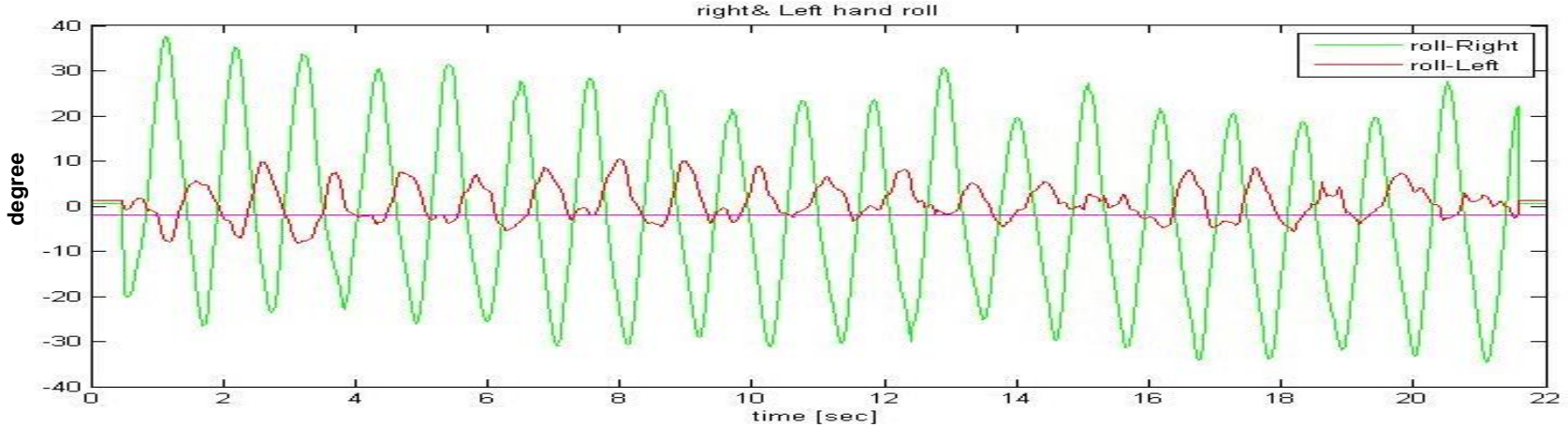


Arm swing- PD compared to Healthy

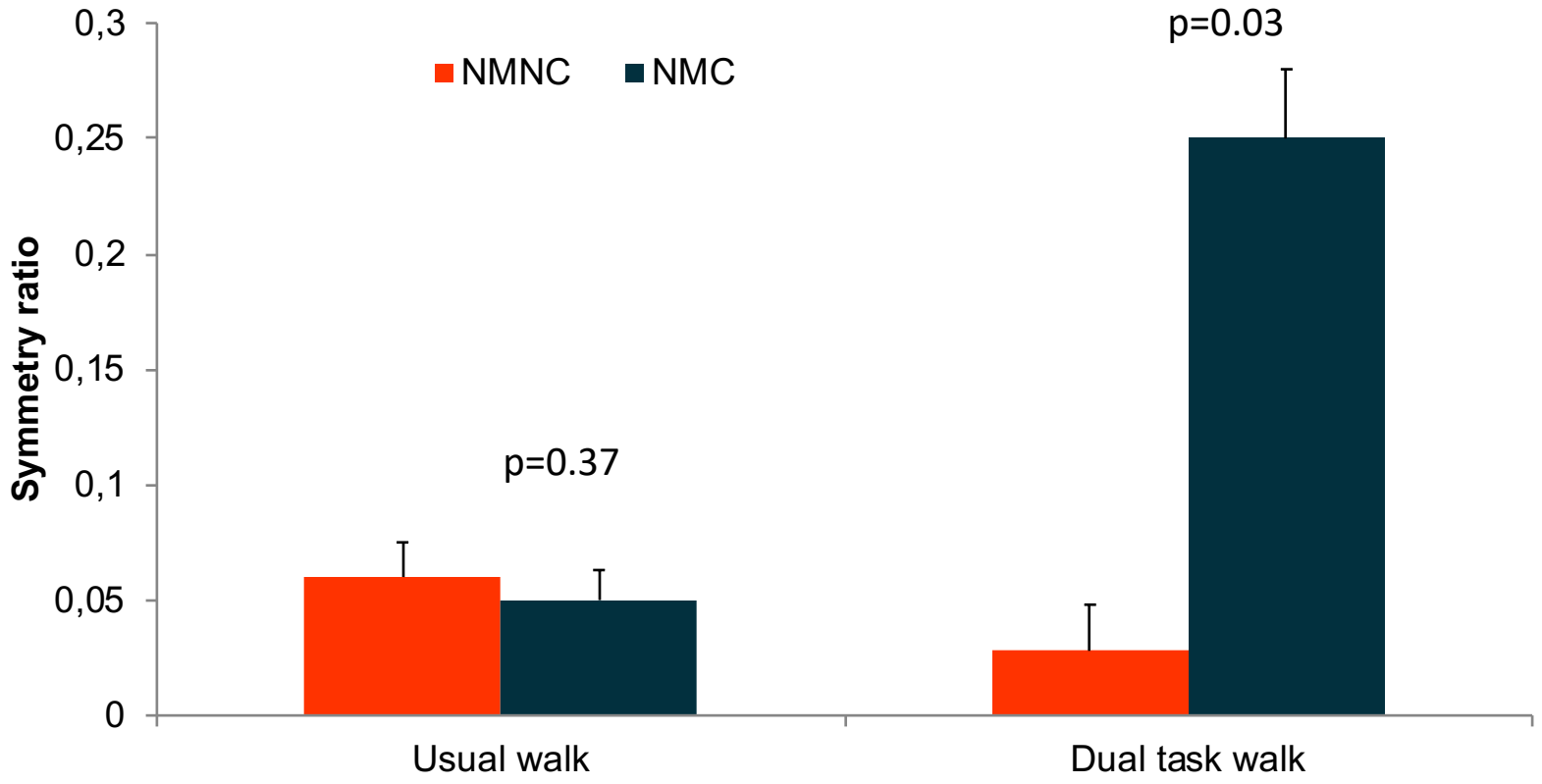
First Degree (age=52)



Patient with PD (age =53)



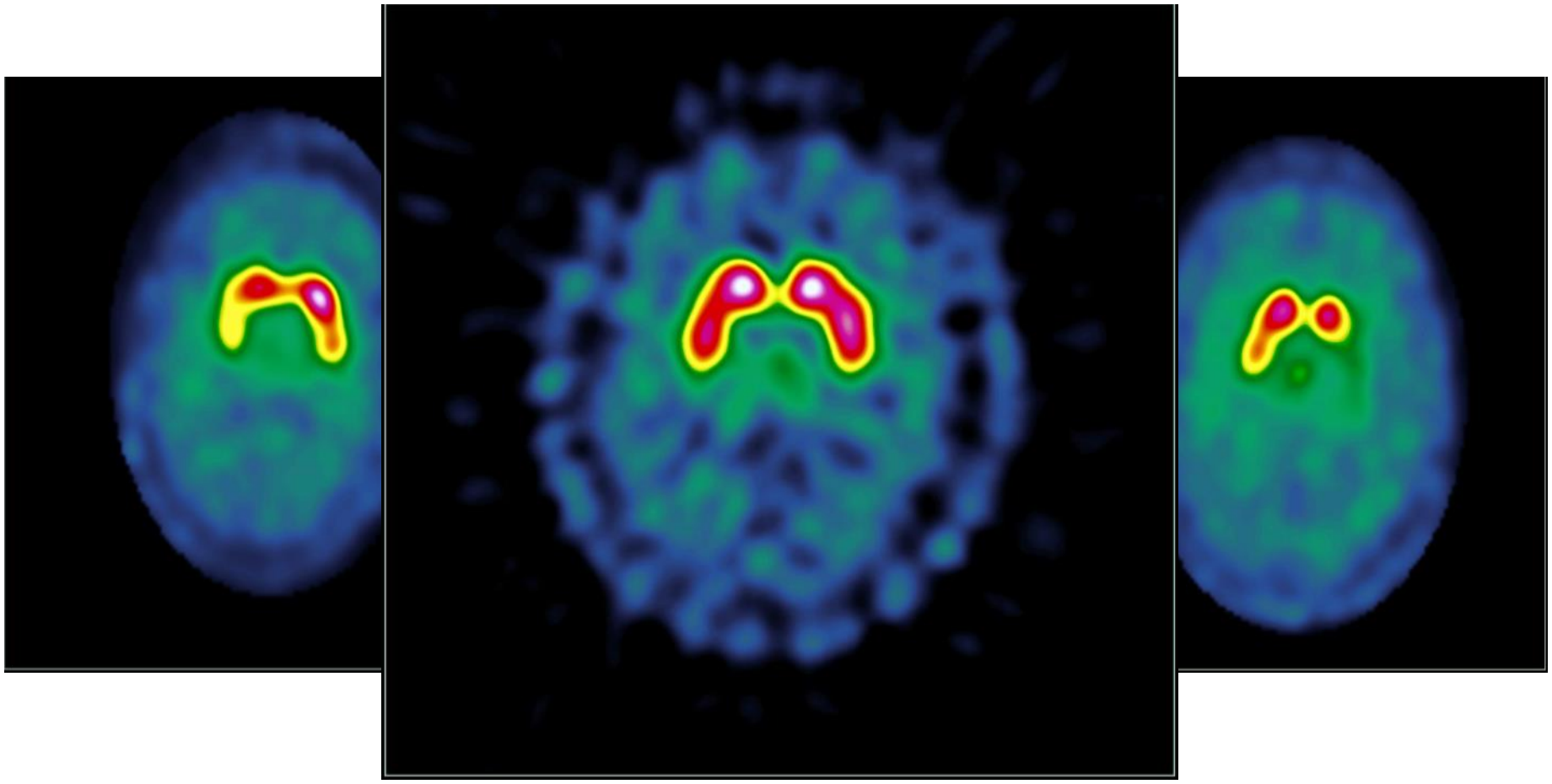
Arm swing asymmetry during walking as a marker for population at risk



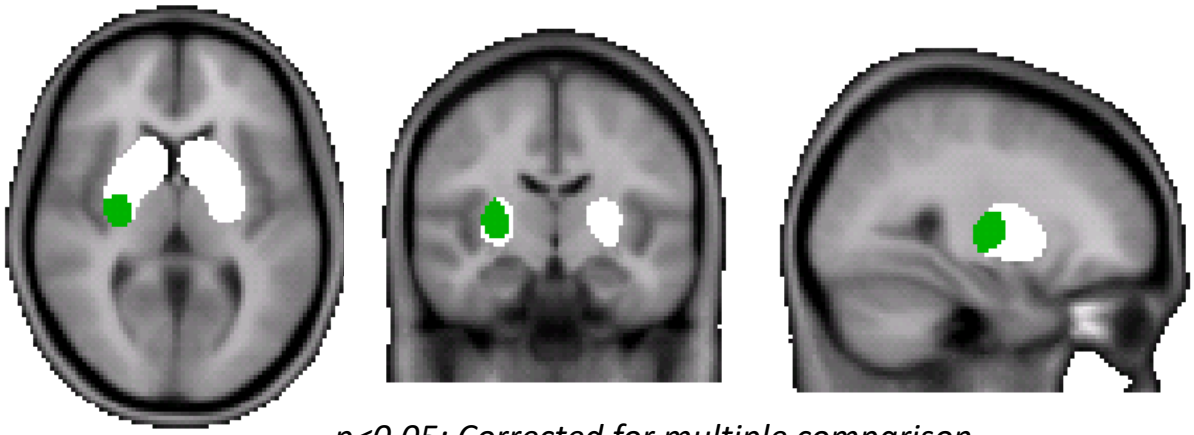
Non carriers = 61, carriers = 62

Mirelman et al, submitted

DaT Scans

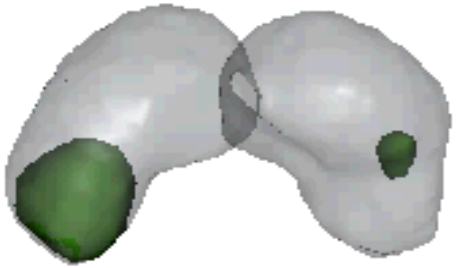


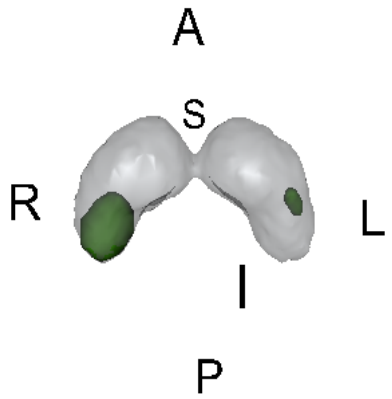
Quantification of DaT uptake using VBM analysis



p<0.05; Corrected for multiple comparison

LC = First-degree relatives, carriers
NC = First-degree relatives, non carriers

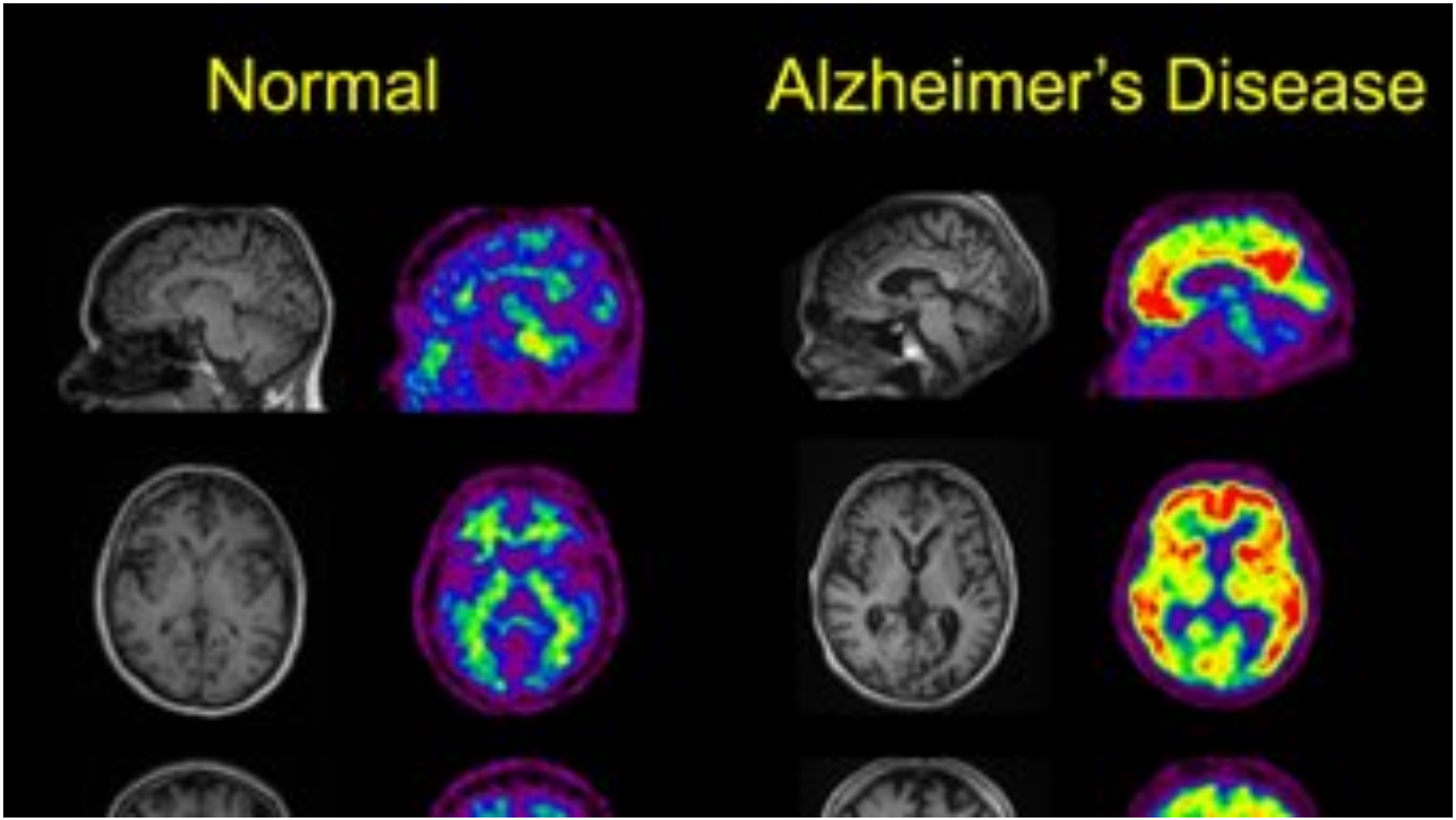




Non Carriers > carriers

Artzi et al. in preparation

Imaging of the brain



PET tracers under evaluation for HD

PET tracers being evaluated or under consideration

Target	PET Ligand	Localization	Preclinical Evaluation Status	Clinical Evaluation Status
D1 receptor	11C-NNC112	Basal ganglia/cortex	**Studies completed (uPET)**	*Currently no planned studies*
D2 receptor	11C-raclopride	Striatum/cortex	**Studies completed (uPET)**	**Studies completed and ongoing**
PDE10A enzyme	18F-MNI659/ [11C]IMA107	Basal ganglia	**Studies completed (uPET)**	**Studies ongoing and planned**
CB1 receptor	18F-FMPEP-d2/ [11C]MePPEP	Basal ganglia/cortex	**Studies ongoing (ARG)**	**Studies completed** and planned
5HT2a receptor	11C-MDL100097	Basal ganglia/cortex	**Studies completed (uPET)**	Studies planned
H3 receptor	11C-GSK189254/ [11C]MK-8278	Basal ganglia/cortex	**Studies ongoing (ARG)**	Studies planned
Glucose uptake	18F-FDG	Cortex and subcortical	**Limited profiling (uPET)**	**Studies completed** and planned
GABA-A receptor	11C-Flumazenil	Basal ganglia/cortex	Studies planned (ARG)	*Currently no planned studies*
mGluR5 receptor	18F-FPEB	Basal ganglia/cortex	Studies planned (uPET)	*Currently no planned studies*
M1 receptor	11C-GSK1034702	Basal ganglia/cortex	*Currently no planned studies*	*Currently no planned studies*
5HT1a receptor	11C-WAY100635	Cortex	*Currently no planned studies*	*Currently no planned studies*
NK1 receptor	18F-FE-SPA-RQ	Basal ganglia/cortex	*Currently no planned studies*	*Currently no planned studies*

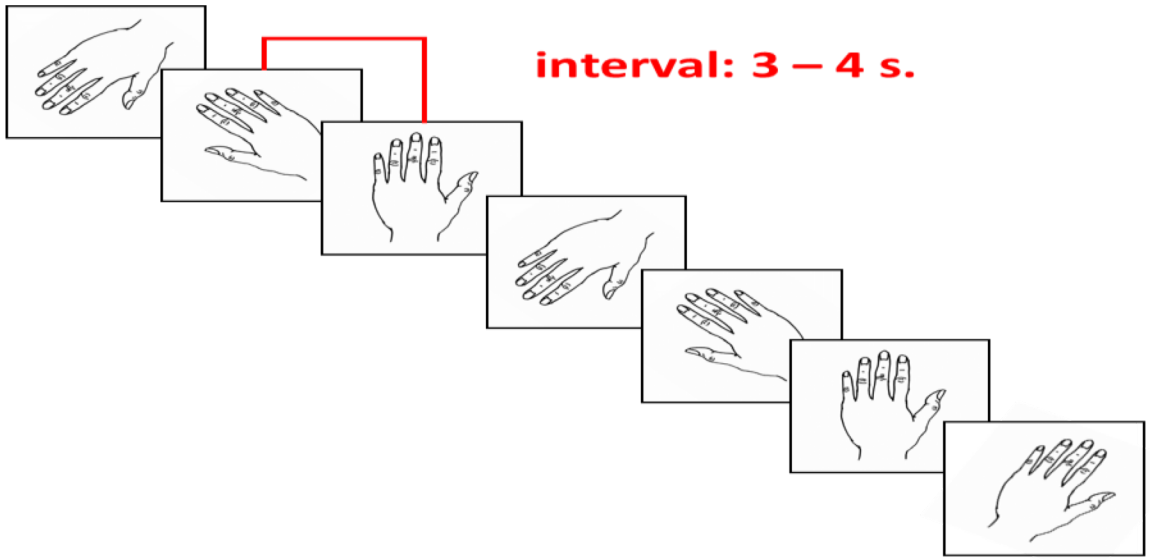
Measuring functional reserve, compensatory mechanisms

doi:10.1093/brain/aws288 Brain 2012: 135; 3687–3698 | 3687

BRAIN
A JOURNAL OF NEUROLOGY

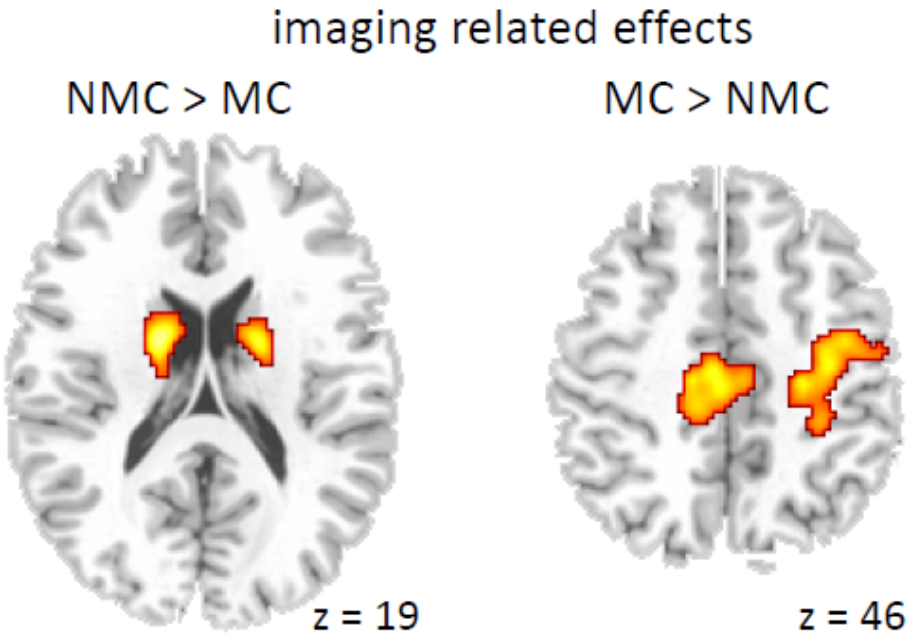
Cerebral pathological and compensatory mechanisms in the premotor phase of leucine-rich repeat kinase 2 parkinsonism

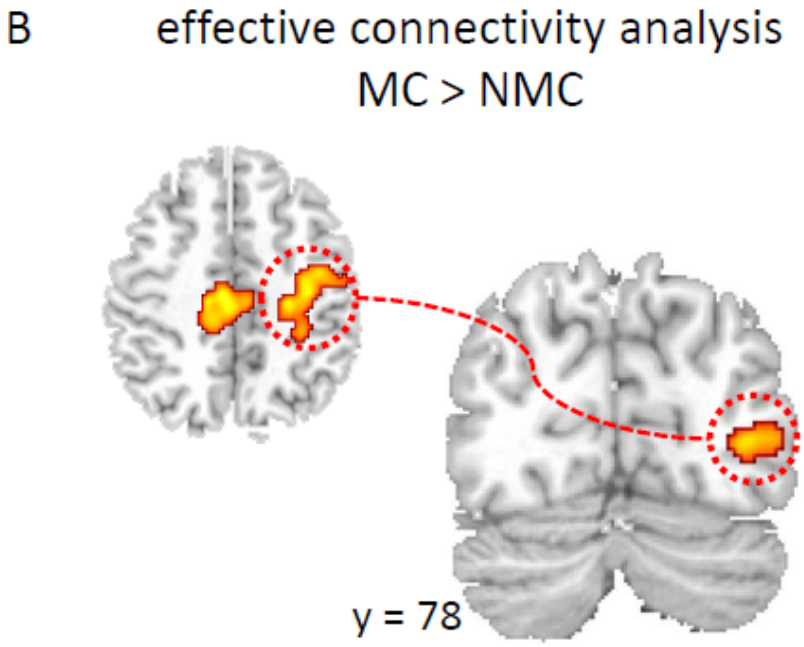
Bart F. L. van Nuenen,[1,2] Rick C. Helmich,[1,2] Murielle Ferraye,[2] Avner Thaler,[3] Talma Hendler,[3] Avi Orr-Urtreger,[4] Anat Mirelman,[3] Susan Bressman,[5] Karen S. Marder,[6] Nir Giladi,[3] Bart P. C. van de Warrenburg,[1] Bastiaan R. Bloem[1] and Ivan Toni[2] on behalf of the *LRRK2* Ashkenazi Jewish Consortium[1]*



Foot response (left / right big toe)

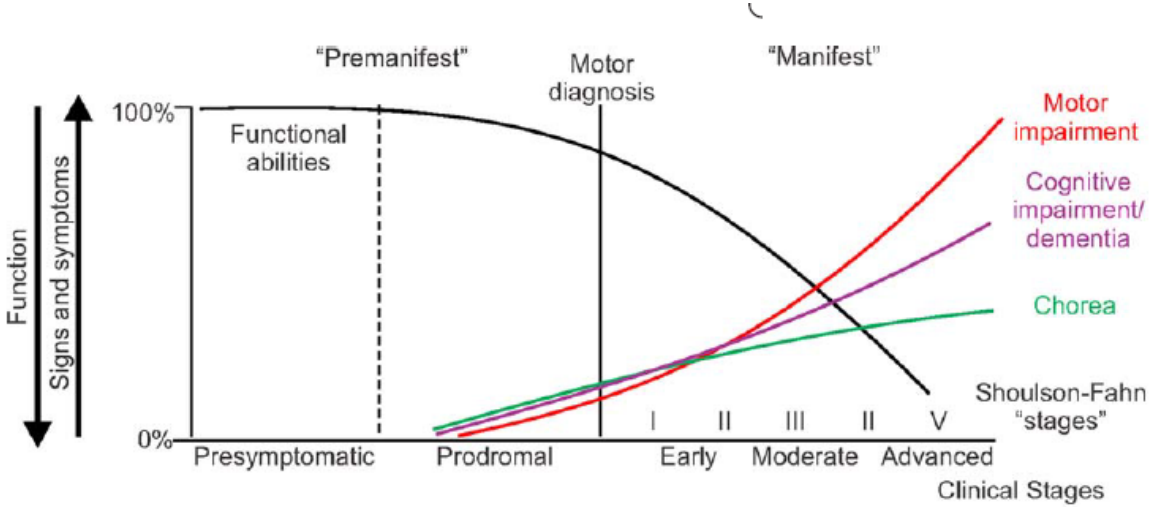
G2019S mutation carriers use the brain differently to solve motor imagery problems



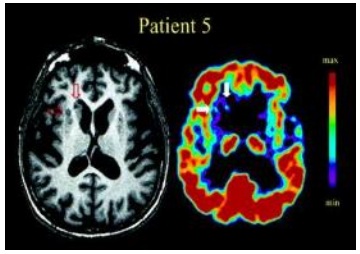


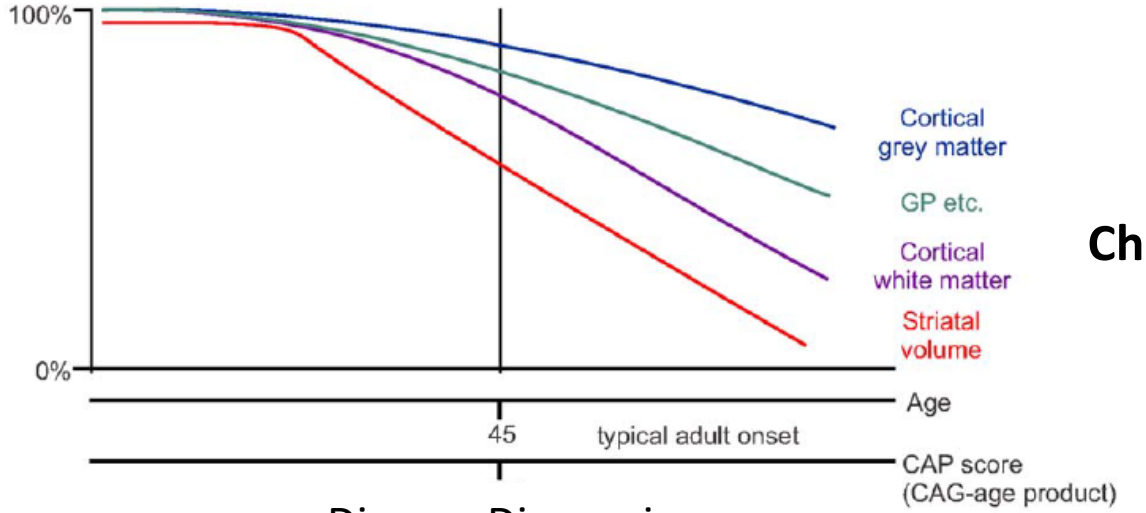
Bart F.L. van Nuenen et al, Brain, 2012

Huntington's disease progression



Clinical signs

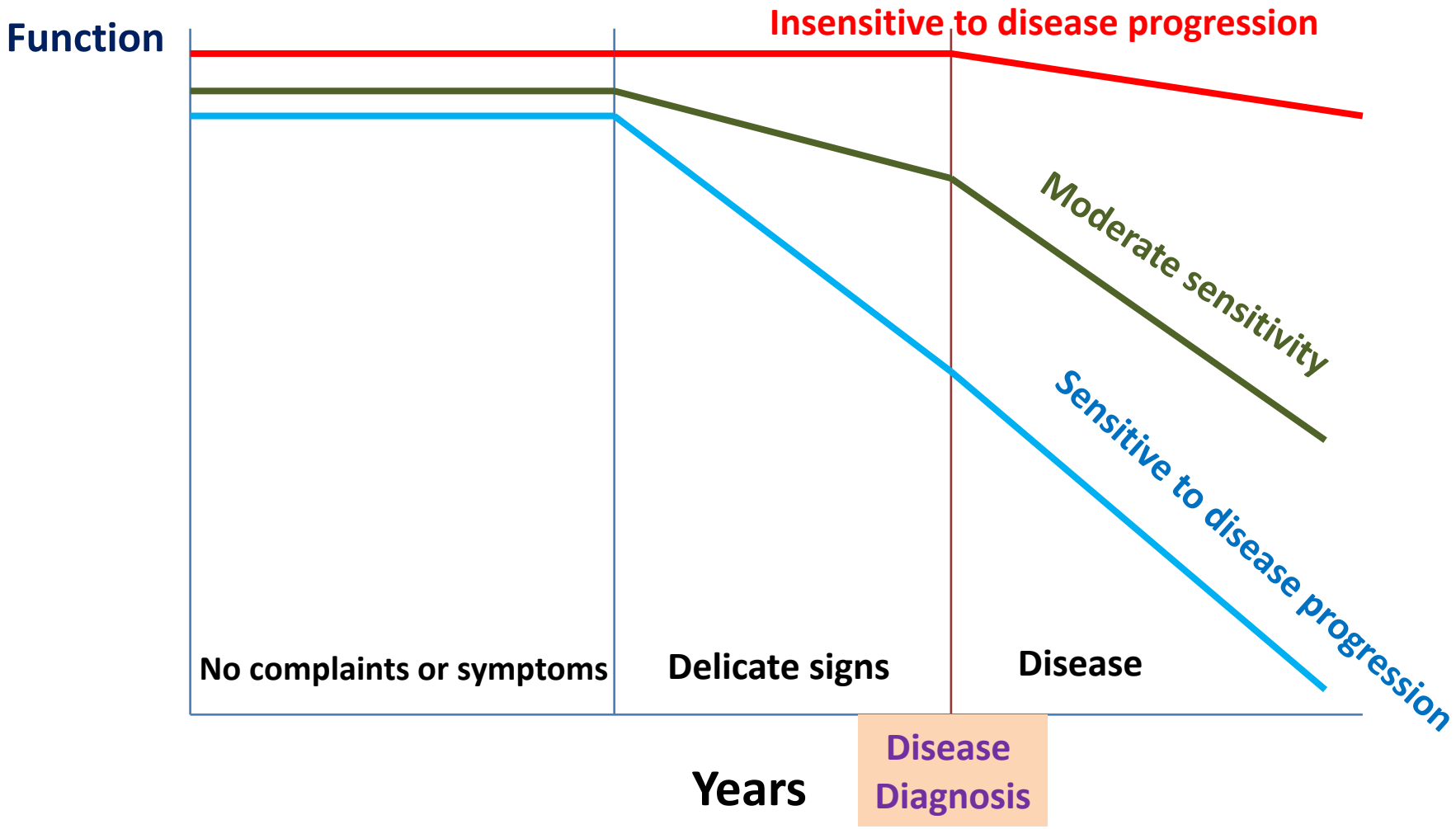




Changes in MRI

Disease Diagnosis

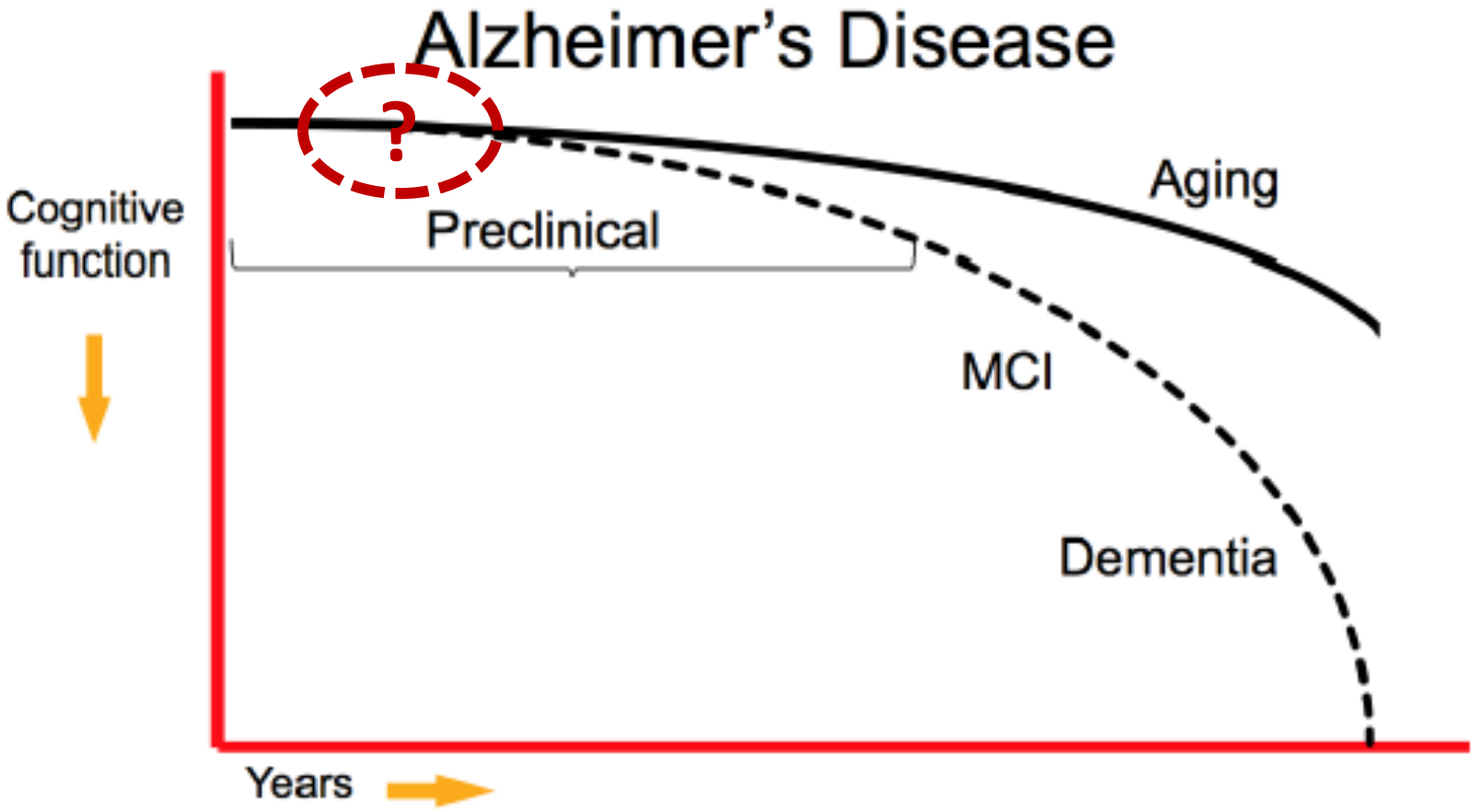
Biological markers of disease state



What initiates the neurodegenerative process?

Understanding the cause can lead to preventive therapy

Alzheimer's disease is NOT just accelerated aging



Where can we intervene and prevent neurodegenerative diseases?

GENETICS

Age

Exposure to pesticides

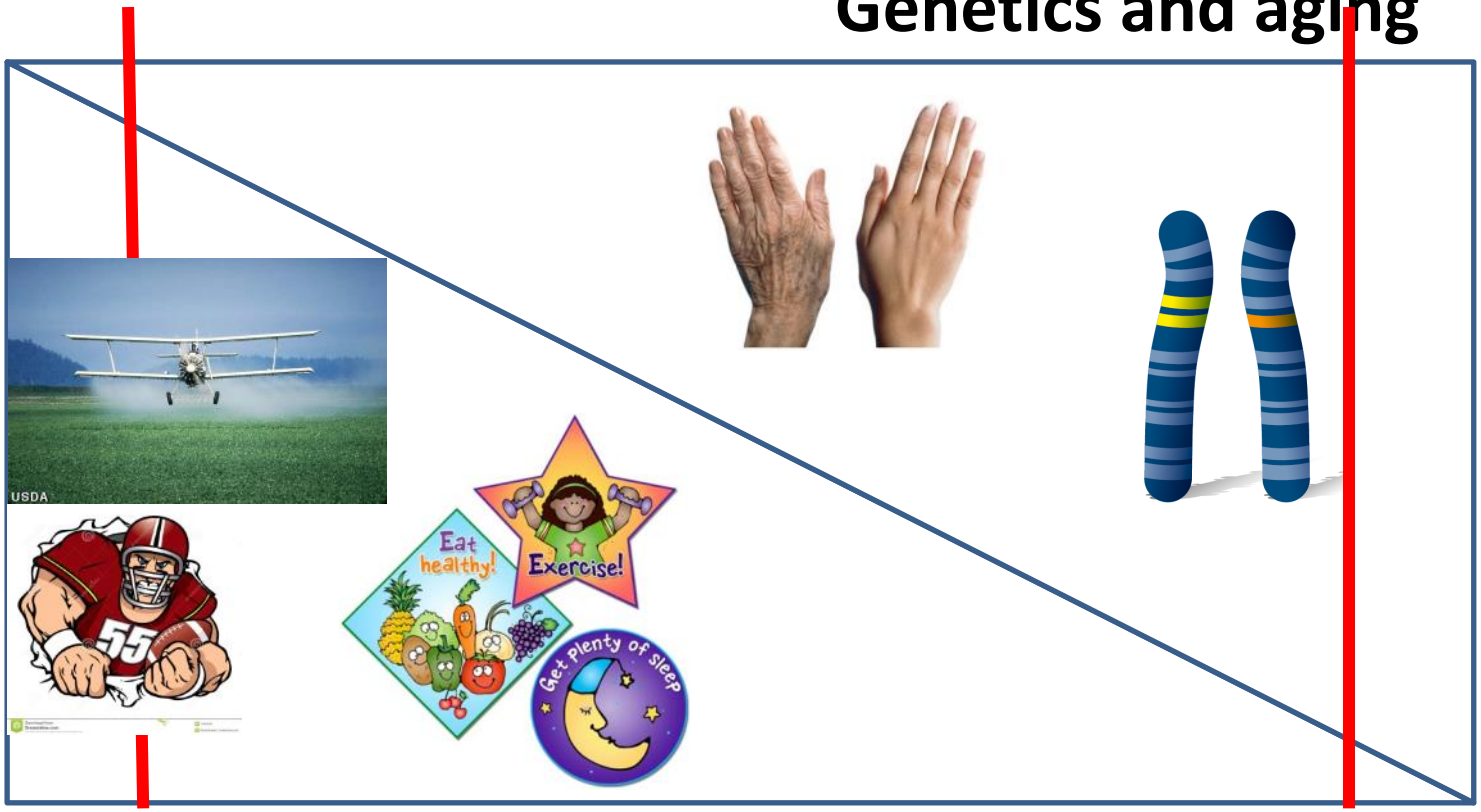
Head injuries

Environment

Lifestyle

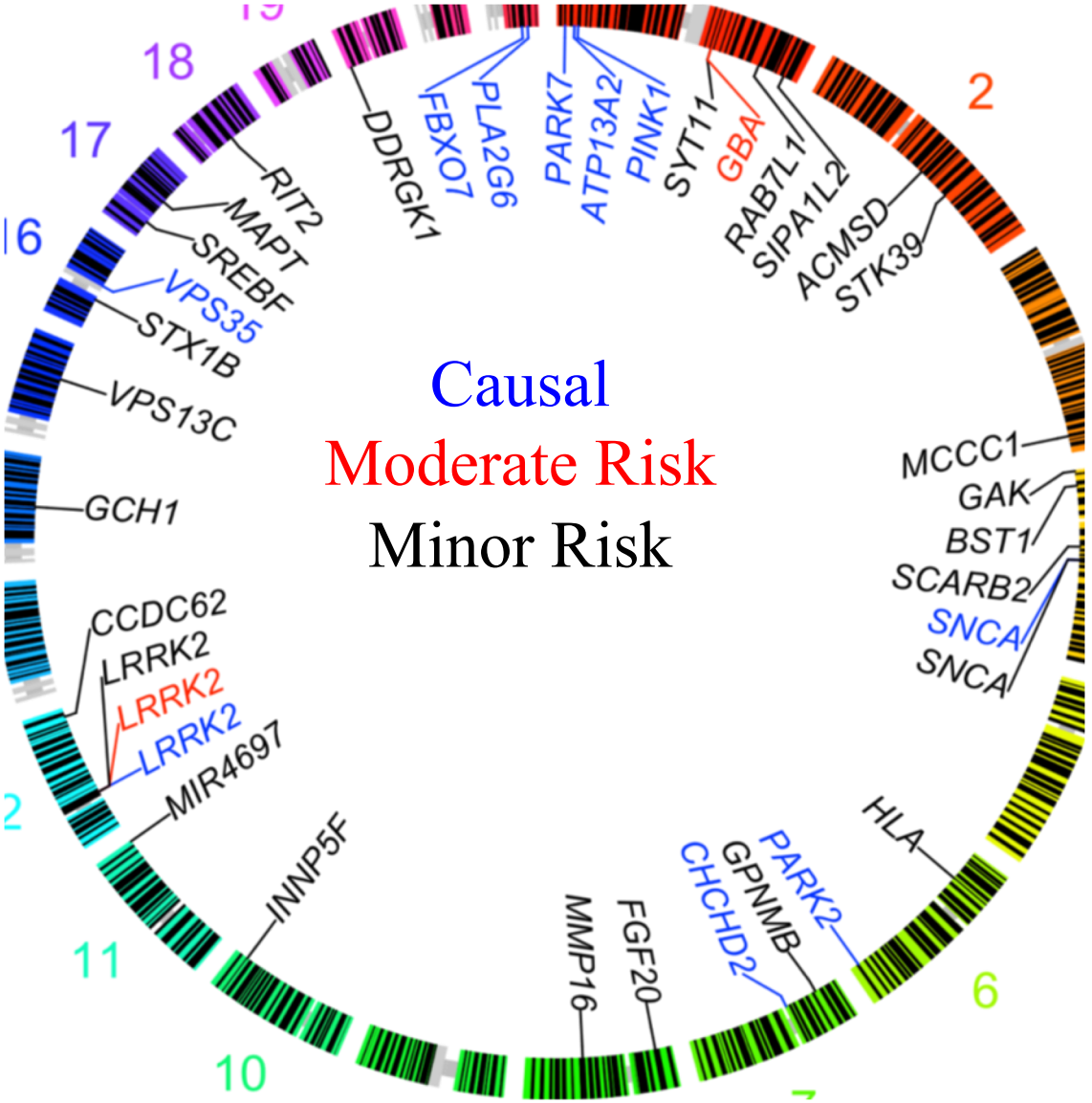
Factors contributing to the development of neurodegenerative diseases

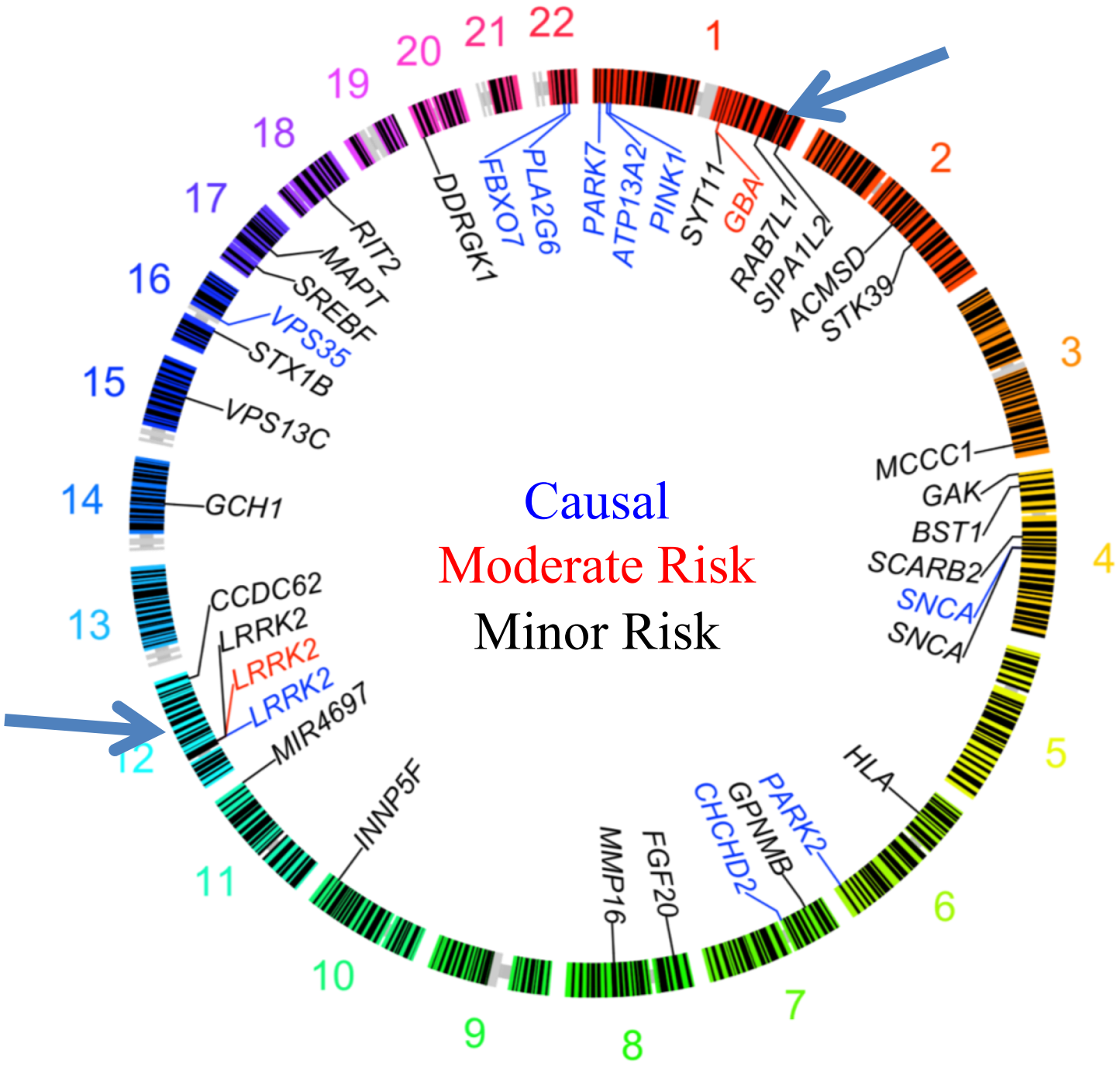
Genetics and aging



Environment and lifestyle

Genetic contribution to Parkinson's disease




Causal
Moderate Risk
Minor Risk
1
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4
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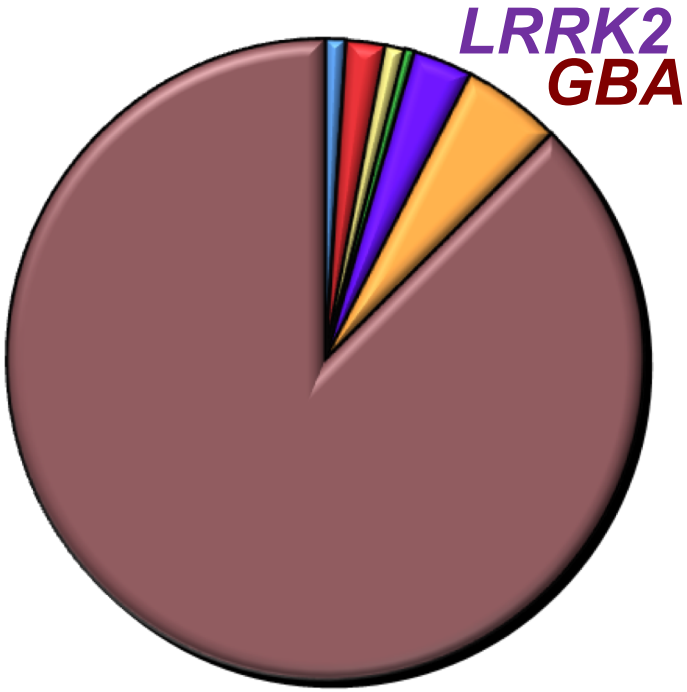
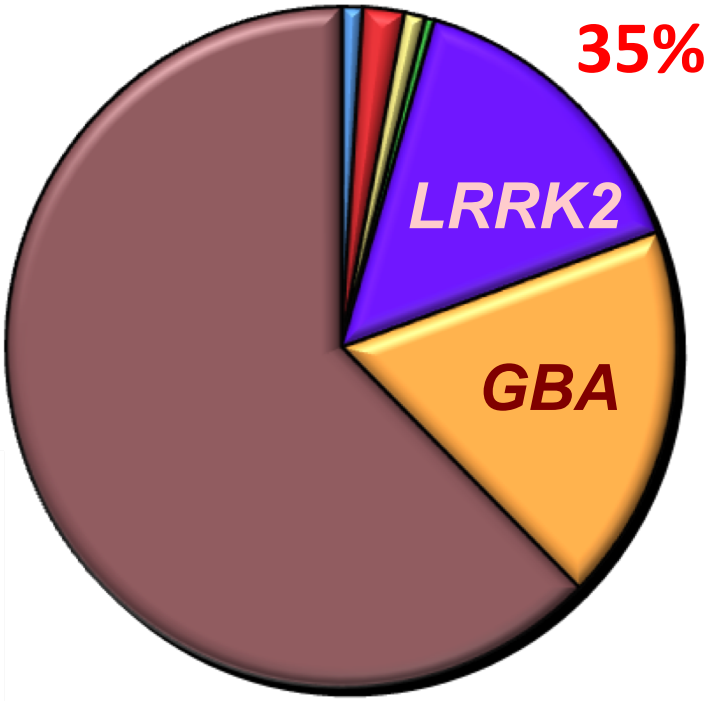
17
18
19
20
21
22
PARK7
ATP13A2
PINK1
SYT11
GBA
RAB7L1
SIPA1L2
ACMSD
STK39
MCCC1
GAK
BST1
SCARB2
SNCA
SNCA
HLA
PARK2
GPNMB
CHCHD2
MMP16
FGF20
INPP5F
MIR4697
LRRK2
LRRK2
LRRK2
CCDC62
GCH1
VPS13C
STX1B
VPS35
SREBF
MAPT
RIT2
DDRGK1
FBXO7
PLA2G6

Genetics of Parkinson's disease
The Ashkenazi Jews story

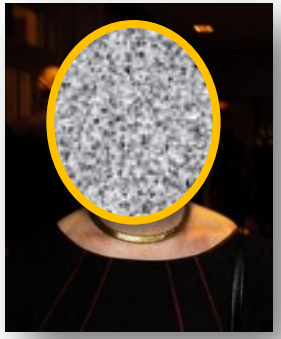
Worldwide



In Ashkenazi Jews



The story of the family members:
The Brin Family's story



Genetic research in Tel-Aviv Parkinson's disease

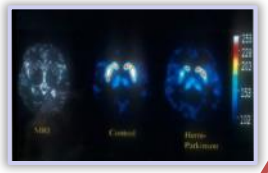
1520 patients with Parkinson's disease

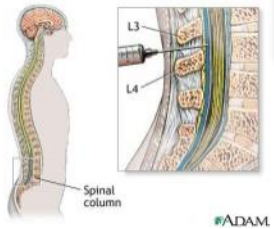
1100 Ashkenazim

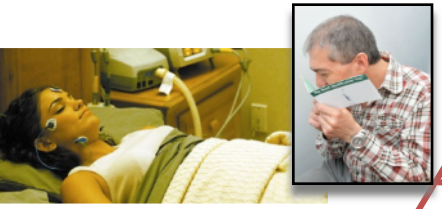
450 healthy first degree relatives of patients with Parkinson who carry a known mutation in the *GBA* or *LRRK2* genes

The pyramid of Parkinson's disease

From population at risk to diagnosed disease







Parkinson's

Subclinical disease

Biological disorders

Non-motor symptoms

Population at risk

Every year a number of healthy individuals become sick

The goal: Following a population at risk for developing PD and learning about the mode of progression and conversion

The method: Examine patients and healthy relatives who carry the PD related mutations, in order to identify early biological markers for the development of the disease.

Recommendations for minimizing the chance of getting Parkinson's disease and dementia for population at risk

- Exercise
- Intellectual stimulation
- Social interaction
- Balance the risk factors for Atherosclerosis
- Sleep well
- Drink coffee
- Avoid becoming overweight
- Avoid depression
- Medications?? Anti-inflammatory ?
- Mediterranean Diet

There's a lot that can be done!!!

Intensive physical activity as medicine: A healthy way to activate neutrotrophic factors that promote regeneration of brain cells

Prescription

28/2/2016

Name: Israel Israeli
Age: 45

Medication: Aerobic physical activity

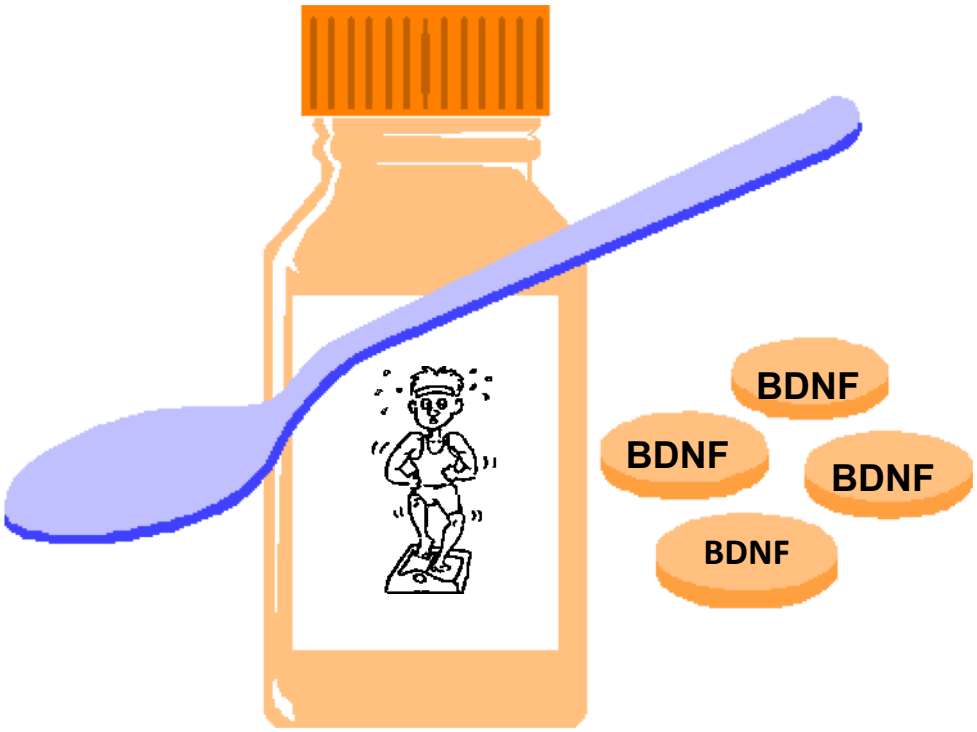
Dosage: 5 times a week – 60 minutes (200-300 minutes a week)

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

Nir Giladi, MD

Nir Giladi

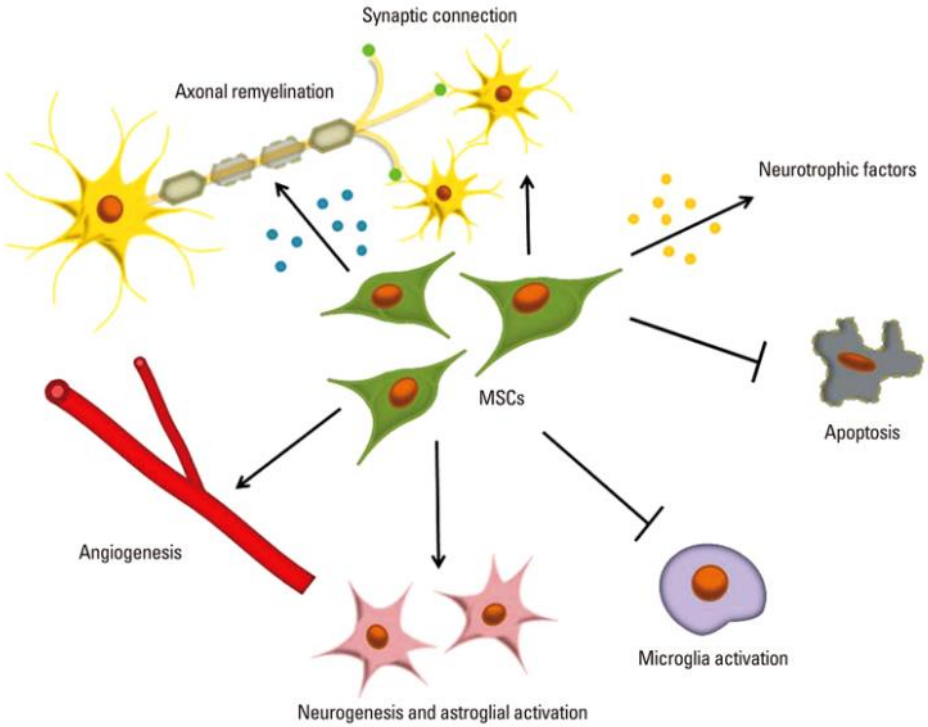
License No. 12345

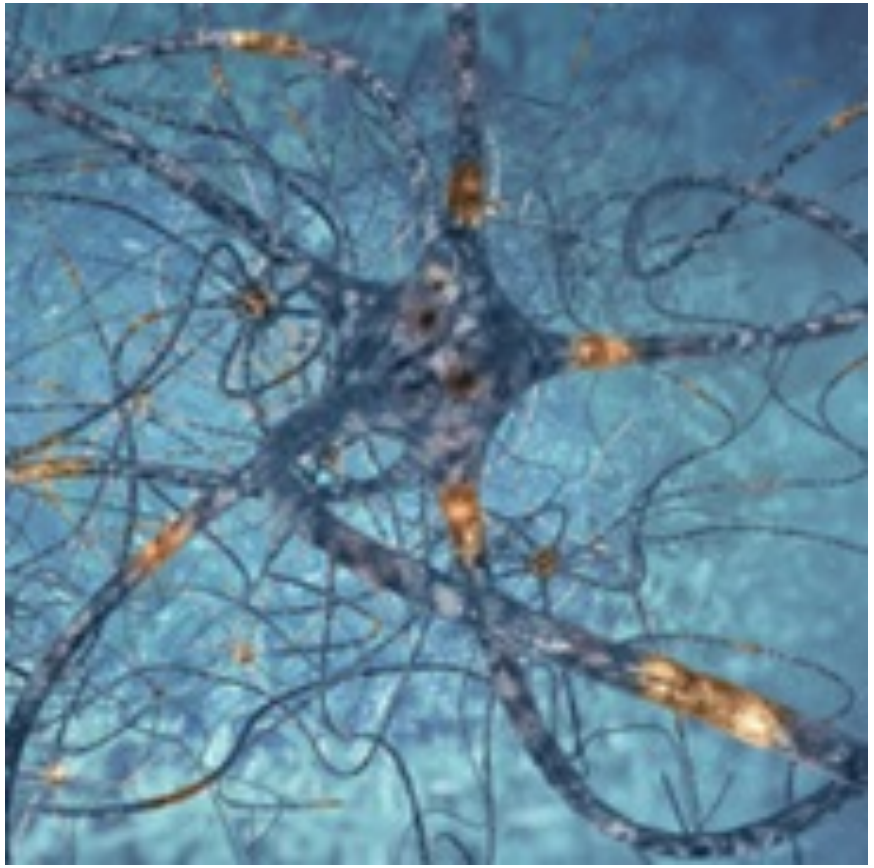


Tel-Aviv Sourasky Medical Center

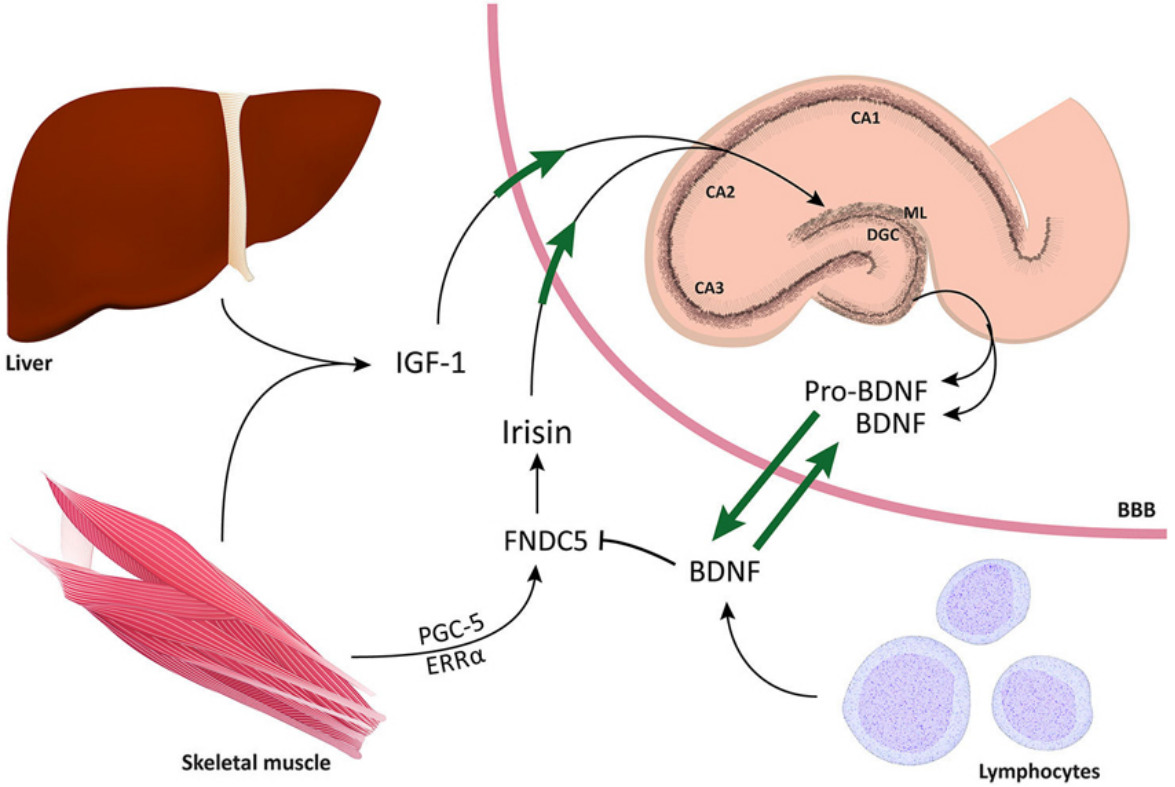
An entire brain is developed in 9 months the product of trophic factors

Trophic factors that promote neuronal, synaptic and vascular regeneration





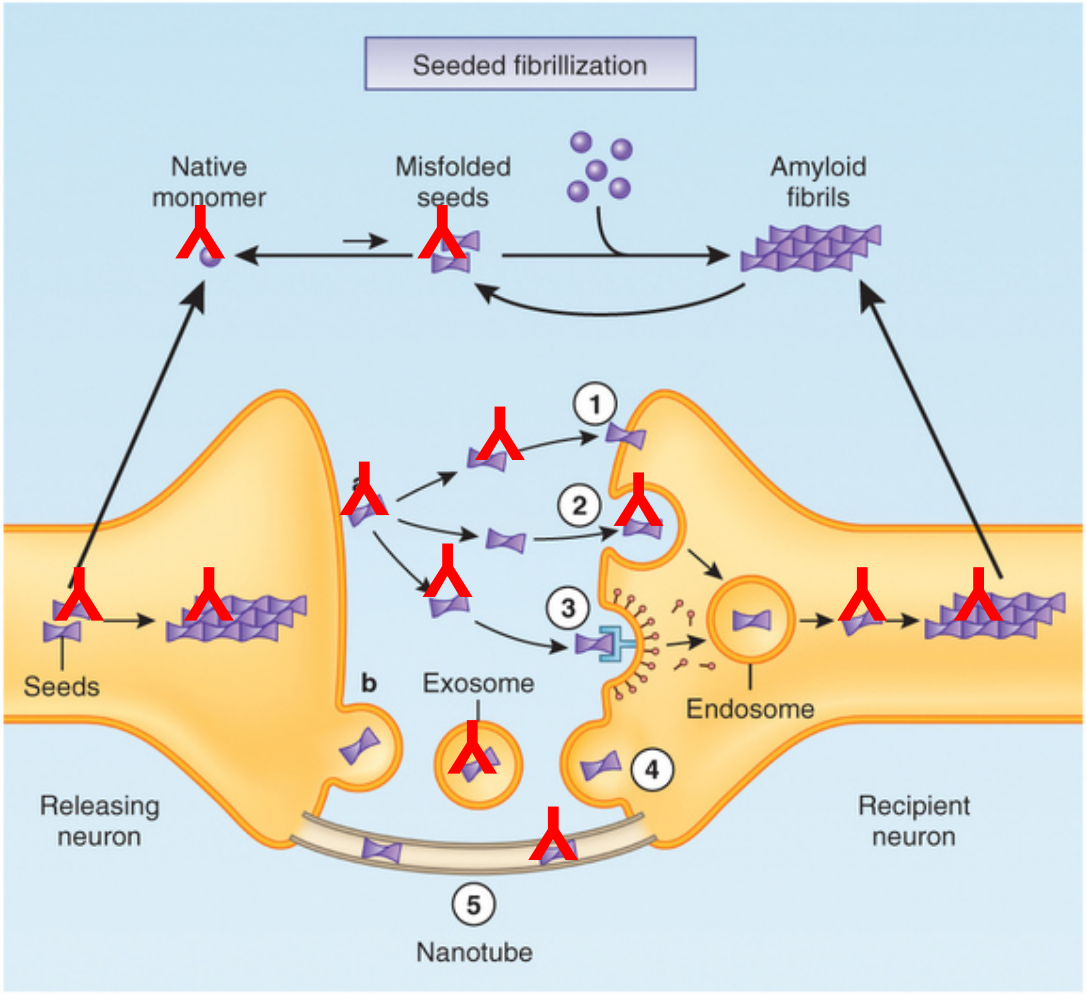
Trophic factors produced by skeletal muscles and the liver promote neuronal-regeneration



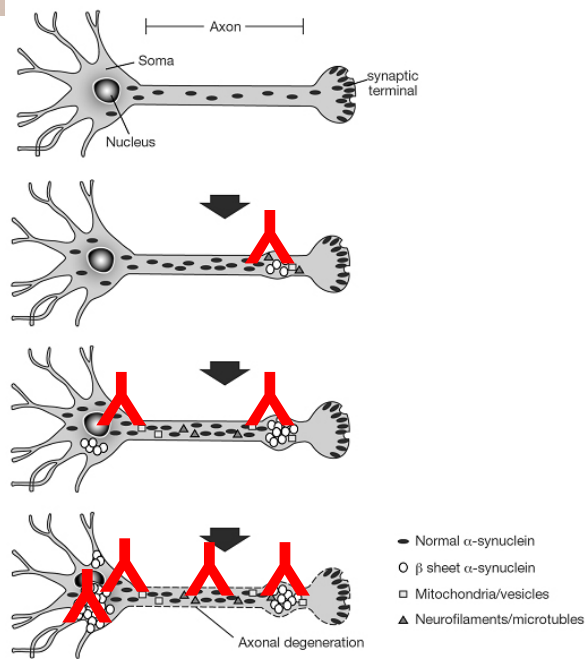
Novel therapeutic approaches for stopping neurodegeneration

- **Vaccines**
- **Gene silencing\ RNA silencing**
- **Enzymatic activity promoting substances – small molecules**
- **Stem cell**
- **Administration of trophic factors that promote regeneration**

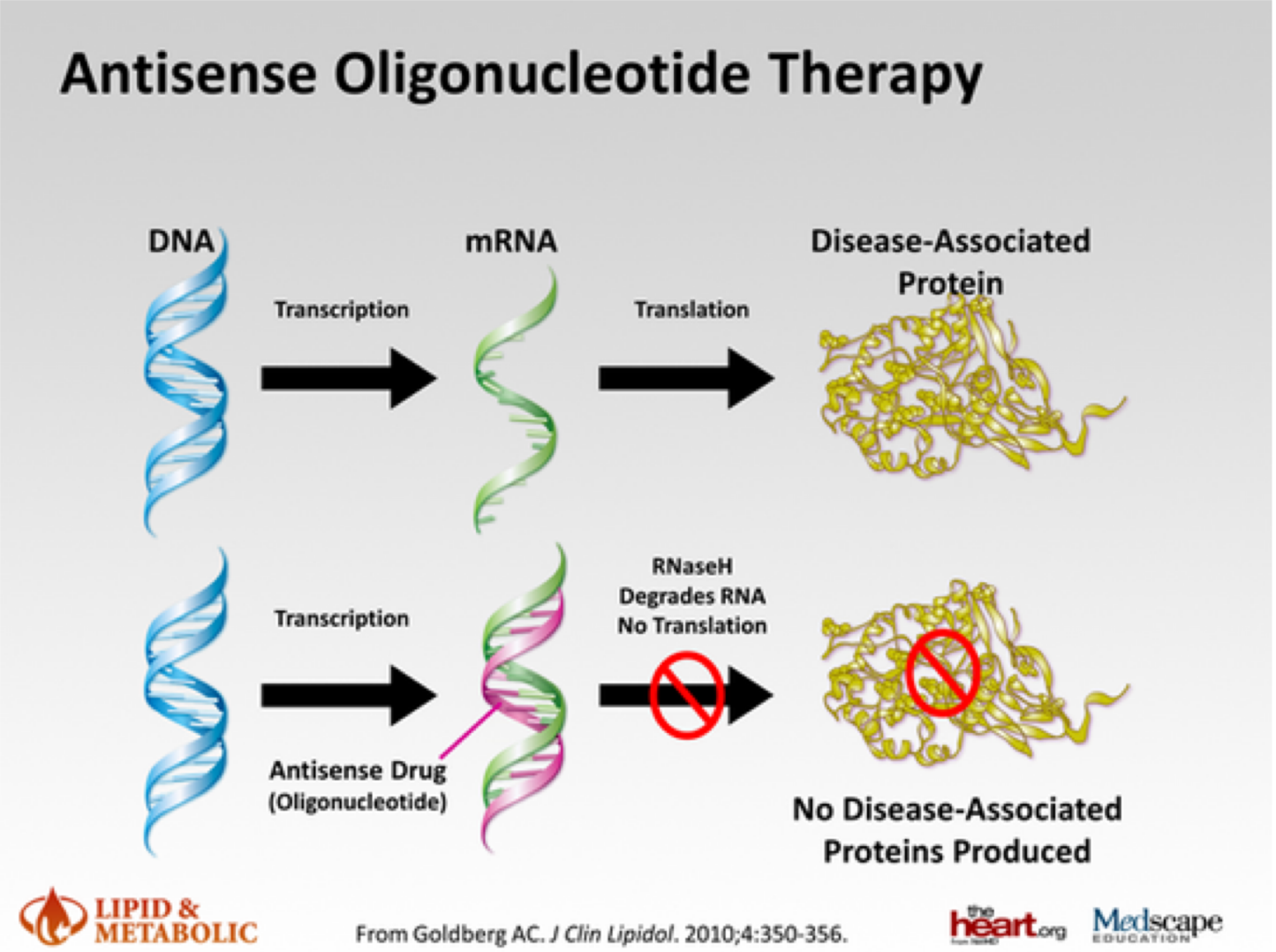
In development:
Dozens of medications and vaccines for the stopping or prevention of Parkinson's disease, Alzheimer's disease and Huntington's disease



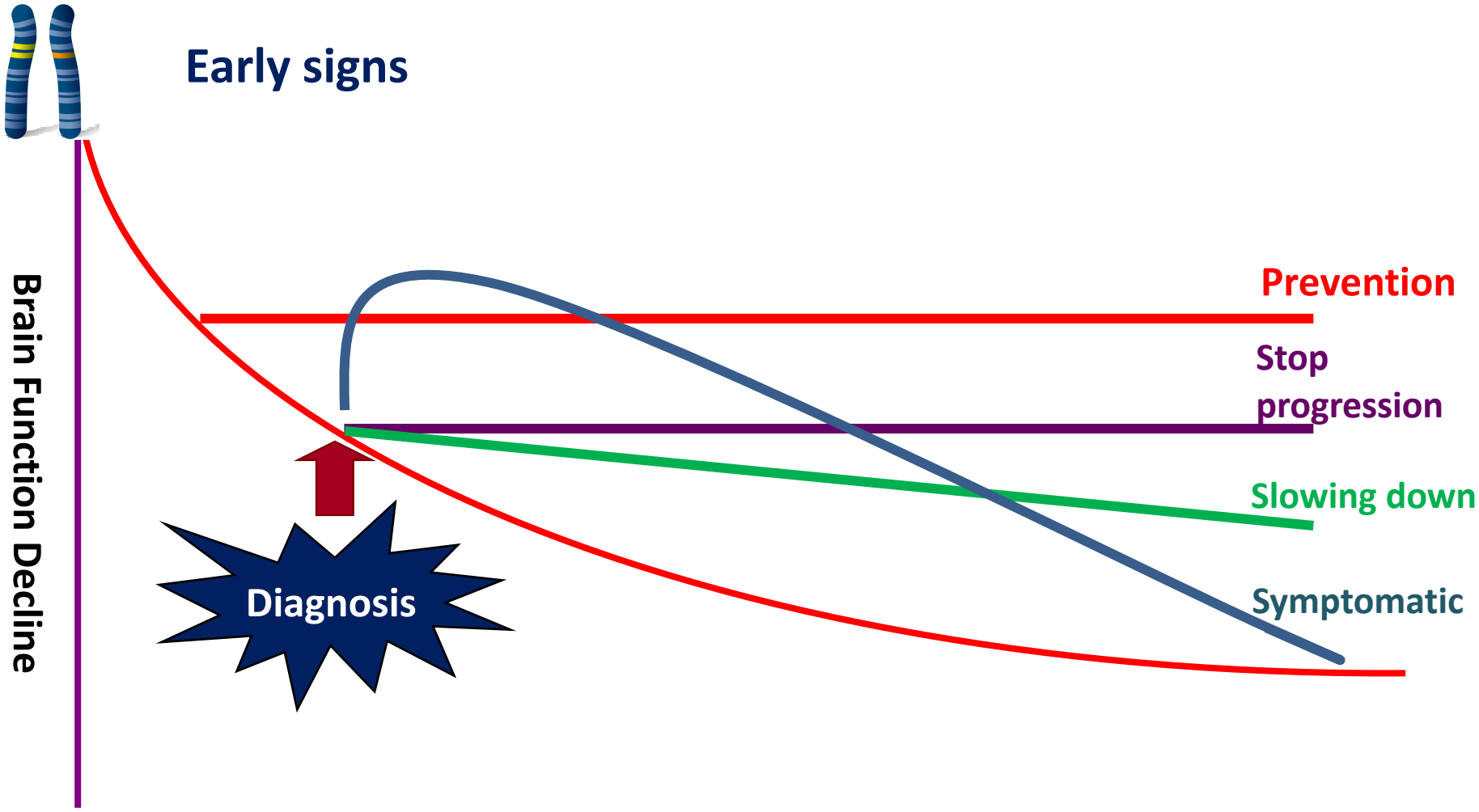
Debbie Maizels



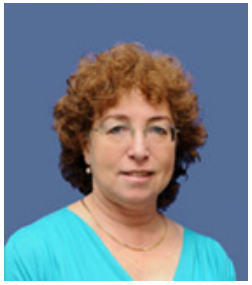
Gene silencing – prevention of toxic protein production

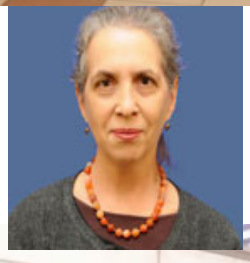


The goal: Prevention




Collaborative Proj
EXIT





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Patients and relatives are waiting…

Thank you

Tel Aviv Medical Center