Amsterdam Neuroscience

Amsterdam UMC
University Medical Centers

Alzheimer Center Amsterdam

Diagnostiek van dementie op jonge leeftijd

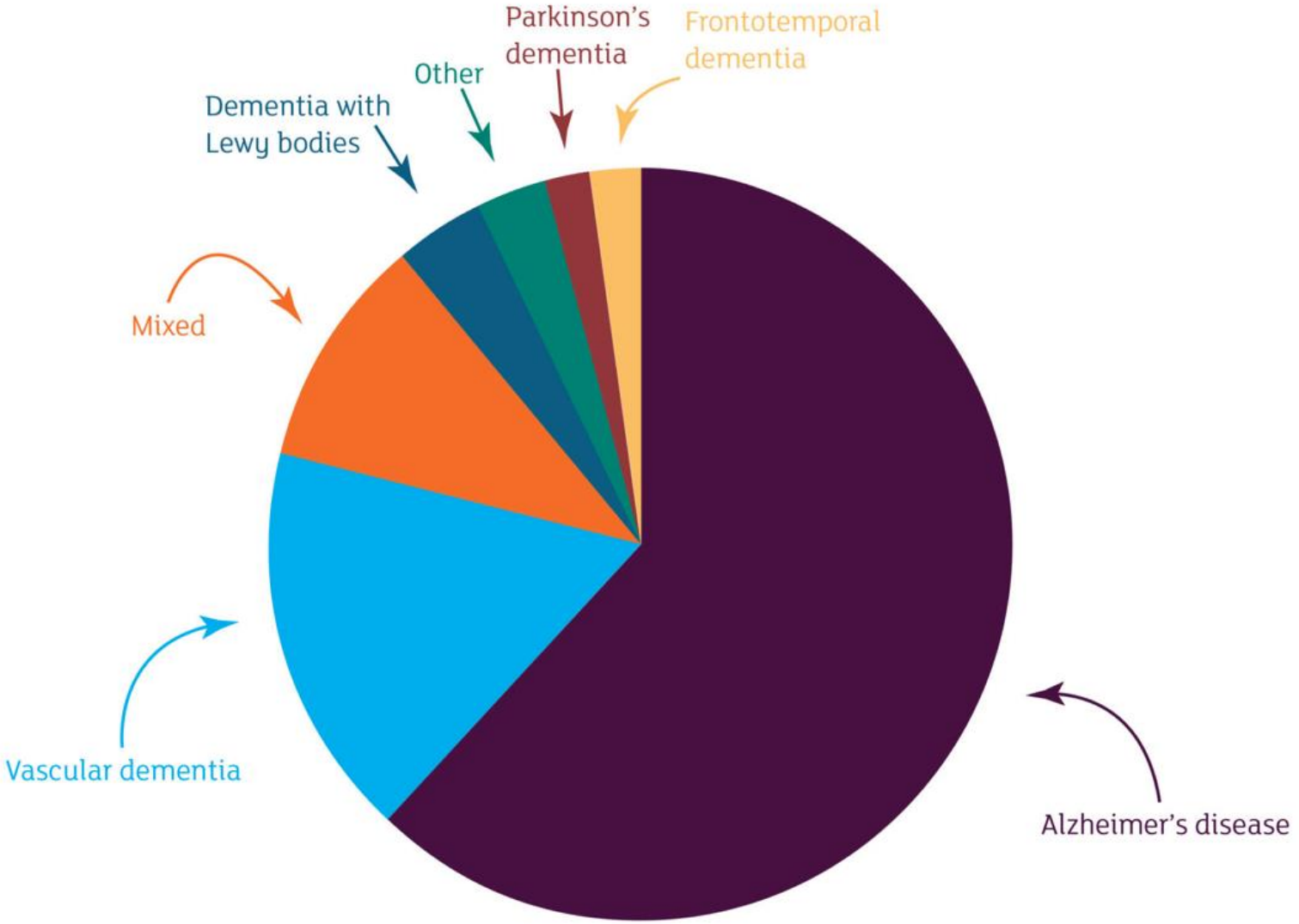
Yolande Pijnenburg

Dementie op jonge leeftijd

- Dementie die ontstaan is voor het 65e jaar
- Overeenkomsten in psychosociale gevolgen en behoeften
- Grote diversiteit aan oorzaken
- Diagnose relatief laat gesteld
- Niet-klassieke symptomen

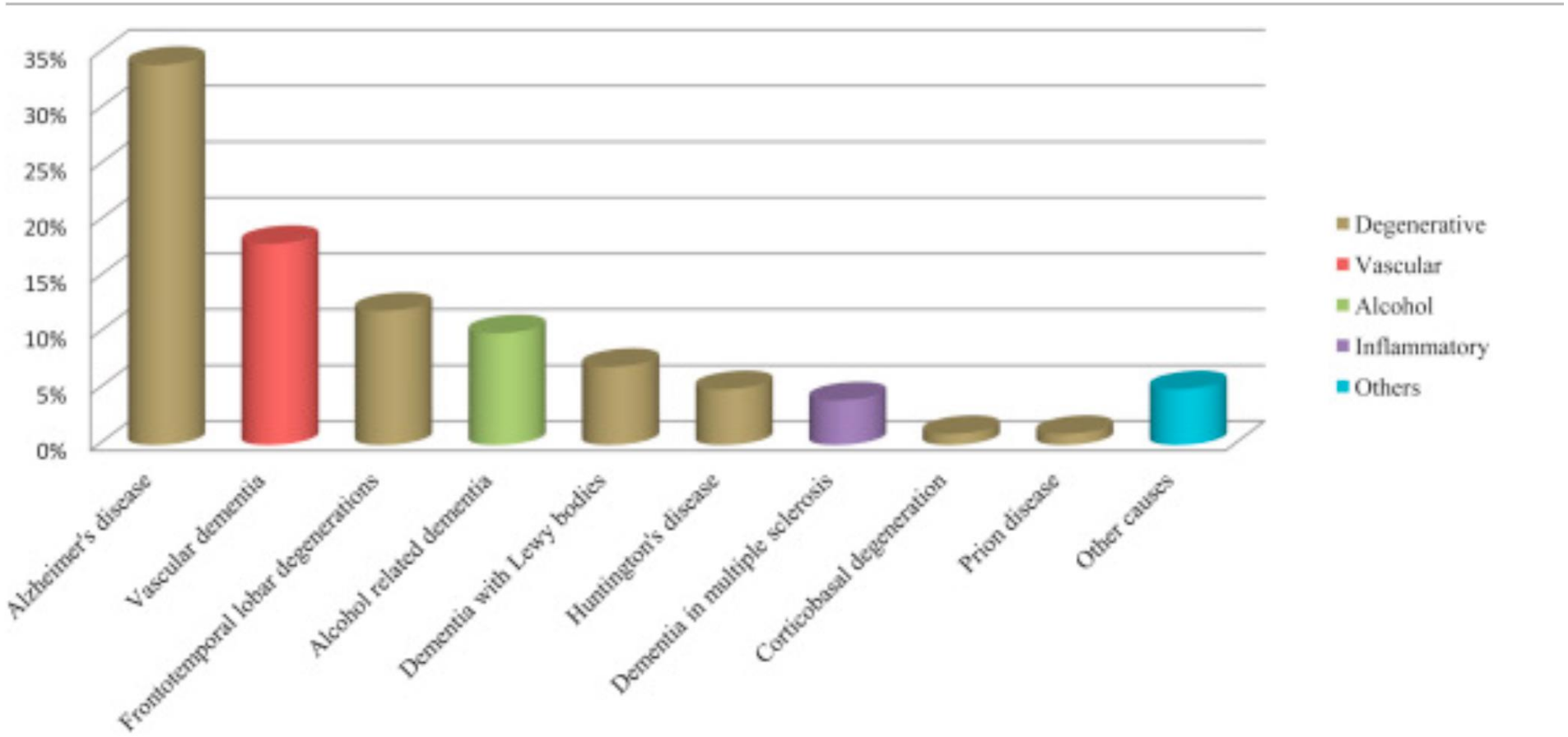
Dementie op jonge leeftijd

Causes of dementia



Alzheimers research UK

Oorzaken van dementie op jonge leeftijd

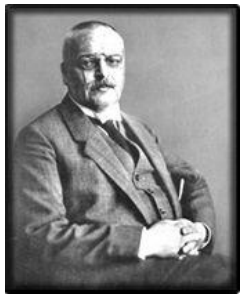


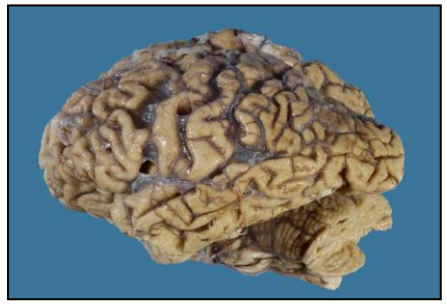
- Quach et al., 2014

Diagnostiek van oorzaken van dementie op jonge leeftijd

- Minder co-morbiditeit → ‘pure’ vormen van ziekte
- Grotere component van genetica
- Focaal versus diffuus
- Individueel patient management

Ziekte van Alzheimer: klassiek





- korte termijn geheugenstoornis
- langere termijn geheugenstoornis, taalstoornissen, moeite met handelingen, waarneming, plannen en organiseren
- Gedragsverandering: apathie, achterdocht, wanen, hallucinaties, aggressie, zwerven
- Geen lichamelijke klachten behalve laat in het beloop

Ziekte van Alzheimer

Table 2
Subdivision of non-memory symptoms by patient groups

	Early-onset Alzheimer's disease	Late-onset Alzheimer's disease	Level of significance
Apraxia/visuospatial dysfunction	33 (12%)	1 (1%)	$p = 0.002$
Language syndrome	25 (9%)	1 (1%)	$p = 0.01$
Aphasic-apraxic-agnosic syndrome	22 (8%)	2 (2%)	$p = 0.05$
Dysexecutive syndrome	4 (2%)	1 (1%)	$p = 0.80$
Posterior Cortical Atrophy	3 (1%)	0 (0%)	$p = 0.30$

Data are presented as N (%).

Koedam et al., 2010

Ziekte van Alzheimer: atypische varianten

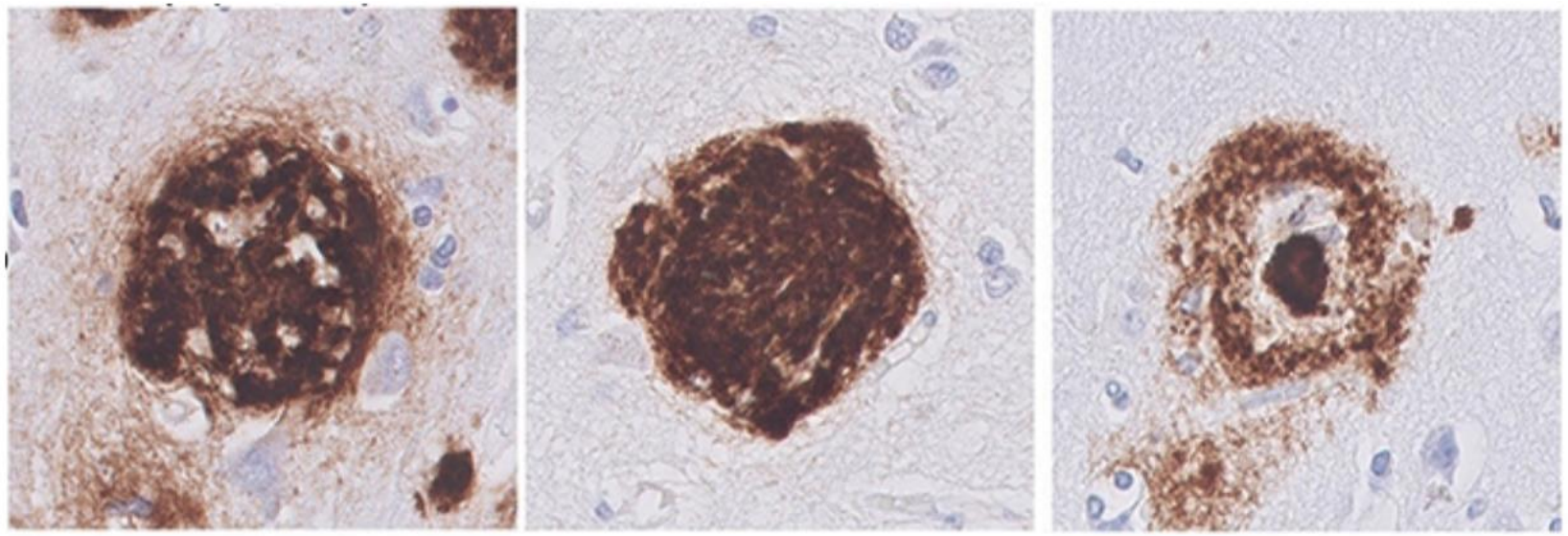
- Posterior cortical atrophy (visuospatieel)
- Logopene progressieve afasie (taal)
- Frontale / dysexecutieve variant (gedrag)
- Corticobasaal syndroom (motoriek)

Atypische ziekte van Alzheimer

Pathologie:

Distributie verschillen

Coarse grained plaque



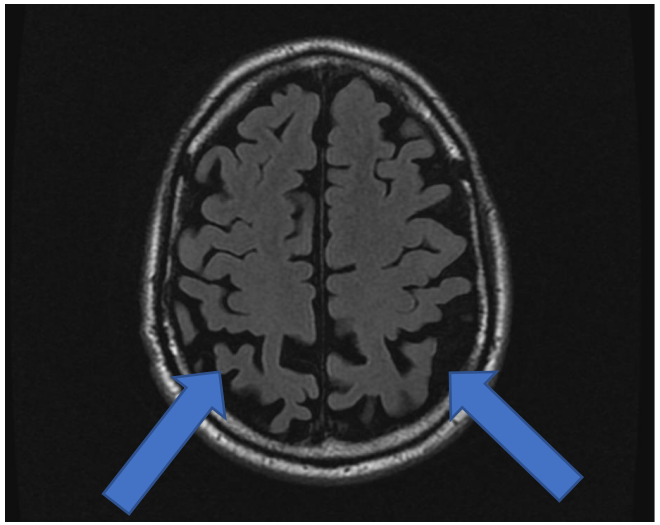
***Variation on a Plaque**. Coarse-grained plaques (left) lack the clearly delineated borders of the cotton-wool plaques (center) and the compact centers of the dense-core plaques (right). [Courtesy of Boon et al., Acta Neuropathologica 2020.]*

Genetica:

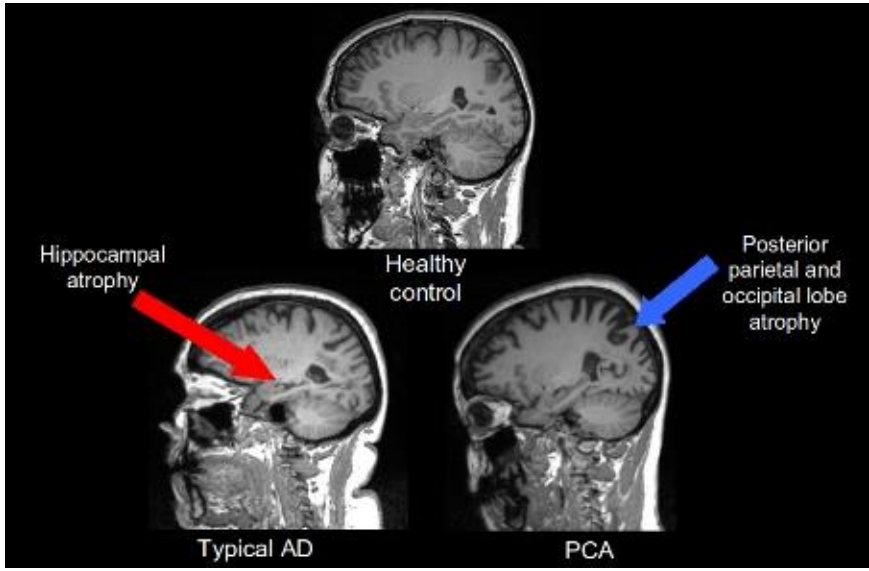
EOAD minder APOE4 gedreven

Boon et al., 2020

Posterior cortical atrophy



- Genoemd naar radiologisch kenmerkende beeld
- Onderliggende pathologie bijna altijd Alzheimer
- Op voorgrond staande visuospatiële stoornissen
- Apraxie, dyscalculie
- Inzicht gespaard



Visuospatiële functies

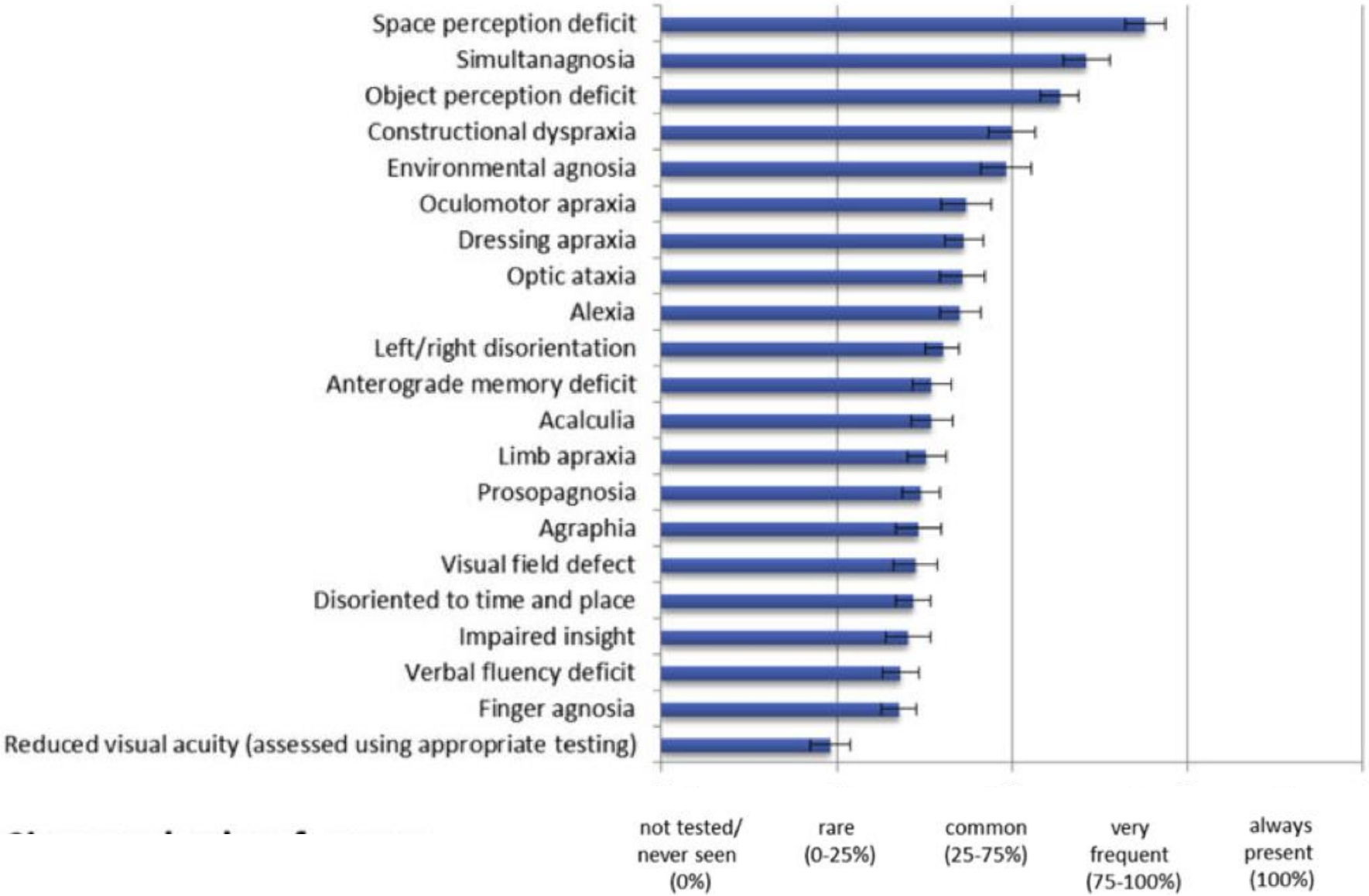
- Object benoemen
- klok tekenen
- kubus tekenen
- ruimtelijke oriëntatie
- tafereel overzien

Core features of the PCA clinico-radiological syndrome (classification level 1)

Clinical, cognitive, and neuroimaging features are rank ordered in terms of (decreasing) frequency at first assessment as rated by online survey participants (see Fig. 2)
Clinical features:
Insidious onset
Gradual progression
Prominent early disturbance of visual ± other posterior cognitive functions
Cognitive features:
At least three of the following must be present as early or presenting features ± evidence of their impact on activities of daily living:
Space perception deficit
Simultanagnosia
Object perception deficit
Constructional dyspraxia
Environmental agnosia
Oculomotor apraxia
Dressing apraxia
Optic ataxia
Alexia
Left/right disorientation
Acalculia
Limb apraxia (not limb-kinetic)
Apperceptive prosopagnosia
Agraphia
Homonymous visual field defect
Finger agnosia
All of the following must be evident:
Relatively spared anterograde memory function
Relatively spared speech and nonvisual language functions
Relatively spared executive functions
Relatively spared behavior and personality
Neuroimaging:
Predominant occipito-parietal or occipito-temporal atrophy/hypometabolism/hypoperfusion on MRI/FDG-PET/SPECT
Exclusion criteria:
Evidence of a brain tumor or other mass lesion sufficient to explain the symptoms
Evidence of significant vascular disease including focal stroke sufficient to explain the symptoms
Evidence of afferent visual cause (e.g., optic nerve, chiasm, or tract)
Evidence of other identifiable causes for cognitive impairment (e.g., renal failure)

Crutch et al., 2017

Symptoms



Crutch et al., 2017

Slowly Progressive Aphasia Without Generalized Dementia

M.-Marsel Mesulam, MD

Six right-handed patients experienced a slowly progressing aphasic disorder without the additional intellectual and behavioral disturbances of dementia. The symptoms almost universally started in the presenium. The initial difficulty was an anomic aphasia in five of the patients and pure word deafness in the sixth. Continuous and gradual deterioration occurred in the five patients who presented with an anomic aphasia. They eventually experienced additional impairment of reading, writing, and comprehension. In four patients, other areas of comportment were not involved within the 5 to 11 years of follow-up. A more generalized state of dementia may have emerged in the other two patients, but only after 7 years of progressive and debilitating aphasia. Neurodiagnostic procedures were consistent with preferential involvement of the left perisylvian region. In one patient, cortical biopsy did not show any pathognomonic change; specifically, no neurofibrillary tangles, amyloid plaques, neuronal inclusions, or gliosis were seen. This condition may constitute a syndrome of relatively focal cerebral degeneration with a predilection for the left perisylvian region.

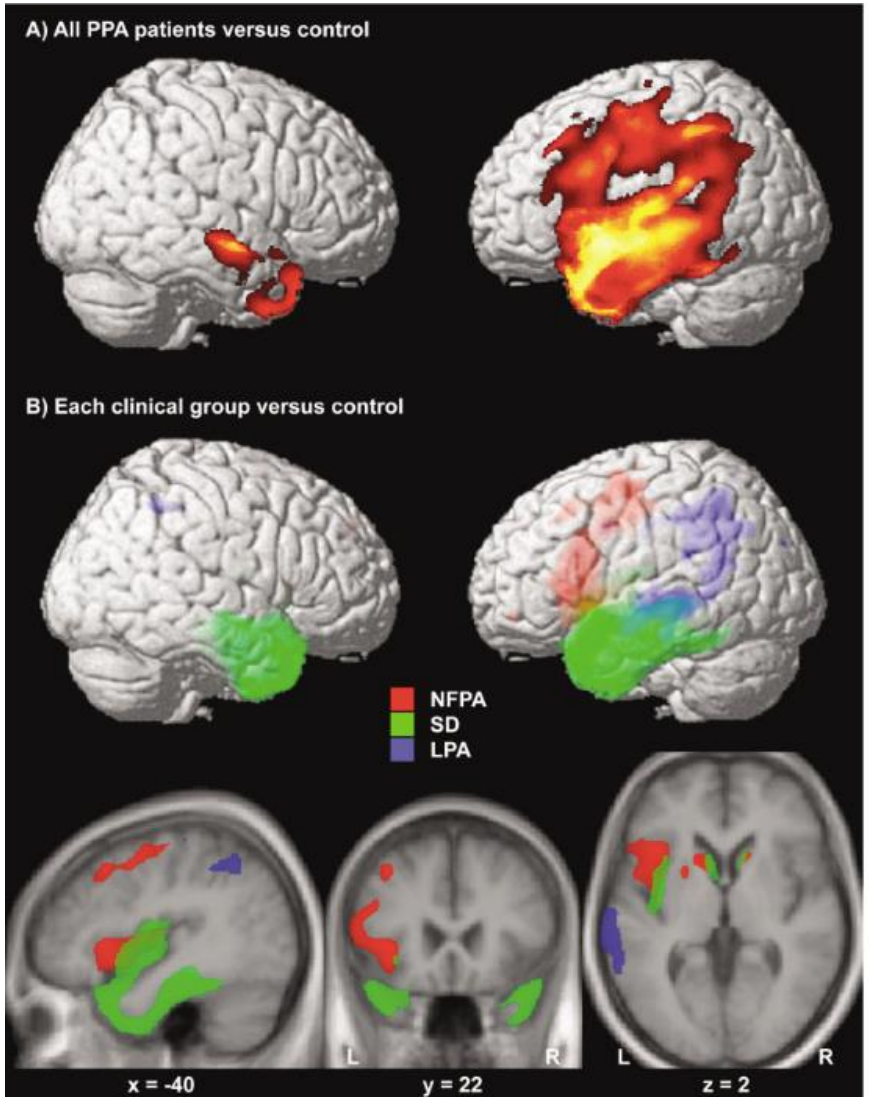
Mesulam M-M: Slowly progressive aphasia without generalized dementia. Ann Neurol 11:592–598, 1982

Primair progressieve afasie

Logopene variant

Semantische variant

Progressieve niet-vloeiende variant



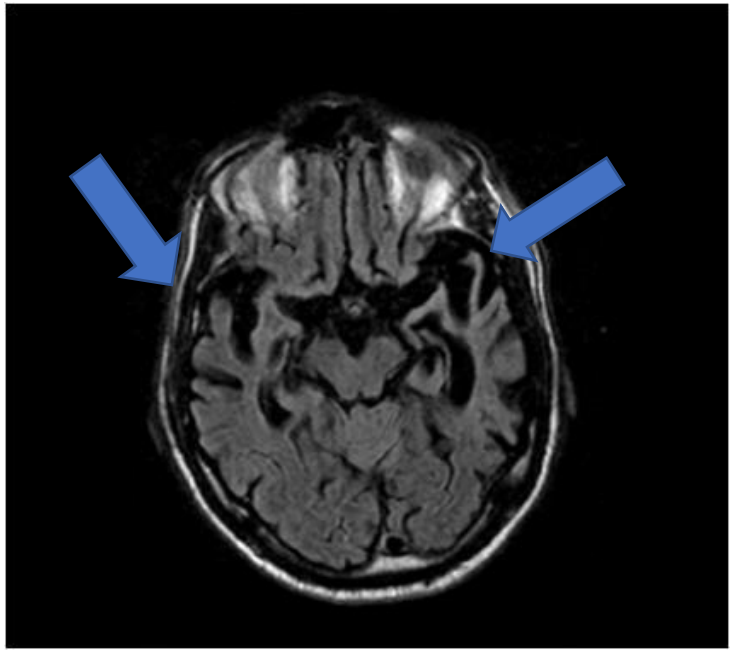
Gorno-Tempini et al., 2011

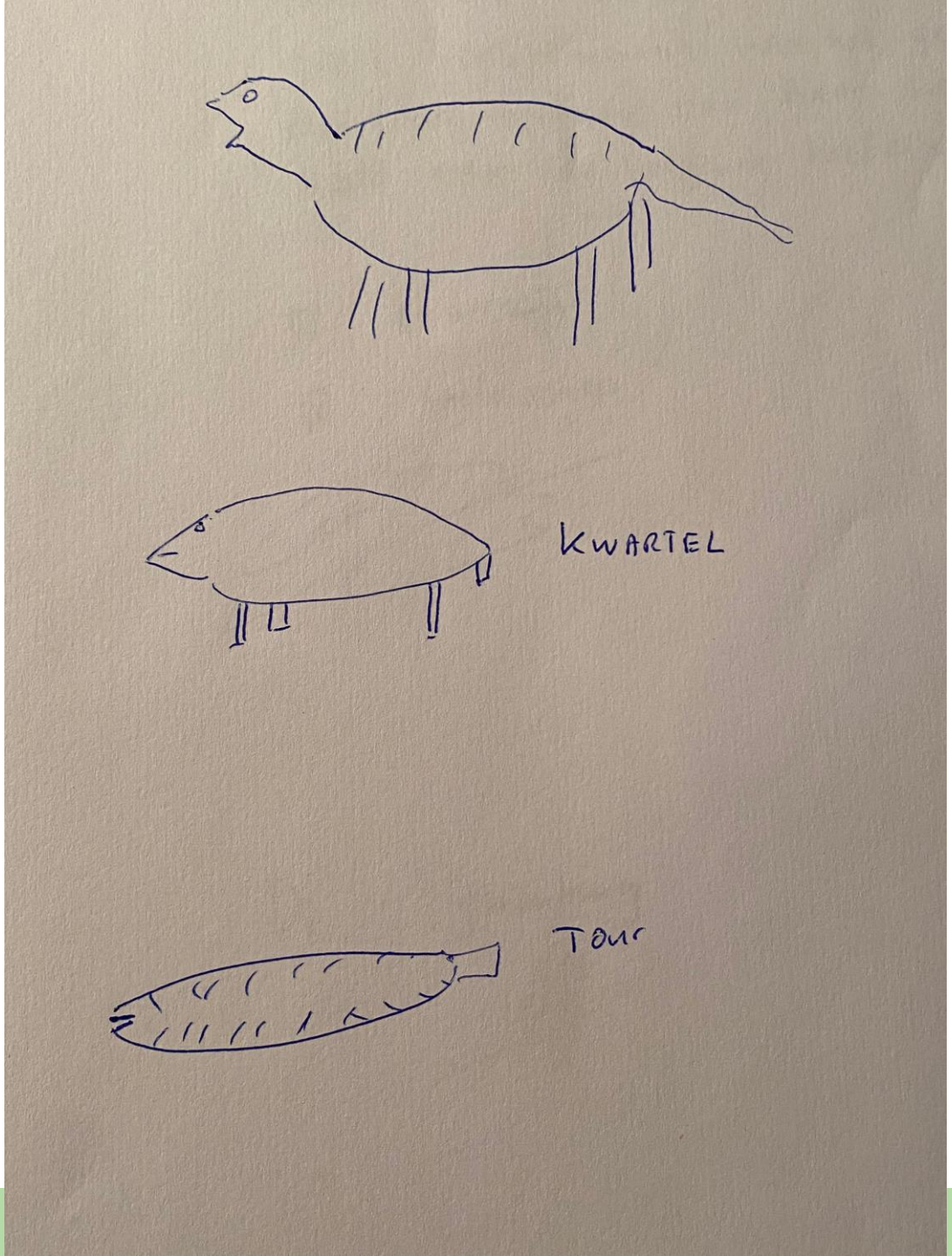
Logopene variant

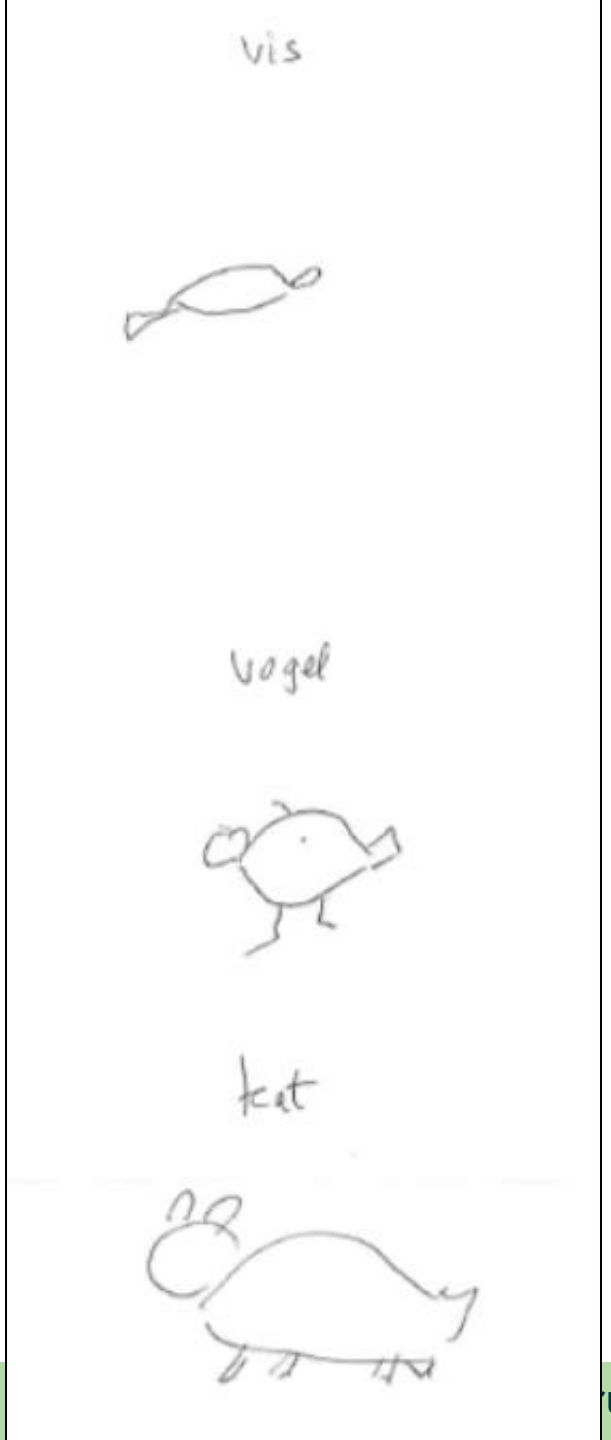
- Vloeiende spraak met woordvindpauzes
- Moeite met nazeggen van langere zinnen
- Vaak ook andere aspecten van taalstoornis (LPA-plus / LPA mixed)
- Meestal op basis van ziekte van Alzheimer

Semantische variant / semantische dementie

- Benoemstoornis
- Begripsstoornis op woordnivo
- Vloeiende spraak
- Inhoudsarm
- Verlies van conceptuele kennis buiten het taaldomein
- Gedragsverandering
- Op basis van frontotemporale dementie




KWARTEL
Tour


vis
vogel
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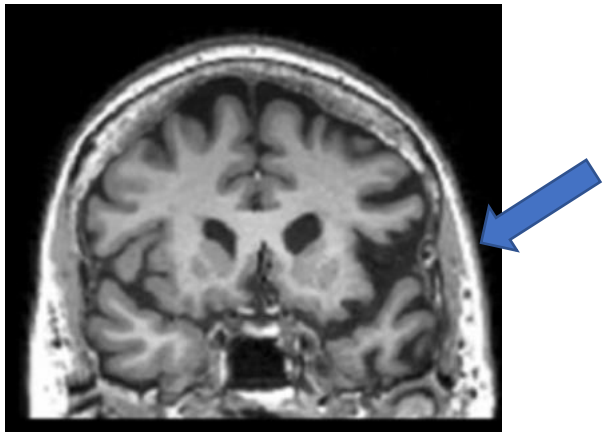
Niet-vloeiende variant

- Niet-vloeiende spraak
- Haperend, dysartrisch
- Grammaticale fouten
- Soms alleen spraakapraxie (PAOS)
- Meestal op basis van frontotemporale dementie



Beloop van PPA

- LPA: snelle ontwikkeling richting Alzheimer dementie
- PnvA: ontwikkeling van motorische symptomen: PSP/ CBD
- SD: ontwikkeling van gedragssymptomen: dwangmatig, egocentrisch

Journal of Neurology
https://doi.org/10.1007/s00415-021-10689-1

ORIGINAL COMMUNICATION

Check for updates

The natural history of primary progressive aphasia: beyond aphasia

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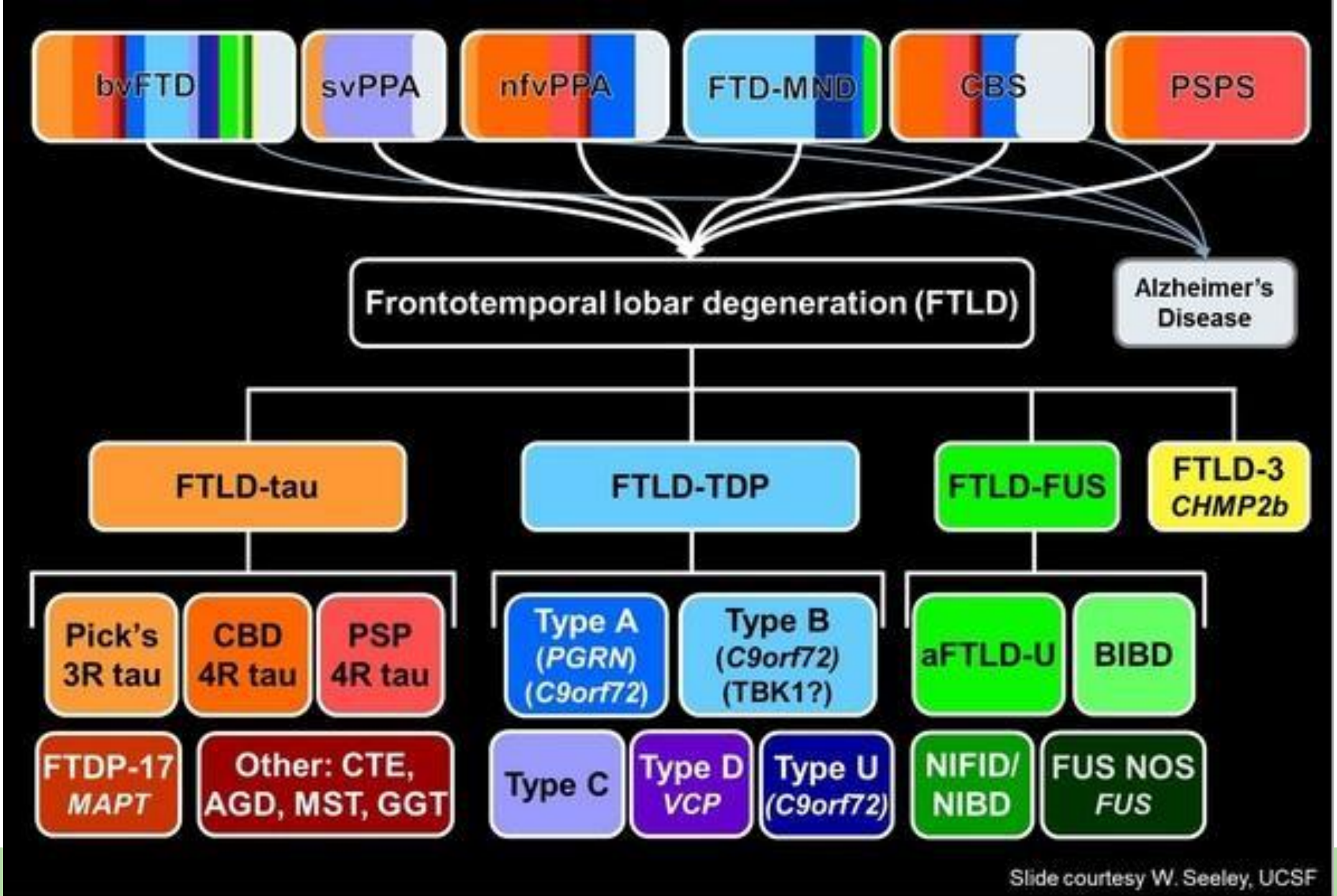
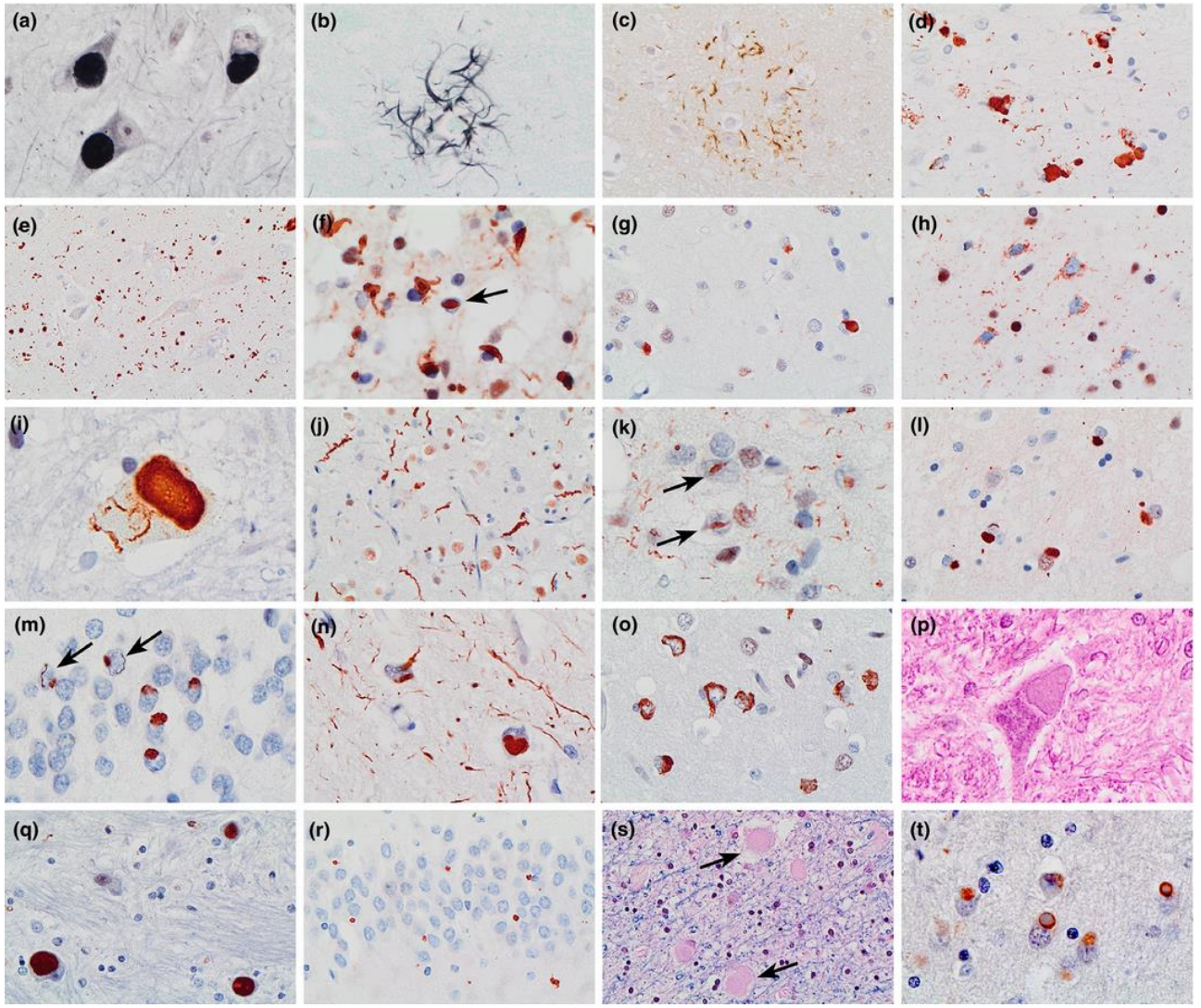
Frontotemporale dementie (gedragsvariant)

- Presentatie vaak tssen 49 en 69 jaar
- Sluipende gedragsverandering
- Stoornissen sociale cognitie/ empathie verlies
- Apathie
- Ontremming
- Dwangmatig-ritualistisch gedrag
- Veranderd eetgedrag
- Executieve stoornissen
- Taalstoornissen
- Geen inzicht


bvFTD
svPPA
nfvPPA
FTD-MND
CBS
PSPS
Frontotemporal lobar degeneration (FTLD)
Alzheimer's Disease
FTLD-tau
FTLD-TDP
FTLD-FUS
FTLD-3
CHMP2b
Pick's 3R tau
CBD 4R tau
PSP 4R tau
FTDP-17 MAPT
Other: CTE, AGD, MST, GGT
Type A (PGRN) (C9orf72)
Type B (C9orf72) (TBK1?)
Type C
Type D VCP
Type U (C9orf72)
aFTLD-U
BIBD
NIFID/ NIBD
FUS NOS FUS
Slide courtesy W. Seeley, UCSF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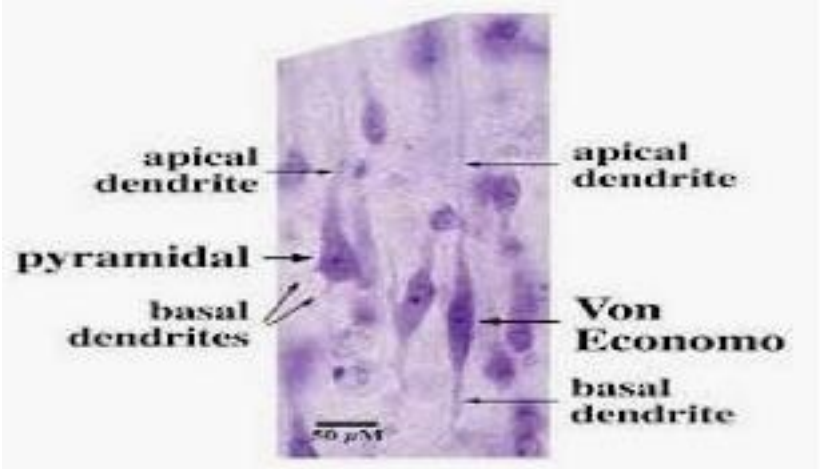
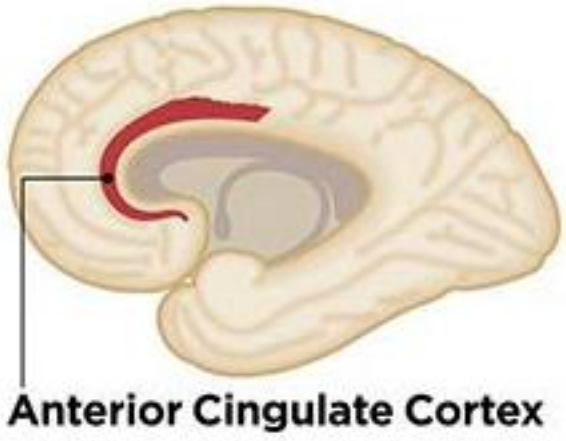
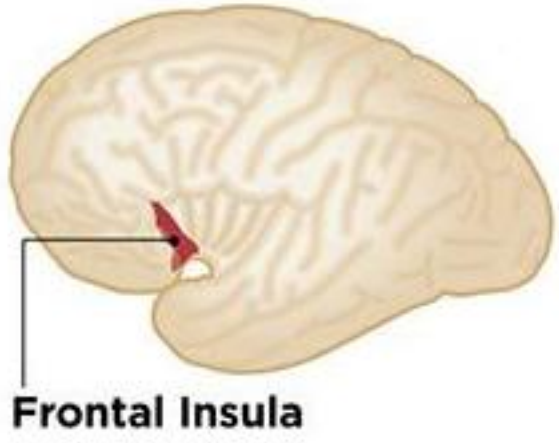
Kernsymptoom FTD: Sociale cognitie

Is geassocieerd met bepaalde hersengebieden

Is geassocieerd met bepaalde hersencellen







Sociale cognitie gestoord bij FTD

- Conflicten
- Ontslag
- Echtscheiding /relatieproblematiek
- Politiecontacten

- In het algemeen: inadequaat gedrag
- Belang van psycho-educatie !

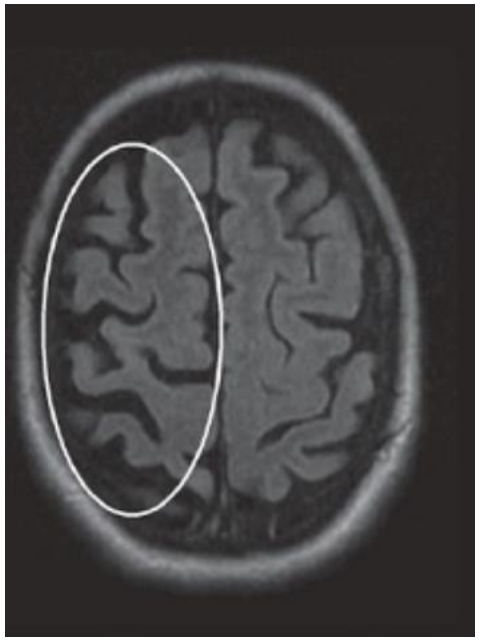
Rechts temporale variant van FTD

- Uniek klinisch profiel
- Combinatie van gestoorde gezichtsherkenning, geheugenstoornis, taalstoornis en gedragsverandering
- Relatief vaker depressie
- Complex dwangmatig / inadequaat probleemoplossend gedrag

Ulugut Erkoyun 2020

Corticobasaal syndroom

- Corticaal: afasie, apraxia, executive stoornissen
- Basaal: motoriek: stijfheid, minder functionaliteit, ‘alien limb’
- Asymmetrische corticale en basale degeneratie



Diagnostiek- fase 1

- Anamnese, hetero-anamnese
- Familie-anamnese: dementie (type/symptomen), ALS, Parkinson, psychiatrie
- Sociale achtergrond
- Klinisch onderzoek & NPO: Aandacht voor alle domeinen inclusief gezichtsherkenning, sociale cognitie en gedrag. Taal. Praxis !
- MRI hersenen
- Amyloid biomarker

Tips: welke testen doen het nou goed in de spreekkamer ?

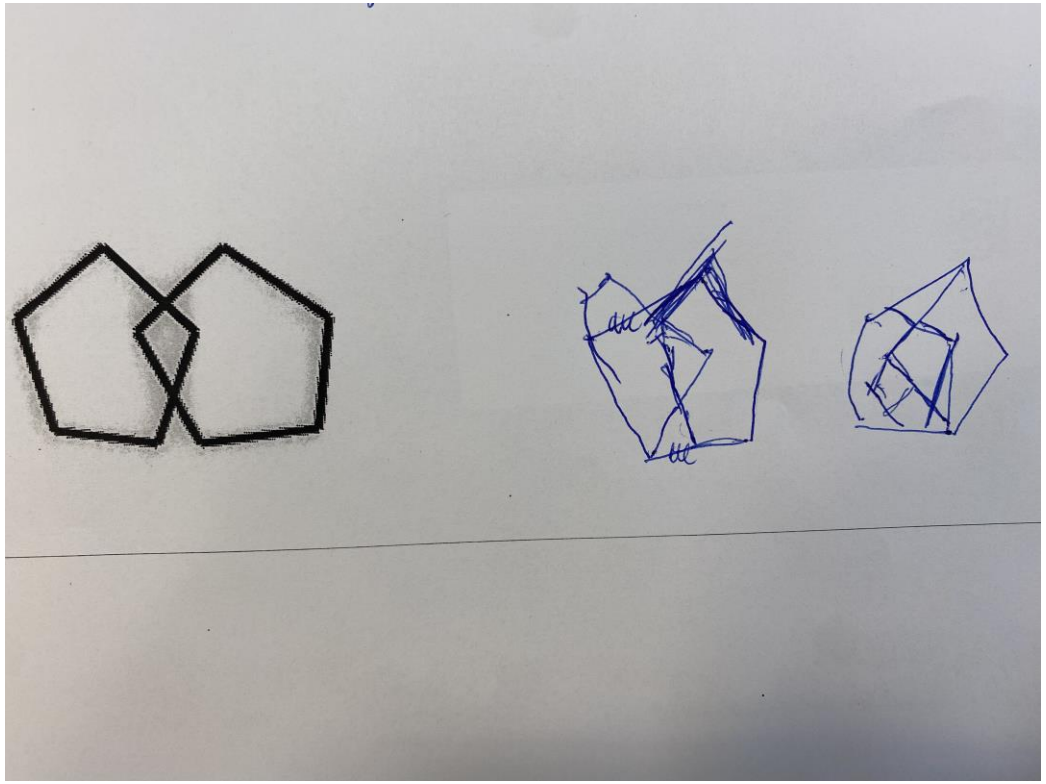
Zelfomschrijving

Sociale cognitie

Grijpreflex

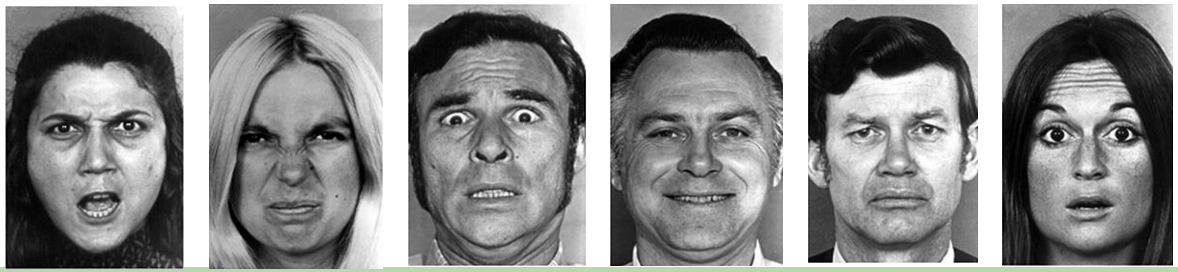
Praxis

PANT

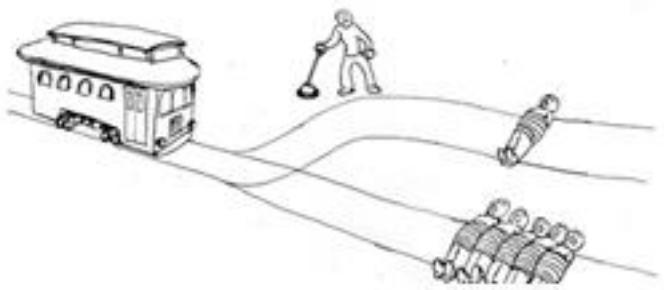


Meten van sociale cognitie

- Subjectief vs objectief
- Vragenlijsten
- Cultuur
- Testsituatie



Switch condition



Footbridge condition

Naam: _____ Geboortedatum: _____ Datum: __ __/__ __/__ __ __ __

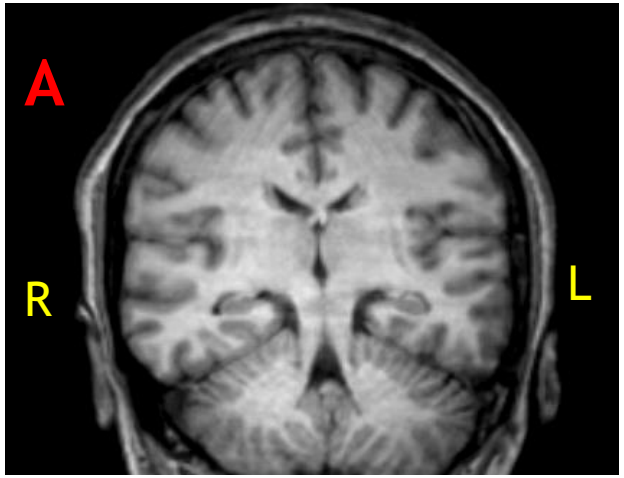
Vragenlijst Sociaal Gedrag (SNQ-NL)

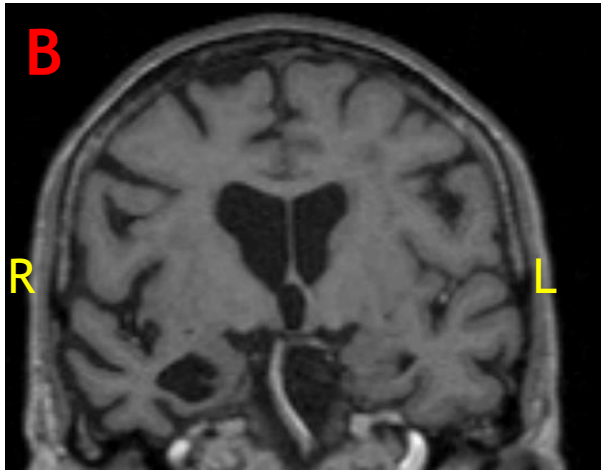
Hieronder vindt u een lijst van gedragingen van mensen. Wilt u aangeven of dit gedrag **naar uw mening** gepast of geaccepteerd is in de sociale cultuur van Nederland? Kruis bij elke vraag JA of NEE aan. Let op: stelt u zich voor dat dit gedrag gebeurt tegenover een kennis of vreemde, niet tegenover een goede vriend of familielid.

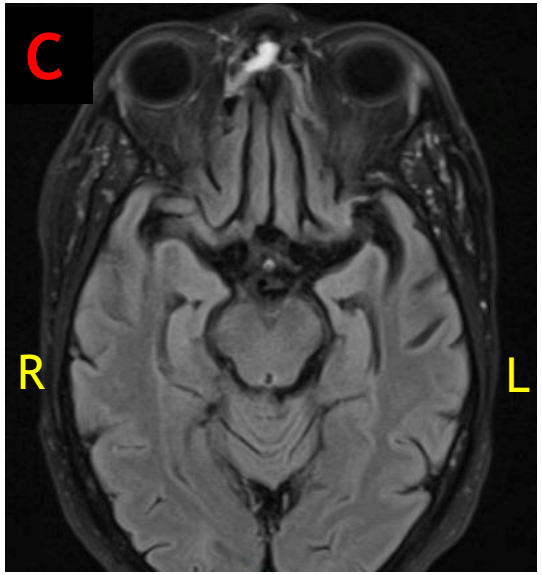
Zou het netjes/maatschappelijk geaccepteerd zijn om:

1.	Een vreemde te vertellen dat u zijn kapsel niet leuk vindt?	☐ NEE	☐ JA
2.	Op de grond spugen?	☐ NEE	☐ JA
3.	Uw neus te snuiten in het openbaar?	☐ NEE	☐ JA
4.	Een collega naar zijn leeftijd te vragen?	☐ NEE	☐ JA
5.	Te huilen tijdens een film in de bioscoop?	☐ NEE	☐ JA
6.	Voor te dringen in een rij als u haast heeft?	☐ NEE	☐ JA
7.	Te lachen wanneer uzelf struikelt en valt?	☐ NEE	☐ JA
8.	Pasta te eten met uw vingers?	☐ NEE	☐ JA
9	Een collega uw leeftijd te vertellen?	☐ NEE	☐ JA

Diagnose obv observatie ?







Diagnostiek- fase 2

- FDG-PET
- DAT-SPECT
- Autoimmuun antilichamen
- EEG
- Ergotherapeutische observatie
- Linguistisch onderzoek
- Genetische diagnostiek

Casus 1

- Man, 61 jaar, vertegenwoordiger
- VG blanco
- Familie-anamness: gb
- Reden bezoek Alzheimercentrum:

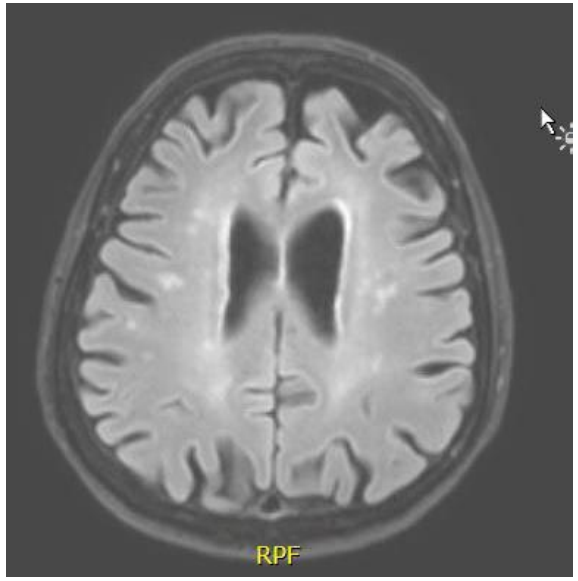
Sinds 2 jaar vergeetachtig, opgevallen na overlijden partner

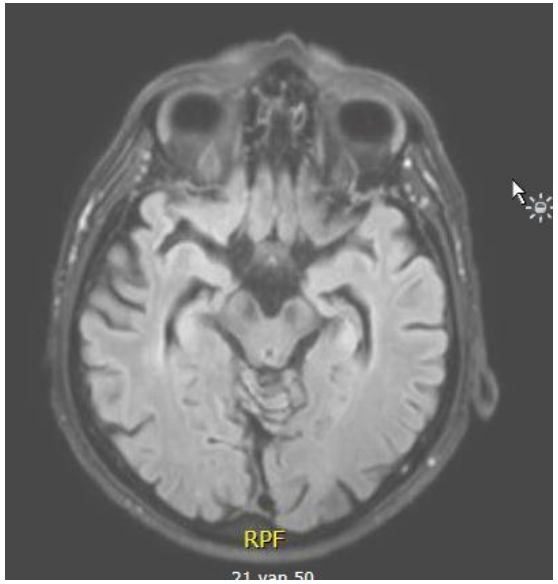
- Minder initiatief
- Empathie behouden
- Geen desorientatie
- Geen motorische klachten; rent 21 km/dag

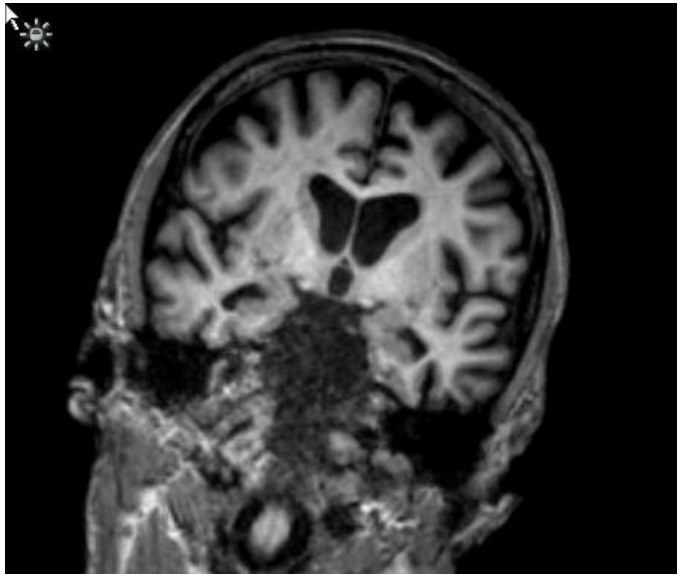
Onderzoek

- Licht ontremd
- Emotioneel tav verlies partner (2 jaar geleden)
- CAMCOG 78/103
- MMSE 26/30
- FAB 11/18

Aanvullende diagnostiek







EEG: normaal AGP, milde focale afwijkingen bitemporaal
Neuropsychologisch onderzoek: geheugen-, taal- en executieve stoornissen

CSF: normaal !!

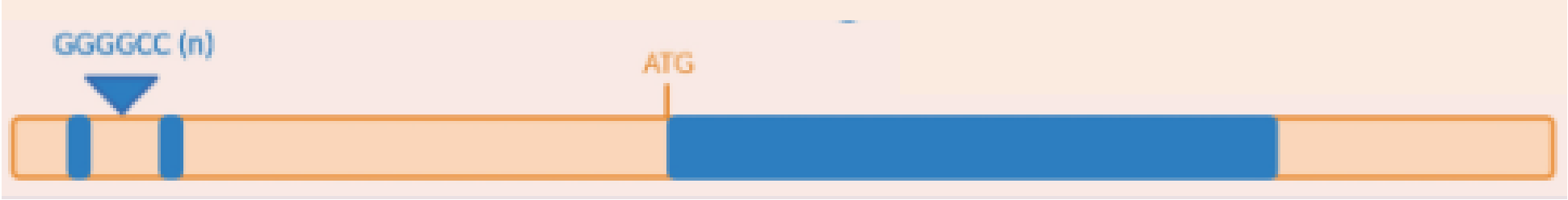
Genetische test:
C9orf mutatie !

Diagnostische criteria (Rascovsky et al., 2011)

A Disinhibitie
B Apathie
C Verlies van empathie
D Stereotypie
E Hyperoraliteit
F Neuropsychologisch profiel

C9orf mutatie

- Presentatie met psychiatrisch beeld
- Langzaam beloop
- Geen of atypische afwijkingen op scan
- Negatieve familie-anamese
- ALS



Snowden et al., Brain 2012

somatoform psychosis or paranoid schizophrenia. Patient 5 presented to the Accident and Emergency department of his local hospital complaining of pieces of plastic emanating from his head. He had been noted in preceding months to being increasingly suspicious and to pluck repetitively at his skull. He carried a pocket-knife with which he threatened to cut out the offending plastic. Patient 6 described visions of the devil and had developed behavioural strategies for keeping him at bay. She reported pain and spent all day in bed, saying that bed-rest would allow her 'nerves to heal'. Despite her symptoms she showed no distress and her affect was of 'belle indifference'. Patient 10 developed persecutory delusions. He threw lit fireworks though his neighbour's letterbox, and carried a knife and pistol for self-defence. He telephoned the police at the same time each night demanding protection. Patient 11 acquired a mono-delusion of weakness of the gluteal muscles, necessitating that he maintain his finger in his anus to prevent incontinence. Patient 12 believed that he was under surveillance and reported hearing the voice of God. Patient 13 exhibited delusional parasitosis believing that he was infested by mites, which crawled under his skin and into his extremities. He reported that the mites congregated in his ear lobe, and that he could reduce their number by pinching his ear lobe at regular 10-min intervals. Patient 14 contacted the police complaining of men hiding in her garden, including a man dressed in a gorilla outfit. Thereafter she reported seeing disembodied faces, which she believed to be spirits. Patient 16 barricaded himself into his home in the belief that his son was trying to kill him. Patient 17 believed that he was being contacted by letter or phone by dead friends and hatched plans to meet them. Patient 22 became suspicious about relatives and believed characters on the television screen to be communicating with her. Patient 23

Casus 2

- Vrouw 73 jaar
- Sinds 2 jaar sombere gevoelens, zonder aanleiding. Kan niet genieten.
- Gevoel van spanning
- Onzeker, twijfelzucht
- Dwangmatige handelingen (tikken op matras terwijl ze in bed ligt)
- Grof in de mond (vloeken)
- Ontremd met eten
- Geen interesse in anderen, toont geen emoties
- Concentratie slecht

Neuropsychiatrisch onderzoek

Geheugen goed

Taal goed

Head turning sign

Fluistert de hele tijd ‘zo, zo, zo’

Tikt frequent met handen op stoel

MMSE 23/30, MOCA 20/30, FAB 13/18, GDS 12/15

Aanvullend onderzoek

MRI-hersenen: leeftijdsconform

NPO: milde stoornissen leervermogen, executieve functiestoornissen, perseveraties in taal

Liquor biomarkers: normaal

FDG-PET: normaal

Auto-immuun antistoffen: negatief

Genetica: negatief

Depressie belangrijke DD bij presentatie met cognitieve klachten

Ziekte van Alzheimer

Frontotemporale Dementie

Dementie met Lewy Lichaampjes

Vasculaire Dementie

NB depressie kan ook co-morbide zijn

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REVIEW ARTICLE

Recommendations to distinguish behavioural variant frontotemporal dementia from psychiatric disorders

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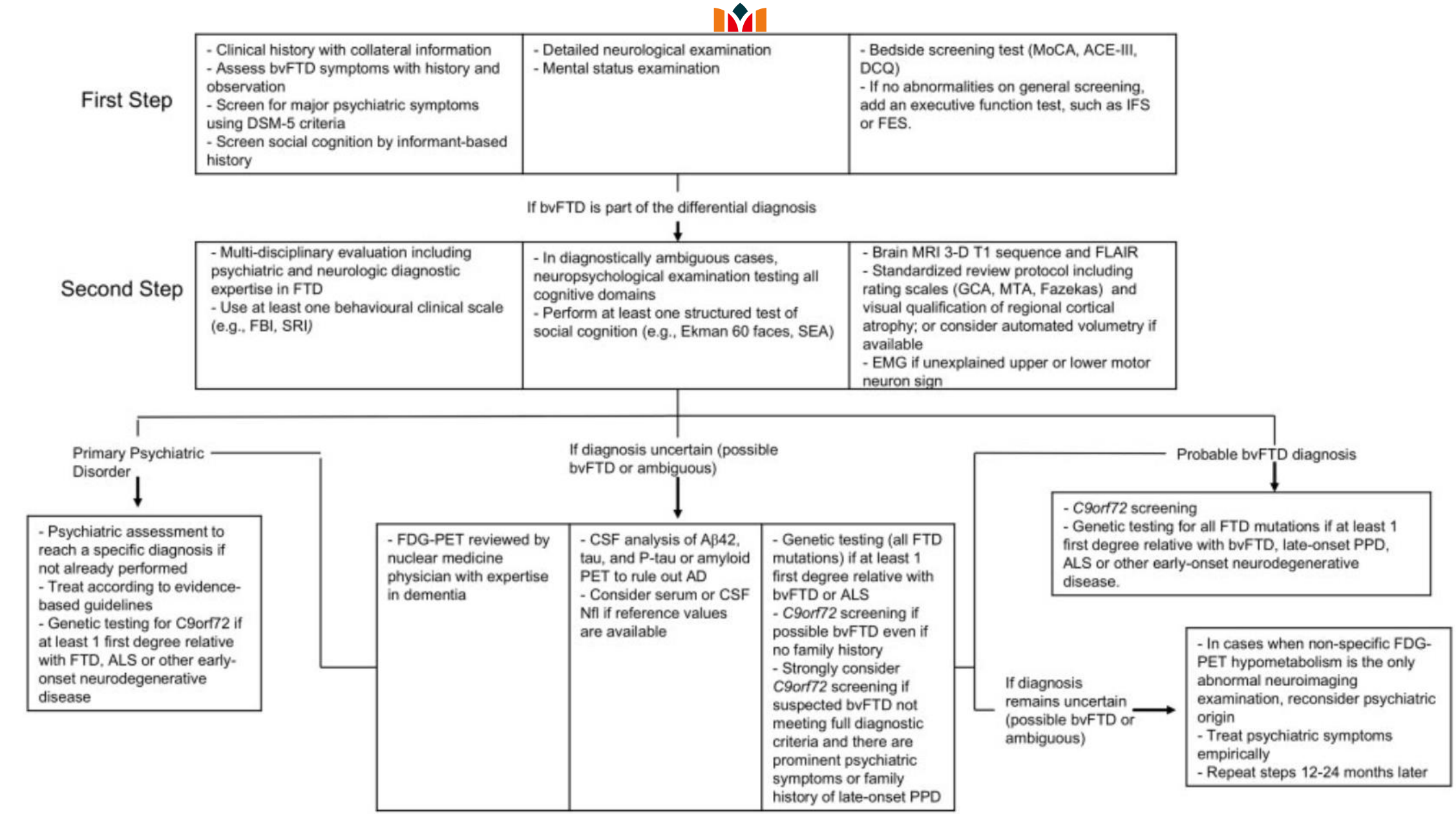
First Step
- Clinical history with collateral information
- Assess bvFTD symptoms with history and observation
- Screen for major psychiatric symptoms using DSM-5 criteria
- Screen social cognition by informant-based history
- Detailed neurological examination
- Mental status examination
- Bedside screening test (MoCA, ACE-III, DCQ)
- If no abnormalities on general screening, add an executive function test, such as IFS or FES.
If bvFTD is part of the differential diagnosis
Second Step
- Multi-disciplinary evaluation including psychiatric and neurologic diagnostic expertise in FTD
- Use at least one behavioural clinical scale (e.g., FBI, SRI)
- In diagnostically ambiguous cases, neuropsychological examination testing all cognitive domains
- Perform at least one structured test of social cognition (e.g., Ekman 60 faces, SEA)
- Brain MRI 3-D T1 sequence and FLAIR
- Standardized review protocol including rating scales (GCA, MTA, Fazekas) and visual qualification of regional cortical atrophy; or consider automated volumetry if available
- EMG if unexplained upper or lower motor neuron sign
Primary Psychiatric Disorder
- Psychiatric assessment to reach a specific diagnosis if not already performed
- Treat according to evidence-based guidelines
- Genetic testing for C9orf72 if at least 1 first degree relative with FTD, ALS or other early-onset neurodegenerative disease
If diagnosis uncertain (possible bvFTD or ambiguous)
- FDG-PET reviewed by nuclear medicine physician with expertise in dementia
- CSF analysis of Aβ42, tau, and P-tau or amyloid PET to rule out AD
- Consider serum or CSF Nfl if reference values are available
- Genetic testing (all FTD mutations) if at least 1 first degree relative with bvFTD or ALS
- C9orf72 screening if possible bvFTD even if no family history
- Strongly consider C9orf72 screening if suspected bvFTD not meeting full diagnostic criteria and there are prominent psychiatric symptoms or family history of late-onset PPD
Probable bvFTD diagnosis
- C9orf72 screening
- Genetic testing for all FTD mutations if at least 1 first degree relative with bvFTD, late-onset PPD, ALS or other early-onset neurodegenerative disease.
If diagnosis remains uncertain (possible bvFTD or ambiguous)
- In cases when non-specific FDG-PET hypometabolism is the only abnormal neuroimaging examination, reconsider psychiatric origin
- Treat psychiatric symptoms empirically
- Repeat steps 12-24 months later

Onderzoek naar diagnostiek dementie op jonge leeftijd

- Specifieke biomarker voor FTD
- DD FTD-psychiatrie
- KIC-NWO: digitale YOD test batterij
- Nationale Dementie strategie: YOD cohort (icm PRECODE, ABOARD), YOD toolkit voor geheugenpoliklinieken
- Diagnose en dan…?
- Postmortem diagnostiek: kwaliteitscontrole ; nazorg

Mariam Badou
Monique Stavenuiter
Marije Voorwinden
Jessica van den Toorn

Omgaan met zeldzamere vormen van dementie DLB, FTD, PCA & PPA

Gids met ervaringen en tips voor patiënten en mantelzorgers

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