Industrial Partners

… and many others

EBC Seminar

“Criteria for success: The future of collaborative brain research”

The researcher perspective

Brussels, March 03 - 2015

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European Academy of Neurology (EAN)

Chair- Subcommittee on European Affairs - EAN

Member of the Scientific Panel for Health (SPH - DG XII - EU)

Hertie Senior Research Professor

Full Professor of Neurology

University Marburg, Germany

Past President of the German Society of Neurology

Major barriers of communication between scientists and policy makers

- absence of personal contact

- poor timely relevance

- mistrust of policy makers and scientists

We are not trained to explain

We are not paid to explain

There is no visible reward for explaining

Long term: personal engagement and time investment

versus

Short term: reelection

Trust me I am brain scientist

your most complex and precious organ

your most expensive organ

Trust me I am brain scientist

Brain science and brain disorders

are more complex

than any other disease

our nervous system

central nervous system

peripheral nervous system

autonomous nervous system

gastrointestinal nervous system

EU spent 3 (2) billion € on brain research in FP7

EU – we spent XX billion € on cancer research –

and the result ?

Health research spending including foundations:

Cancer versus brain disorders: UK 1000:1

Neurology – the fastest growing field in medicine –

1970: stone age

2015: middle age

• MS	disease modifying drugs
• Stroke unit	clear improvem ent
• Parkinson	DBS, preclinical diagnosis
• Alzheimer	preclinical diagnosis
• RLS (10%)	effective drug treatment
• Migraine (15%)	tryptans

Basic neuroscience

Disease oriented neuroscience

Patient oriented clinical science

Health care and health economic science

my

neuroscientific and neurological

background

Neuroscience Vol. 6, No. 12, pp. 2689 to 2700, 1981
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Pergamon Press Ltd

PRODUCTION OF A SPECIFIC ANTISERUM TO RAT BRAIN GLUTAMIC ACID DECARBOXYLASE BY INJECTION OF AN ANTIGEN–ANTIBODY COMPLEX

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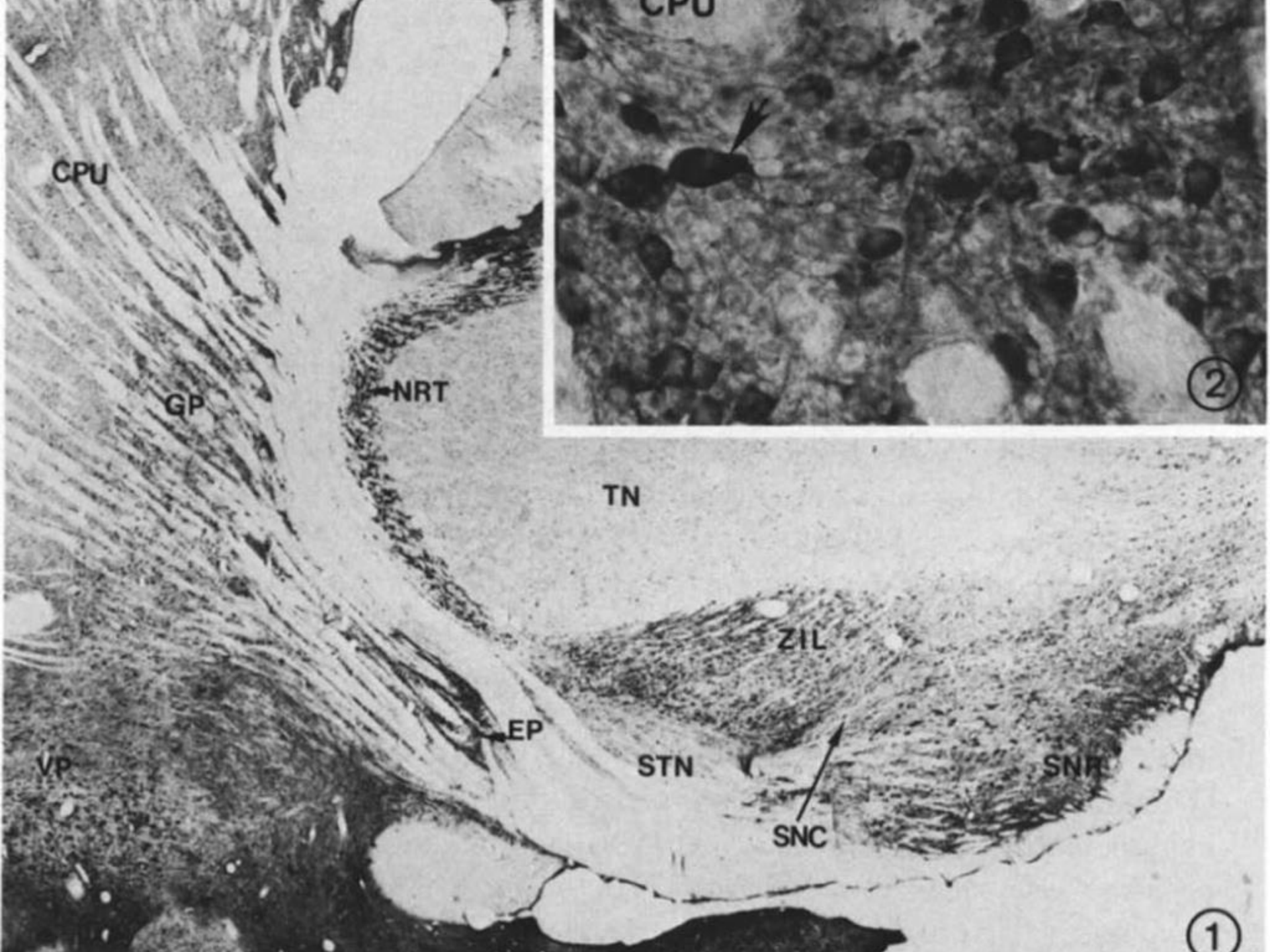
Abstract—Production of an antiserum specific to rat brain L-glutamic acid decarboxylase is described, featuring the injection of an antigen–antibody complex. Partial purification of glutamate decarboxylase was first achieved through differential centrifugation, ammonium sulfate fractionation, chromatography on Sephadex G-150, preparative isoelectric focusing in sucrose gradient and polyacrylamide gel electrophoresis for the production of a preliminary polyvalent, so called 'trapping' glutamate decarboxylase antiserum in sheep. In rat brain homogenate supernatant this antiserum maximally inhibited glutamate decarboxylase activity by 80% and totally precipitated enzyme activity on centrifugation. This antiserum, however, was polyvalent, as in crossed immunoelectrophoresis it detected four antigens in rat brain homogenate supernatant and three antigens in a partially purified preparation of glutamate decarboxylase. One of these three precipitin lines could be radioactively labelled by 2-[^{3}H]-γ-acetylenic γ-aminobutyrate, an irreversible inhibitor of glutamate decarboxylase. Injection of this antigen-antibody-precipitin line into a new non-immunized sheep yielded a new antiserum, which slightly inhibited but maximally precipitated 85% of the glutamate decarboxylase activity in rat brain homogenate supernatant. In crossed immunoelectrophoresis the latter antiserum detected one antigen in the partially purified preparation of glutamate decarboxylase. In crossed immunoelectrophoresis with intermediate gel the antiserum altered the mobility of a single antigen in brain homogenate supernatant.

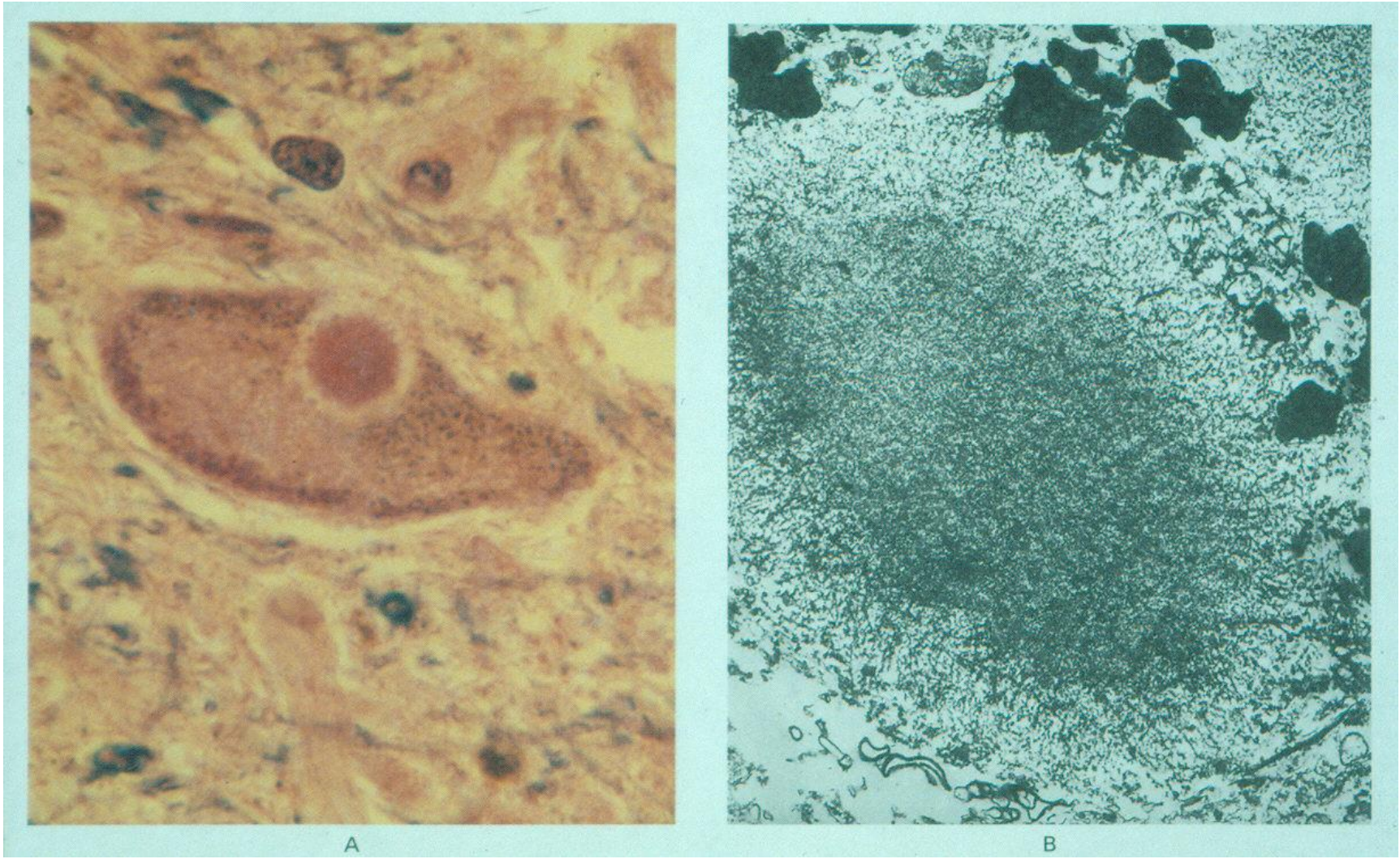

CPU
GP
NRT
TN
ZIL
EP
VP
STN
SNR
SNC
1
CPU
2

Translational neurology

Example:

From Parkinson‘s disease patient to mouse and back from mouse to man

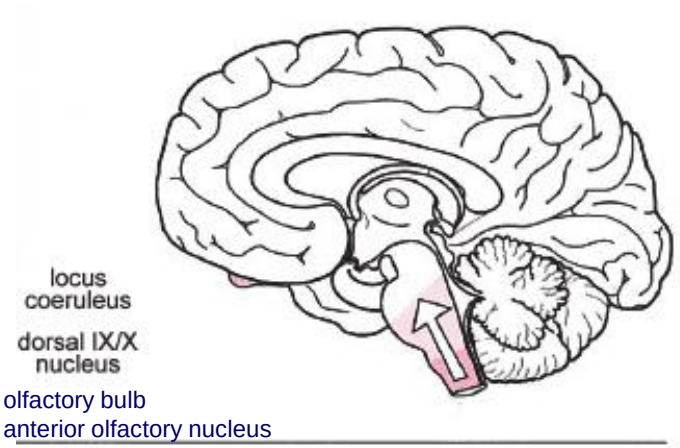
PD - Lewy body, Lewy neurites 1912
protein aggregation

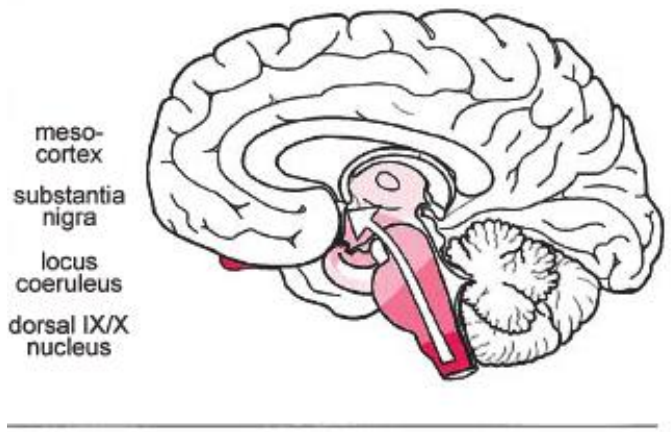


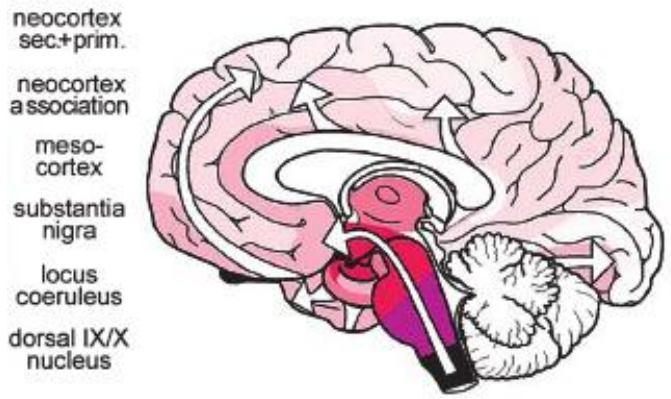
Pathoanatomical stages of Parkinson‘s disease

Braak et al. 2003

J NEURAL TRANSM 2003
NEUROBIOL AGING 2003





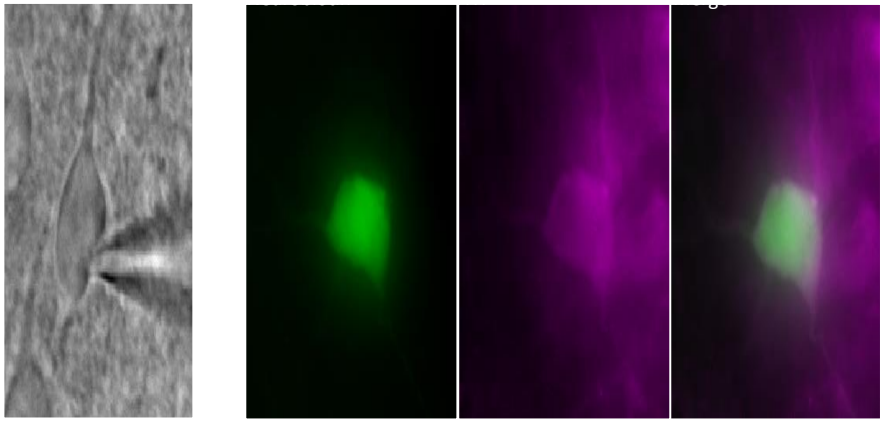


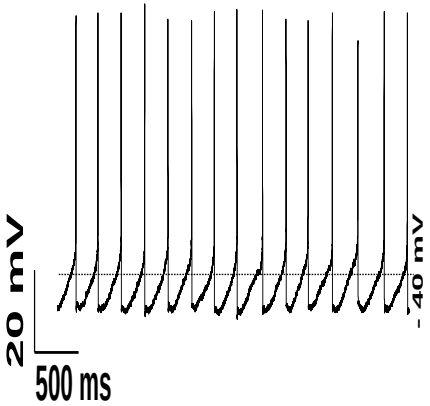
Non-motor symptoms in the premotor phase of PD

Premotor symptoms	*Related brain structures*	*Braak staging*
Constipation	**vagal nucleus** **enteric plexus neurones**	**1**
BRAIN **Impairment or loss of smell**	**olfactory bulb;** **anterior olfactory nucleus**	**1**
Depression	**locus coeruleus** **raphe nuclei**	**2**
REM sleep behaviour Disorder (RBD)	**dorsal midbrain and pons;** **locus coeruleus**	**2 ?**
Akinesia	**substantia nigra**	3

Patch clamp: vagal nucleus , locus coeruleus, sub. nigra

(A) (B) (C)





Parameters	Measured values
Resting membrane potential (mV)	-49 ± 1.5
Firing frequency (Hz)	3.6 ± 0.7
AP-height (mV)	107.3 ± 5.3
AP-width (ms)	1.8 ± 0.4
AHP amplitude (mV)	32.1 ± 2.4

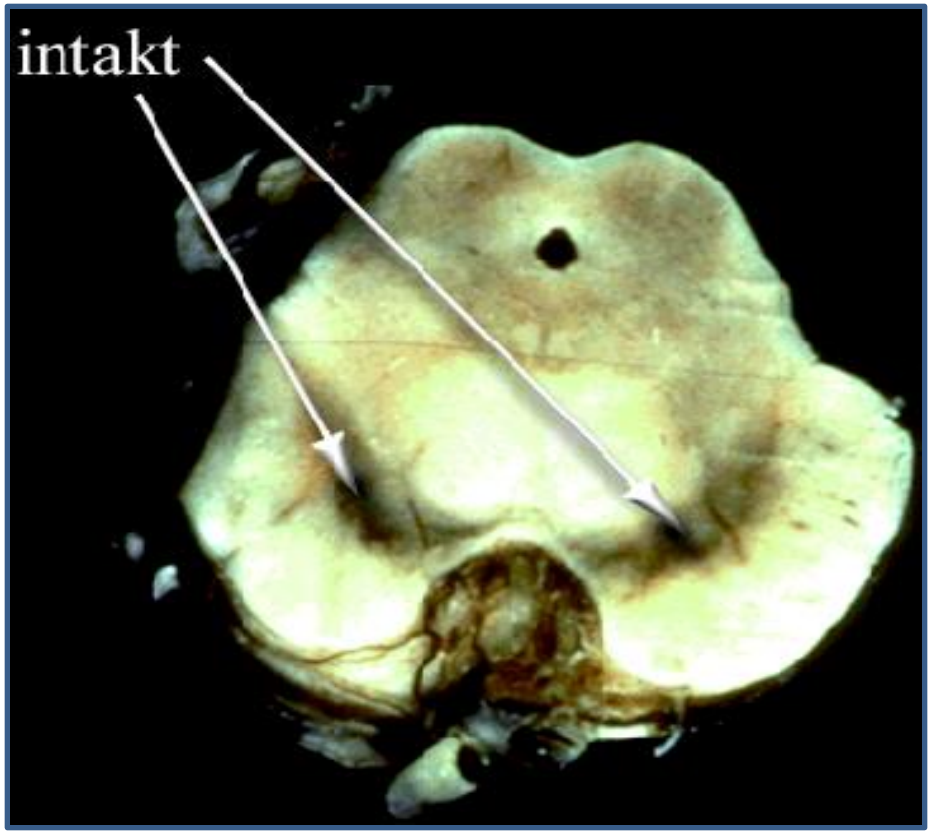
Unpublished data - example of patch clamp recording of normal LC neurons
(A) A single LC neuron recorded by a patch electrode is visually identified. **(B)** Immuno-fluorescent double-staining demonstrates colocalization of neurobiotin and TH in the same LC neuron. **(C)** Spontaneous spiking in the whole cell configuration. **(D)** Electrophysiological properties of LC neurons (n=28). AHP: afterhyperpolarization; AP: action potential.

MRI-Video

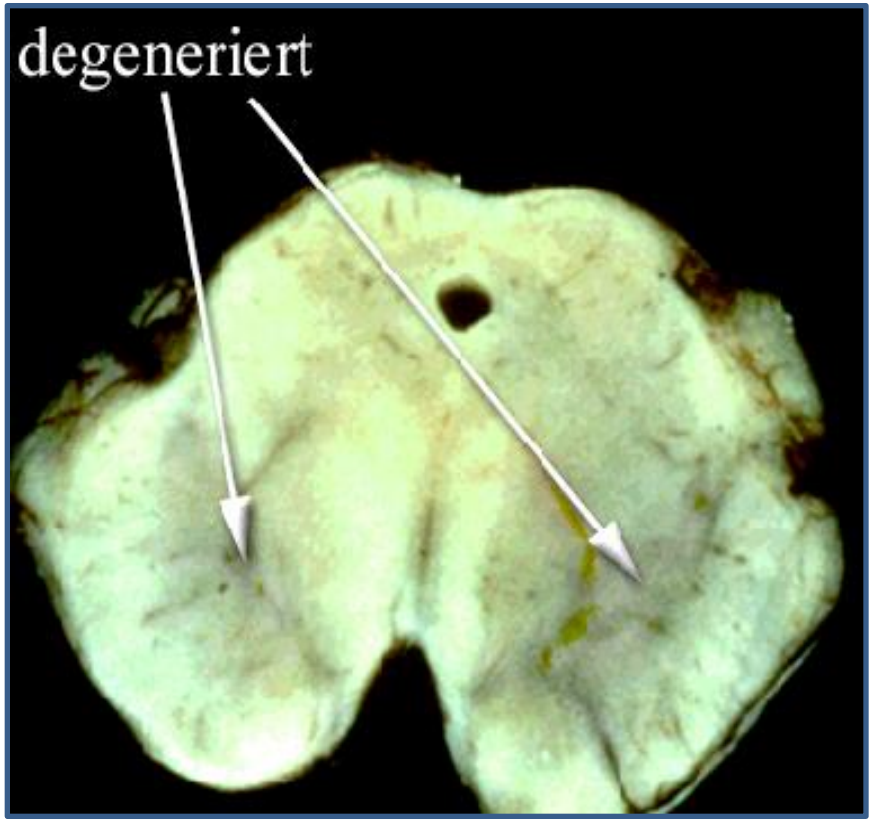
Fast

forward

Postmotor: neurodegeneration - 1919

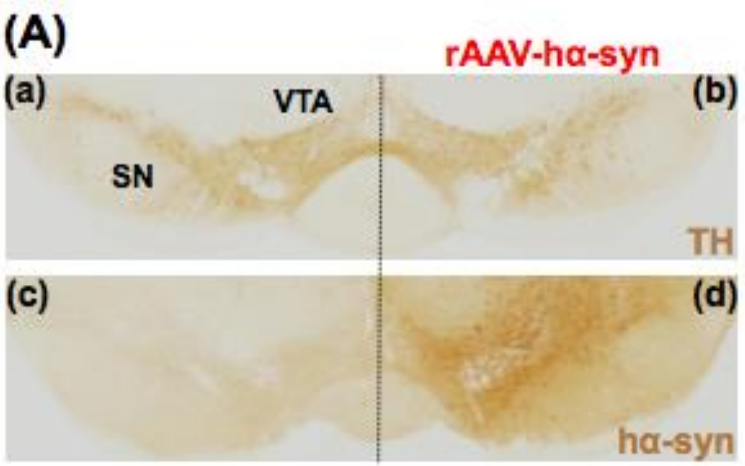


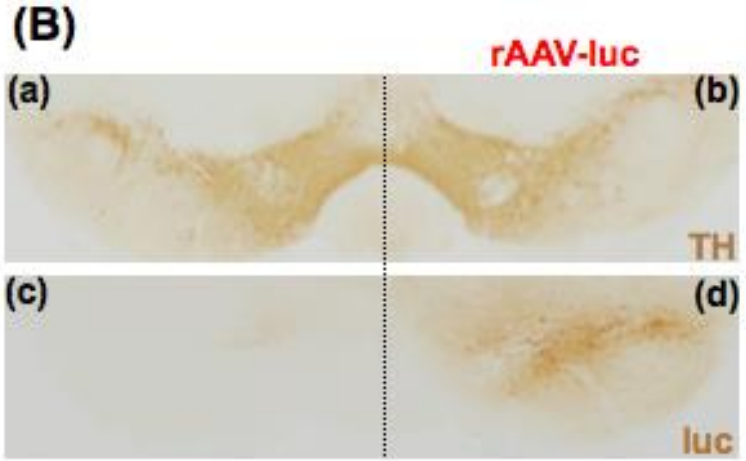
‘Healthy‘ Control

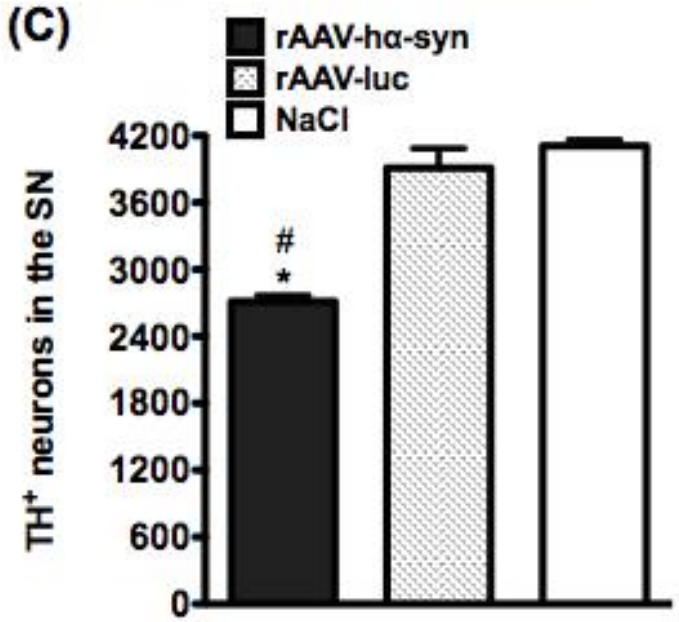


Parkinson‘s disease

Protein aggregation model of Parkinson‘s disease in mouse







(D)

	rAAV6-hα-syn	rAAV6-luc
Viral titer (x10^{13} vg/ml)	1	1
Injected volume in the SN (ul)	2	2

Brain, Mind and **Pain**

- headache *(migraine – 15 %)*

(female : male - 4 : 1)

- backpain

- sleepless painful nights

(restless legs syndrome – 10 %)

patent, Phase I – III, EMA, FDA

Restless Legs Syndrome

Clinical Trials - approved

L-DOPA	Trenkwalder et al.,1996
	Collado-Seidel er al.,1999
	Benes et al., 1999
	Stiasny-Kolster et al., 2004
Cabergoline	Stiasny-Kolster et al., 2002
	Stiasny-Kolster et al., 2004
	Oertel et al., 2006 - **PSG**
	Trenkwalder et al., 2006
Pramipexole	Partinen et al., 2006
	Winkelmann et al., 2006
	Oertel et al., 2006
	Trenkwalder et al., 2006
Ropinirole	Allen et al., 2004
	Trenkwalder et al., 2004
	Walters et al., 2004
	Garcia-Borreguero et al., 2007
Rotigotine	Stiasny-Kolster et al., 2004
	Oertel et al., 2008a
	Trenkwalder et al., 2008
	Oertel et al., 2008b **PSG**
	Oertel et al., 2010 – 5 years
	Bauer et al., 2015 - PSG
GABApentine	Garcia-Borreguero et al., 2008
Pregabaline	Allen et al. 2014
	Garcia-Borreguero et al.2014 - PSG
Opioids	Trenkwalder et al., 2013

Basic neuroscience
Disease oriented neuroscience

Patient oriented clinical science

Health care/health economic science

Study nurse – recruiting
Speed Quality Value

EBC Seminar

"Criteria for success: The future of collaborative brain research"

Academia
Industry
Researcher/Physician
Policy maker
Program planer and administrator
Patient
Researcher/Physician

Brussels, March 03 - 2015

Am I prepared for a collaboration in brain research between academia and industry ?

Kindergarden

School

University

Postgraduate period

Professorship

Public awareness

Reputation

The view of journalism ?

Cooperation between

- Pharmaceutical industry and academia is bad

- Airbus and Technical University is good
- GE and Technical University is good
- Apple and UCLA
- Samsung and Seoul University

  - no problem

smartphones change our way of thinking

„Pharma is bad – corrupts people“

- Cars are good and sexy –

  and kill people and nature

  (motorways seal earth)

  Journalists report on banks

  and how important they are,

  on cars and affairs of celebrities

„The milk comes from a violet cow“

Which child knows where the tablets come from -

- grandmother takes for her depression
- grandfather takes for his Alzheimer dementia

Hardly no awareness, how research and drug development belong together

Which child knows:

Where is my brain

What is my brain

What does my brain do

The big book on research on the body

Patrick Bäuerle – SPH
Amgen-Germany

- Boys - soccer player

- Girls - top stars on the charts ?

- Who knows the nobel prize winners for neuroscience in the last 5 years ?

Who knows the head ? of

- Innovative pharmaceutical companies
- Big Pharma
- Big car companies
- Which major national or EU politician appears at an international conference on drug development or brain diseases

  (ECNP, EAN, EPA)

- Who knows Prof. Ruxandra Draghia-Akli
- Who knows Dr. Robert-Ian Smits
- Who knows Dr. Carlos Moedas

There is not a single course in the bachelor or master curricula or in medical undergraduate training on:

- What is the life of a scientist ?
- What is the life of a neurologist ?
- What is the difference between a urologist and a neurologist ?
- How to explain science to policy makers
- How to collaborate in Europe

BRAIN DISORDERS

Public visibility

Public awareness

Public reputation, respect

Child and Youth Psychiatrist
Neuroscientist
Neurologist
Neuropharmacologist
Neurosurgeon
Psychiatrist

„Good example“ (leadership, supervisor)

Medical students do not see medical professors in the preclinical phase of their curriculum any more

- They all wait to get their hands onto patients (healer) and slowly loose the appreciation for science
- The loss of scientific background in the medical profession

There is not a single course in the bachelor or master curricula or in medical undergraduate training on:

- How does research function
- How to finance research
- How to write a grant
- The role of the pharmaceutical industry
- The role of the regulatory bodies in Europe
- How to collaborate in Europe

All national ministers on Research and Innovation in Europe on one picture

All national ministers on Research and Innovation in Europe on national TV

The three commissioners together

- DG CONNECT
  Communications Networks,
  Content&Technology

- DG Research and Innovation

- DG SANCO
  Health and Consumers

Public appearance – brain science ?

Publish a picture of the

- brain of
- Junker
- Merkel
- Varoufakis

EBC Seminar

“Criteria for success: The future of collaborative brain research”

Am I prepared for a collaboration in brain research between academia and industry ?

NO

Brussels, March 03 - 2015

EBC Seminar

“Criteria for success: The future of collaborative brain research”

What do I get out of a collaboration ?

Incentives :

Financial award

Reputation

Intellectual freedom

Brussels, March 03 - 2015

Evaluation of neuroscientific research performance

Factors which impact on your carrier in academia ?

MD, PhD, tenure track, assistent professor. associate professor, full professor

Hirsch factor – depends also on field
(Alzheimer, stroke versus Tulio-phenomen)

Impact factor –unadjusted specific
(1. author, last author etc)

- number of collaborations with industry ? - no
- number or clinical trials, you help to design, participate or implement ? no
- Patent may be

Evaluation of medical research performance

- Funding from public agencies - 100%
- Funding from industry - 30 %
- Funding from private foundations - ?

- Clinical trial research is considered second class research

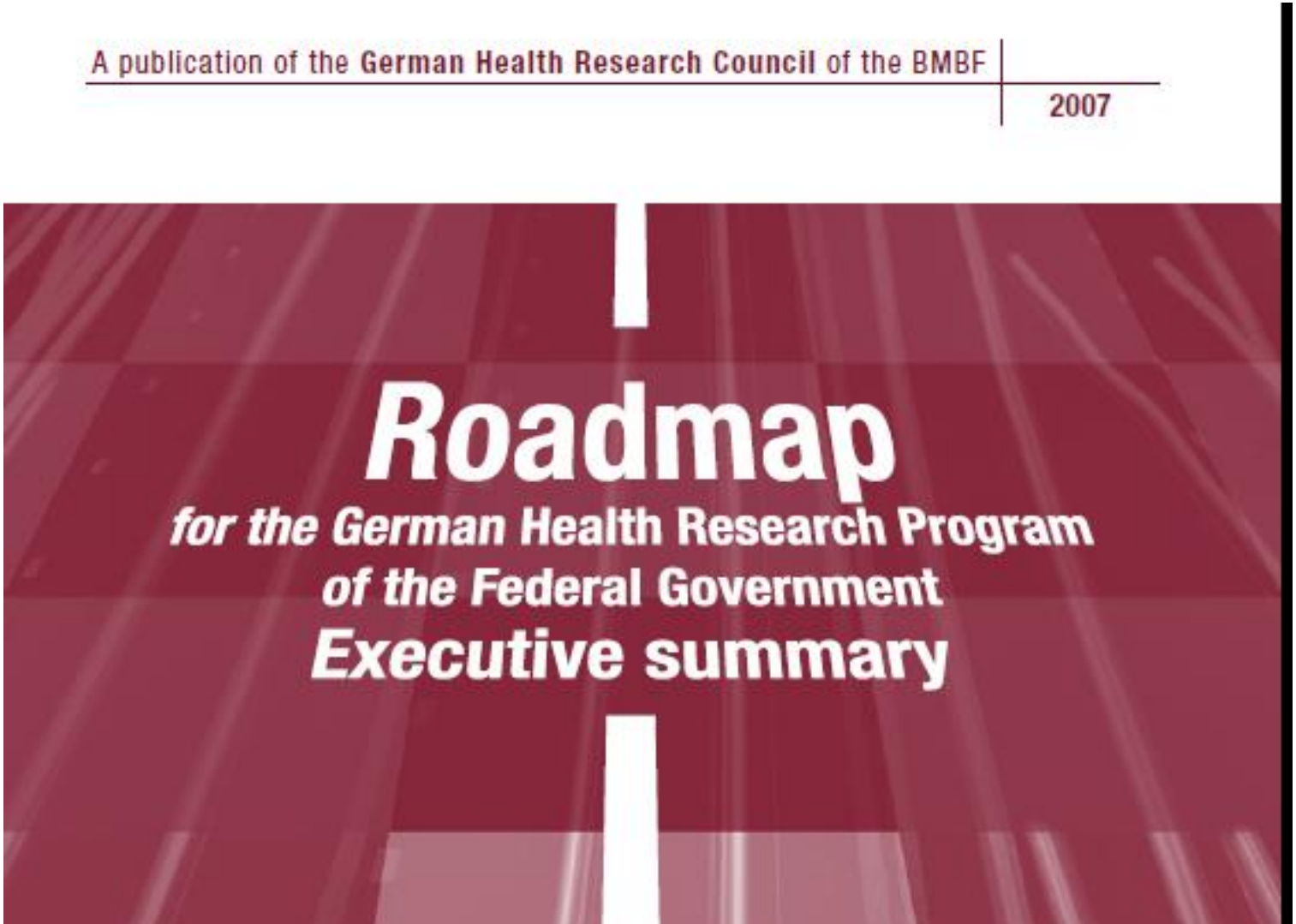
- Germany: BMBF, DFG –
- clinical research group (6-8)
- research area (> 12)

The evaluation of medical research performance shall mainly focuse on three core areas:

- The "impact" of research activities in a broader sense, i.e. their contribution to scientific, medical/clinical and other societal progress
- The "input", i.e. especially the performance in generating competitive third party funds
- The "attraction and promotion of young scientists" as a crucial factor of sustainability

For items 1 and 3 hardly a financial reward is giving (DE)

The topic „collaboration between adacemia and industry“ is not mentioned



Observation in the laboratory
Observation in the clinic

- Neuroscientist
- Physician scientist

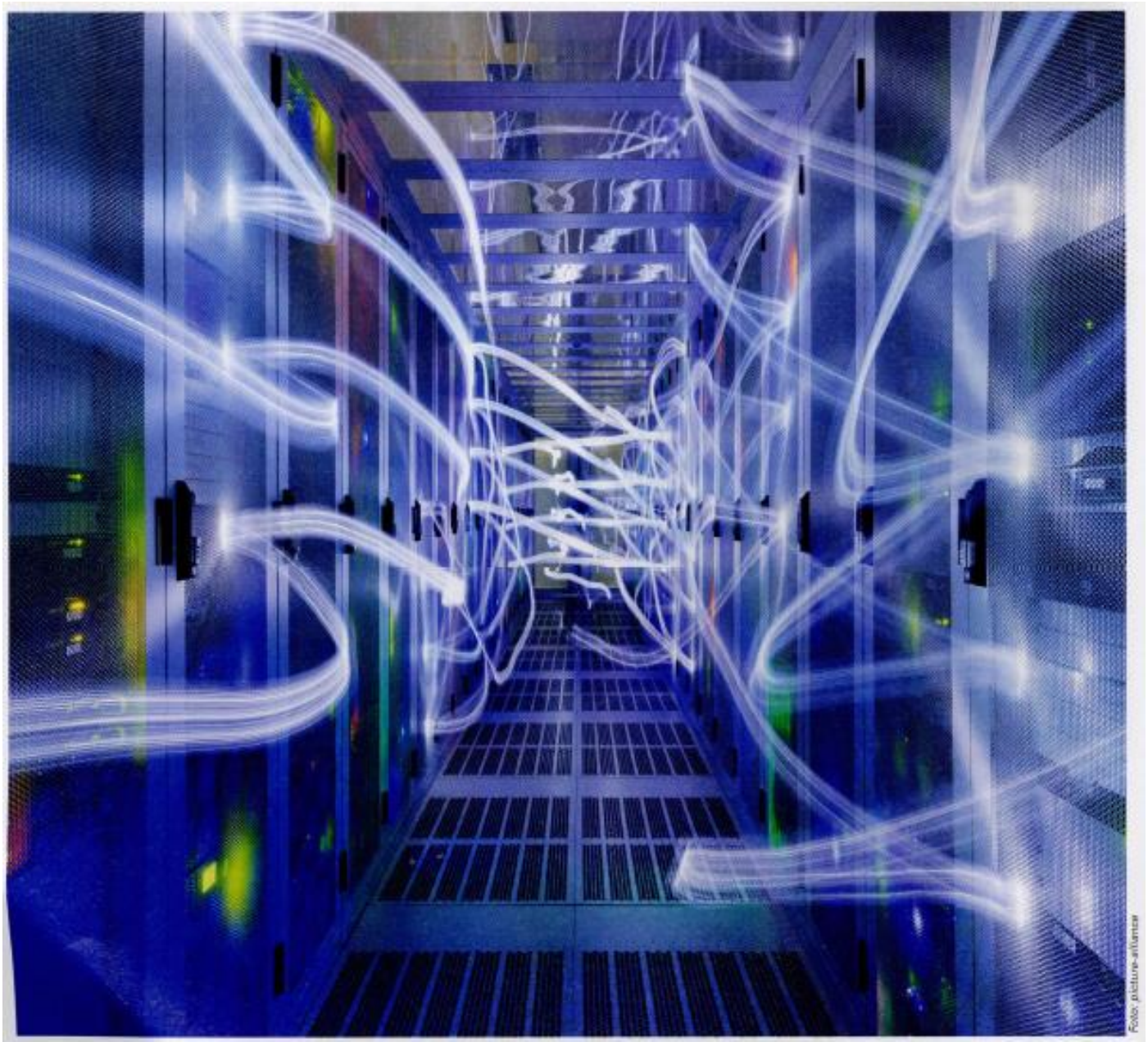
- Trained to carefully obbserve
- Trained to critically observe
- Trained to question a given situation

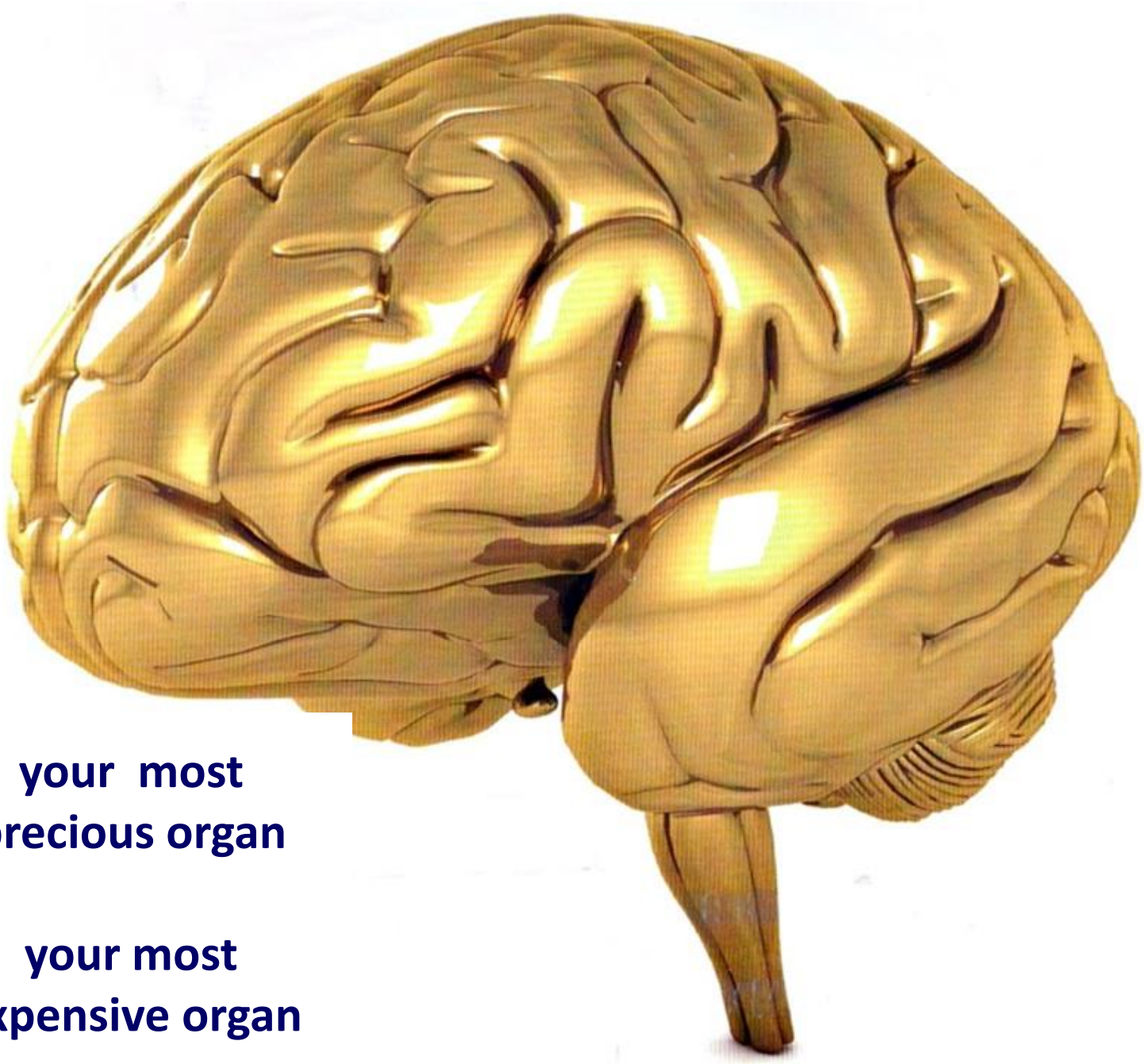
- Not trained to explain science
to lay people or policy makers

Economic pressure very high in clinical services – at least in central Europe

if you have to make a choice:
„take care of the patient or go to the laboratory“ –
you normally serve the patient

Big data – the solution ?

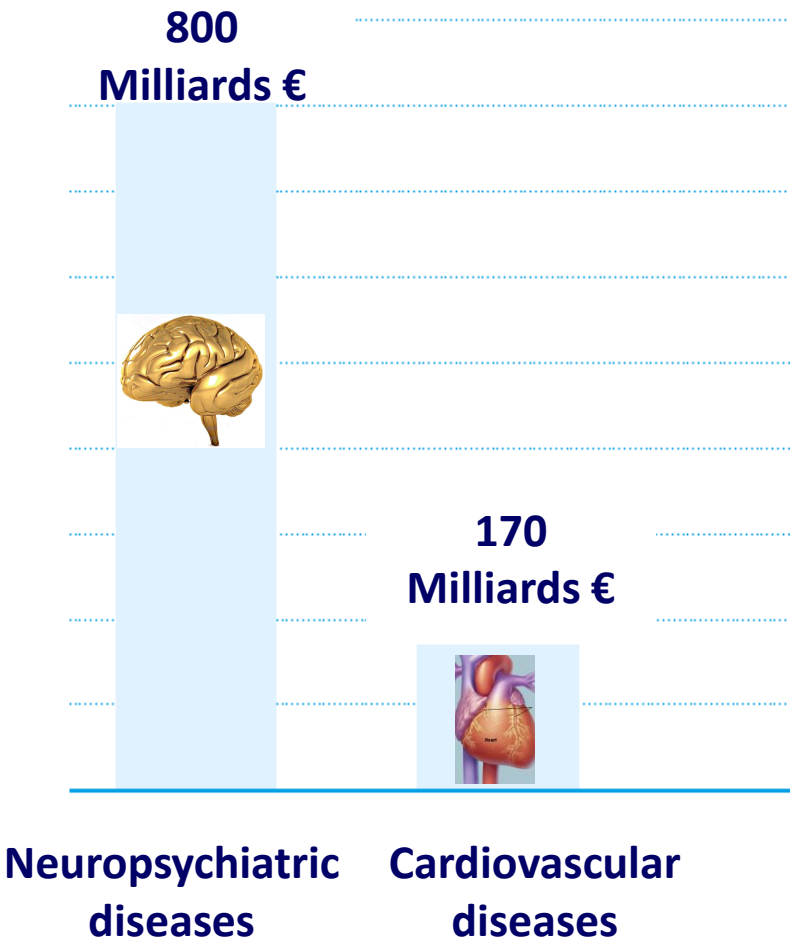




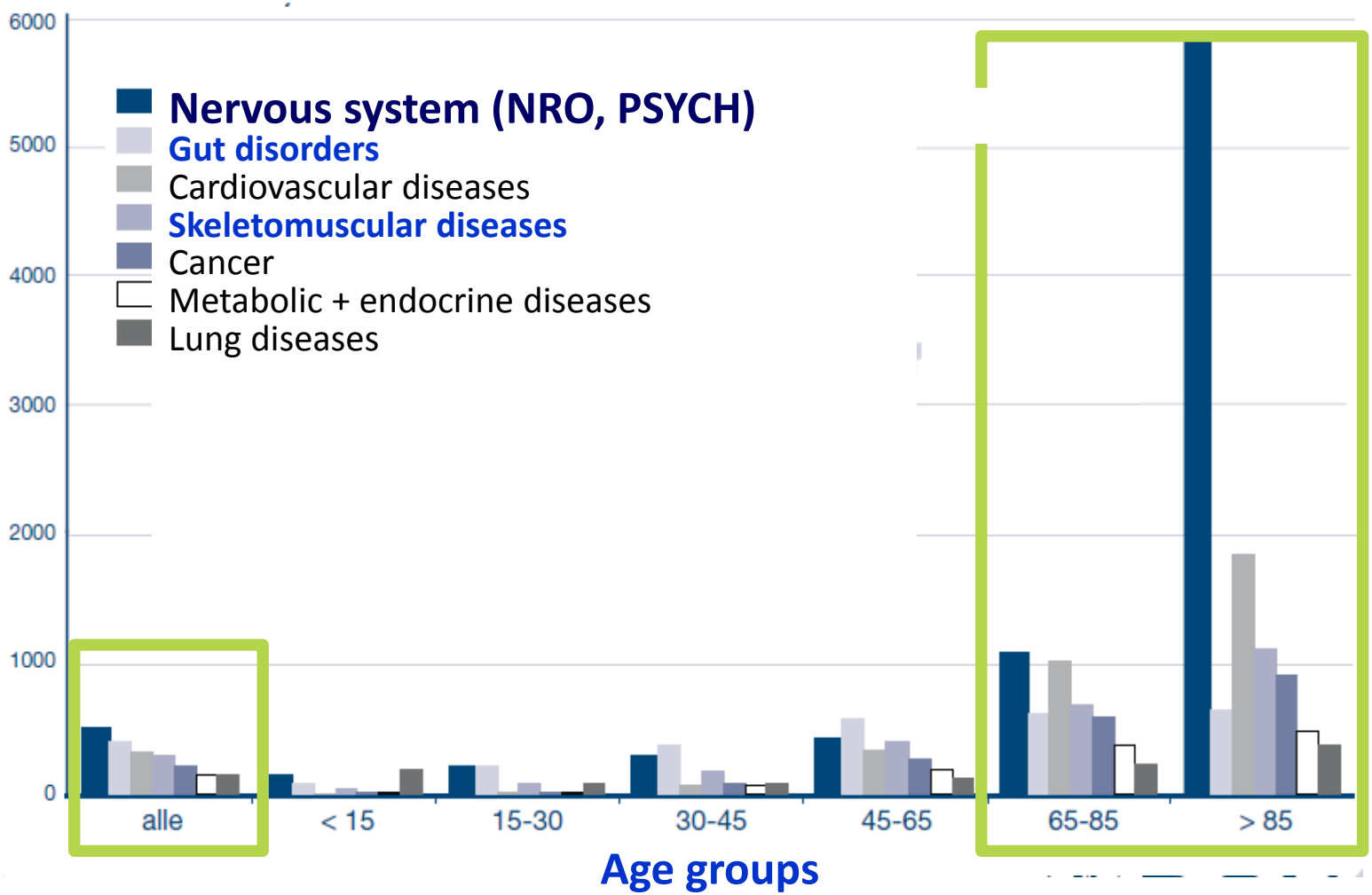
your most
precious organ

your most
expensive organ

Costs of major diseases in Europe 2010



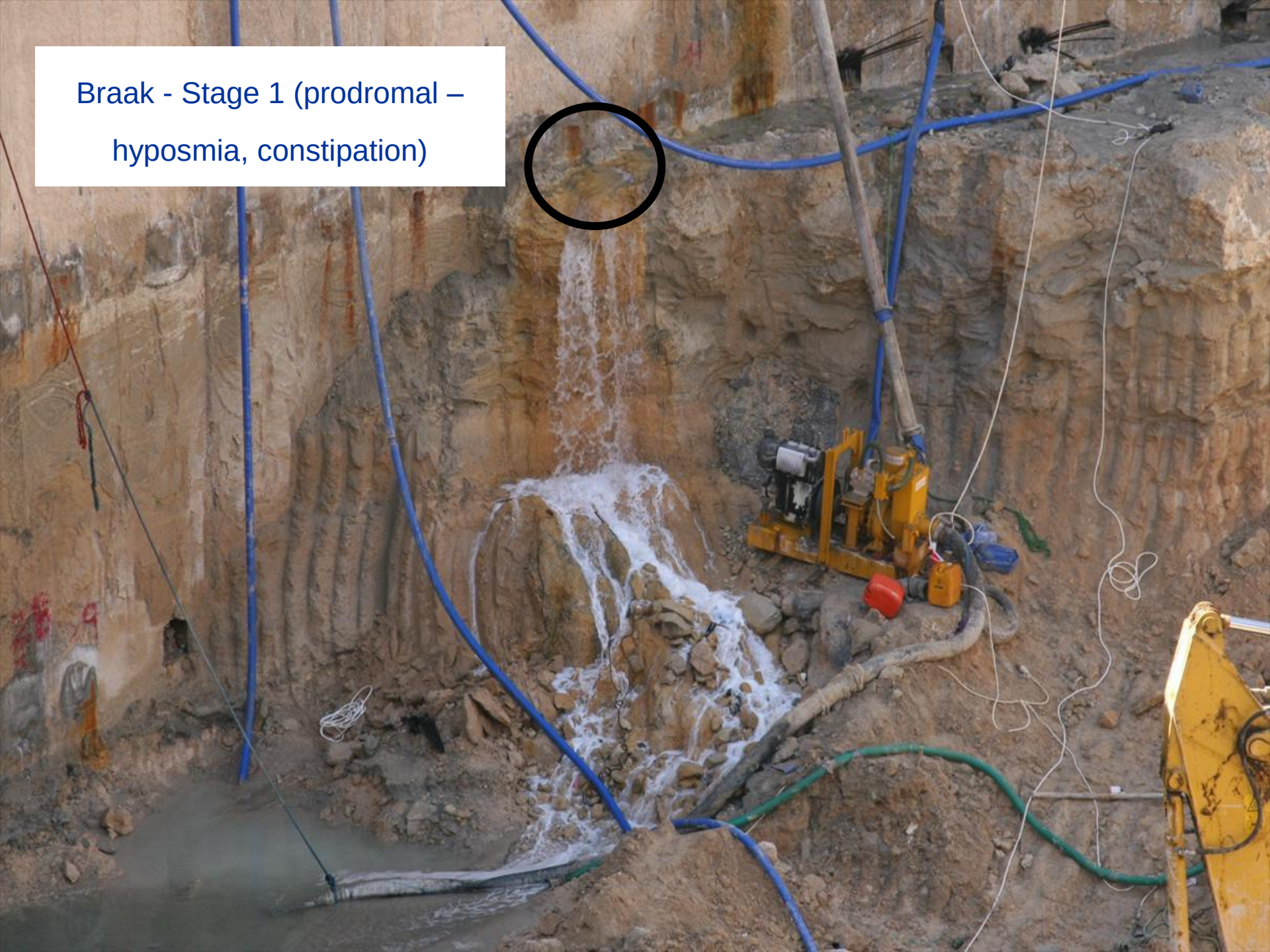
Costs of disease per person/voter per year



chronic medicine

medicine from child to grandgrandmother

Braak - preclinical


Braak - Stage 1 (prodromal –
hyposmia, constipation)

Braak - Stage 2 (prodromal - RBD)

Braak - Stage 3

(prodromal – subclinical nigrostriatal degeneration)

– the view of the classic neurologist

Braak - Stage 4

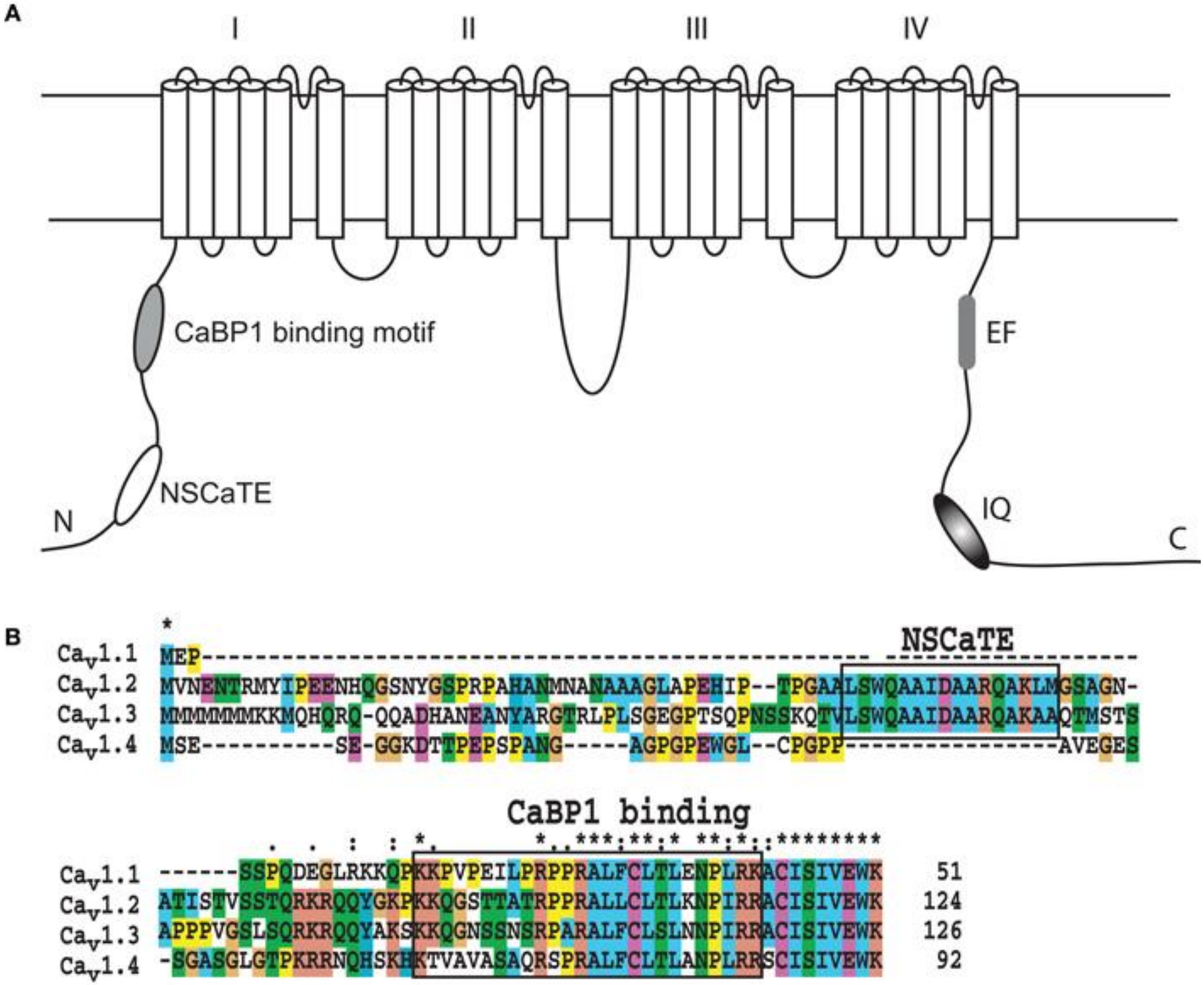
first motor sign is noticed

Brain health or Car

car check every year

€

Brain check ?



A
I
II
III
IV
CaBP1 binding motif
NSCaTE
N
EF
IQ
C
B
NSCaTE
Cav1.1 MEP---
Cav1.2 MVNENTRMYIPEENHQGSNYGSPRPAHANMNANAAAGLAPEHIP--TPGAALSWQAAIDAARQAKLMGSAGN-
Cav1.3 MMMMMMMKKMQHQRQ-QQADHANEANYARGTRLPLSGEGPTSQPNSSKQTVLSWQAAIDAARQAKAAQTMSTS
Cav1.4 MSE----------SE-GGKDTTPEPSPANG-----AGPGPEWGL--CPGPP----------------AVEGES
CaBP1 binding
Cav1.1 ------SSPQDEGLRKKQPKKPVPEILPRPPRALFCLTLENPLRKACISIVEWK 51
Cav1.2 ATISTVSSTQRKRQQYGKPKKQGSTTATRPPRALLCLTLKNPIRRACISIVEWK 124
Cav1.3 APPPVGSLSQRKRQQYAKSKKQGNSSNSRPARALFCLSLNNPIRRACISIVEWK 126
Cav1.4 -SGASGLGTPKRRNQHSKHKTVAVASAQRSPRALFCLTLANPLRRSCISIVEWK 92

$Ca^{2+}v1.3$ Na^{2+}

Brain, Mind and Pain

Alzheimer dementia

Parkinson‘s disease

stroke

epilepsy

multiple sclerosis

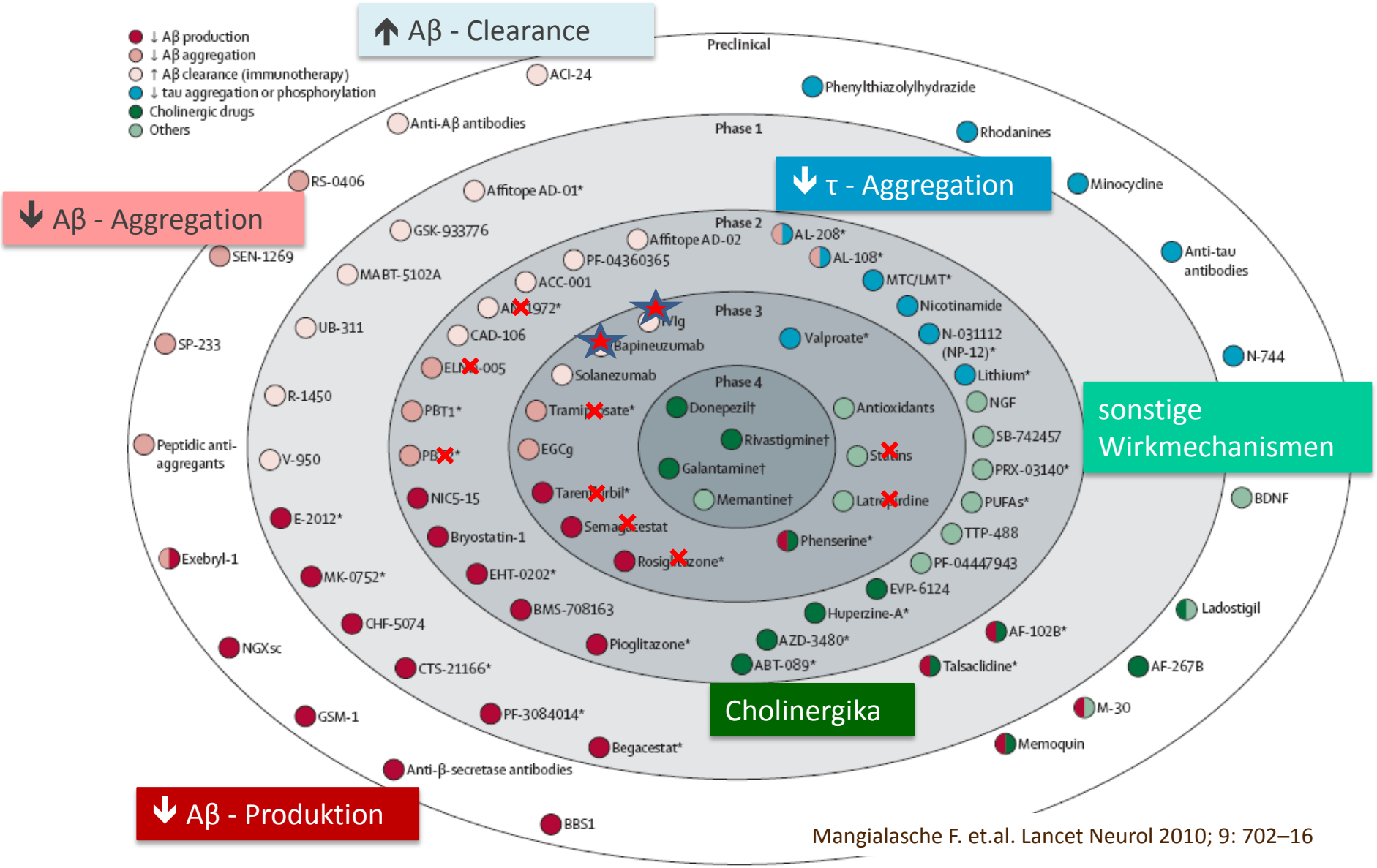
sleep disorders

Alzheimer dementia when economical disaster strikes

Greece debts are cheap

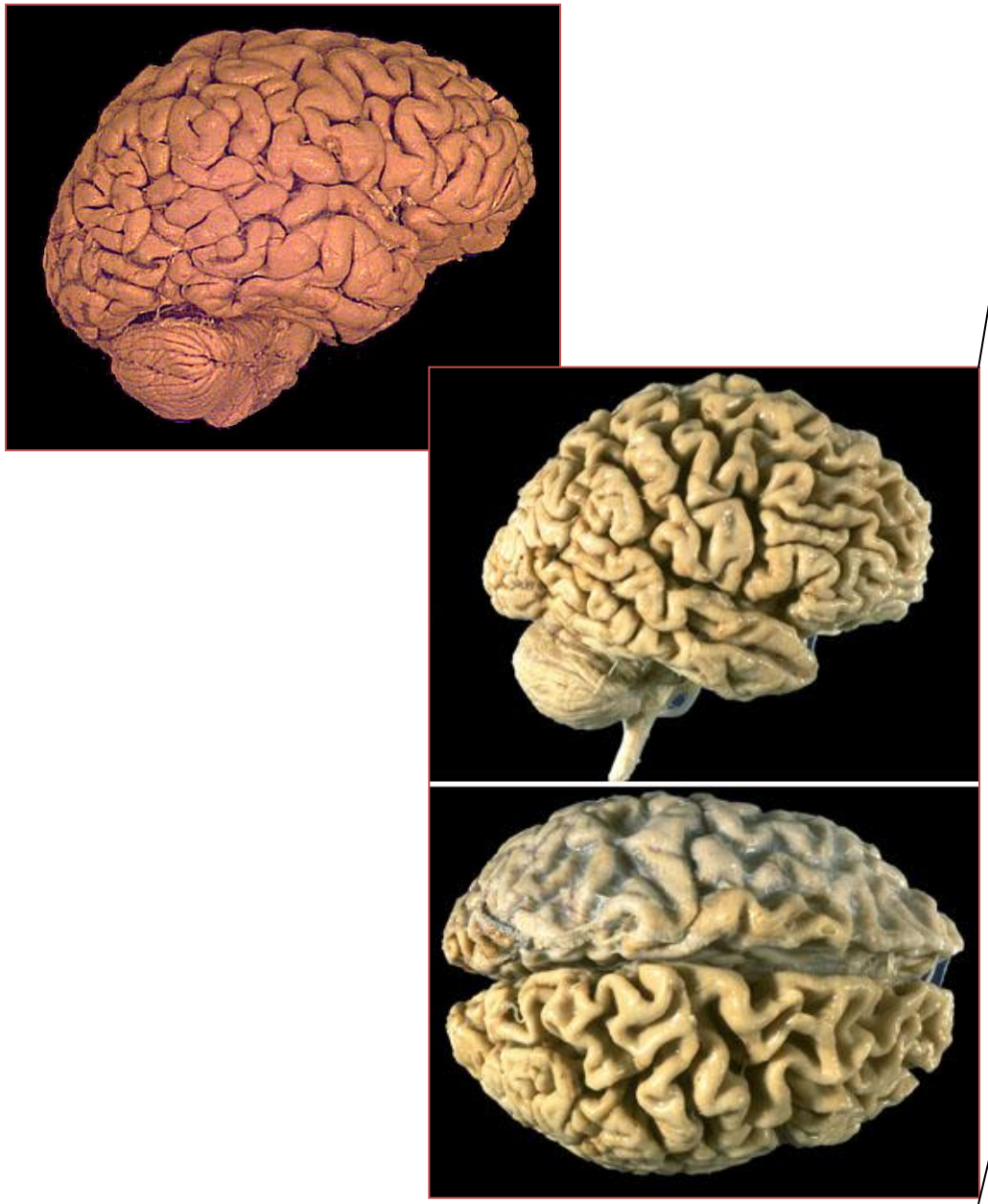
European debts are cheap

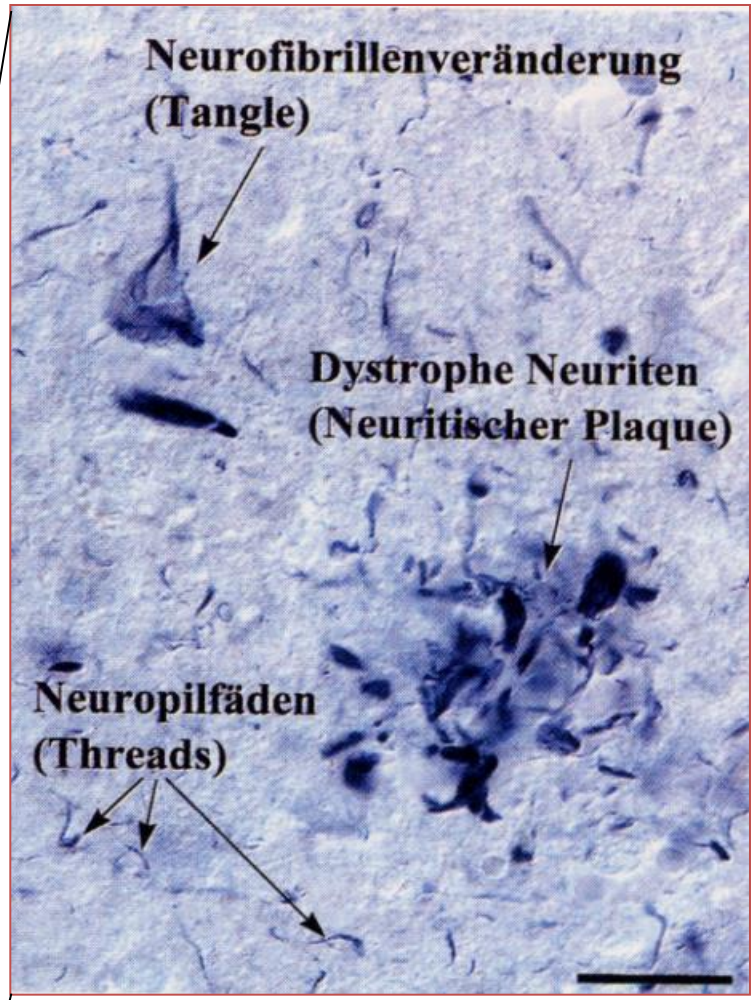
Therapeutical developments for Alzheimer-Dementia



Mangialasche F. et.al. Lancet Neurol 2010; 9: 702–16

Alzheimer Krankheit: Pathologie





EMA

FDA

Experts – advisory boards

Preventing neurological disease

- a dream or a realistic aim ?

Example Parkinson’s disease

Genetics in PD – 1994

Protein Aggregation

- Park 1 - alpha-Synuclein

- Park 8 (LRRK2 (Leucine rich region kinase 2)

- Tau

- ß Amyloid

Mitochondrial Dysfunction

- Parkin

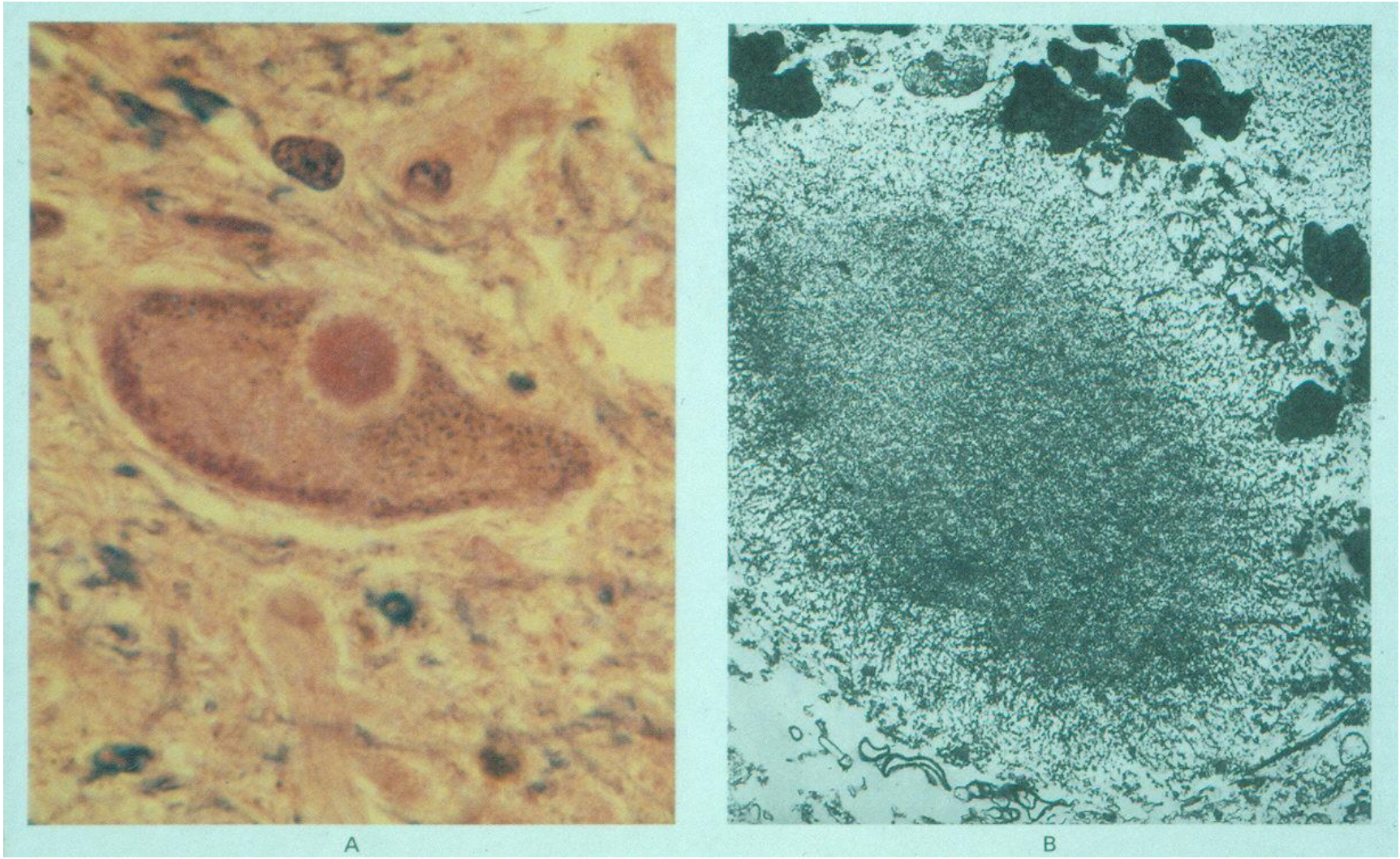
- Pink1

- DJ1

Glucocerebrosidase (GBA) –

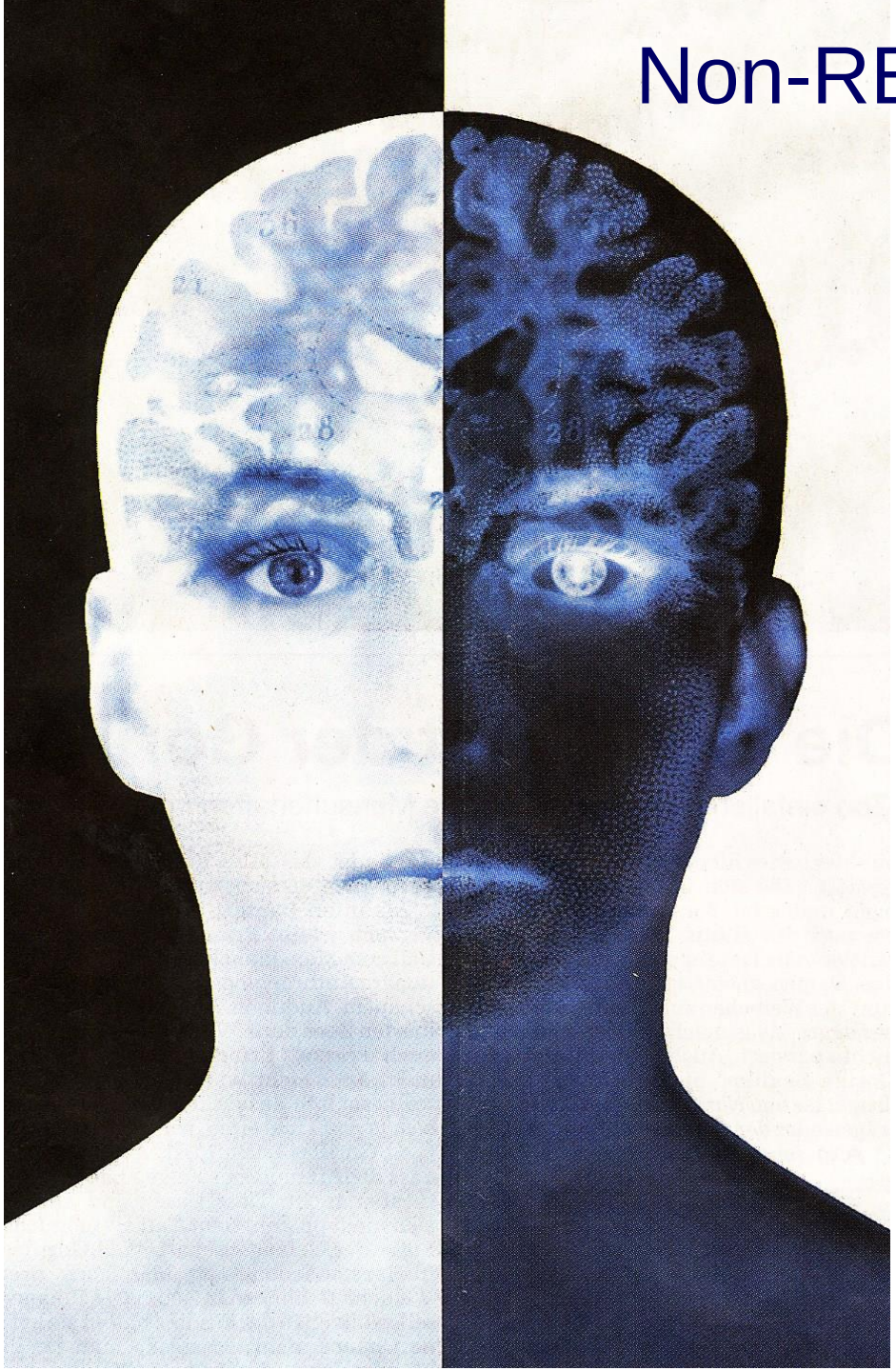
(3 % -7 % of idiopathic Parkinson-Syndrome-Patients show a mutation – role of GBA (degradation of glucocerebroside to glucose and ceramide) and of glycosphingolipids on the mitochondrial function or alpha-synuclein

Lewy body, Lewy neurites 1912
protein aggregation



REM-Sleep

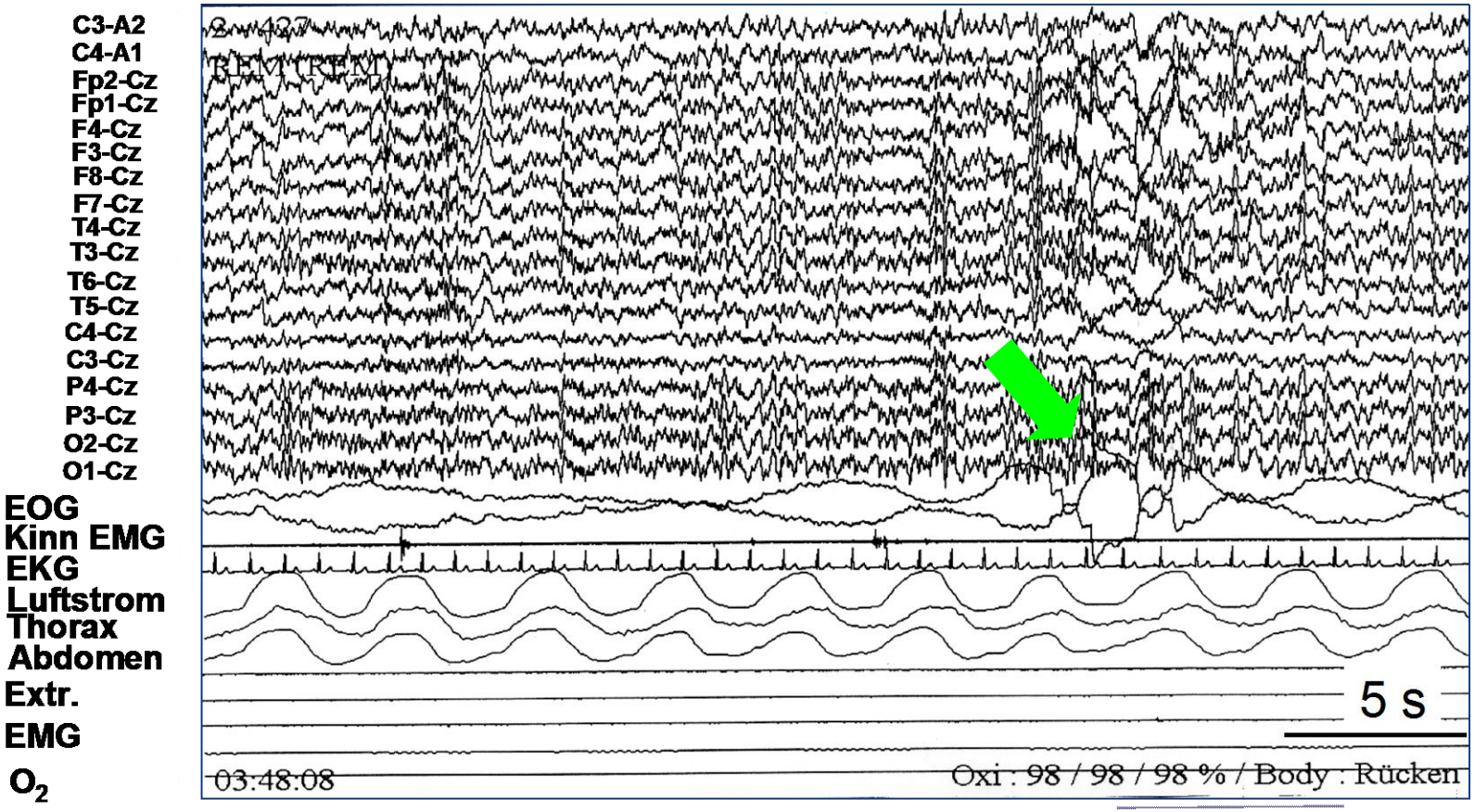
1986



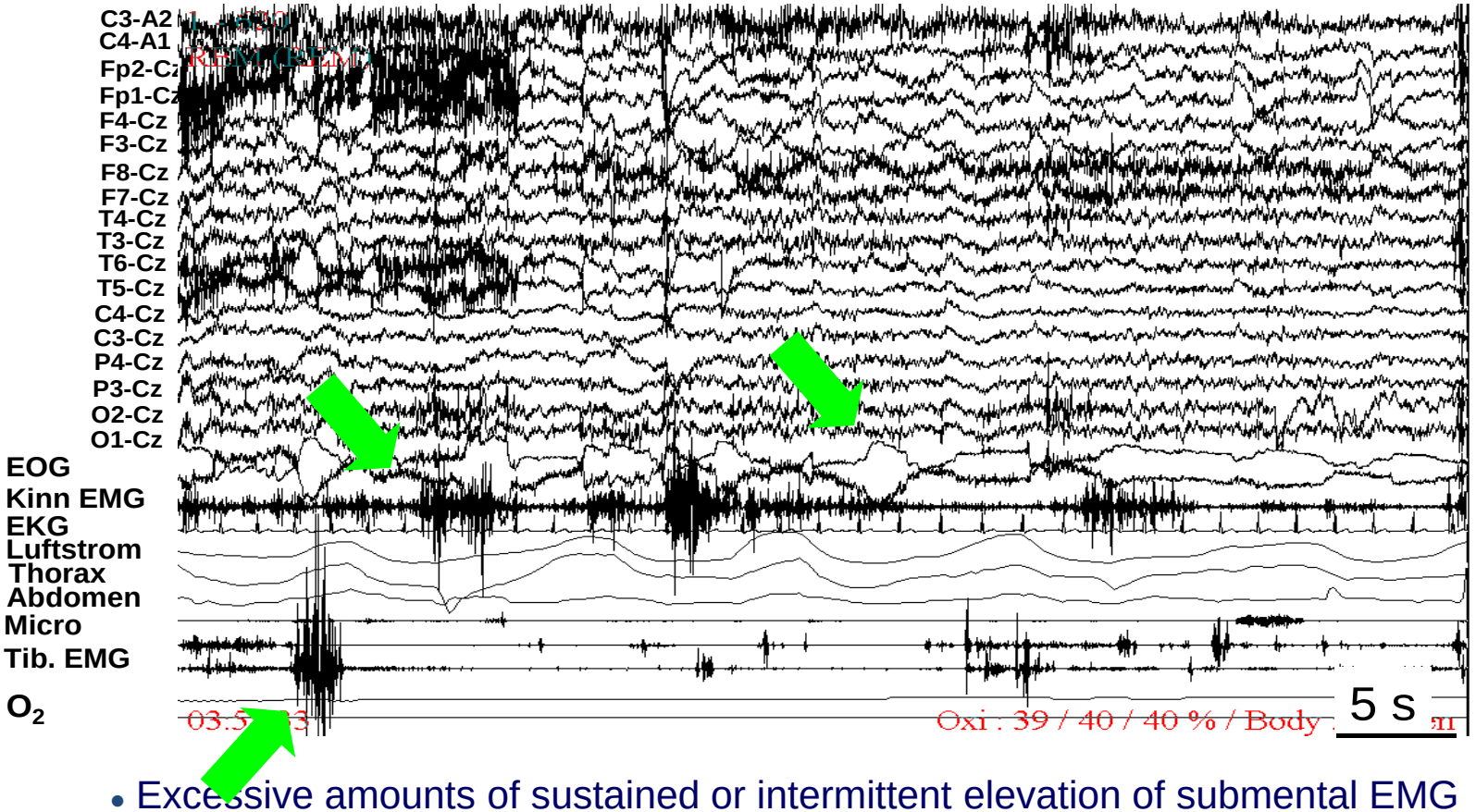
Non-REM Sleep

Normal REM sleep – REM Atonia

(Rapid-Eye-Movement)



Polysomnography (PSG) in clinical RBD
(ICSD 2005 rev.)



- Excessive amounts of sustained or intermittent elevation of submental EMG tone and/or excessive phasic submental or limb twitching
- Presence of sleep related injuries, potential injurious, or disruptive behaviors, and/or documentation of abnormal REM sleep behavior during polysomnography
- Absence of EEG epileptiform activity during REM sleep

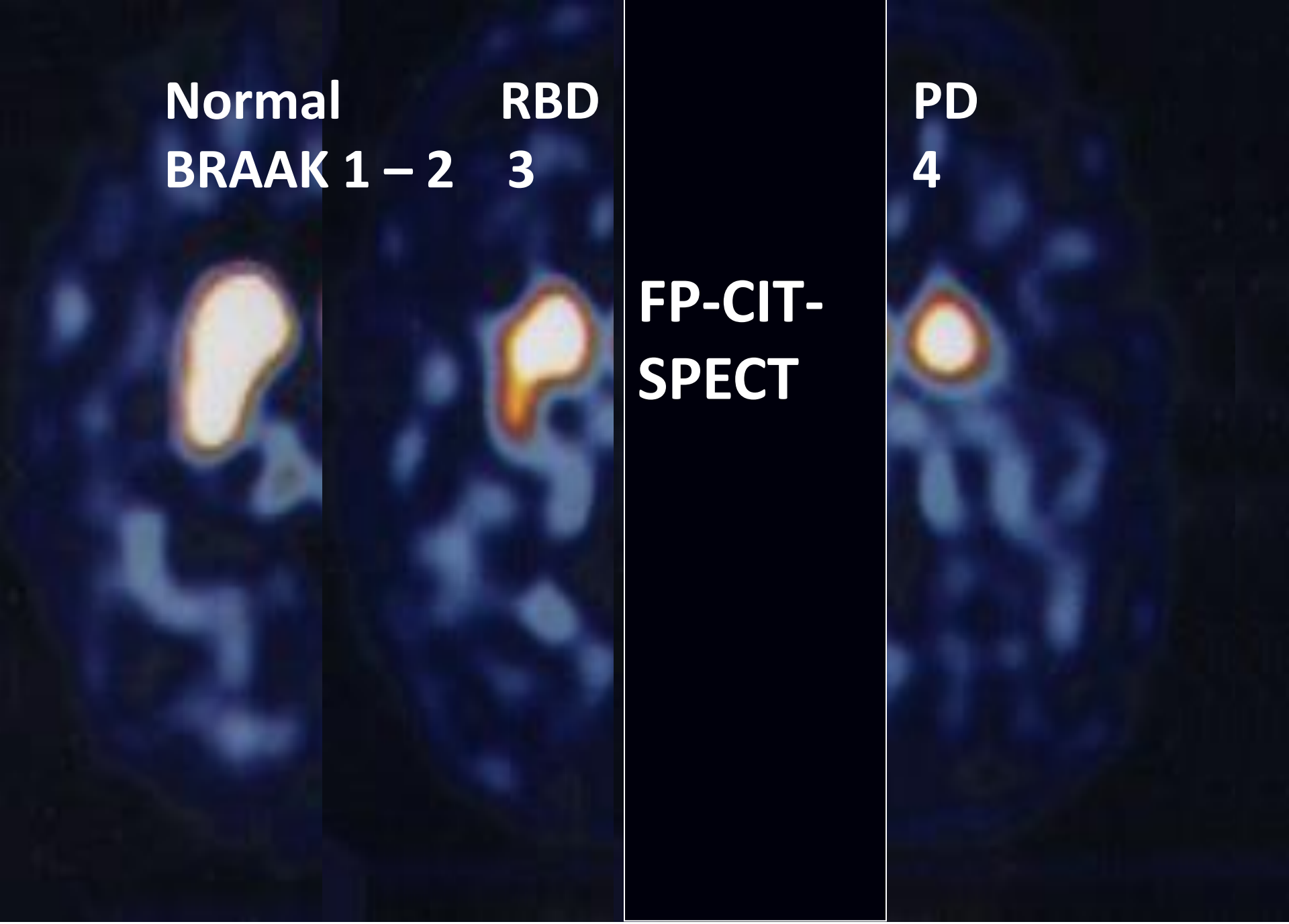
REM-sleep behaviour disorder (RBD) - 2015

these patients will develop in

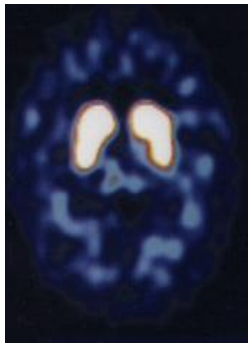
> 85 %

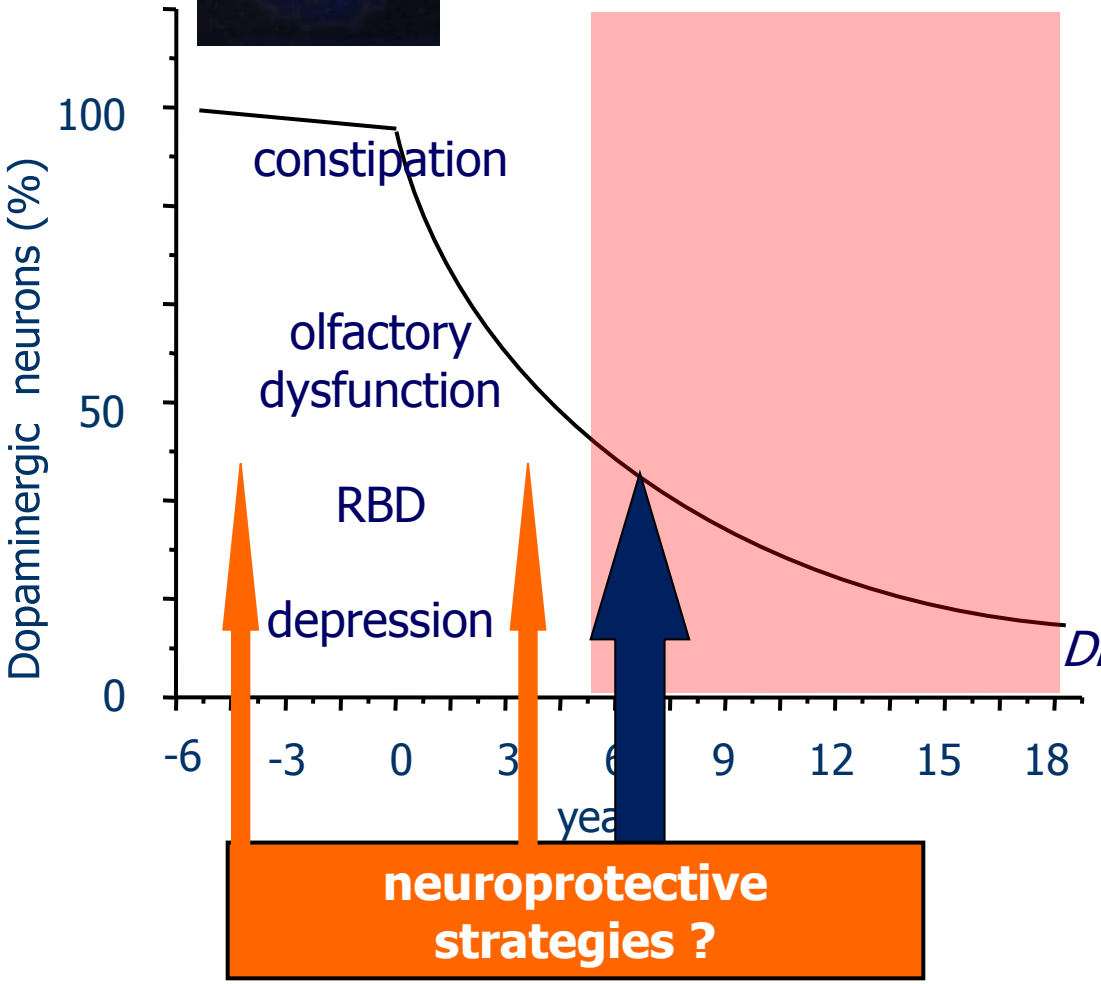
a Parkinson syndrome

after 15 – 20 years

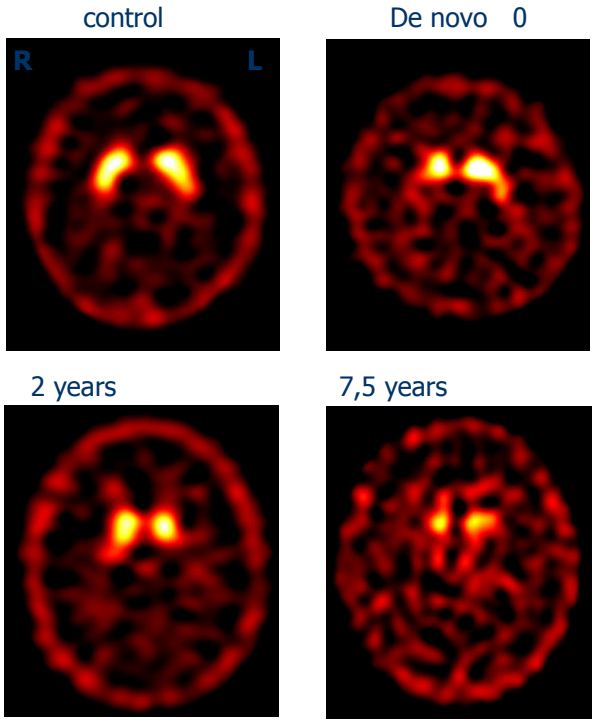

Normal
BRAAK 1 – 2
RBD
3
FP-CIT-
SPECT
PD
4

Symptomatic therapy (motor) phase





Disease progression



(modified from Schwarz et al., 2004)

Preventing neurological disease

- a dream or a realistic aim ?

Example Parkinson’s disease

The power of patients in science

These people will drive the discovery

of a cure for Parkinson‘s disease


UKGM

The development /course of Parkinson‘s disease

Preclinical PD
prodromal

Olfactory dysfunction
Constipation
RBD
Anxiety, Depression

Early treated PD (stabil)

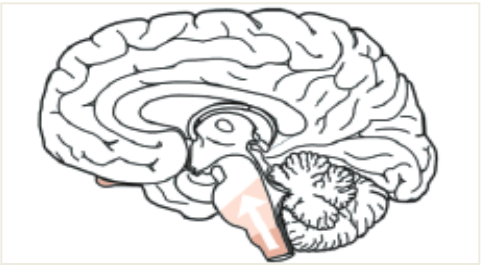
Bradykinesia
Rigidity
Tremor at rest
(+/- non-motor-symptoms)

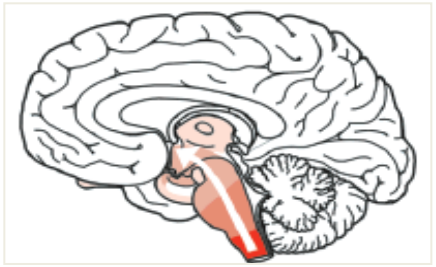
Advanced PD

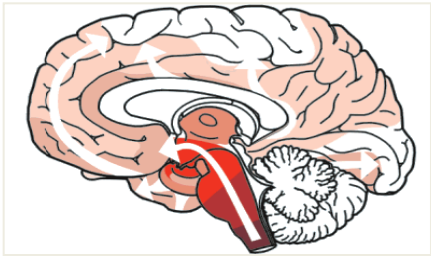
Motor complications
wearing off/dyskinesia
Gait disorder- and postural instability
Dysphagia

Non-Motor complications
dementia, psychosis, autonomic dysfunction, sleep wake distubances

-10 - 20 | 0 | 2 | 5 | 10 years

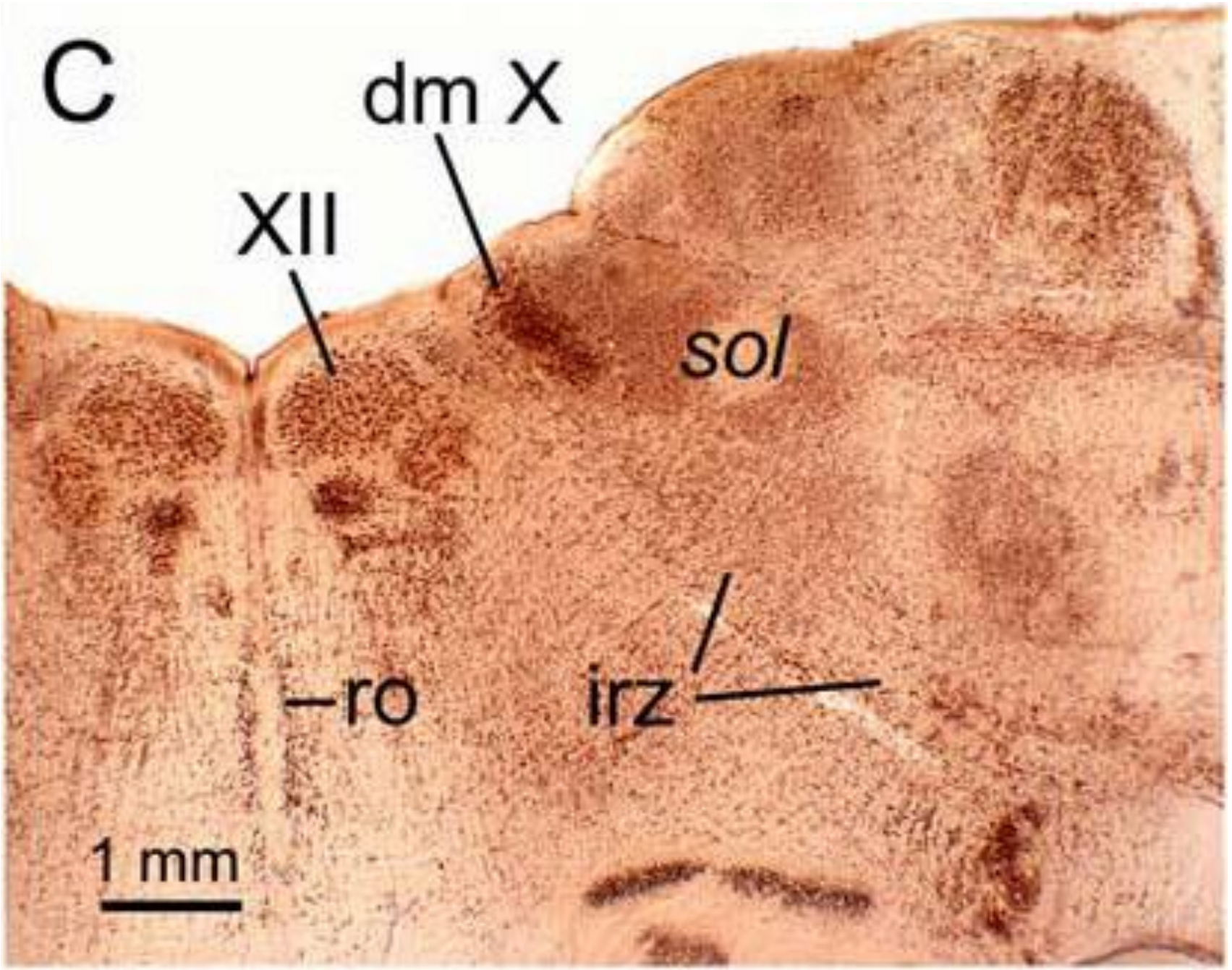






Non-motor symptoms in the premotor phase of PD

Premotor symptoms	*Related brain structures*	*Braak staging*
Constipation	**dorsal motor nucleus of the vagus; enteric plexus neurones**	**1**
BRAIN Impairment or loss of smell	**olfactory bulb; anterior olfactory nucleus**	**1**
Depression	**locus coeruleus; raphe nuclei**	**2**
REM sleep behaviour Disorder (RBD)	**dorsal midbrain and pons; locus coeruleus**	**2 ?**
Akinesia	Substantia nigra	3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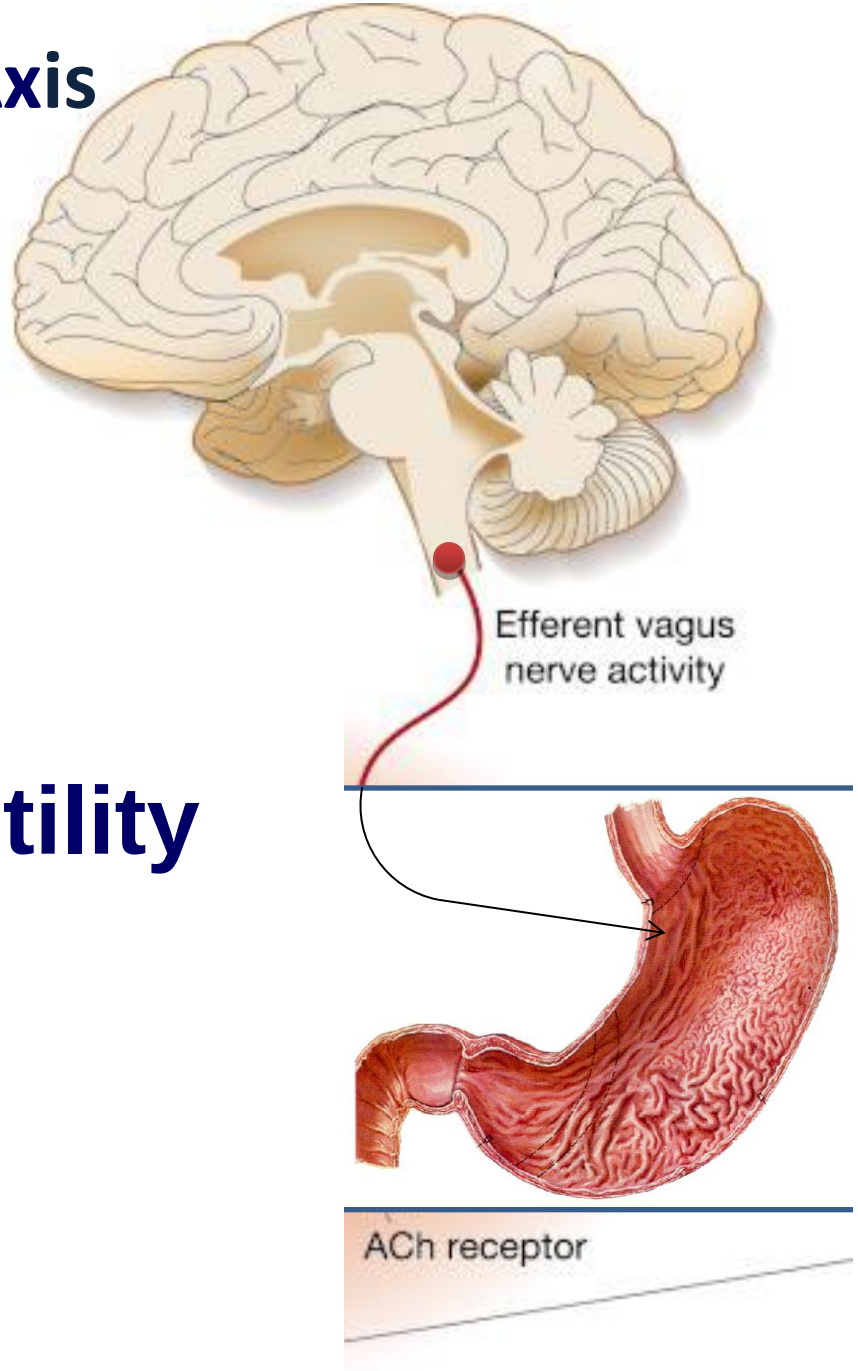
1 mm

The Brain-Gut-Axis



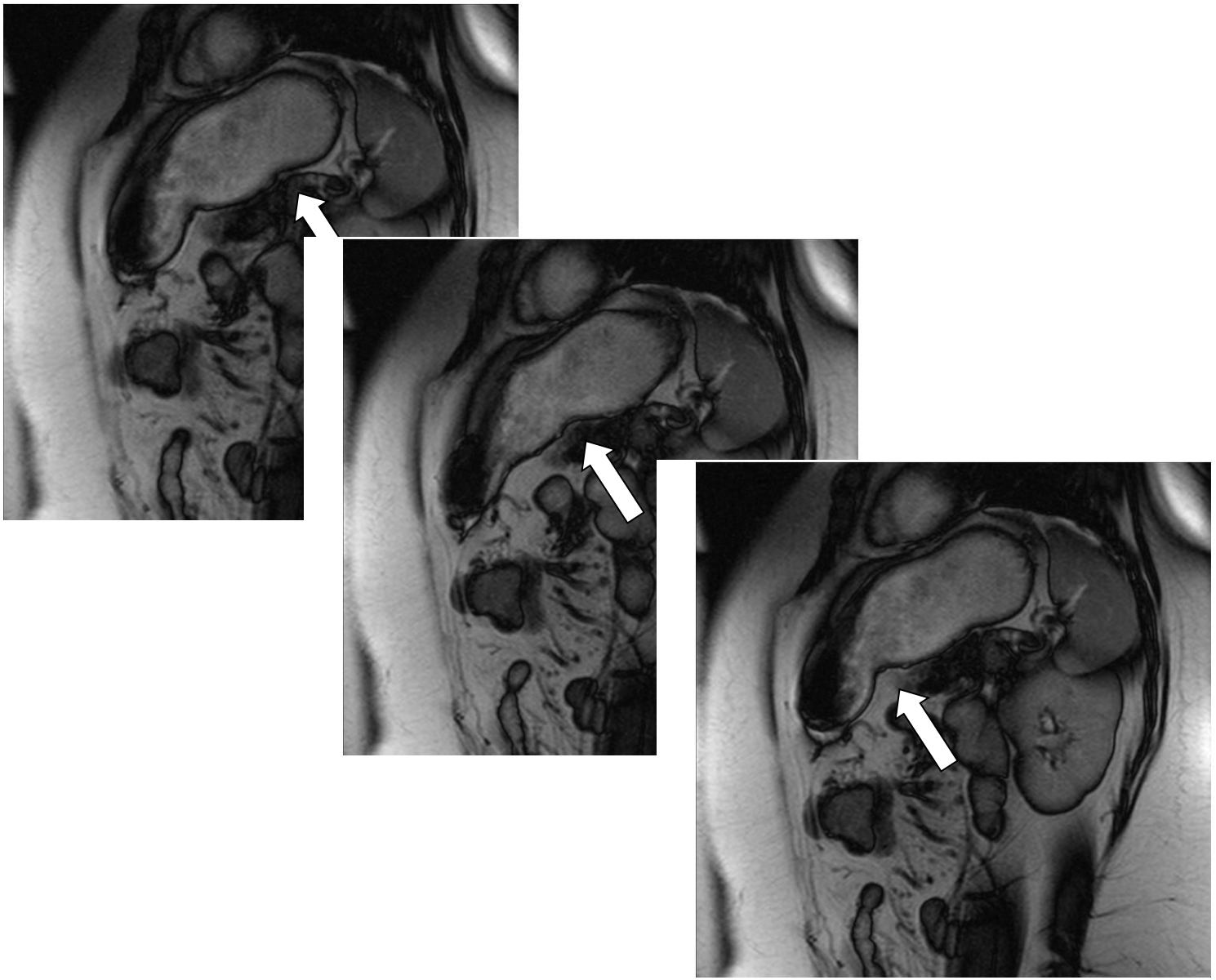
Dorsal motor nucleus of the vagal nerve

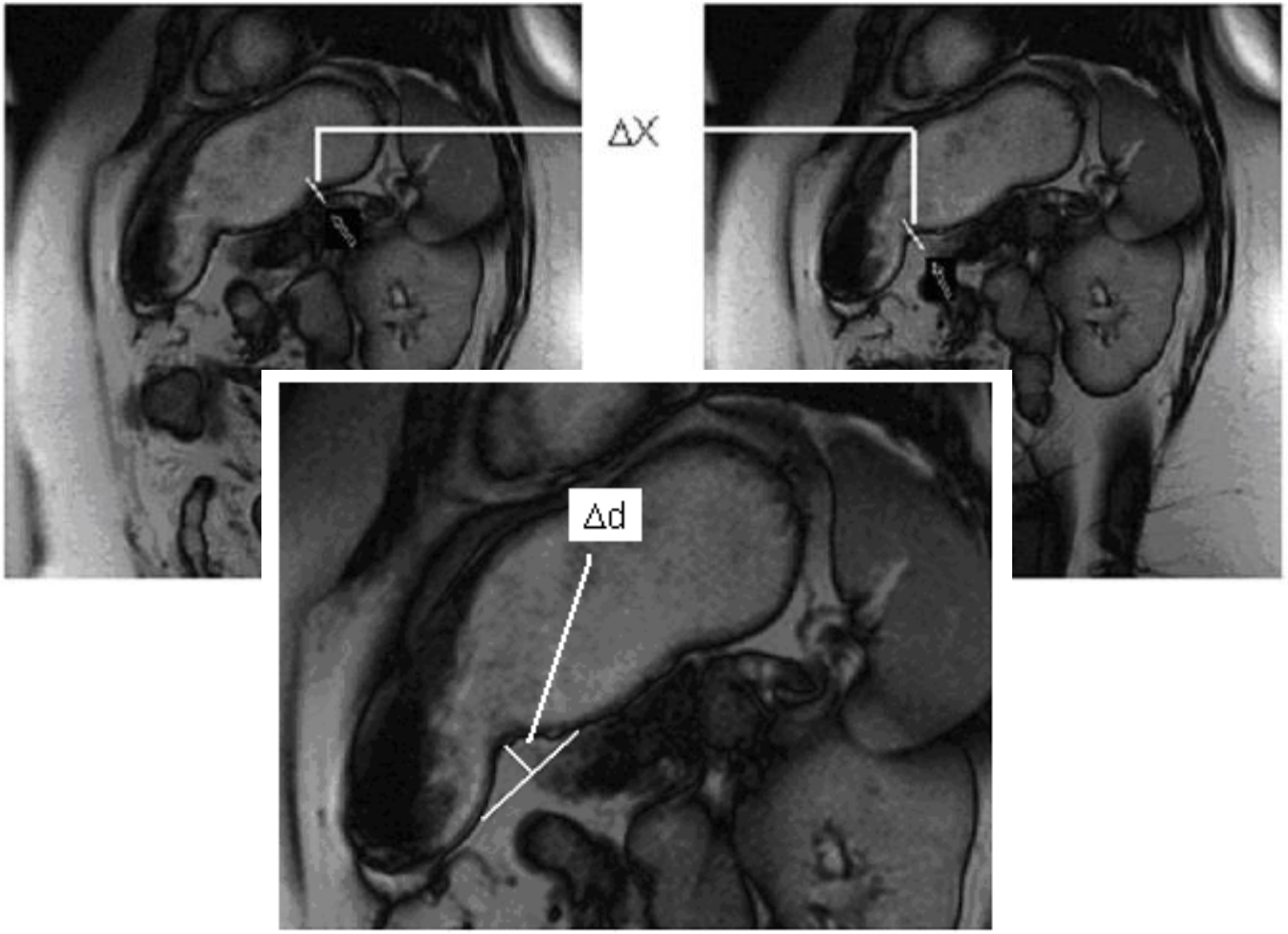
Gastric motility

MRI-Video

Fast

forward




ΔX
Δd

MRT Results Unger et al., Mov Disord 2010

p= 0,059 → non significant difference

	PD	Controls
GMI (mm^2/s)	11 ± 6,9	16,5 ± 5,1
Velocity (mm/s	2,08 ± 0,63	2,07 ± 0,45
Amplitude (mm)	5,35 ± 2,85	8,06 ± 2,31

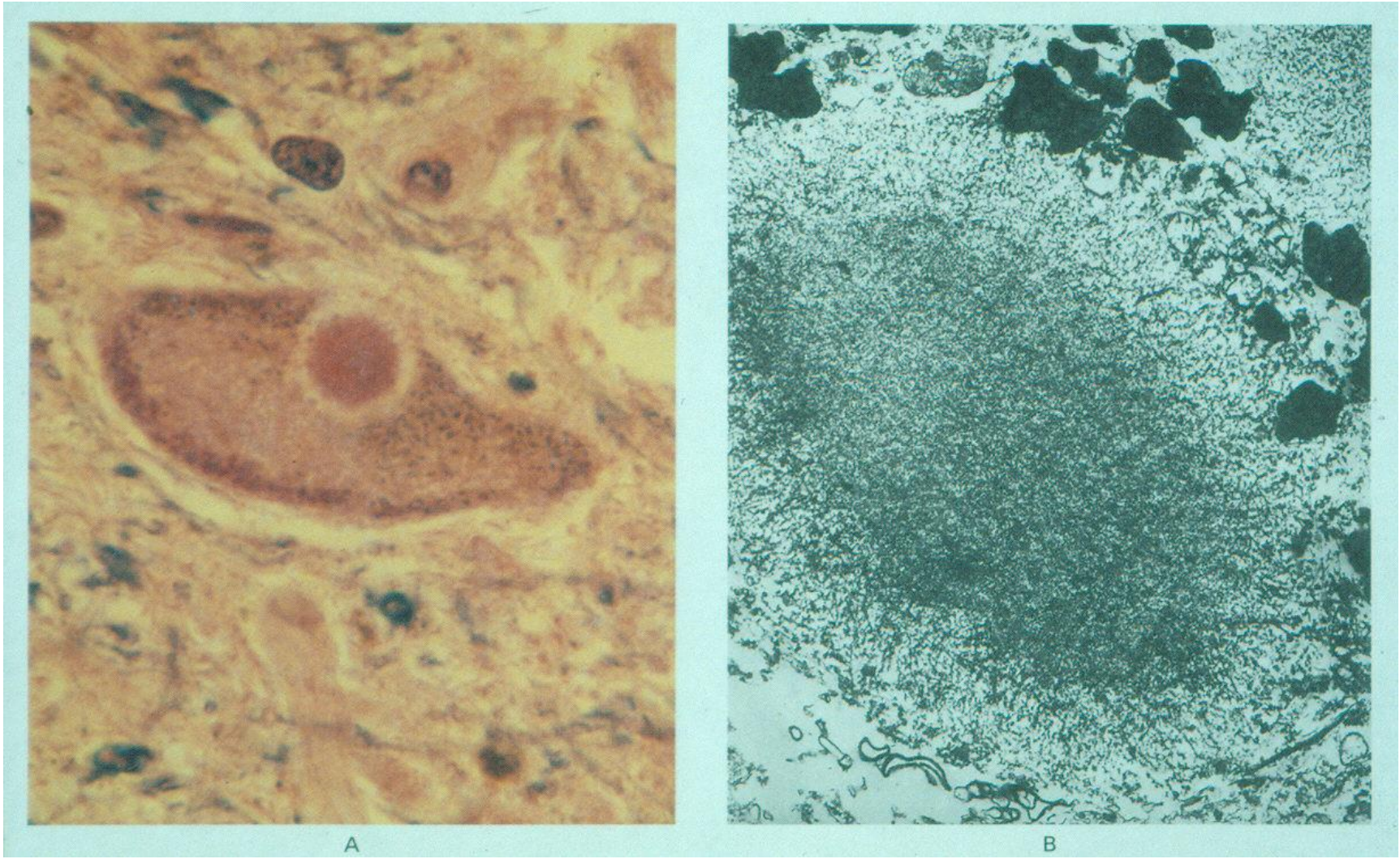
p=0,97 → non significant difference

p=0,029 → significant difference

Non-motor symptoms in the premotor phase of PD

Premotor symptoms	*Related brain structures*	*Braak staging*
Constipation	**dorsal motor nucleus of the vagus; enteric plexus neurones**	**1**
BRAIN Impairment or loss of smell	**olfactory bulb; anterior olfactory nucleus**	**1**
Depression	**locus coeruleus; raphe nuclei**	**2**
REM sleep behaviour Disorder (RBD)	**dorsal midbrain and pons; locus coeruleus**	**2 ?**
Akinesia	Substantia nigra	3

PD - Lewy body, Lewy neurites 1912
protein aggregation



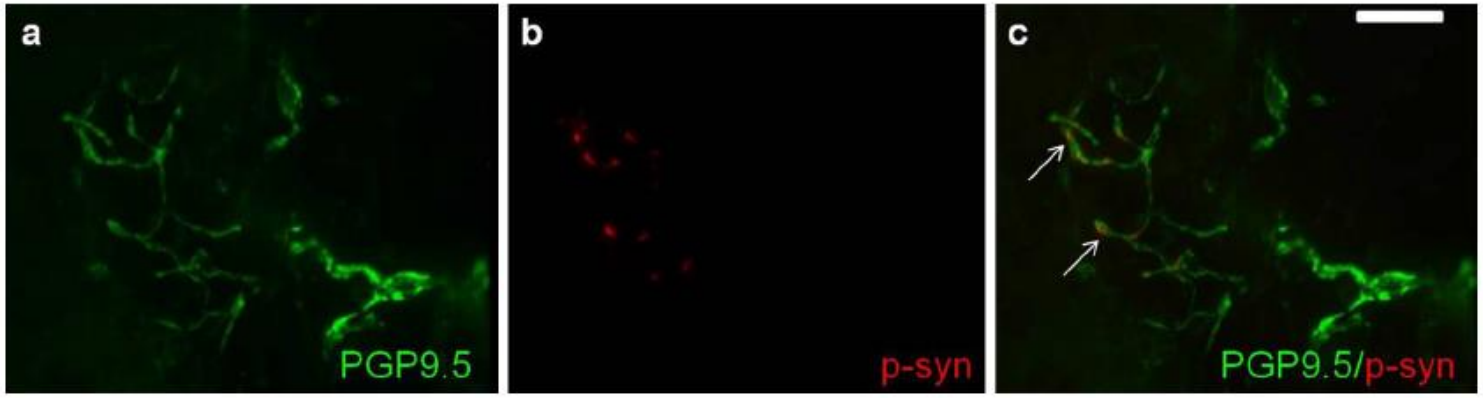
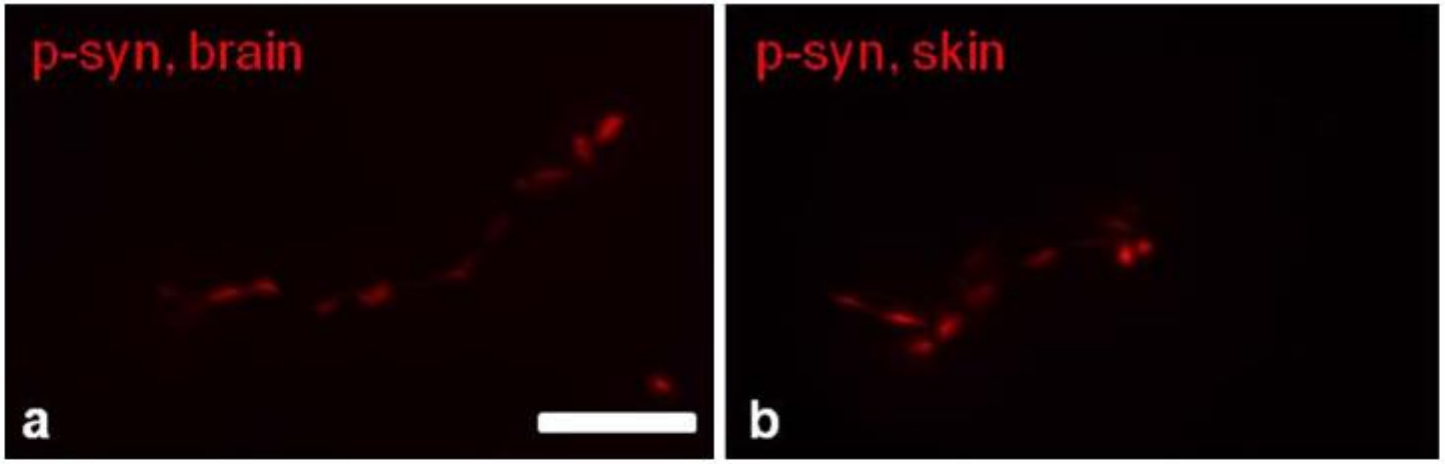


Fig. 1 Photomicrograph of a skin biopsy of a PD patient double stained with anti-PGP9.5 and anti-p-alpha-synuclein. Note colocalization (*arrows*) of PGP9.5 (**a**, **c**) and phosphorylated alpha-synuclein (**b**, **c**) in a nerve fiber of the subepidermal plexus. *Bar* 50 μm



ig. 3 Photomicrograph of p-alpha-synuclein immunolabeling of the substantia nigra of a PD patient (**a**) and of a skin biopsy of another PD atient (**b**). Morphology of p-alpha-synuclein deposits of dermal nerve fibers (**b**) resembles CNS Lewy neurites (**a**). *Bar* 10 μm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Skin biopsy

Healthy people 0 %

Parkinson‘ s disease > 90 %

Prodromal Parkinson‘s disease:

REM sleep behaviour disorder ?? %

Development of preventive therapy ?

INCUBATOR

Boston, USA
Harvard University - MIT
Research Park – Companies

Seoul
Shanghai
Singapur

INCUBATOR - Europe

The Golden Triangle, UK
Cambridge - London - Oxford

Munich and Bavaria /
Heidelberg-Tübingen-Ulm

Paris Metropol area

Berlin Metropol area

The biotechnology and pharmaceutical industries in the Munich Metropolitan Region (EMM)

IHK München und Oberbayern

City of Munich
Department of Labor and Economic Development

BioM

Incubator - Europe

The Golden Triangle, UK

Cambridge - London - Oxford

Munich and Bavaria /

Heidelberg-Tübingen-Ulm

Allianz, Audi (close), BMW, Linde,
Munich Rück Insurance, Siemens
Octoberfest, Bayern Munich

Overcome barriers of communication

Skill set

7 languages

Policy maker
Industry
Physican (NRO,PSY)
Neuroscientist
Patient
Investment banker/foundation
Journalist

Overcome barriers of communication

Brain7

B7

In 2020 the currency of the

European Union will be the

NEURO

Marburg NPF CENTER OF EXCELLENCE

Collaboration

Deutsche Forschungsgemeinschaft DFG

THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH

Brussel
March 03 - 2015

Bundesministerium für Bildung und Forschung

DLR

EU –
JP-Neurodegeneration

GPS German Parkinson Study Group

Internationaal Parkinson Fonds

Wolfgang H Oertel, Karla Eggert, David Vadasz,
Christoph Best, Geert Mayer
Hertie Senior Research Professor
Klinik für Neurologie, Universität Marburg
International and German RBD Study Group
Landscape (DLB,PDD) Coordination Center

Kompetenznetz Parkinson Demenz

Gemeinnützige Hertie-Stiftung

PHILIPPS-UNIVERSITÄT MARBURG 15 27

KKS Koordinierungszentrum für Klinische Studien Marburg