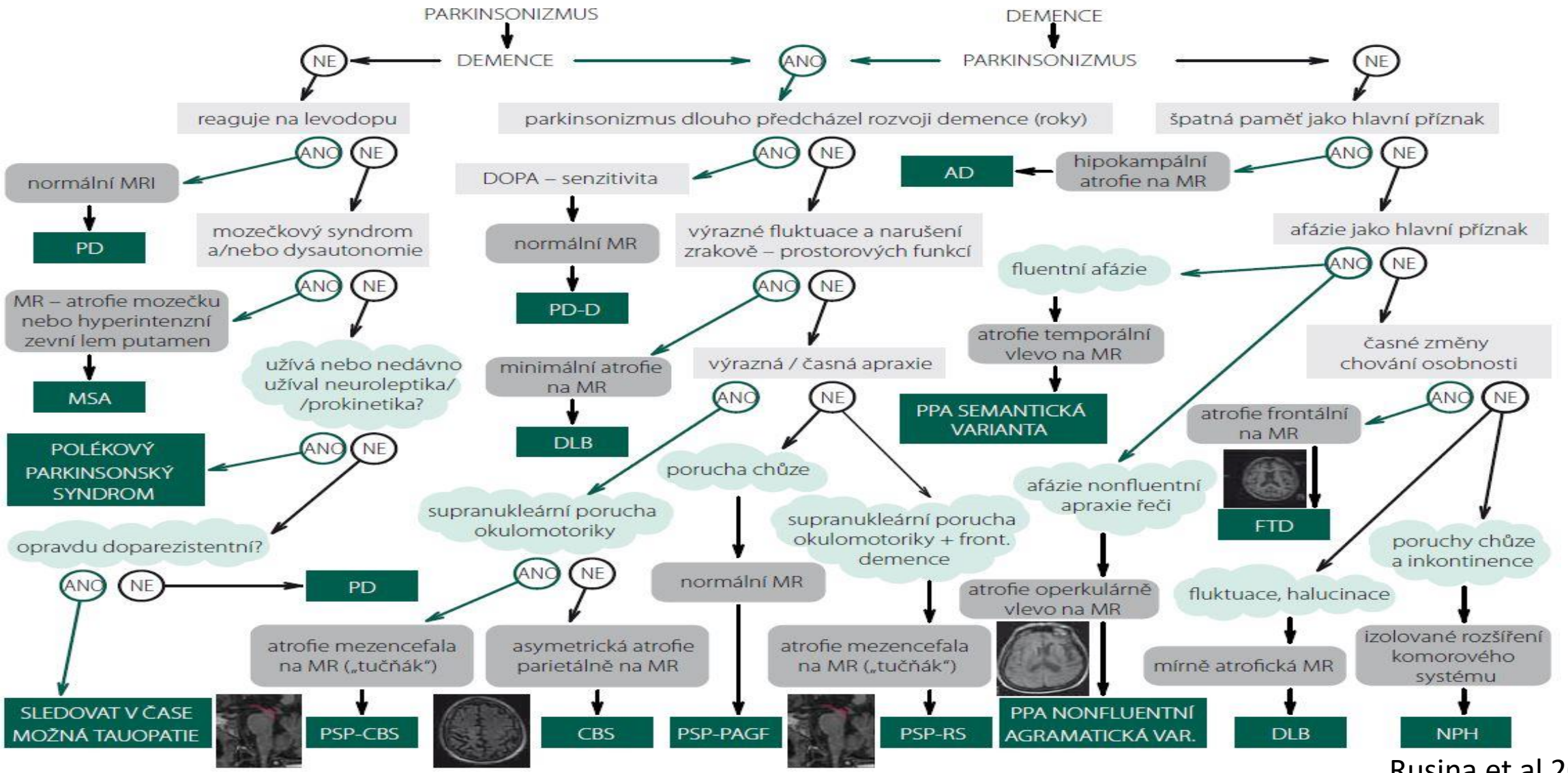
Neuropsychiatry: Cognitive disorders

Tomáš Glaser

Neuropsychiatry

- Multidisciplinary team
- Neurologist + Psychiatrist + Neuropsychologist

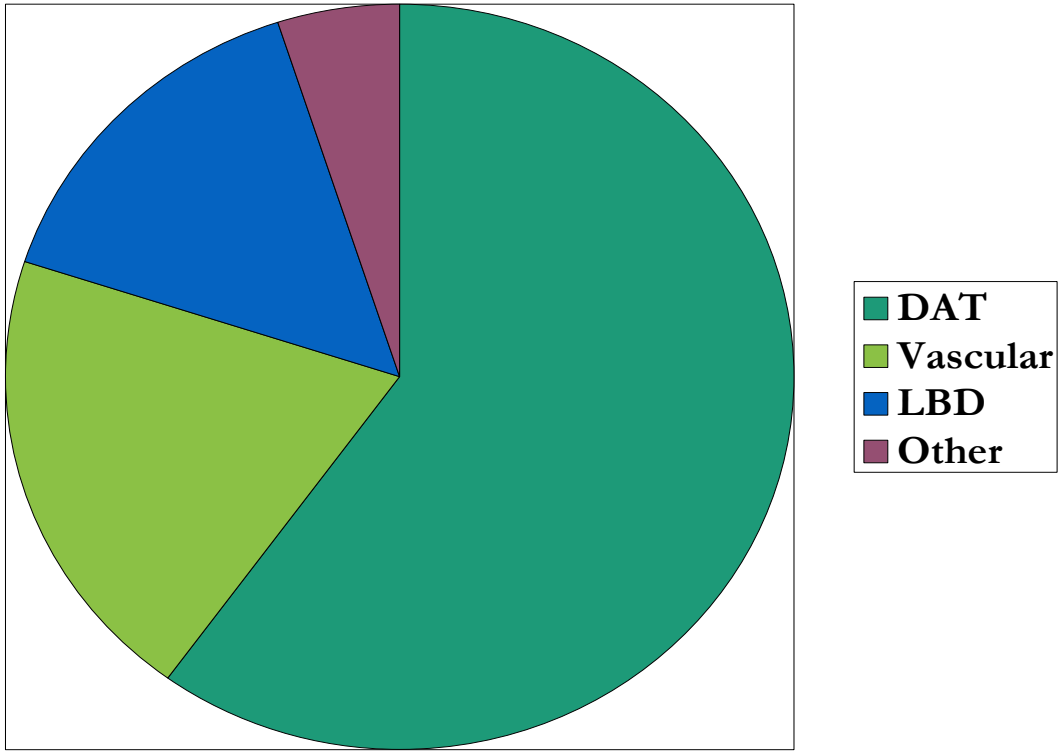
- + social workers, nurses, cognitive trainers, radiologist….



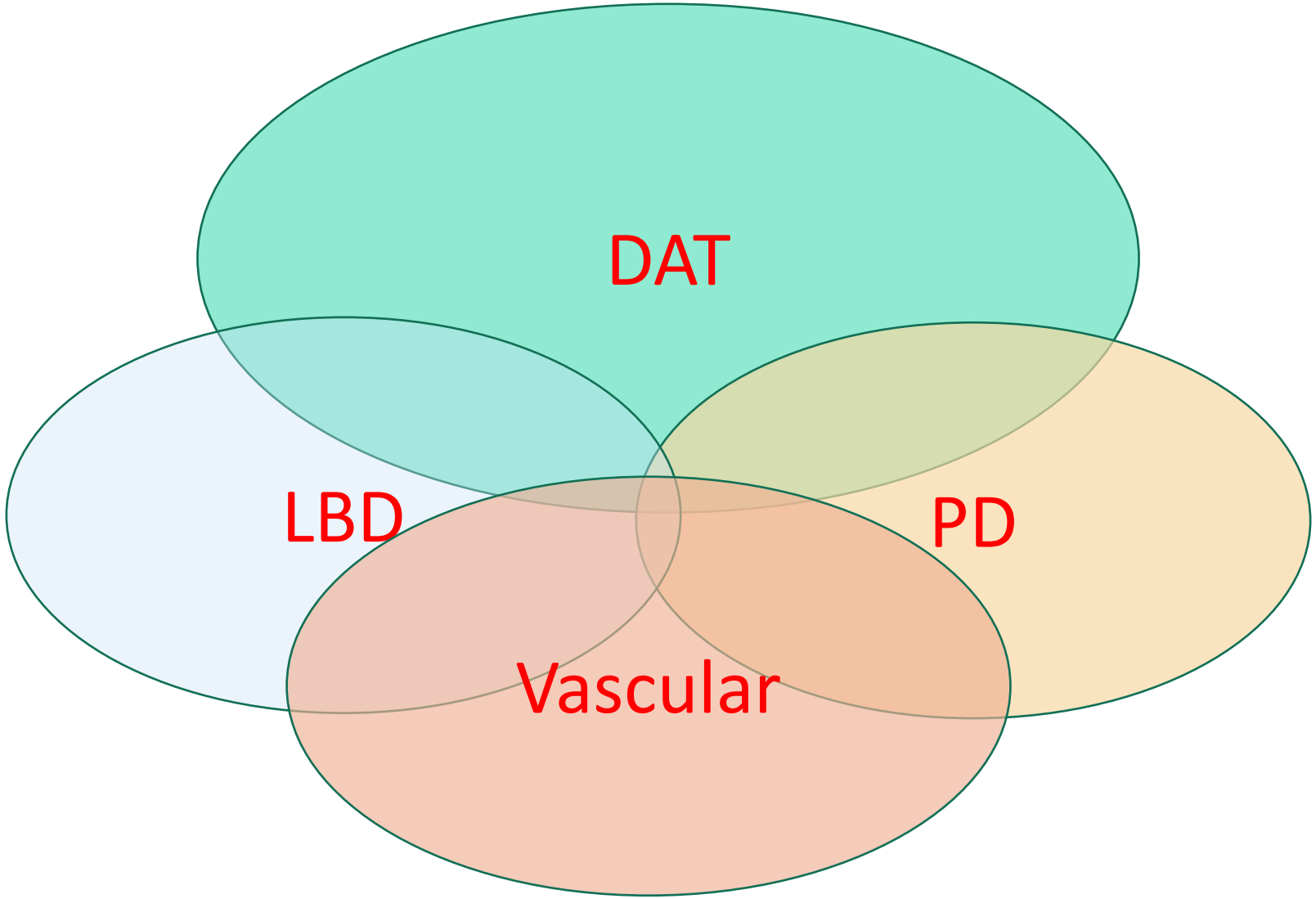
Rusina et al 2015

Institut neuropsychiatrické péče - komplexní léčba / mezioborový přesah / individuální přístup
Neurologie, psychiatrie, dětská neurologie, dětská psychiatrie, klinická psychologie, psychoterapie a lékárna.

INEP



- AD 50 - 70%
- VD 10 - 30%
- LBD 10 - 20%
- FTLD 1 - 20%
- PD 1 - 10%
- PSP, NPH 1 - 10%

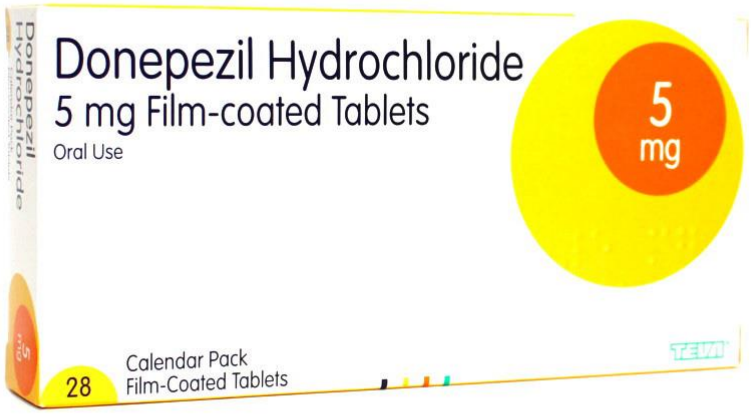

DAT
LBD
PD
Vascular

Therapy?

- Cholinesterase inhibitors
- Memantine

- Egb 761

- SSRI, AP (quetiapine, tiapride)



Section 1: Early-Stage Clinical Drug Development

Amyloid beta

Project Name	Trial Name on CT.gov	Principal Investigator/ Institution	Intervention	Population	Anticipated Completion Date
Discover Study (CSF Sampling: Safety, Tolerability, PK and PD of Posiphen[1] in Subjects With Early Alzheimer's Disease (DISCOVER)	Safety, Tolerability, PK and PD of Posiphen[1] in Subjects With Early Alzheimer's Disease (DISCOVER)	Douglas Galasko, University of California, San Diego	Posiphen (inhibitor of amyloid precursor protein (APP) processing)	People with amnestic Mild Cognitive Impairment or mild Alzheimer's disease (Ages 55-85)	2021
Generation Study: Alzheimer's Prevention Initiative Apolipoprotein E4 Trial	A Study of CAD106 and CNP520 Versus Placebo in Participants at Risk for the Onset of Clinical Symptoms of Alzheimer's Disease (Generation E4)	Eric Reiman and Pierre Tariot, Banner	CAD106 (anti-amyloid β immunotherapy) CNP520 (beta-secretase inhibitor)	Cognitively healthy individuals with two copies of the APOE ε4 gene (Ages 60-75)	2025
Active Immunotherapy for Cognitive Decline in Adults with Down Syndrome	Safety, Tolerability and Immunogenicity of ACI-24 Vaccine in Adults With Down Syndrome (I Star)	Howard Feldman, University of California San Diego	ACI-24 (anti- amyloid β vaccine)	Down syndrome adults age (Ages 35-55)	2020
Solid oral dosage form and chronic tox for PTI-125	A Phase I Study in Healthy Volunteers	Lindsay H. Burns Pain Therapeutics, Inc.	PTI-125 (Vitamin A (FVNA), a protein critical to beta amyloid's toxicity)	Healthy volunteers (Ages 18-45)	2020
A Pilot Synaptic Vesicle Glycoprotein 2A (SV2A) PET Study to Evaluate the Effect of CT1812 Treatment on Synaptic Density in Subjects with Mild to Moderate Alzheimer's Disease	Effect of CT1812 Treatment on Brain Synaptic Density	Susan Catalano, Cognition Therapeutics, Inc.	CT1812 (sigma2 receptor antagonist)	People with Alzheimer's disease (Ages 50-85)	2020
A Pilot CSF Catheter Study to Evaluate the Effect of CT1812 Treatment on Aβ Oligomer Clearance Into CSF in Subjects with Mild to Moderate Alzheimer's Disease	Study to Evaluate the Effect of CT1812 Treatment on Amyloid Beta Oligomer Displacement Into CSF in Subjects With Mild to Moderate Alzheimer's Disease	Susan Catalano, Cognition Therapeutics, Inc.	CT1812 (sigma2 receptor antagonist)	People with Alzheimer's disease Ages 50-80)	2020
Multiple Ascending Dose clinical trial of PTI-125, a novel AD therapeutic candidate	Open-label, PK and Safety Study in Mild-to-moderate Alzheimer's Disease Patients	Lindsay H. Burns Pain Therapeutics, Inc.	PTI-125 (Vitamin A (FVNA), a protein critical to beta amyloid's toxicity)	Mild to Moderate Alzheimer's Disease (Ages 50-85)	2020
Randomized, Double-blind, Placebo-Controlled, Parallel-Group, Phase II Study to Evaluate the Safety and Efficacy of CT1812 in Subjects with Mild to Moderate Alzheimer's Disease	A Study to Evaluate the Safety and Efficacy of CT1812 in Subjects With Mild to Moderate Alzheimer's Disease	Susan Catalano, Cognition Therapeutics, Inc.	CT1812 (sigma2 receptor antagonist)	Mild to Moderate Alzheimer's Disease Ages 50-85)	2022
A Seamless Phase 2A-B Randomized Double Blind Placebo Controlled Trial to Evaluate the Efficacy and Safety of PQ912 in Patients with Early Alzheimer's Disease	A Trial to Evaluate the Efficacy and Safety of PQ912 in Patients With Early AD	Howard Feldman, University of California San Diego	PQ 912 (glutaminyl cyclase (QC) inhibitor) (treats both amyloidopathy and neuroinflammation)	Adults with MCI or mild probable AD (Ages 50-89)	2025
Pilot Electroencephalography (EEG) Study to Evaluate the Effect of CT1812 Treatment on Synaptic Activity in Subjects with Mild to Moderate Alzheimer's Disease	TBD	Susan Catalano, Cognition Therapeutics, Inc.	CT1812 (sigma2 receptor antagonist)	Adults with Mild to Moderate Alzheimer's Disease (Ages 50-80)	2021

Receptors

Project Name	Trial Name on CT.gov	Principal Investigator/ Institution	Intervention	Population	Anticipated Completion Date
The delivery of essential fatty acids to the Brain in Alzheimer's disease	DHA Brain Delivery Trial (Prevent E4)	Yassine, Hussein, University of Southern California	Docosahexaenoic acid (DHA) (lipid)	Healthy adult carriers and non-carriers of APOE ε4 (Ages 60-80)	2022
Long Term Nicotine Treatment of Mild Cognitive Impairment	Memory Improvement Through Nicotine Dosing (MINO) Study (MINO)	Paul Newhouse, Vanderbilt University Paul Aisen, Alzheimer's Therapeutic Research Institute	Nicotine (Nicotinic receptor agonist)	People with Mild Cognitive Impairment (Ages ≥ 55)	2021
Network-Level Mechanisms for Preclinical Alzheimer's Disease Development	Network-Level Mechanisms for Preclinical Alzheimer's Disease Development	Shi-Jiang Li, Medical College of Wisconsin	Levetiracetam (LEV) (synaptic vesicle protein (SV2A) modulator)	Healthy adults, carriers of APOE ε4 (Ages 55-75)	2020
Treating hyperexcitability in Alzheimer's disease with levetiracetam to improve brain function and cognition	Treating Hyperexcitability in AD With Levetiracetam	Moustafa Shaef Harvard	Levetiracetam (synaptic vesicle protein (SV2A) modulator)	Adults with probable AD (Ages 50-90)	2024

Synaptic plasticity/Neuroprotection

Project Name	Trial Name on CT.gov	Principal Investigator/ Institution	Intervention	Population	Anticipated Completion Date
Neuron regenerative therapeutic, NNI-362, for first-in-human safety and PK for AD	TBD	Judith Kellner-Anderson, Neuronascent, INC.	NNI – 362 (modulates the phosphorylation of p70S6K) (drug functions as neuron regenerative therapy)	Healthy volunteers (Ages 50-72)	2020
Safety and modulation of ABCC9 pathways by nicorandil for the treatment of hippocampal sclerosis of aging (SMART-HS)	TBD	Gregory A. Jicha, University of Kentucky Peter Nelson, University of Kentucky	Nicorandil (agonist for sulfonyl urea receptor 2 protein (SUR2))	Adults with probable Hippocampal sclerosis (HS)-aging (Ages ≥ 75)	2024
(-)-Phenserine inhibition of neuronal death in Alzheimer's disease and developing brain-labeled plasma exosomes assays as biomarkers for a phenserine phase 1B ascending dose trial	TBD	Lon S. Schneider, University of Southern California	(-)-Phenserine (inhibits neuronal pre-programmed cell death)	Adults with probable AD (Ages 70-82)	2025
A randomized, double blind, placebo-controlled study to evaluate the impact of Nilotinib treatment on safety, tolerability, pharmacokinetics and biomarkers in Dementia with Lewy Bodies (DLB)	TBD	Chartel Moussa, Georgetown University	Nilotinib (inhibits CSF tyrosine kinase Abelson (facilitates autophagic degradation of neurotoxic proteins and promotes survival of neurons)	Adults with clinical diagnosis of DLB with both dementia and Parkinsonism (Ages 25-90)	2024

Metabolism and Bioenergetics

Project Name	Trial Name on CT.gov	Principal Investigator/ Institution	Intervention	Population	Anticipated Completion Date
Benfotiamine in Alzheimer's Disease: A pilot study	Benfotiamine in Alzheimer's Disease: A Pilot Study (Benfotiamine)	Gary Gibson, Burke Medical Research Institute	Benfotiamine (synthetic derivative of thiamine (Vitamin B1))	People with Mild Cognitive Impairment or Alzheimer's disease (Ages ≥ 60)	2020
Phase 2 Randomized, Double-Blind, Placebo-Controlled Clinical Trial of T3D-959 in Mild to Moderate Alzheimer's Disease Subjects	TBD	John Olcsbury, T3D Therapeutics	T3D-959 (PPARγ and PPARδ agonist)	Adults with mild to severe AD (Ages 50-90)	2025

Vasculature

Project Name	Trial Name on CT.gov	Principal Investigator/ Institution	Intervention	Population	Anticipated Completion Date
Hypertension, angiotensin receptor blockers, and cognition: effects and mechanism	CAndesartan vs Lisinopril Effects on the BRain (CALIBREX)	Ihab Hajjar, Emory University	Candesartan (angiotensin II receptor blocker)	Hypertensive adults with Mild Cognitive Impairment (Ages ≥ 60)	2020
A biomarker-driven trial of angiotensin receptor blockers for prodromal Alzheimer	Candesartan's Effects on Alzheimer's Disease And Related Biomarkers (CEDAR)	Ihab Hajjar, Emory University	Candesartan (angiotensin II receptor blocker)	Non-hypertensive adults with Mild Cognitive Impairment (Ages ≥ 40)	2022

Growth Factors and Hormones

Project Name	Trial Name on CT.gov	Principal Investigator/ Institution	Intervention	Population	Anticipated Completion Date
A double-blinded, randomized, controlled phase 2a safety, proof-of-concept and exploratory end point trial of the drug LM11A-31 in patients with mild to moderate Alzheimer's disease	Study of LM11A-31-BHS in Mild-moderate AD Patients	Manfred Windisch, Pharmatrophix-NeuroGlia, Inc.	LM11A-31 (p75 neurotrophin receptor (p75NTR)) (function to increase survival signaling and inhibit amyloid-β-induced degenerative signaling)	People with Alzheimer's disease (Ages 50-85)	2022
The LUCINDA Trial	The LUCINDA Trial: Lupron Plus Cholinesterase Inhibition to Reduce Neurological Decline in Alzheimer's (LUCINDA)	Tracy Butler (contact), New York University School of Medicine James Galvin, Florida Atlantic University Craig Atwood, University of Wisconsin	Lupron (gonadotropin-releasing hormone (GnRH) receptor agonist)	Women with mild-moderate Alzheimer's Disease who are also taking AChEi (Ages 55-92)	2024

Multi-target

Project Name	Trial Name on CT.gov	Principal Investigator/ Institution	Intervention	Population	Anticipated Completion Date
Phase II RCT of High-dose Vitamin D Supplements in Older Adults without Dementia	High-dose Vitamin D Supplements in Older Adults	John Gilchrey, University of California, Davis	Vitamin D (Vitamin D receptor)	People with Mild Cognitive Impairment or mild Alzheimer's disease (Ages 65-90)	2025
Evaluation of Brain and Cognitive Changes in Older Adults with MCI Taking Lithium to Prevent Alzheimer Type Dementia	Lithium Axis Treatment to Prevent Impairment of Cognition in Elders (LATTICE)	Ariel Gildengers, University of Pittsburgh Medical Center	Lithium (GSK3α and GSK3β inhibitor)	People with Mild Cognitive Impairment Age (Ages ≥ 60)	2025

Inflammation

Project Name	Trial Name on CT.gov	Principal Investigator/ Institution	Intervention	Population	Anticipated Completion Date
Assessment of lenalidomide to treat Alzheimer's disease	N/A	Marwan Sabbagh, Cleveland Clinic Earl Dacourt, Arizona State University	Lenalidomide (Anti-inflammatory immunomodulator)	Adults with amnestic Mild Cognitive Impairment (Ages ≥ 50)	2024
First-in-human SAD & MAD trials for NW151, a novel Alzheimer's disease drug candidate that attenuates proinflammatory cytokine dysregulation	TBD	Daniel Martin, Watterson Northwestern University Feinberg School of Medicine	NW151 (selectively suppress proinflammatory cytokines))	Healthy volunteers (Open to all adults meeting inclusion criteria)	2022

Oxidative Stress

Project Name	Trial Name on CT.gov	Principal Investigator/ Institution	Intervention	Population	Anticipated Completion Date
2-Hydroxybenzylamine for the prevention of Alzheimer's disease: Initial Evaluation in Humans	2-HOBA: Multiple Dosing Study in Older Adults (2-HOBA)	John Rathmacher, Metabolic Technologies, Inc.	2-hydroxybenzylamine (γ-ketoaldehyde scavenger)	Healthy volunteers (Ages 50-79)	2020
Age- Related Mild Cognitive Impairment and novel protective role of Glutathione: Implications for Alzheimer's Disease	Glutathione in Mild Cognitive Impairment	Sekhar Rajagopal Vissvanath Baylor College of Medicine	Glutathione (antioxidant)	Adults with MCI (Ages 65-80)	2025

Other

Project Name	Trial Name on CT.gov	Principal Investigator/ Institution	Intervention	Population	Anticipated Completion Date
Evaluating the disease-modifying potential of a sleep intervention for Alzheimer's Disease outcomes	TBD	Nazan Aksan, University of Iowa	Melatonin (regulates sleep cycle)	Older adults (Ages 60-75)	2025
Olfactory deficits and donepezil treatment in cognitively impaired elderly	Olfactory Deficits and Donepezil Treatment in Cognitively Impaired Elderly	Devangere Devanand, Columbia University	Donepezil (acetylcholinesterase (AChE) inhibitor)	People with Mild Cognitive Impairment or Alzheimer's disease (Ages 55-95)	2020
NAD+ therapy for improving memory & cerebrovascular function in patients with MCI	NAD Therapy for Improving Memory and Brain Blood Flow in Older Adults With Mild Cognitive Impairment	Christopher Martens, University of Colorado	Nicotinamide Riboside (precursor to Nicotinamide adenine dinucleotide (NAD+))	People with amnestic Mild Cognitive Impairment (Ages 60-92)	2025
Anti-viral therapy in Alzheimer's disease	Anti-viral Therapy in Alzheimer's Disease	Devangere Devanand, Columbia University	Valacyclovir (Anti-HSV drug)	People with mild Alzheimer's disease (Open to all adults meeting inclusion criteria)	2025
Biomarker Predictors of Memantine Sensitivity in Patients with Alzheimer's Disease	Biomarker Predictors of Memantine Sensitivity in Patients With Alzheimer's Disease	Neal Swerdlow, University of California	Memantine (noncompetitive NMDA receptor antagonist)	Mild to Moderate Alzheimer's Disease	2025
Pathophysiology of postoperative delirium and the use of biomimetic sleep as a treatment strategy in the CSICU	Minimizing ICU Neurological Dysfunction With Dexmedetomidine-Induced Sleep (MINDCIS)	Oluwaseun Johnson-Akeju Massachusetts General Hospital	Preemptive biomimetic sleep induction in reducing the incidence of delirium	>=60 yrs old scheduled for cardiac surgical procedure	2021

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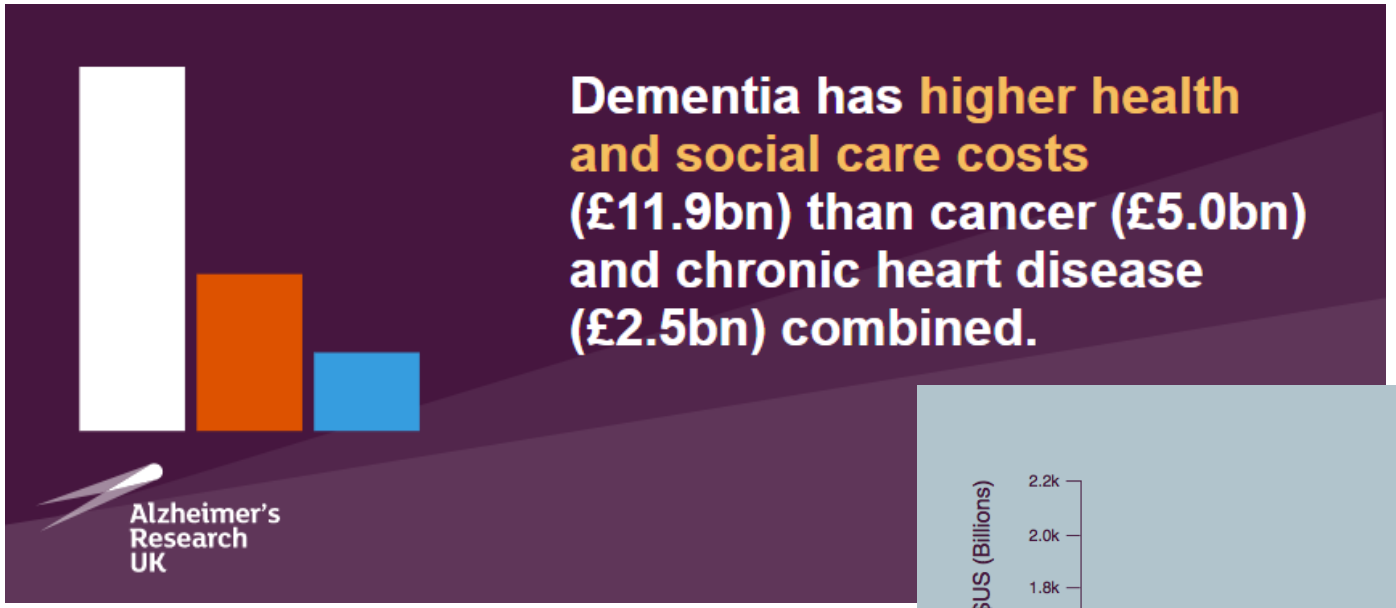
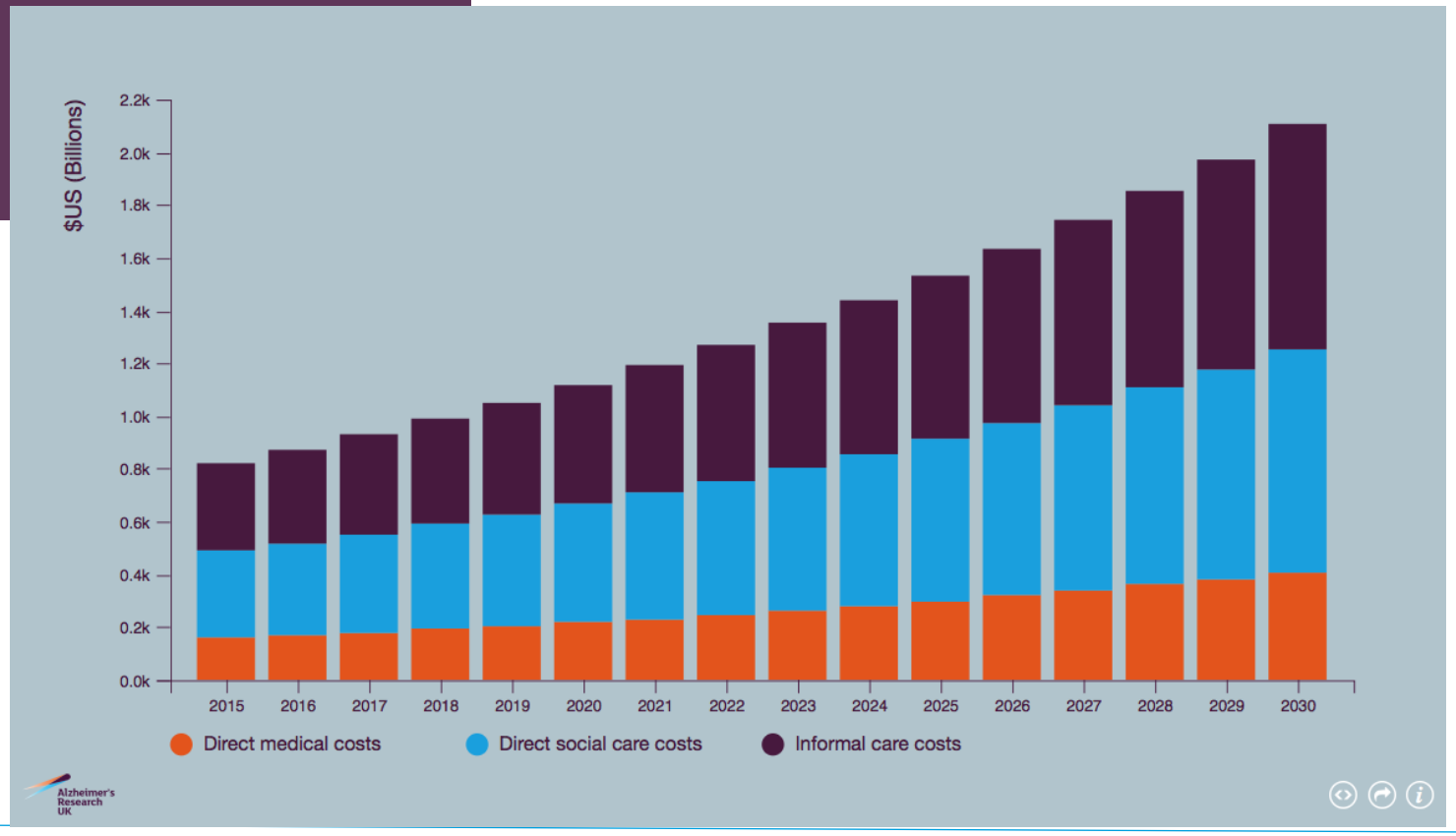
https://www.nia.nih.gov/research/ongoing-AD-trials


Dementia has higher health and social care costs (£11.9bn) than cancer (£5.0bn) and chronic heart disease (£2.5bn) combined.
Alzheimer's Research UK

The cost of dementia in the UK is expected to more than double in the next 25 years, from £26bn to £55bn in 2040.
Alzheimer's Research UK


$US (Billions)
2.2k
2.0k
1.8k
1.6k
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1.2k
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0.6k
0.4k
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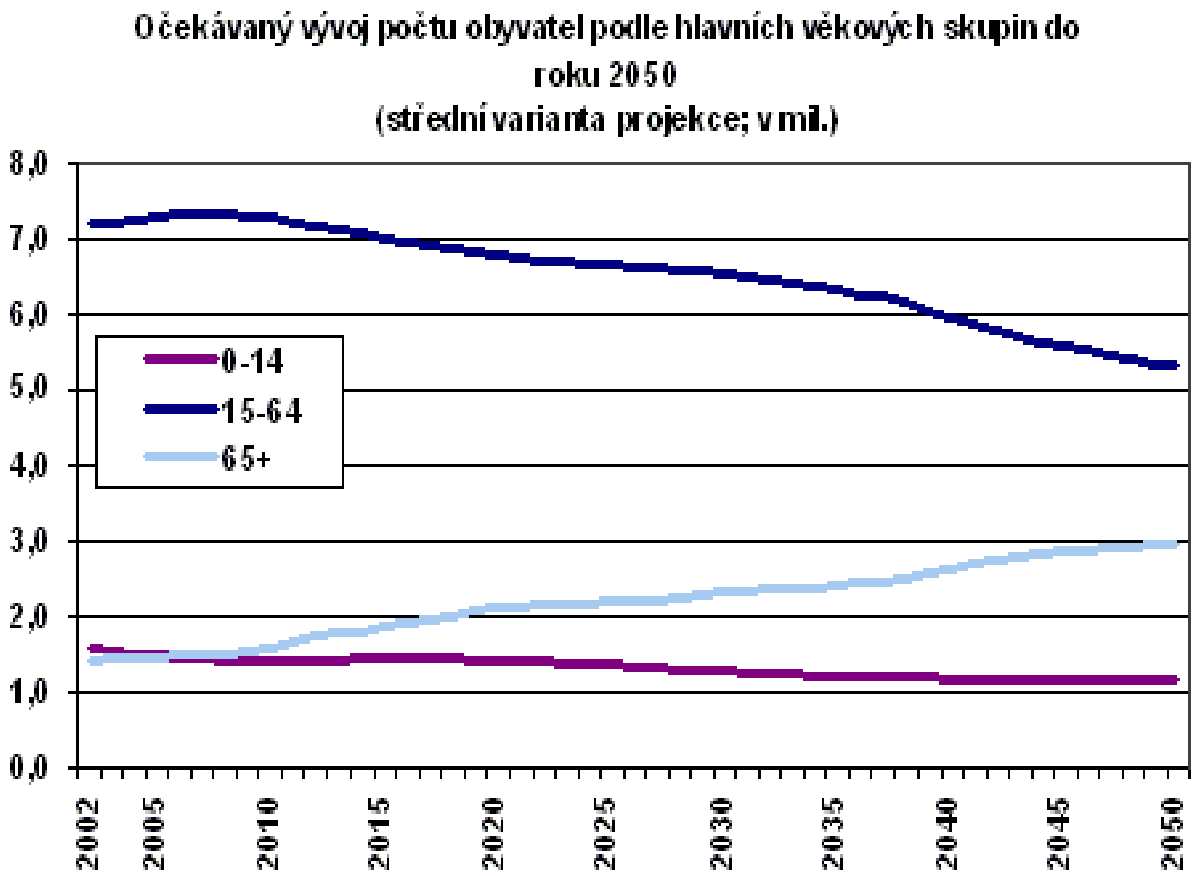
Direct medical costs
Direct social care costs
Informal care costs
Alzheimer's Research UK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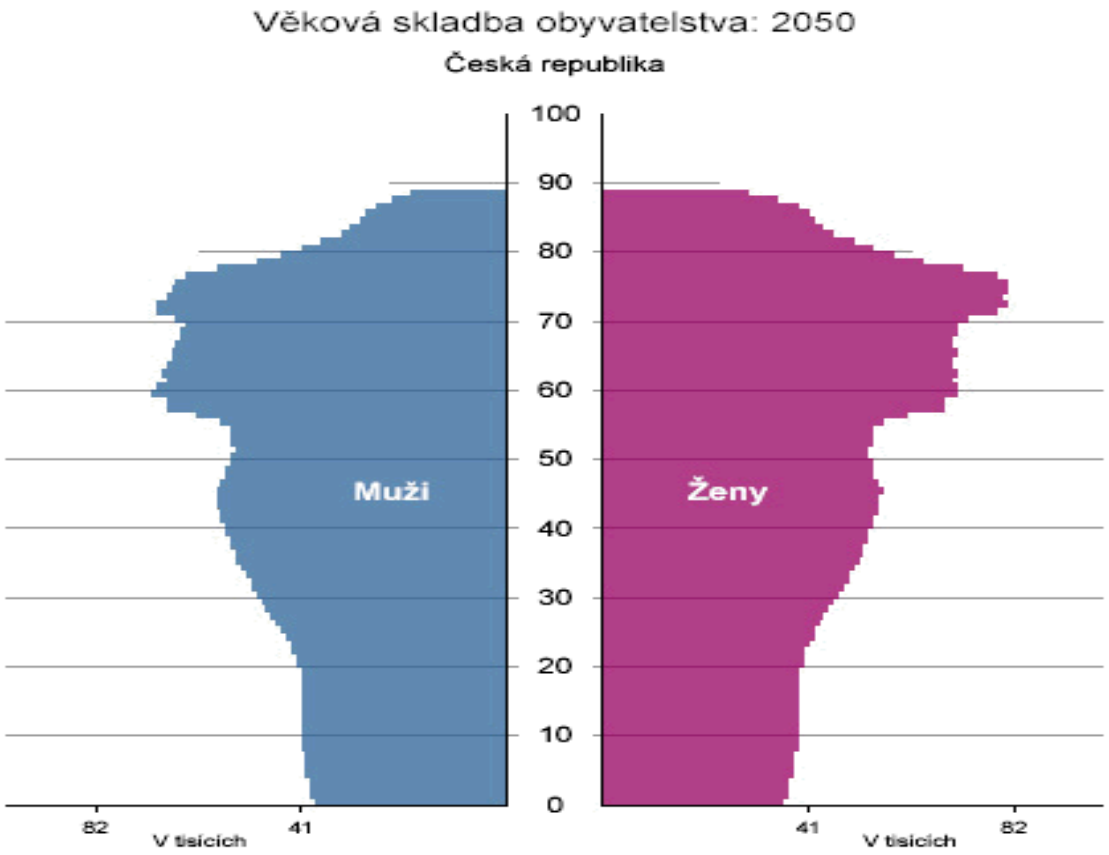
(střední varianta projekce; v mil.)
8,0
7,0
6,0
5,0
4,0
3,0
2,0
1,0
0,0
0-14
15-64
65+
2002
2005
2010
2015
2020
2025
2030
2035
2040
2045
2050


Věková skladba obyvatelstva: 2050
Česká republika
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90
80
70
60
50
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10
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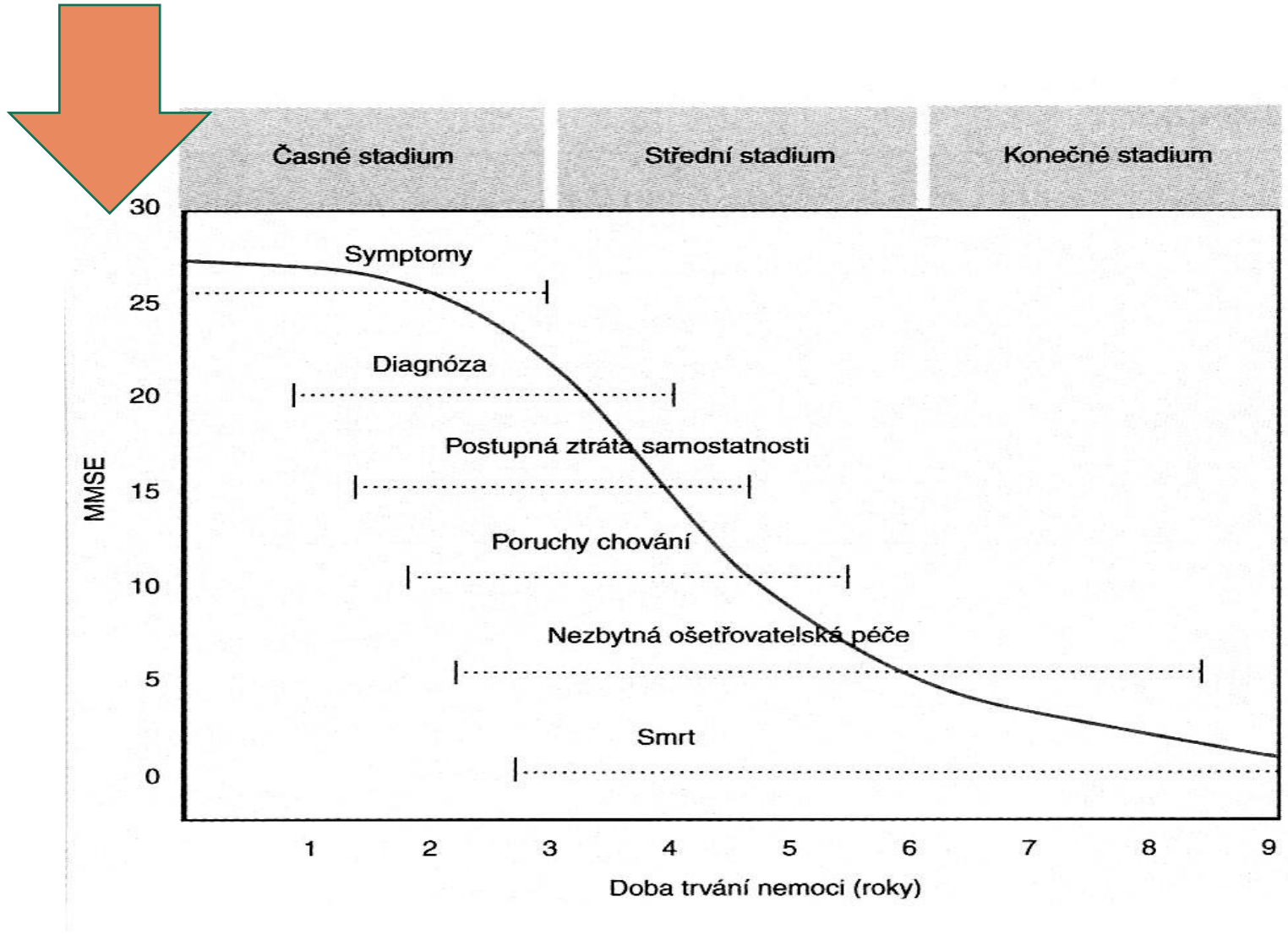
Muži
Ženy
82
41
V tisících
41
82
V tisících



Obr. 4 Klasický průběh AD

Major neurocognitive disorder

~~Dementia~~

- Memory impairment
- Loss of any other cognitive function (judgement, thinking, planing, information processing)
- NOT unconsciousness
- Loss of emotion control, motivation or social behaviour
- Duration - at least 6 months

Major neurocognitive disorder

~~Dementia~~

- A – activities of daily life
- B – behaviour
- C – cognition (memory, judgement, planing, executive function)

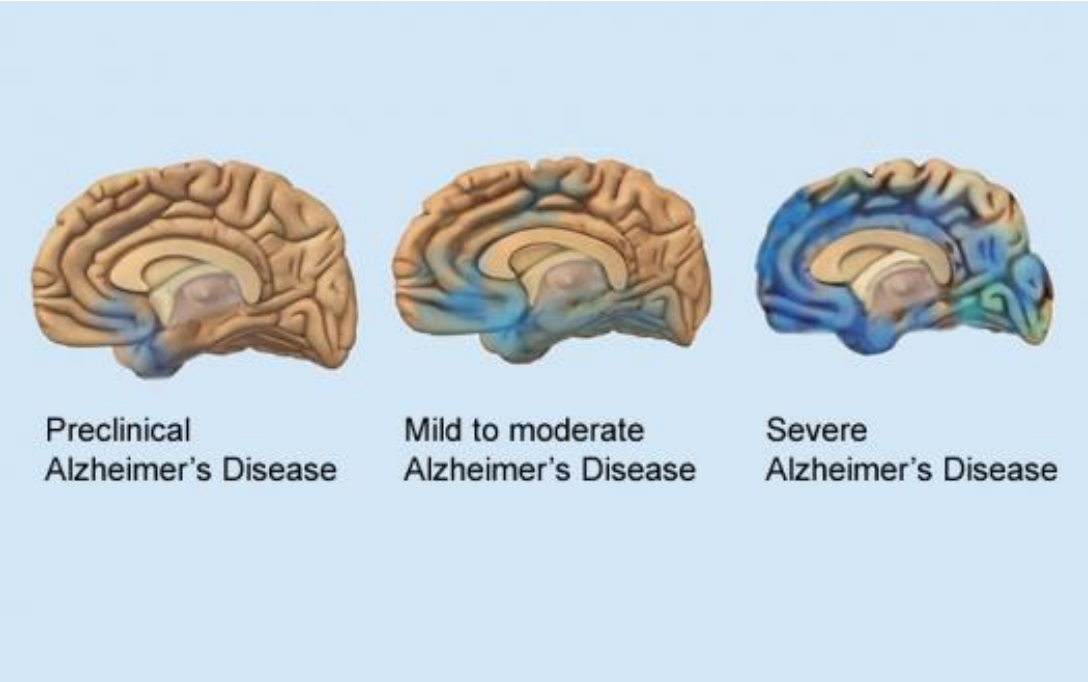
Dementia

- Primary – neurodegenerative - AD, LBD….
- Secondary – vascular, syphilis, HIV, pelagra (B3), alcohol…

- „Pseudodementia“

AD - Mild

- Still able to live on his own
- Difficulties learning new things
- Difficulties recalling basic daily things/activities



AD - Moderate

- Remembers only what is stored deep enough…
- New information kept only for a very short time
- Does not recall basic information about places, people…
- Dependent on other peoples help
- Can do a simple home work etc.

AD - Severe

- Not able to learn anything new
- Only framgents of past information remain
- Does not recognize close relatives
- Can not formulate clear intentions

Item	Score
Abrupt onset	2
Stepwise deterioration	1
Fluctuating course	2
Nocturnal confusion	1
Relative preservation of personality	1
Depression	1
Somatic complaints	1
Emotional incontinence	1
History of hypertension	1
History of strokes	2
Evidence of associated atherosclerosis	1
Focal neurological symptoms	2
Focal neurological signs	2
Total	18

Alzheimer's disease ≤4; Mixed forms = 5-6; Multi-infarct dementia ≥7.

- Hachinsky score

- Onset
- Course
- Medical history
- Neurological signs

- CADASIL – genetic VD

Depression

DEMENTIA	PSEUDODEMENTIA
Insidious onset	Sudden onset
Slow progression	Rapid progression
Lack of insight	Presence of insight
Confabulations	Memory disorders
Tendency to diminish disability	Tendency to emphasize disability
Behavior corresponding to the severity of illness	Behavior often not corresponding to the severity of illness
Lack of answers	General responses (i.e. "I do not know")
Worsening at night	No night changes
Incongruity of affect	Depressed mood
Few vegetative symptoms	Frequent vegetative symptoms
Infrequent psychiatric history	Frequent psychiatric history
Low suicide risk	High suicide risk

- Frequent
- Reversible
- Worth treating!
- SSRI

Geriatric Depression Scale

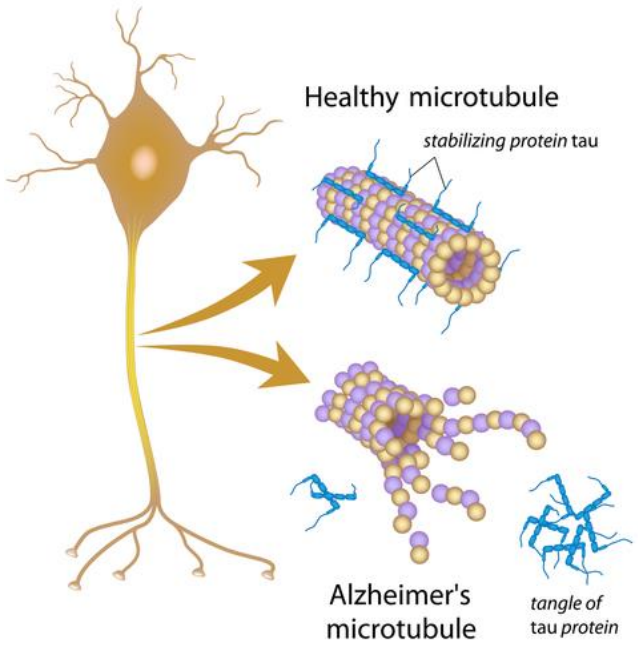
Date: 2016-08-12 Patient Name: TEST, TEST

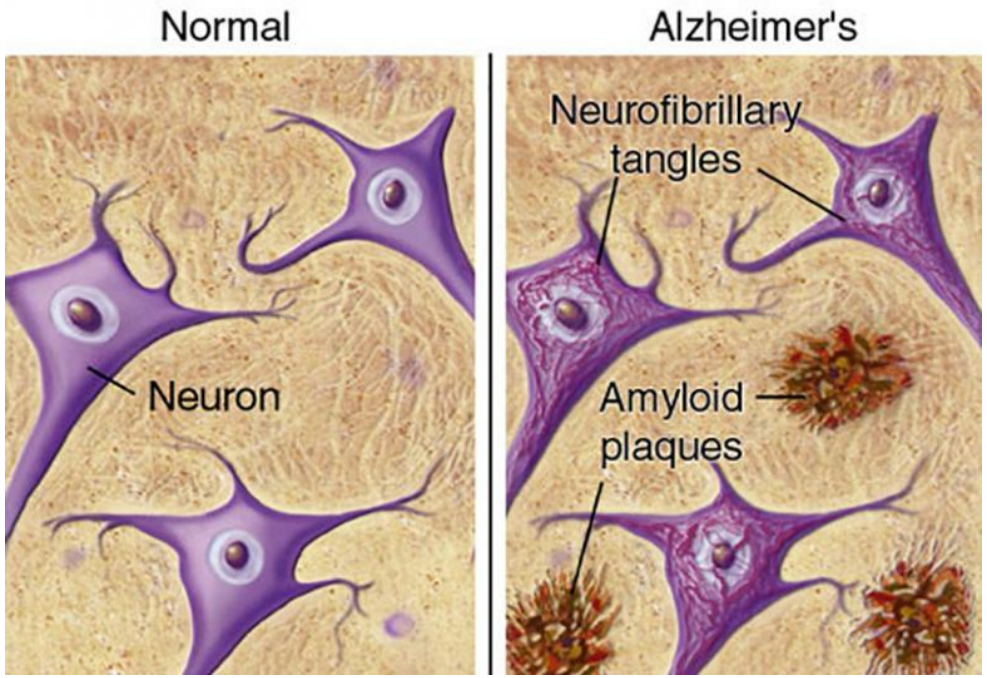
	Yes	No	
1. Are you basically satisfied with your life?	0	1	
2. Have you dropped many of your activities and interests?	1	0	
3. Do you feel that your life is empty?	1	0	
4. Do you often get bored?	1	0	
5. Are you are you in good spirits most of the time?	0	1	
6. Are you afraid something bad is going to happen to you?	1	0	
7. Do you feel happy most of the time?	0	1	
8. Do you often feel helpless?	1	0	
9. Do you prefer to stay at home, rather than going out and doing new things?	1	0	
10. Do you feel you have more problems with memory than most?	1	0	
11. Do you think it is wonderful to be alive?	0	1	
12. Do you feel pretty worthless the way you are now?	1	0	
13. Do you feel full of energy?	0	1	
14. Do you feel your situation is hopeless?	1	0	
15. Do you think that most people are better off than you are?	1	0	
Total (over 5 indicates depression)			

- Frequent
- Reversible
- Worth treating!
- SSRI

Patophysiology

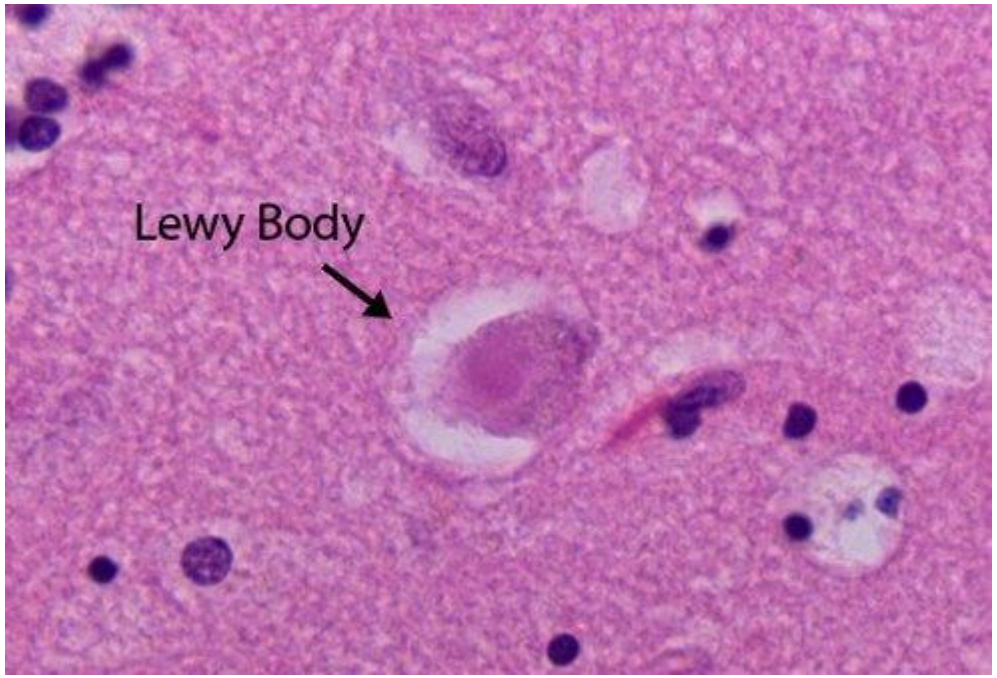
- Proteins: tau, amyloid, alpha – synuclein…



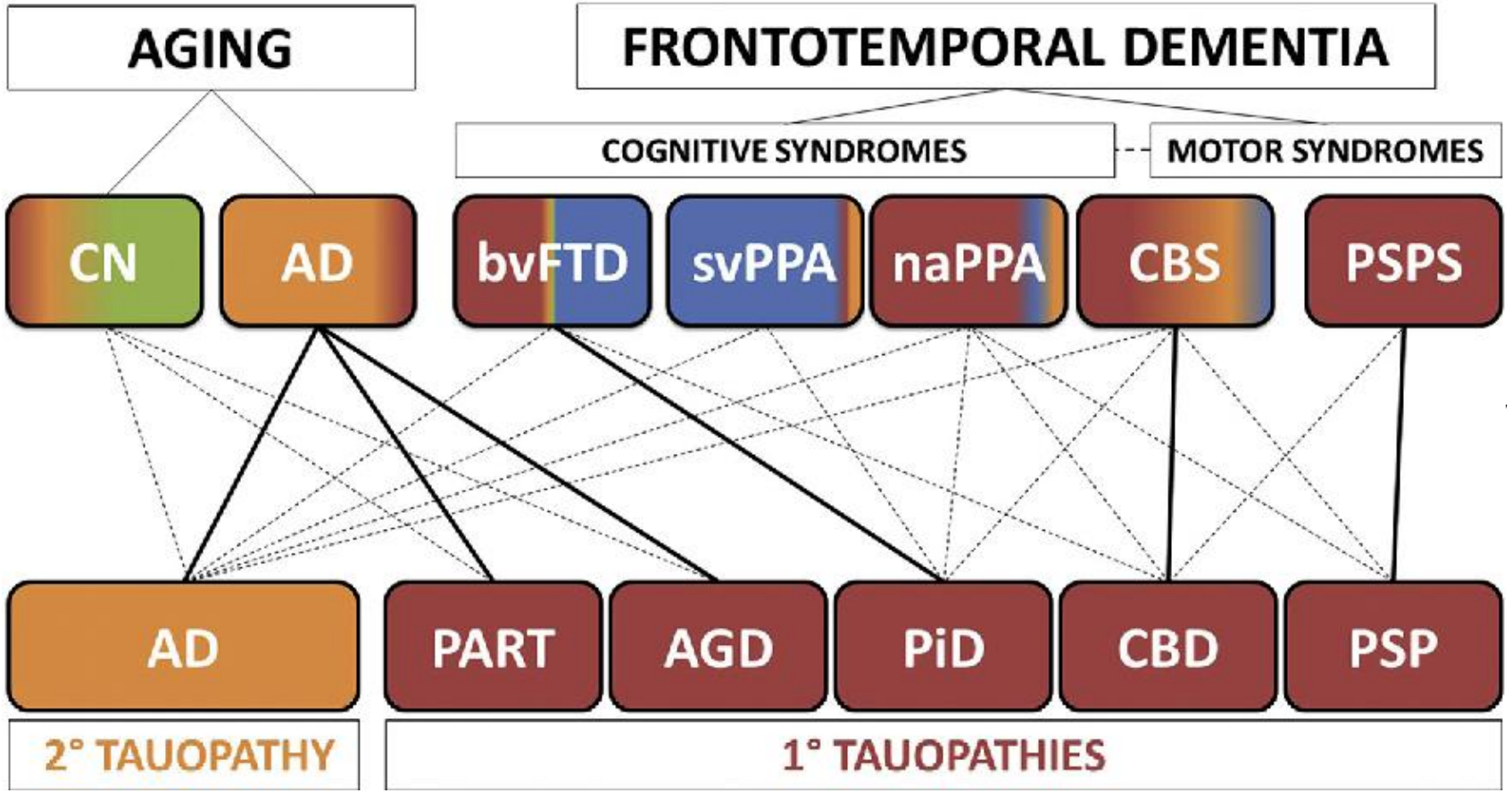


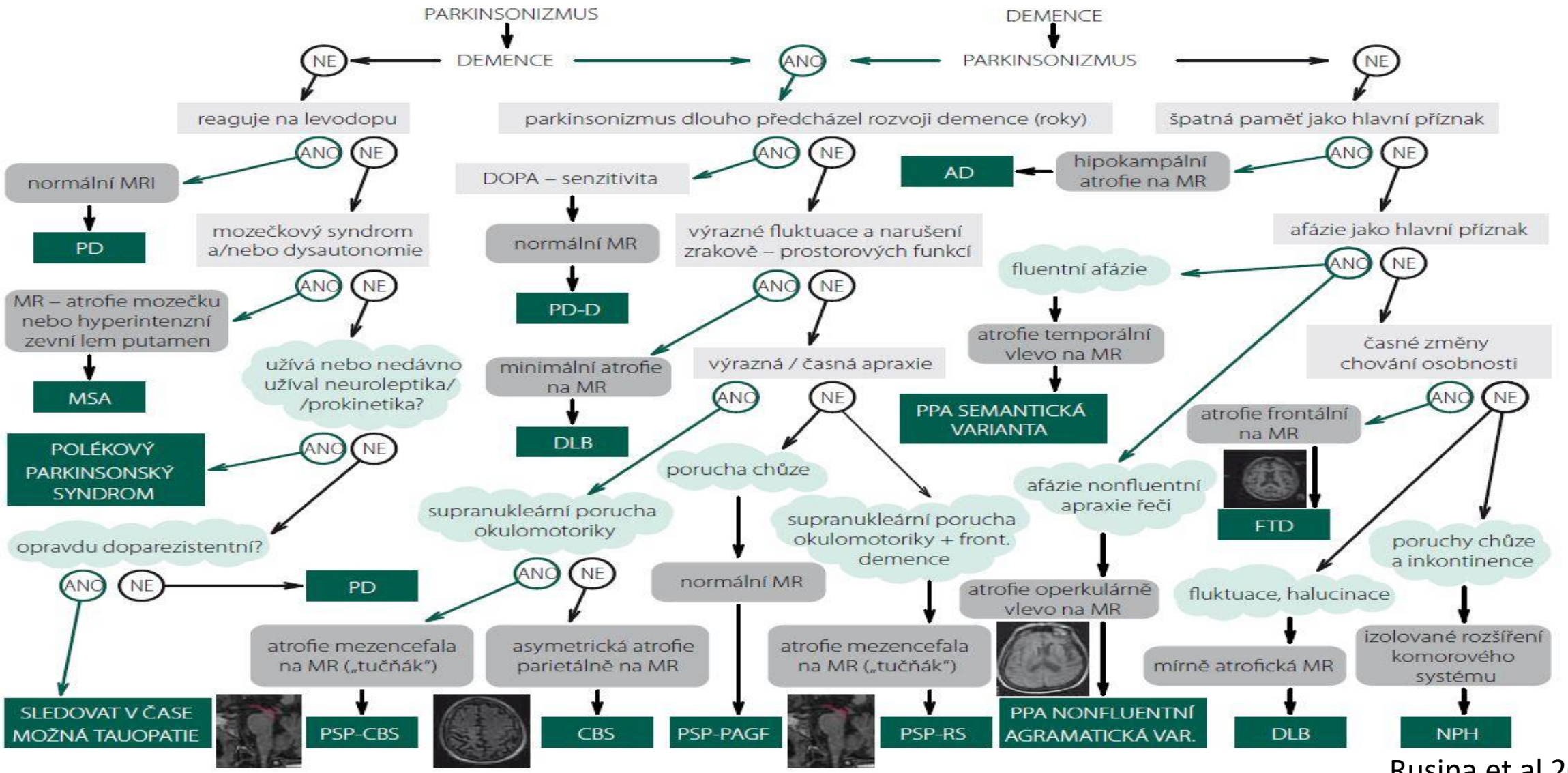
Patophysiology

- Histology



Symptoms vs histopatology





Rusina et al 2015

Institut neuropsychiatrické péče - komplexní léčba / mezioborový přesah / individuální přístup
Neurologie, psychiatrie, dětská neurologie, dětská psychiatrie, klinická psychologie, psychoterapie a lékárna.

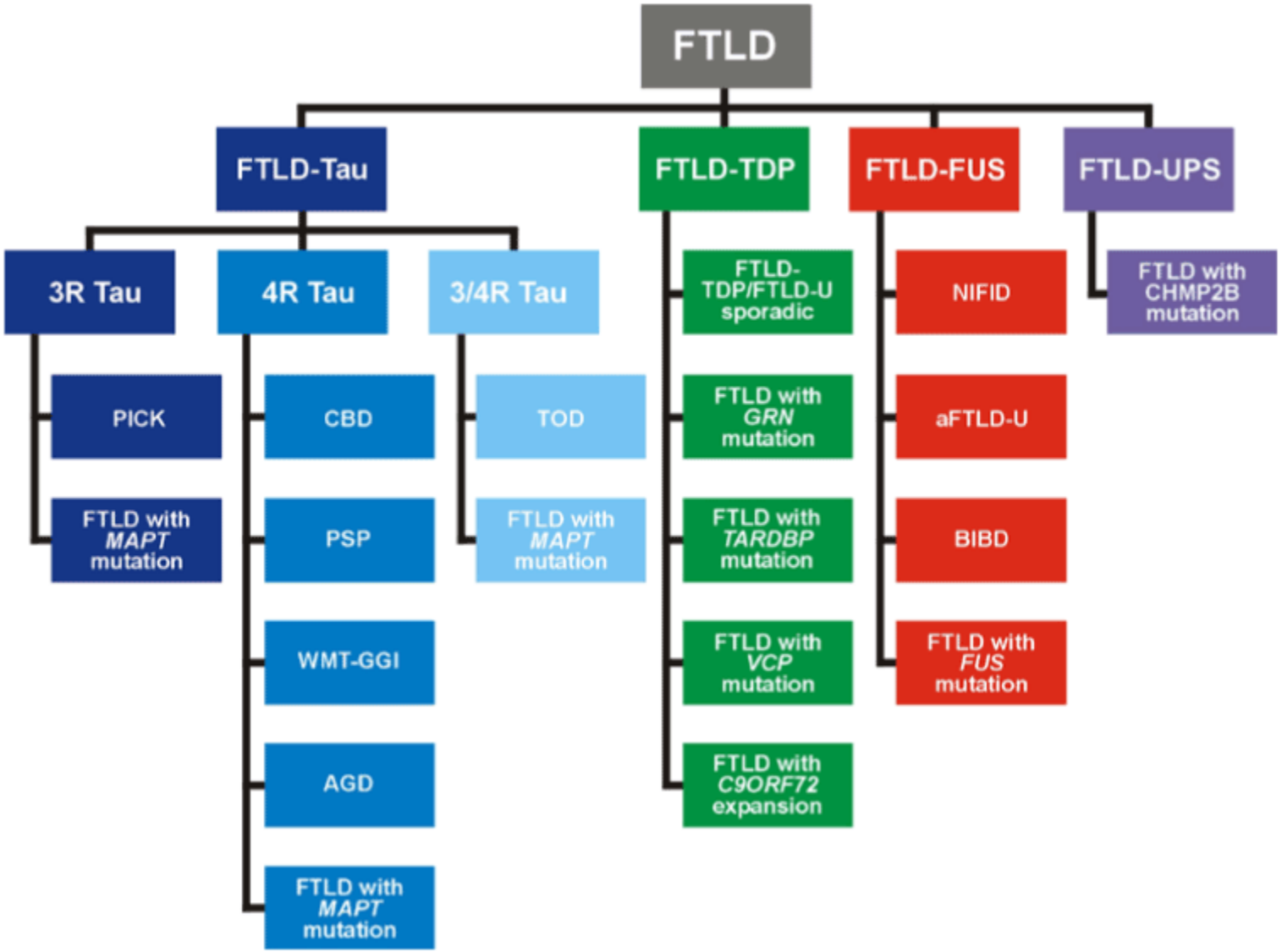
INEP

Localization

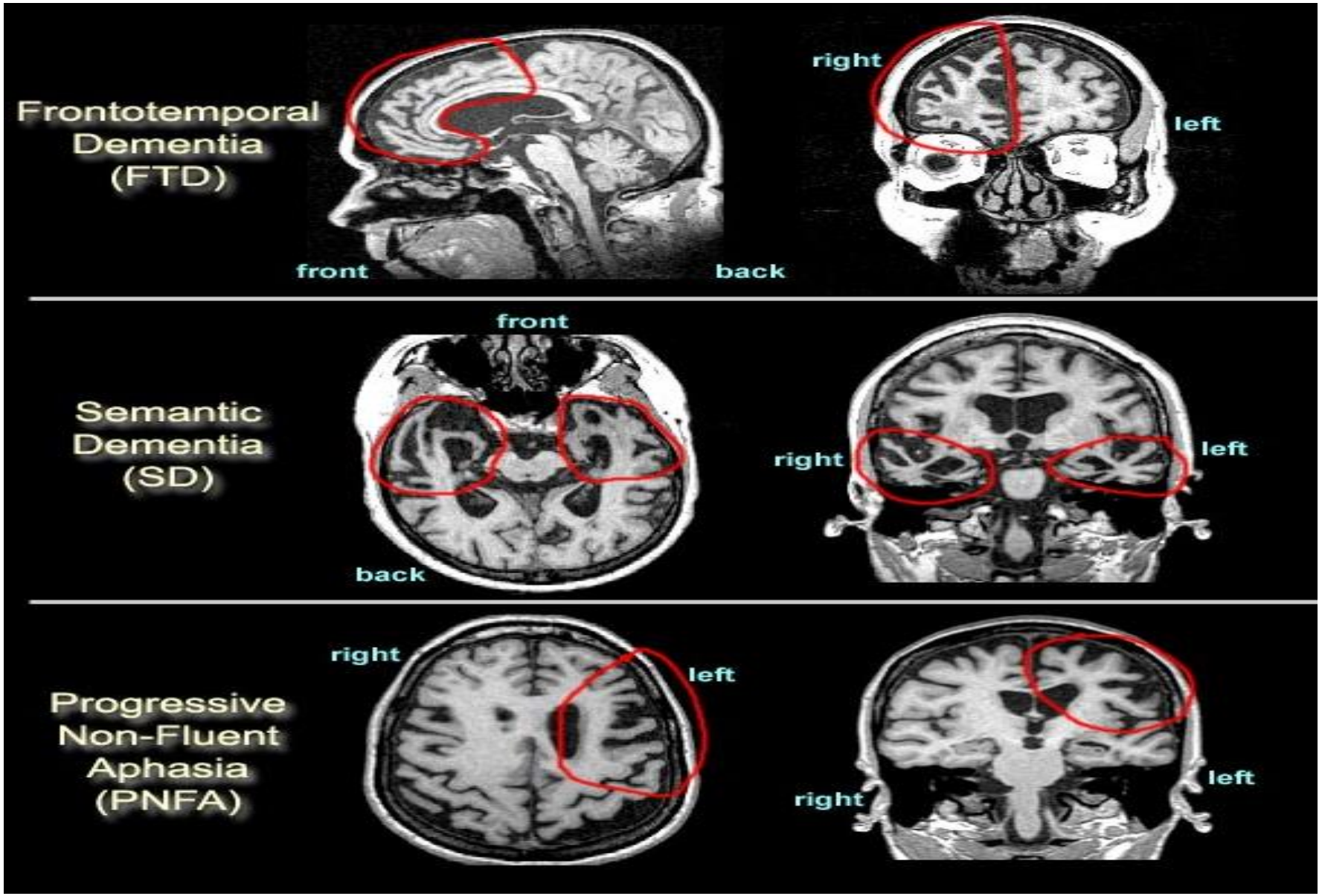
- Brain anatomy + function
- FTLD – frontal + temporal lobe
- AD – hippocampus

- Vascular – subcortical
- Other subcortical (PD, PSP, MSA…)

FTLD


FTLD
FTLD-Tau
FTLD-TDP
FTLD-FUS
FTLD-UPS
3R Tau
4R Tau
3/4R Tau
PICK
FTLD with MAPT mutation
CBD
PSP
WMT-GGI
AGD
FTLD with MAPT mutation
TOD
FTLD with MAPT mutation
FTLD-TDP/FTLD-U sporadic
FTLD with GRN mutation
FTLD with TARDBP mutation
FTLD with VCP mutation
FTLD with C9ORF72 expansion
NIFID
aFTLD-U
BIBD
FTLD with FUS mutation
FTLD with CHMP2B mutation

FTLD


Frontotemporal Dementia (FTD)
front
back
right
left
Semantic Dementia (SD)
front
back
right
left
Progressive Non-Fluent Aphasia (PNFA)
right
left
right
left

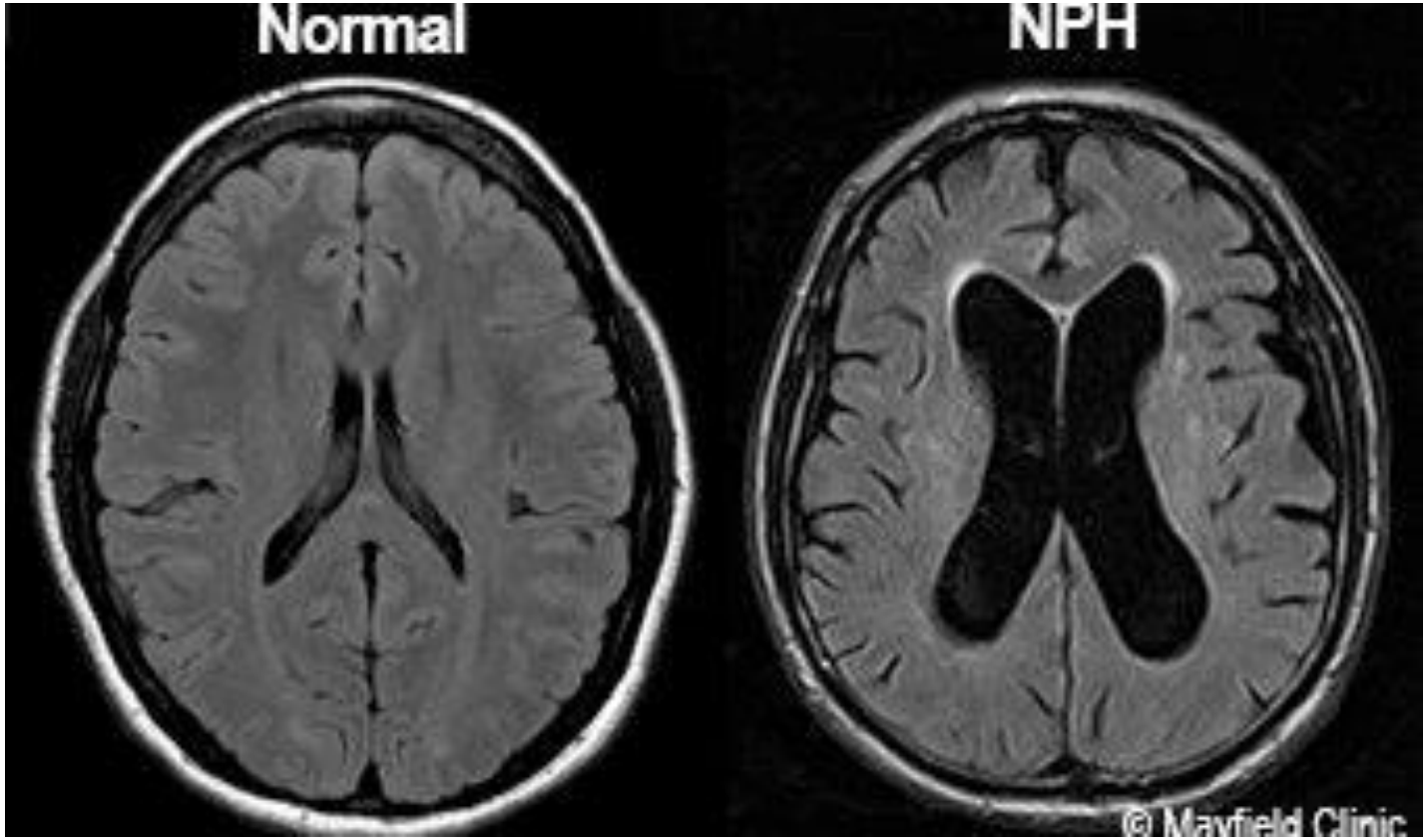
https://www.youtube.com/watch?v=3oef68YabD0

https://www.youtube.com/watch?v=JWC-cVQmEmY

Reversible dementia?

- NPH
- ? Korsakoff sy
- Pellagra

- Pseudodementia



Normal Pressure Hydrocephalus

- Etiology: not clear (trauma, tumor, surgery…)
- Symptoms – „Hakim trias“
  - Dementia
  - Gait disturbance
  - (Urinary) incontinence
- Dg: CT/MRI, LP test

- Treatment: surgical – VP shunt

Parkinson disease

- Motor function – rigidity, tremor
- Depression, anxiety
- Subcortical dementia
- Hallucinations - dopamine
  - ?LBD – sensitive to AP - falls
  - ?MSA – hypotension
- Dopa dysregulation syndrome…

BPSD

- Agitation
- Depression, anxiety
- Abnormal motor behaviour
- Irritability, apathy
- Disinhibition, impulsivity
- Delusions, hallucinations
- Sleep disturbances

Summary

- **„Core“ symptoms**
- PSY: cognition, thinking, memory, hallucinations…
- NEU: tremor, rigidity, oculomotor…

- **Added/possible symptoms**
- PSY: depresion, hallucinations, irritability, insomnia, agression…
- NEU: gait, falls, focal signs…