Primary progressive aphasia subtyping in clinical practice

Rik Vandenberghe
Laboratory for Cognitive Neurology, K.U.Leuven,
Neurology Department University Hospitals
Leuven, Belgium

Q1 What is your background?

1. Patient/family member
2. Speech therapist
3. Neuropsychologist
4. Resident in neurology
5. Practising general neurologist
6. Cognitive Neurologist
7. Researcher in cognitive neuroscience
8. Other

Learning objectives

- Clinically characterize language and speech problems in patients presenting to the clinic
- Select and interpret neurolinguistic tests that are essential for PPA subtyping
- To know the probability of the underlying neuropathological causes for the different PPA subtypes

Outline

- What are the subtypes?
- Six key clinical questions to evaluate

Classification of primary progressive aphasia and its variants

M.L. Gorno-Tempini, MD, PhD
A.E. Hillis, MD
S. Weintraub, PhD
A. Kertesz, MD
M. Mendez, MD
S.F. Cappa, MD
J.M. Ogar, MS
J.D. Rohrer, MD
S. Black, MD
B.F. Boeve, MD
F. Manes, MD
N.F. Dronkers, PhD
R. Vandenberghe, MD, PhD
K. Rascovsky, PhD
K. Patterson, PhD
B.L. Miller, MD
D.S. Knopman
J.R. Hodges, MD*
M.M. Mesulam, MD*
M. Grossman, MD*

ABSTRACT

This article provides a classification of primary progressive aphasia (PPA) and its 3 main variants to improve the uniformity of case reporting and the reliability of research results. Criteria for the 3 variants of PPA—nonfluent/agrammatic, semantic, and logopenic—were developed by an international group of PPA investigators who convened on 3 occasions to operationalize earlier published clinical descriptions for PPA subtypes. Patients are first diagnosed with PPA and are then divided into clinical variants based on specific speech and language features characteristic of each subtype. Classification can then be further specified as "imaging-supported" if the expected pattern of atrophy is found and "with definite pathology" if pathologic or genetic data are available. The working recommendations are presented in lists of features, and suggested assessment tasks are also provided. These recommendations have been widely agreed upon by a large group of experts and should be used to ensure consistency of PPA classification in future studies. Future collaborations will collect prospective data to identify relationships between each of these syndromes and specific biomarkers for a more detailed understanding of clinicopathologic correlations. **Neurology® 2011;76:1006–1014**

GLOSSARY

AD = Alzheimer disease; **FTLD** = frontotemporal lobar degeneration; **PPA** = primary progressive aphasia.

A progressive disorder of language associated with atrophy of the frontal and temporal regions of the left hemisphere was first described in the 1890s by Pick[1] and Serieux.[2] In the modern literature, Mesulam[3] described a series of cases with "slowly progressive aphasia," subsequently

Objective language/speech impairment

Sparing of other cognitive domains

ROOT DIAGNOSIS OF PPA

Speech apraxia and/or agrammatism

Yes

No

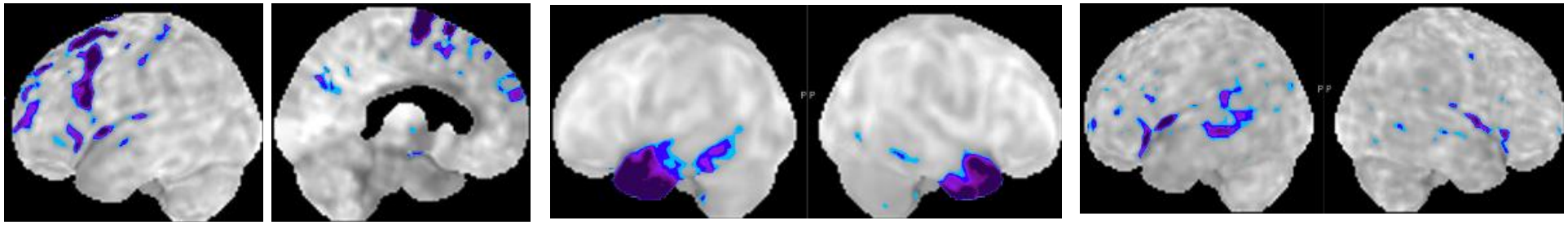
Comprehension deficit

Phonological short-term memory deficit

Nonfluent variant

Semantic variant

Logopenic variant



Vandenberghe R, Alzheimer's Research and Therapy, 2016

Primary progressive aphasia subtyping

- Subtyping helps to distinguish between underlying etiologies in a probabilistic manner
- Important for communication of diagnosis and prognosis
- Important to direct attention during follow-up

- MRI and FDG PET may also show subtype-specific patterns
- Cerebrospinal fluid biomarker tests are also important for an etiological diagnosis

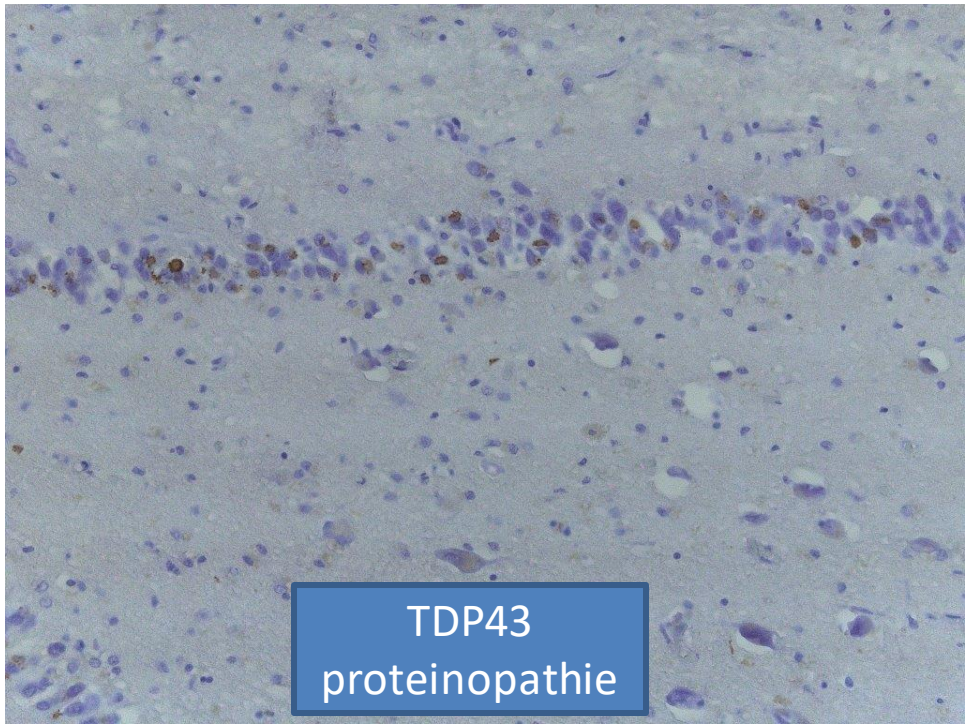
Q2

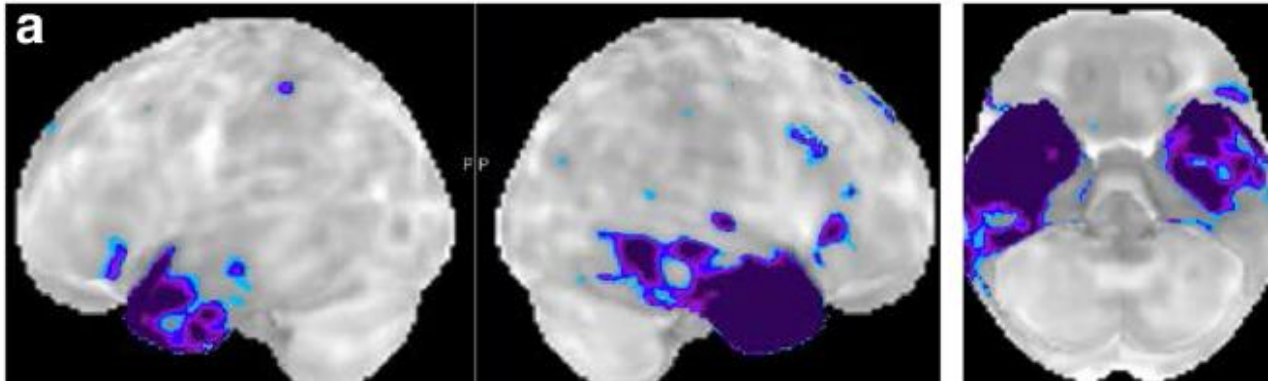
What is the single most frequent etiology of PPA Semantic variant?

1. Alzheimer's disease
2. Pick's disease
3. FTLD-TDP43 type A
4. FTLD-TDP43 type B
5. FTLD-TDP43 type C

Semantic variant

- FTLD-TDP43 in 69-83%

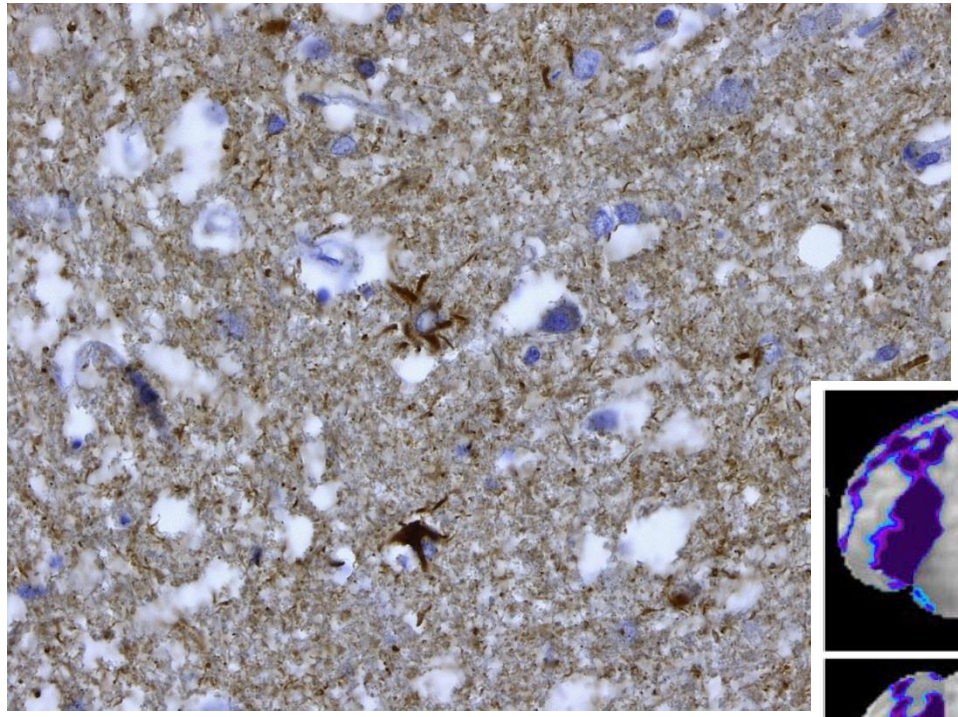


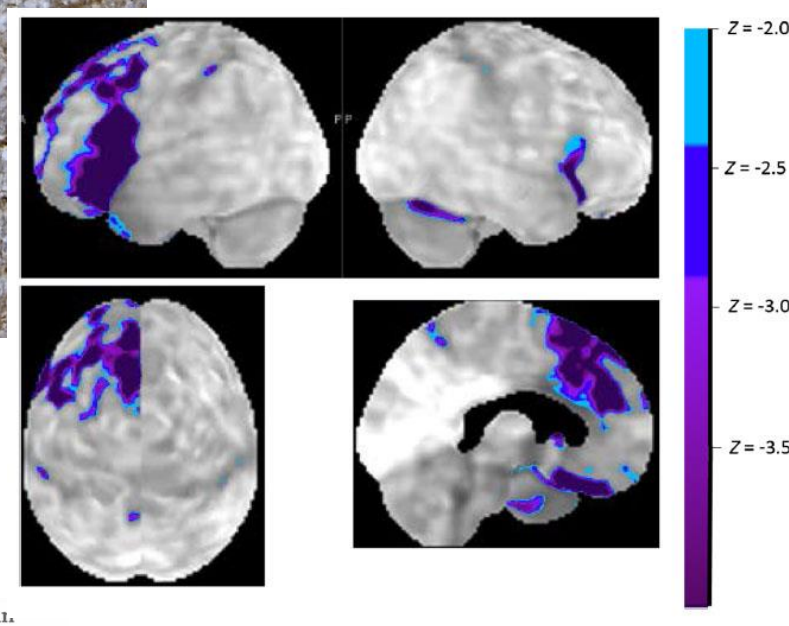


- Alzheimer in 10-20%
- Rarely Pick's diease

Nonfluent variant

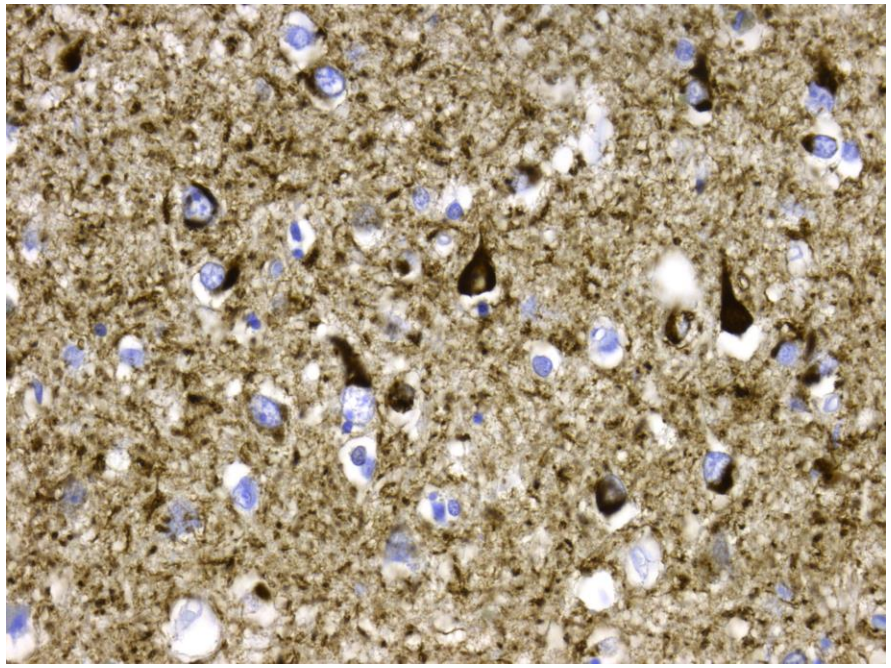
- FTLD-tau (50-70%)
  - Corticobasal degeneration
  - Progressive supranuclear palsy
  - Pick's disease
- FTLD-TDP43 (20%)
- Alzheimer (12-25%)

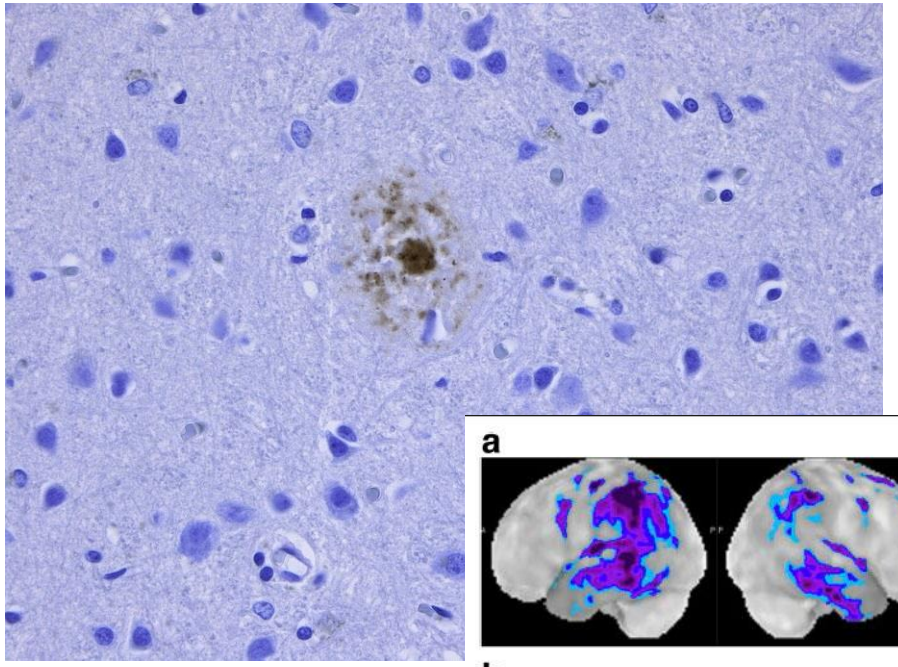


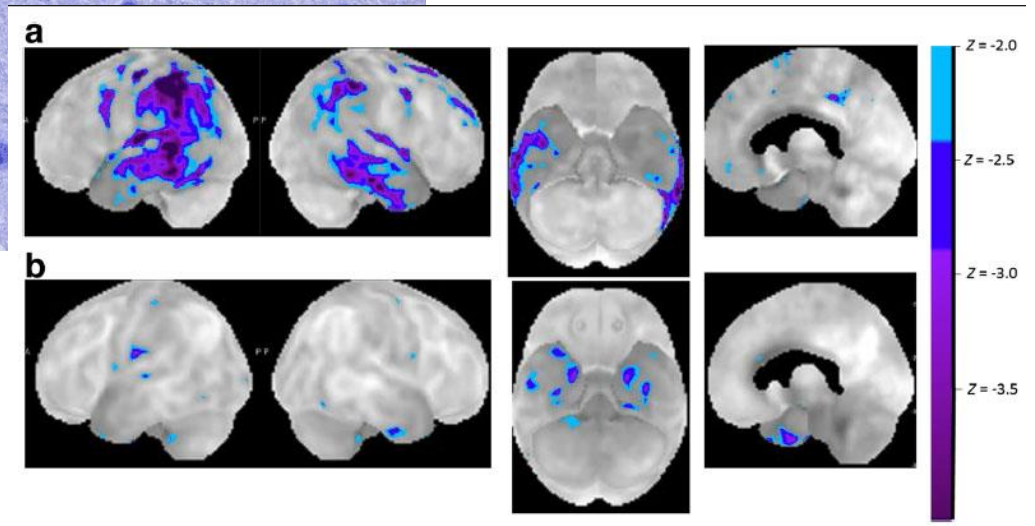


Logopenic variant

- Alzheimer (50-60%)







- FTLD-TDP43 (38%)
- FTLD-tau (5-10%)

Six key questions in primary progressive aphasia

1. Is there a language deficit?
2. Are other cognitive domains relatively preserved?
3. Word finding versus speech problems?
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5. Agrammatism
6. Is comprehension affected?

Types of tests

- Clinical bedside tests
- Standardized normative tests
  - Common: aphasia in general and available in many languages

    Aaken Afasie Test

    Boston Diagnostic Aphasia Examination

    Comprehensive Aphasia Test

    Psycholinguistic Assessment of Language Processing in Aphasia
  - PPA specific

    Sydney Language Battery (SYDBAT)

    Screening for Aphasia in Neurodegeneration (SAND)
  - Language specific
    - E.g. Czech, Dutch, English, French, German, Italian, …

European Reference Network
for rare or low prevalence complex diseases
Network Neurological Diseases (ERN-RND)

Neurolinguistic and cognitive assessment for subtyping of primary progressive aphasia: Current practice

The history

As always in the memory clinic, everything starts with the complaint of the patient and the family, and the concrete examples they provide.

Memory versus language

Language versus speech

Six key questions in primary progressive aphasia

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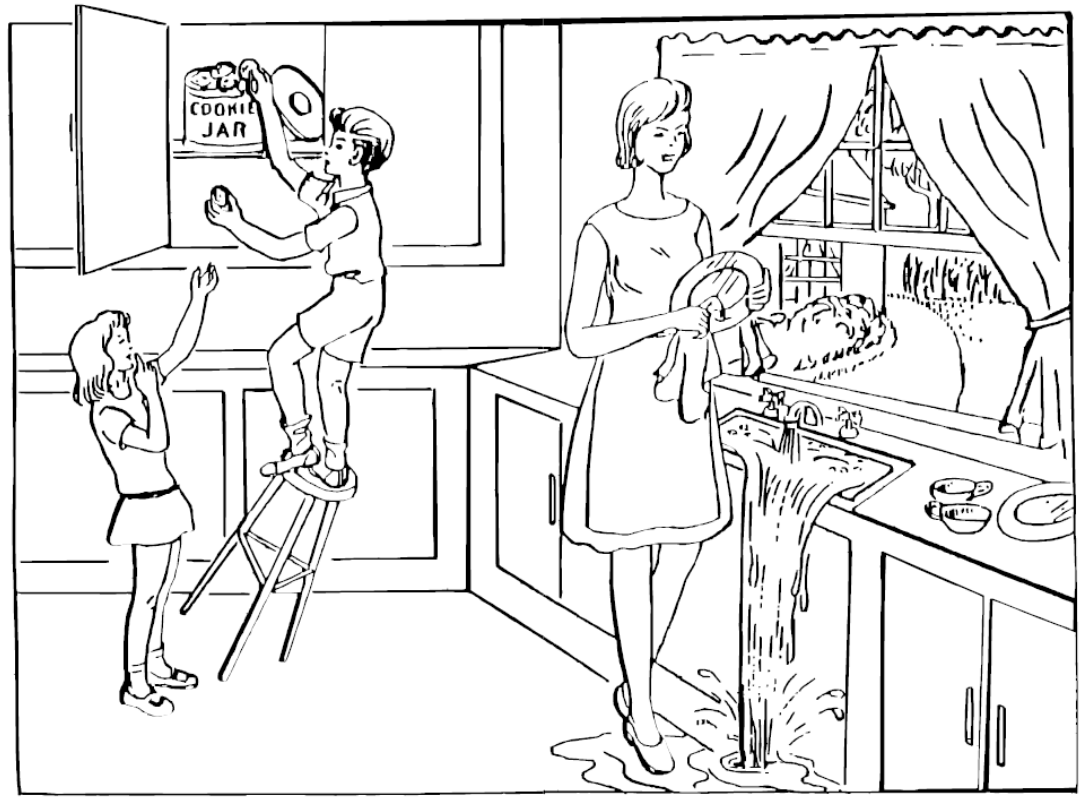
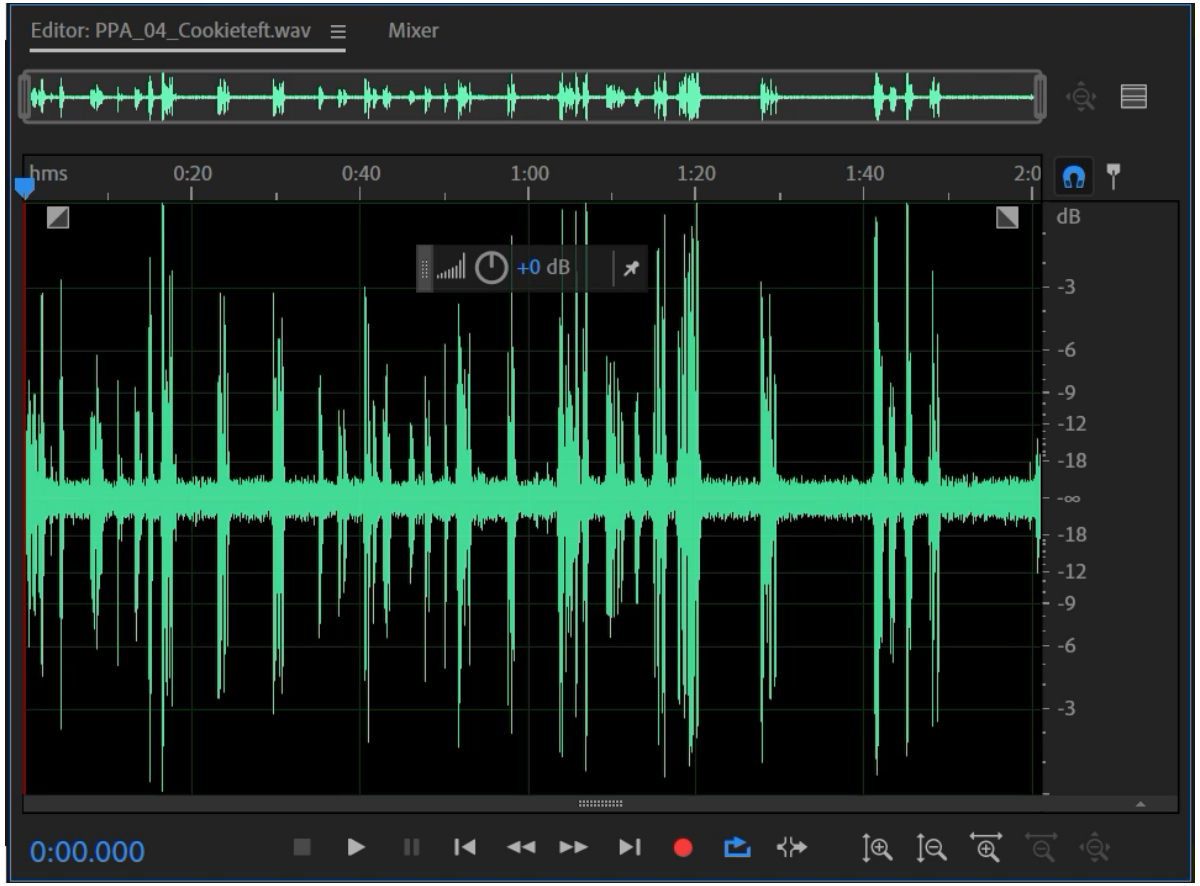
1. Is there a language deficit?

- Spontaneous speech
- Semi-structured speech elicited by pictorial scene
- Boston Naming test, preferably lower-frequency items
- Repetition of longer sentences
- May require extensive neurolinguistic assessment to detect abnormalities

Fluency of semi-structured speech



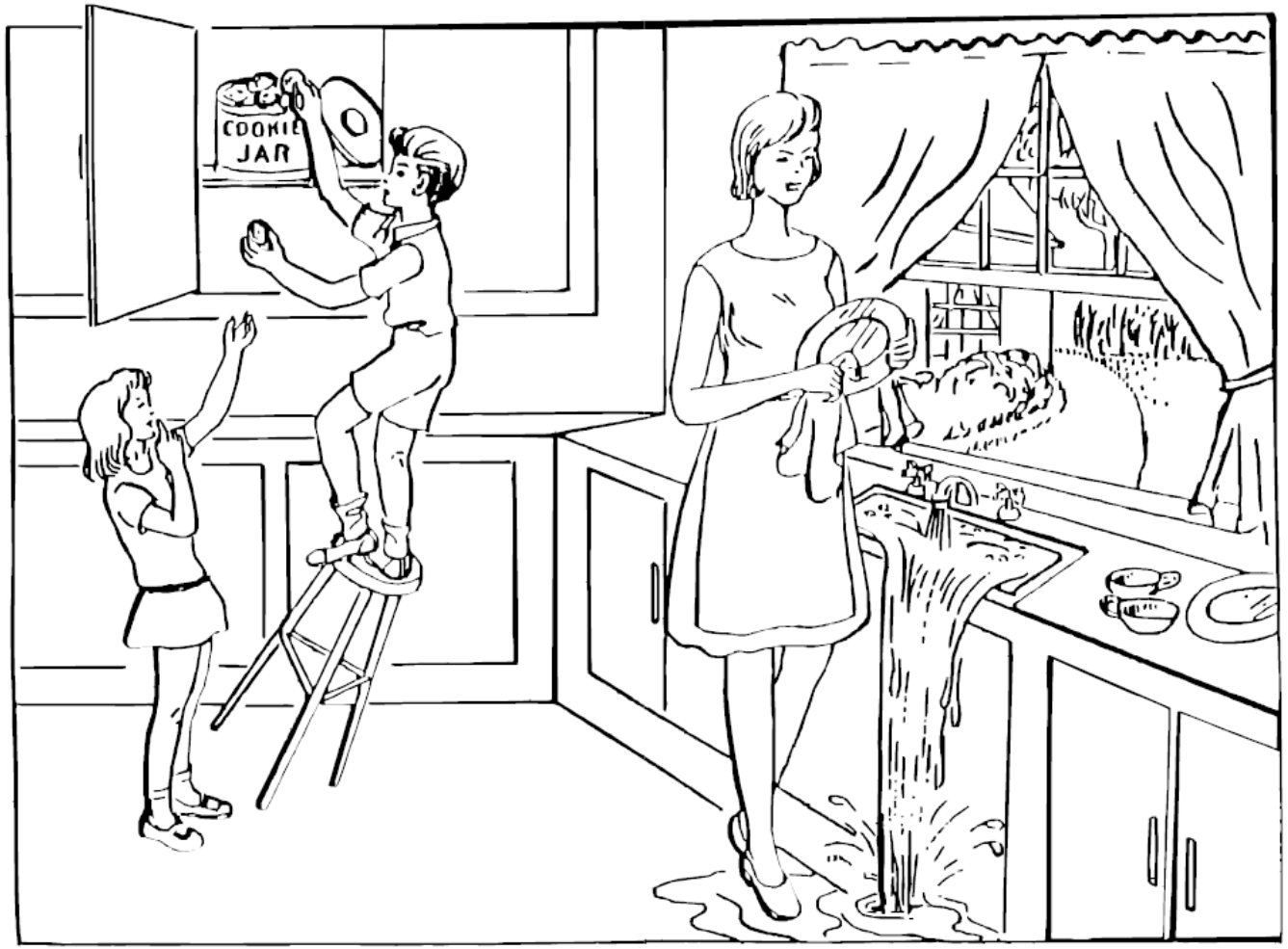
VIGNETTE A



A woman who does the dishes … and … her little son … takes … jar … eum … her little son takes … and that is water … he spills water … and … there stand … saucers and … things … eum … cups … and that is a window … a garden … and he stands on a chair that boy … and that girl stands … next to him … on the chair … stands the boy … and the boy falls … and these are cupboard

Initially, the language difficulties may not be very conspicuous

VIGNETTE B



Ah it is a kitchen *eum* … two children and a mother.

Eum … one child a daughter or a girl *eum* … stands on *eum* … stands on the floor

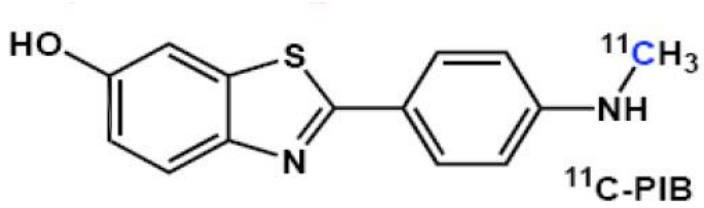
and another stands on a *eum eum eum* … a ta *eum eum* …. stands on <silence> on *eum* … a chair and tries yes he does that he takes cookies

and mother is washing the dishes and the bin with water is spilling *eum* …

and there also stand two *eum* … there stand there stand a litle saucer and two *eum eum* … two little cups

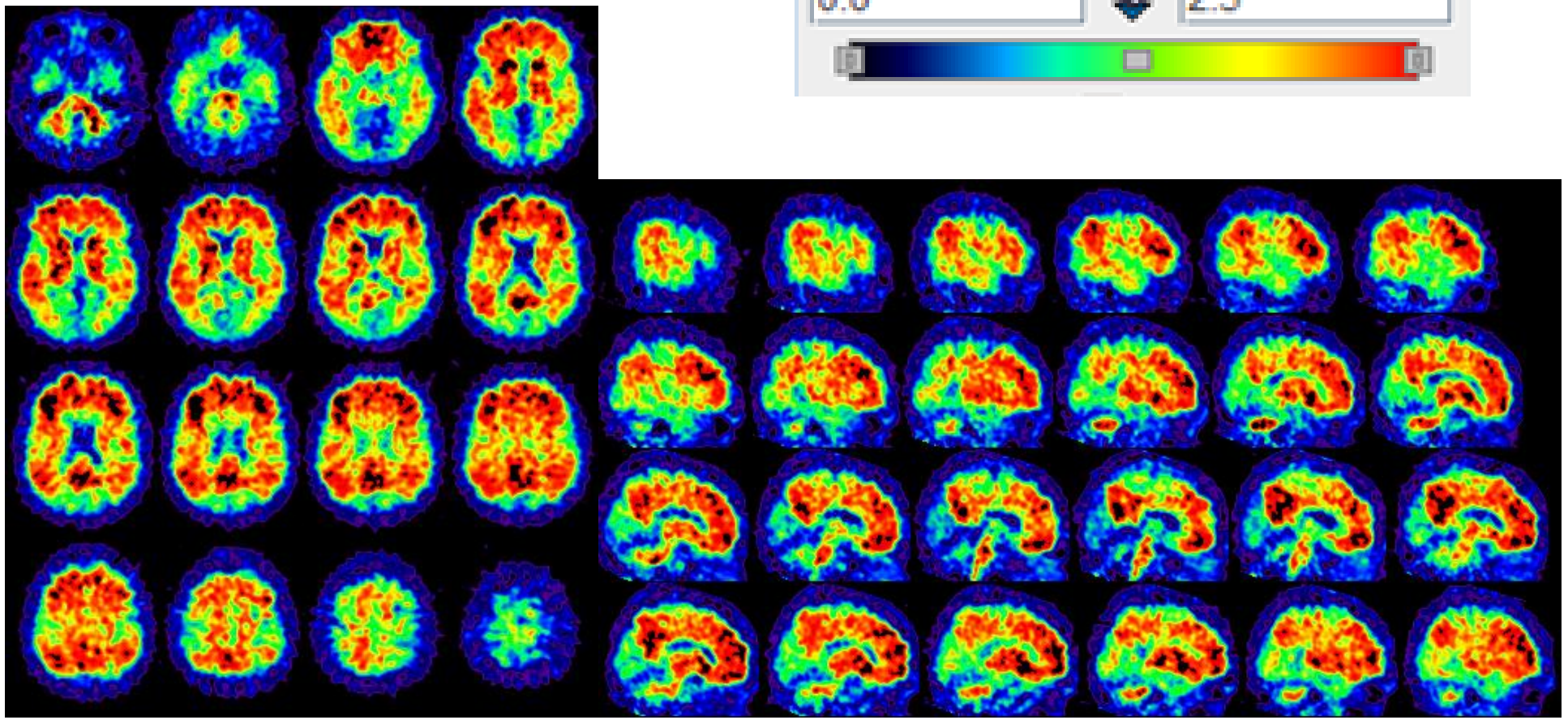
and then you have a view through that window that is open

Logopenic variant



VIGNETTE B

SUVR



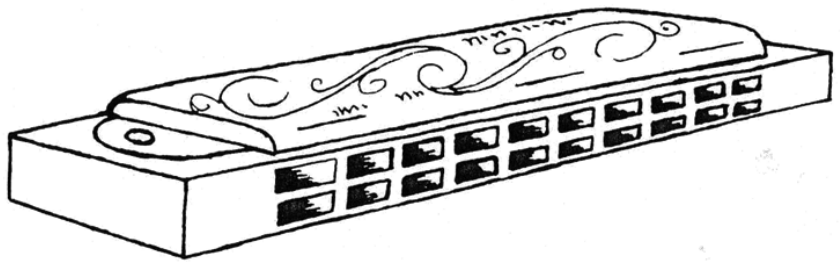
SUVR composite cortical region > 1.22)

2. Are other cognitive domains relatively preserved?

- History
  - Is the change of instrumental activities of daily living entirely attributable to language/speech problems?
  - Is topographical memory affected?
- Constructional disturbances
  - Overlapping pentagons, clock test
- Less discriminative
    - Executive function tests
    - Nonverbal episodic memory tests

3. WORD FINDING VS SPEECH PROBLEMS

Vignette C

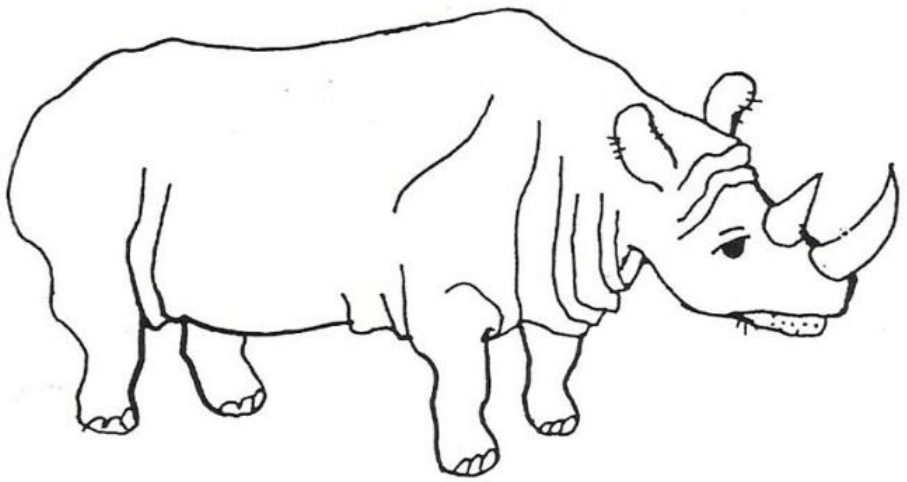


“mondharmonica”

Me me mond har monica

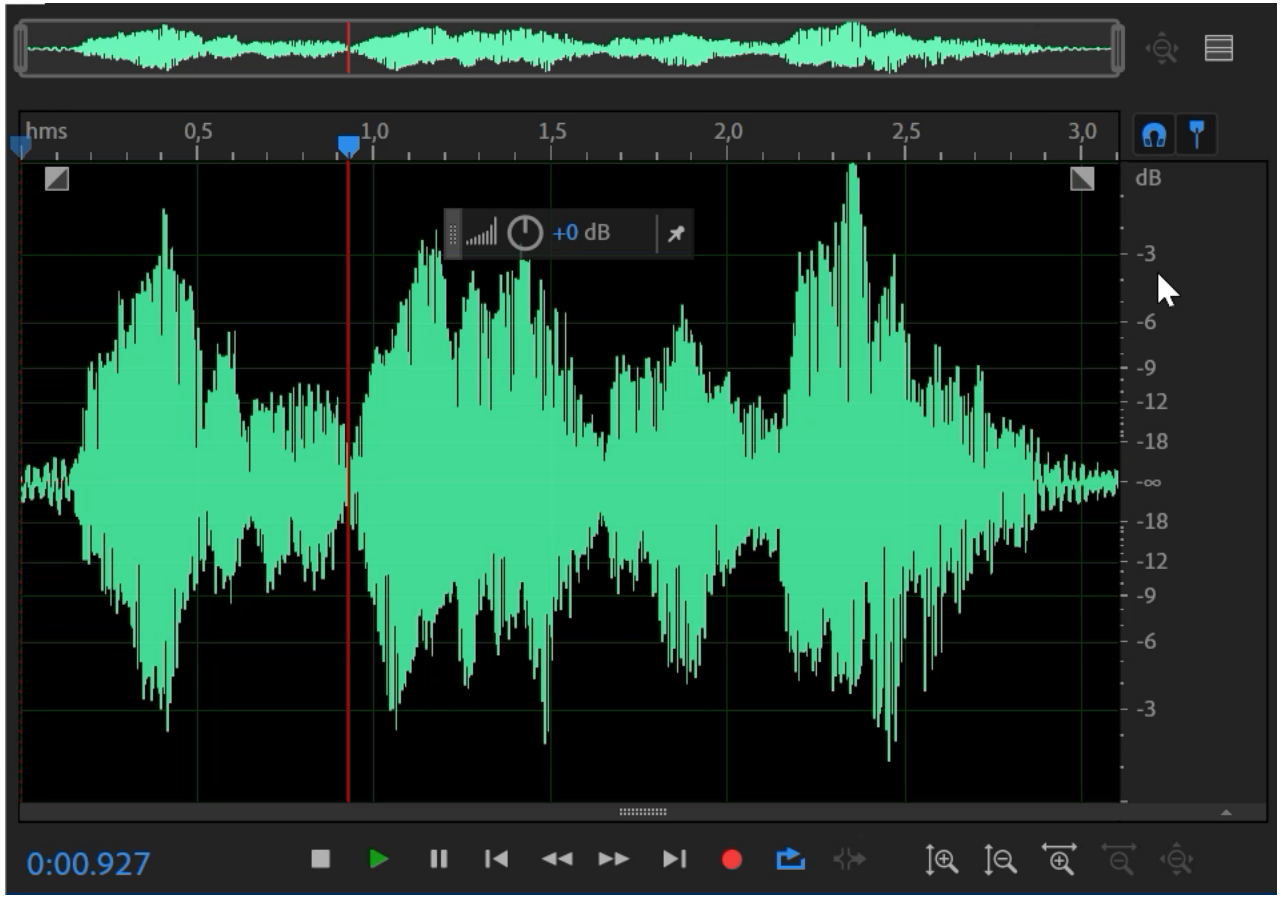
3. WORD FINDING VS SPEECH PROBLEM

Vignette C



“neushoorn”

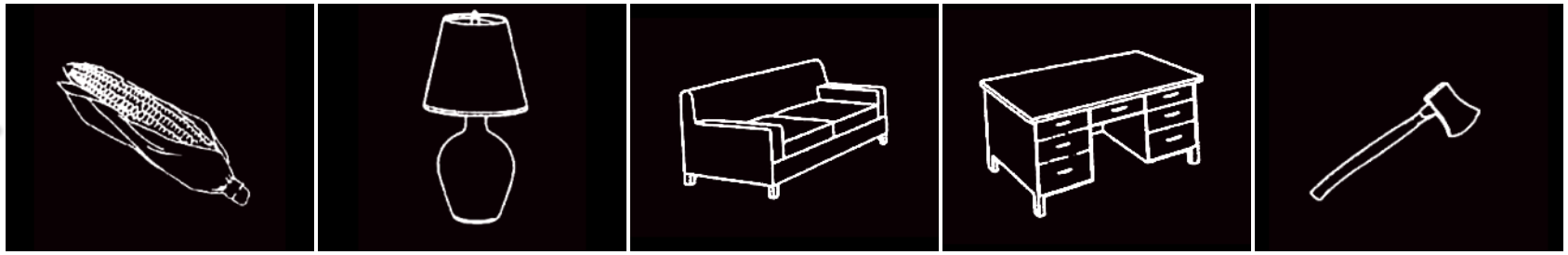
Ne neus eu hoorn



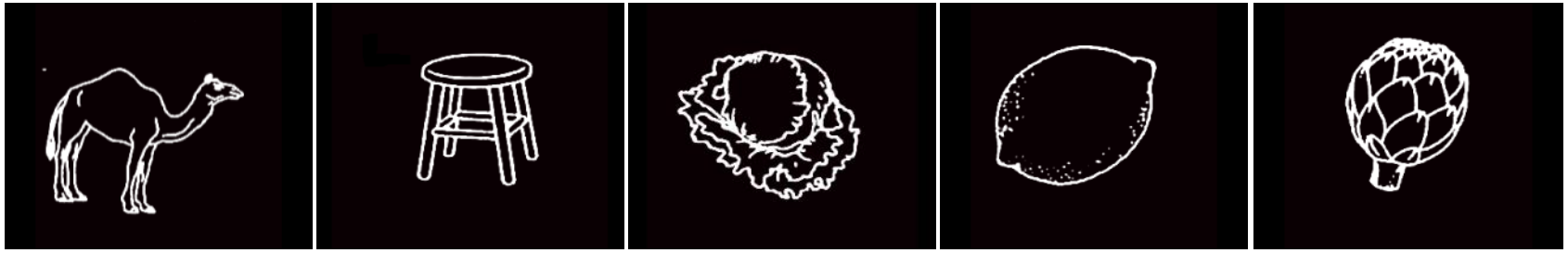
Vignette D

maïskolf

schemer mer schemerlamp



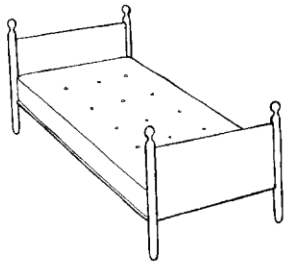
dromedaris



Q3. What was the autopsy diagnosis in vignette D?

1. Alzheimer's disease
2. FTLD-TDP43 type A
3. FTLD-TDP43 type B
4. FTLD-TDP43 type C
5. Corticobasal degeneration
6. Progressive supranuclear palsy
7. Other

Vignette E



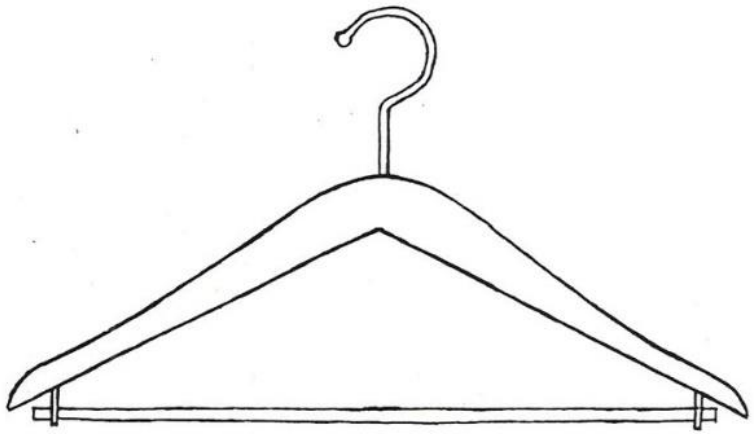
bed

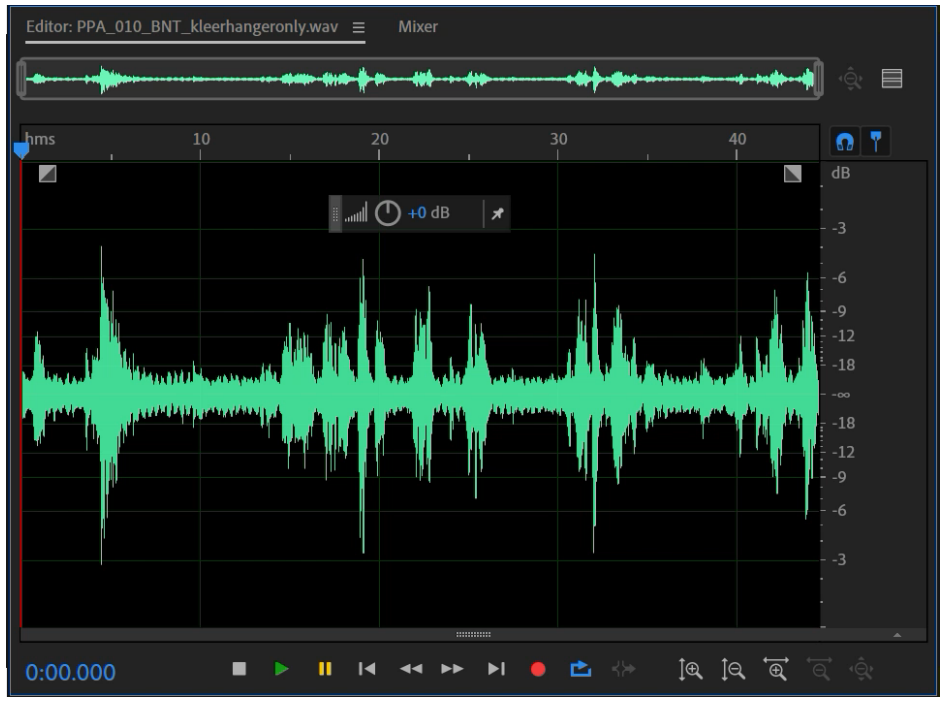
boom

Potlood: <silence> pon pon pont ponto

3. WORD FINDING VS SPEECH PROBLEM

Vignette F

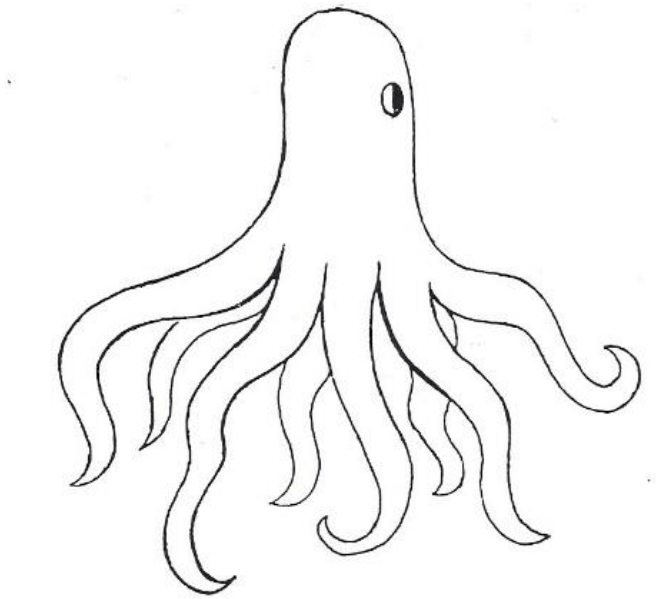




Eum …
Allez to hang clothes on a eu …
I have taken this morning my shirt from it and euh. Bad eh …
Such simple things …
that we see daily …
<klee> kleerdrager
<kleerhanger> kleerhanger

3. WORD FINDING VS SPEECH PROBLEM

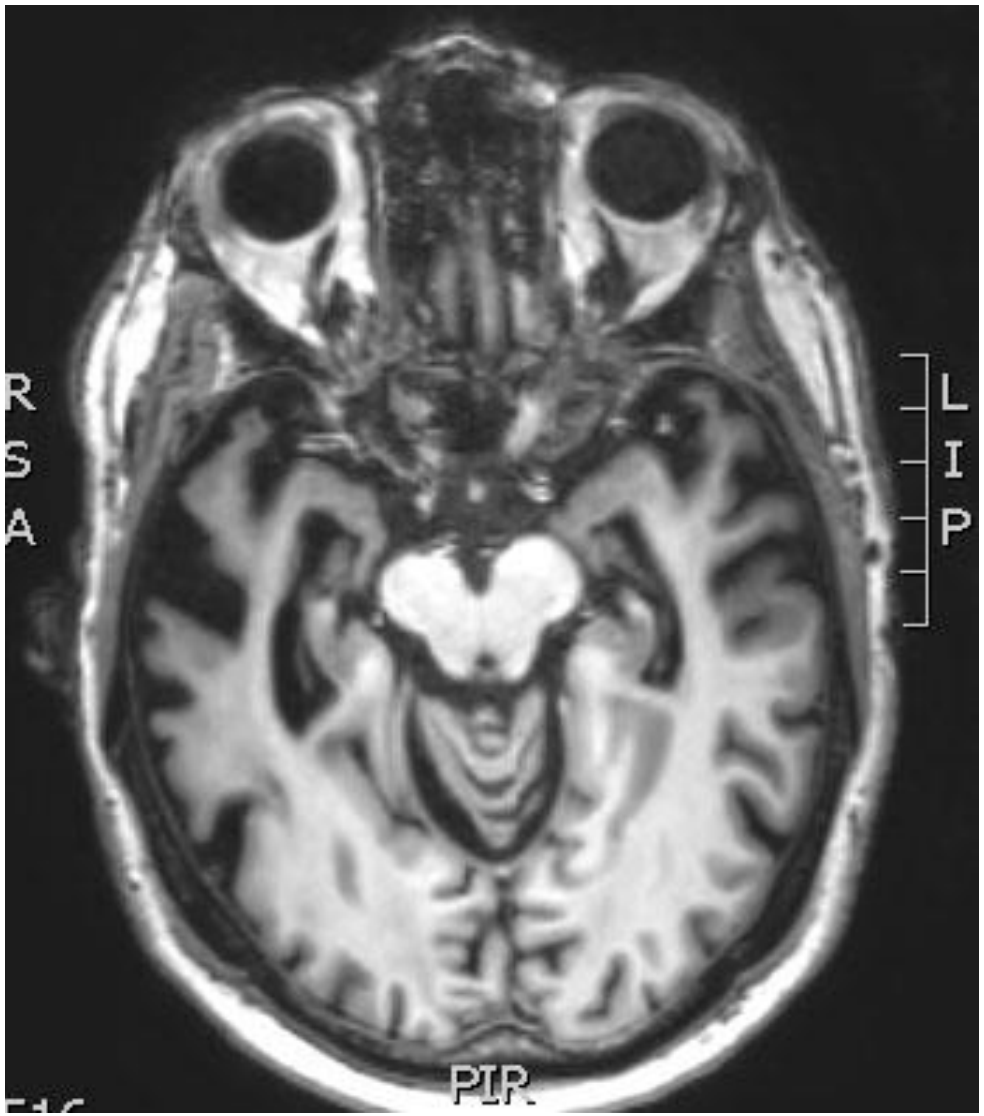
Vignette F

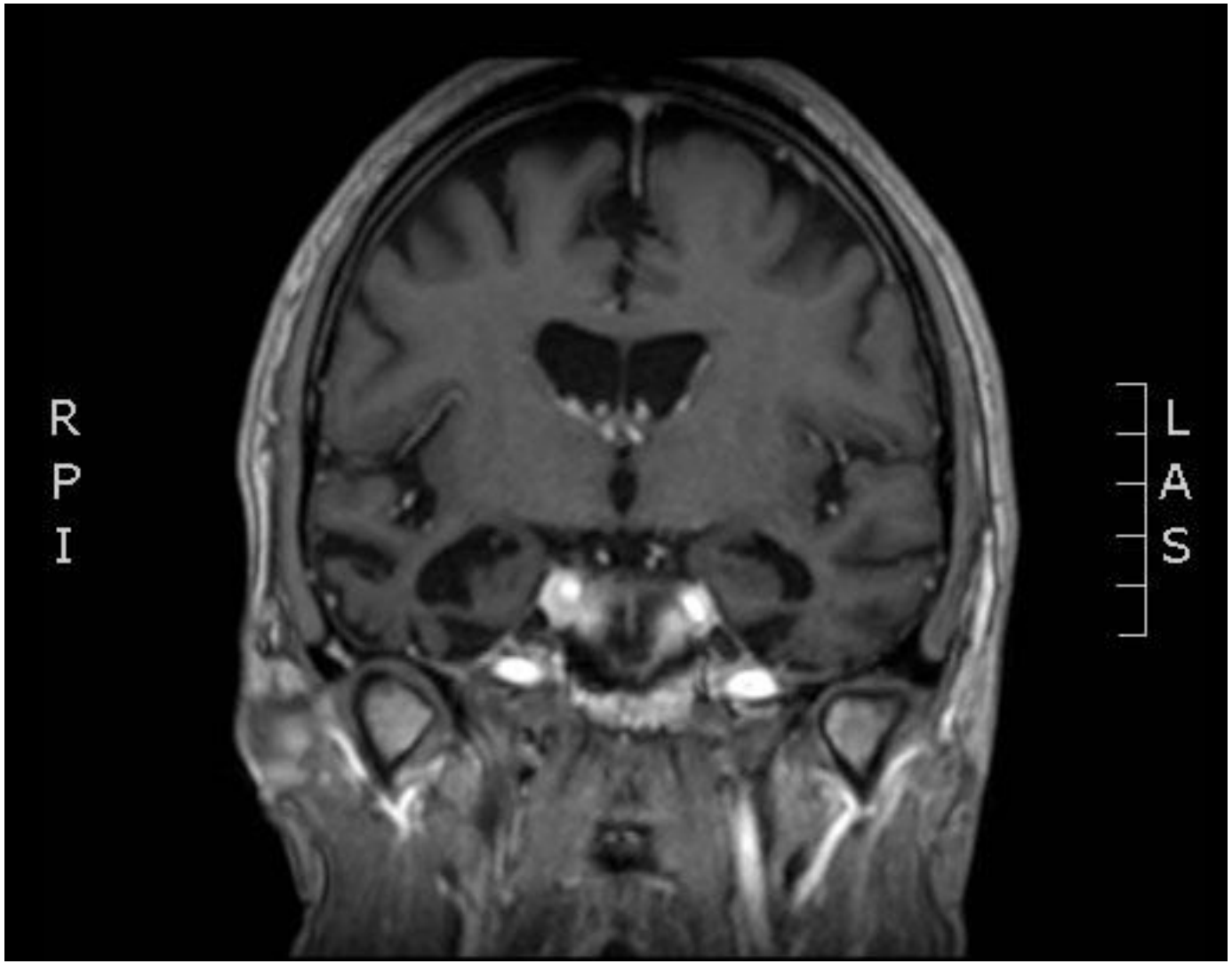


Eum … Allez zo an animal in the sea eum …
A centipede no…
Allez …
<it is indeed a sea animal. It starts with>
Eight-arm
<inkt>
inktvis

Q4. Which region is responsible for the deficit in vignette F?

1. L inferior frontal gyrus
2. Broca's area (pars triangularis)
3. Wernicke's area (posterior superior temporal g./s.)
4. Anterior temporal pole
5. Temporoparietal junction
6. Other


R
S
A
L
I
P
PIR


R
P
I
L
A
S

Six key questions in primary progressive aphasia

1. Is there a language deficit?
2. Are other cognitive domains relatively preserved?
3. Word finding versus speech problems?
4. Repetition of single words versus longer sentences
5. Agrammatism
6. Is comprehension affected?

Repetition

- Can be impaired due to speech apraxia or phonological short-term memory deficit
- Type of materials
  - In speech apraxia: multisyllabic words with consonant clusters
  - In case of phonological short-term memory problems: repetition of longer complex sentences

AAT repetition **vignette E**

a	a
o	o
eu	eu
ui … ui … ui	eu
t	tsut
p	pup
k	ke
s	se
f	se
sh	se
oost	oos
vla	vla
mond	mon
glas	gla
storm	strom
worst	wors
spreuk	sprok
kwarts	k … k… kwart
psalm	psa
stronk	stronk

European Reference Network for rare or low prevalence complex diseases
Network Neurological Diseases (ERN-RND)

ean european academy of neurology

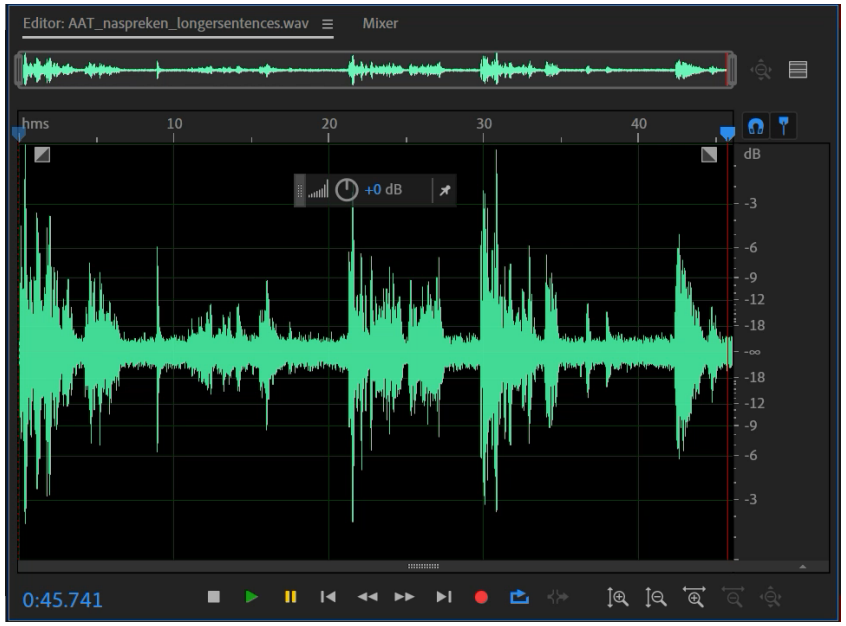
European Reference Network for rare or low prevalence complex diseases
Network Neuromuscular Diseases (ERN EURO-NMD)

Speech apraxia

- Effortful speech
- Articulatory groping and successive approximation of the target form
- Abnormal duration of vowels and intersegmental intervals (segments consisting of sounds, syllables or words), syllable segregation
- Uneven volume or pitch
- Abnormality of intonational stress
- Sound distortions (phonetic errors) and substitutions
- Most prominent for words of increasing length and articulatory complexity

Josephs et al., Characterizing a neurodegenerative syndrome: primary progressive apraxia of speech. Brain 2012; 135: 1522-1536.

Vignette G



<Hij haalde zijn moeder met de nieuwe auto van het station af.>

Hij haalde zijn moeder met de nieuwe auto … euh … hij haalde zijn moeder met de nieuwe auto … aan het station of zoiets

<Er werd gezegd dat steeds meer mensen honger lijden.>

correct

De man die onze auto gekocht heeft, is gisteren getrouwd.

De man die … de man die… dingen

Q3. What is the etiology in vignette G?

1. Alzheimer’s disease
2. FTLD-TDP43
3. Corticobasal degeneration
4. Progressive supranuclear palsy
5. Other

REPETITION

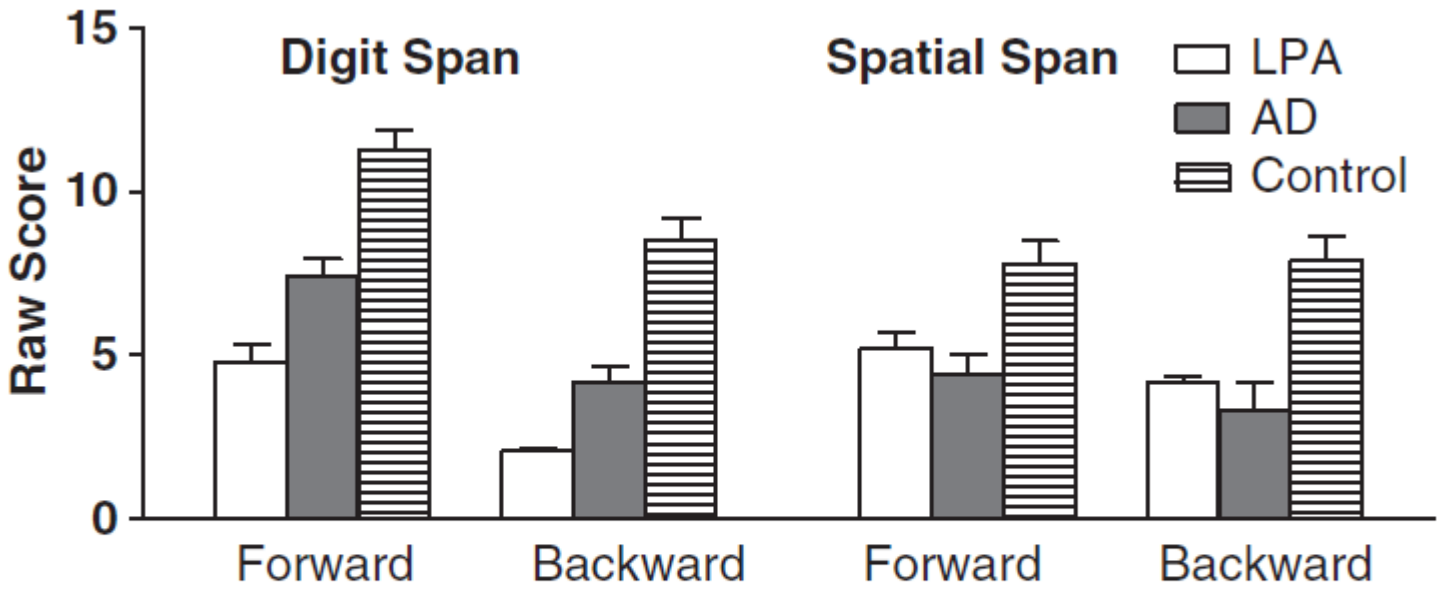


Fig. 1. Performance on the Wechsler Memory Scale-III (WMS3) Digit Span and Spatial Span Forward and Backward tasks. Error bars represent standard errors of the mean.

Foxe et al, Verbal and visuospatial span in logopenic progressive aphasia and Alzheimer's disease, J Int Neuropsychol Soc 2013; 19: 247-253

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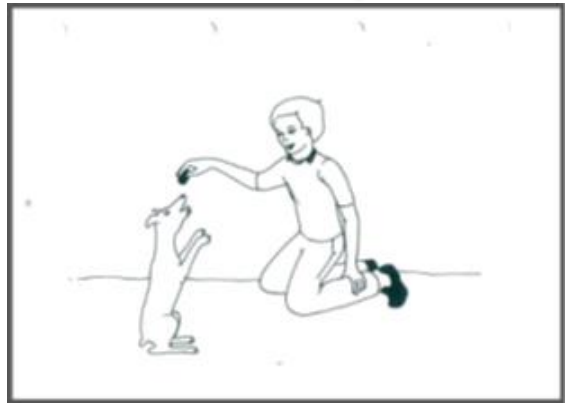
Agrammatism

AAT naming of situations and actions

VIGNETTE E

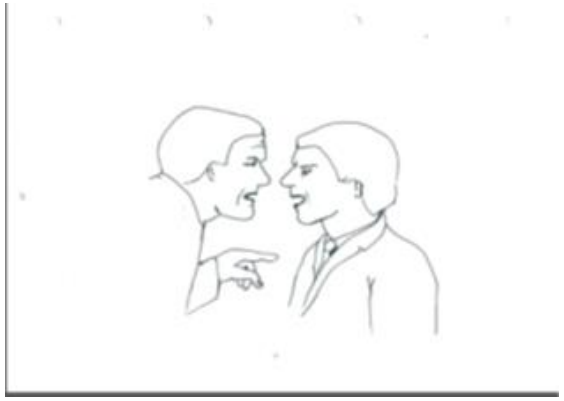
"Man met hoed"

"Man … tuije … vissen"



"Jongen met … spelen met hond"

"jongen spelen met de papa"



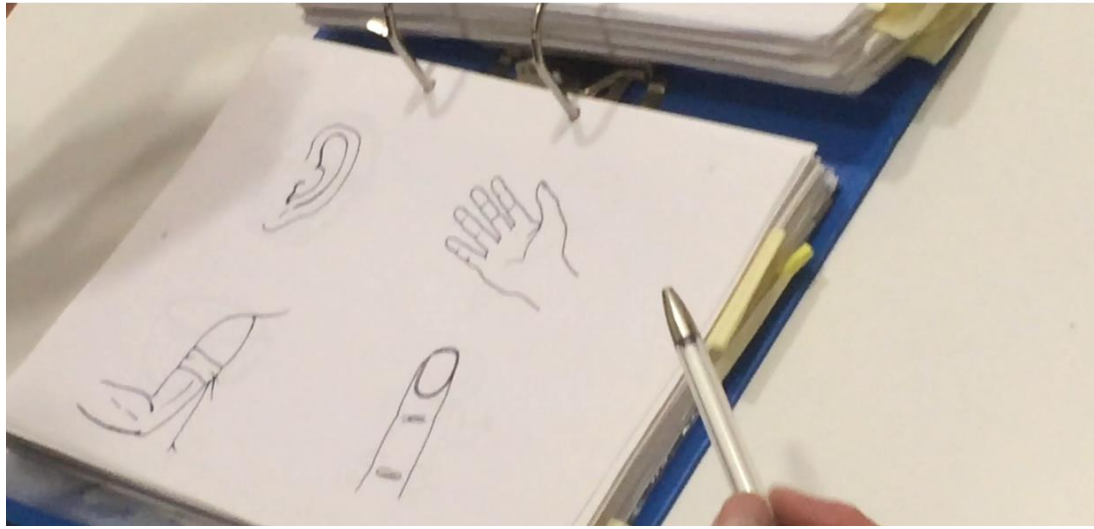
"samen praten"

Token test

6. Is comprehension impaired?

Word Comprehension

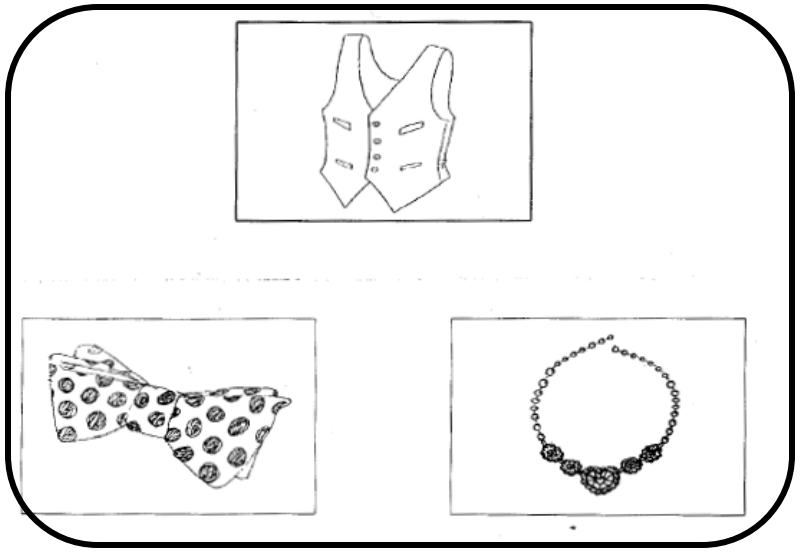
- AAT
  - Auditory word-picture matching
  - Auditory sentence-picture matching
  - Visual word-picture matching
  - Visual sentence-picture matching

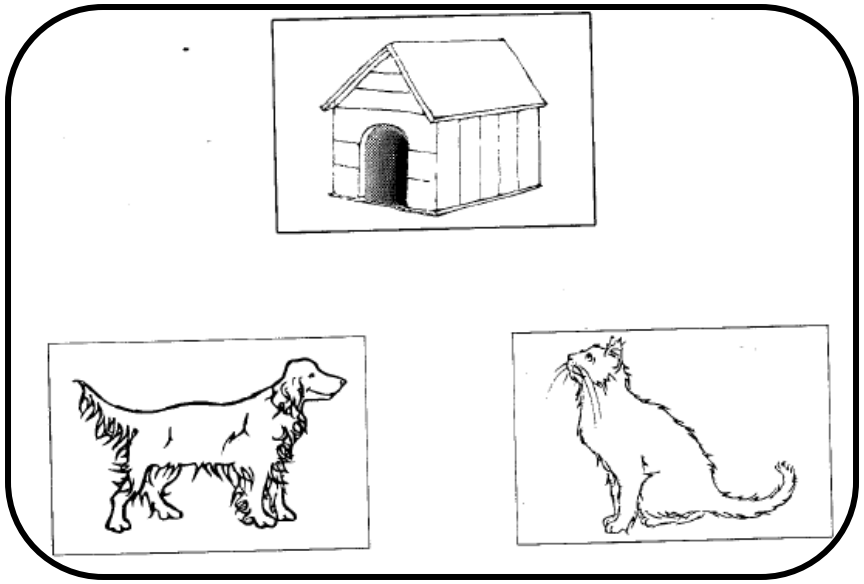


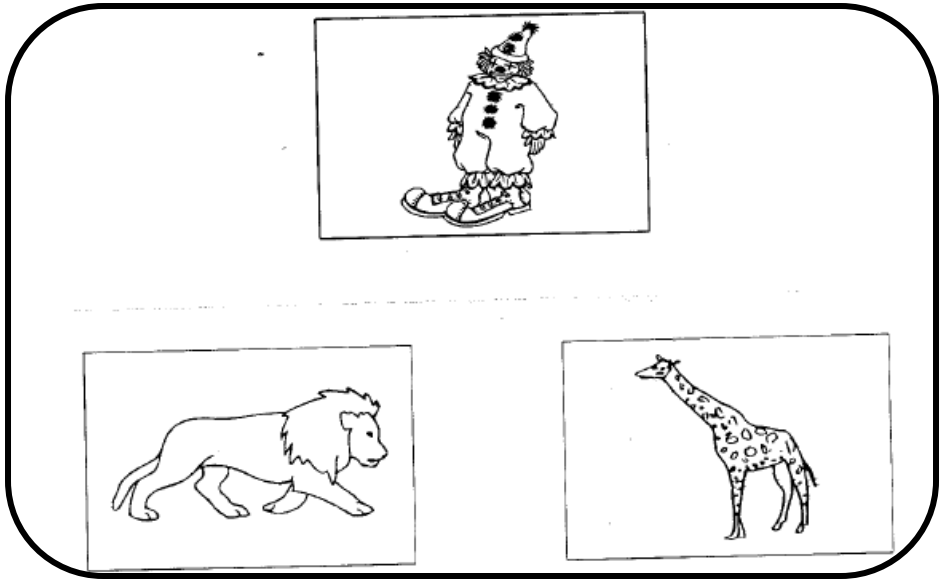
PALPA verbal semantic association test
Low Imageability

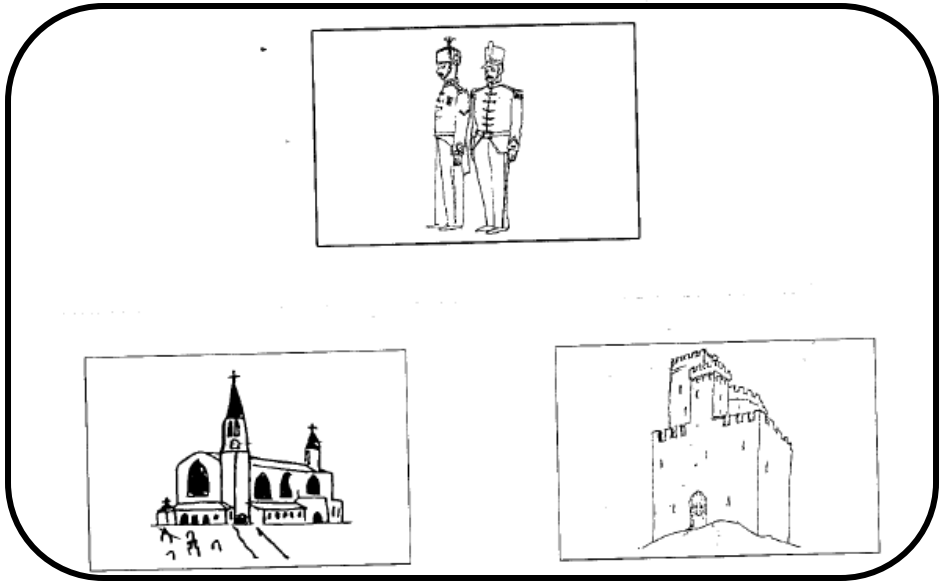
contract	oordeel	afspraak	verdrag	mening
fraude	leugen	bedrog	sein	signaal
aanwijzing	hint	fabel	code	sprookje
thema	cultuur	tekst	kunst	onderwerp
handeling	plek	plaats	daad	wijze
emotie	gevoel	firma	gedachte	bedrijf
humor	plicht	plezier	geluk	taak
kabinet	minister	centrum	kern	regering
lol	melodie	mop	gein	deun
nijd	ijver	vlijt	jaloezie	berouw

Pyramids and Palm Trees test









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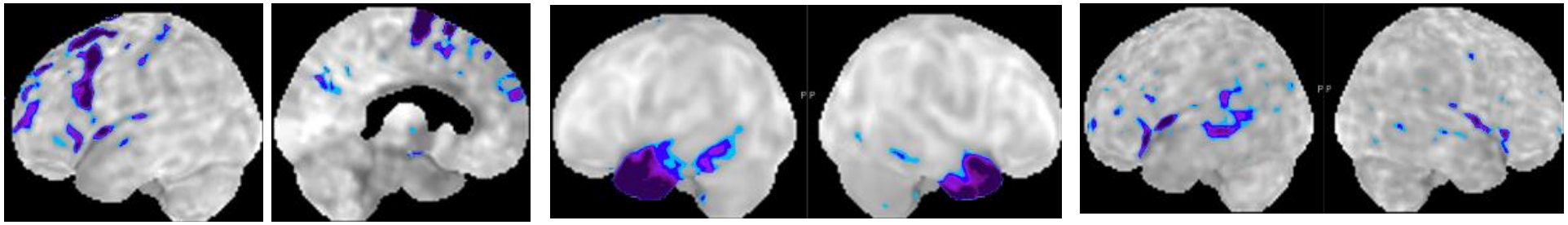
Semantic variant

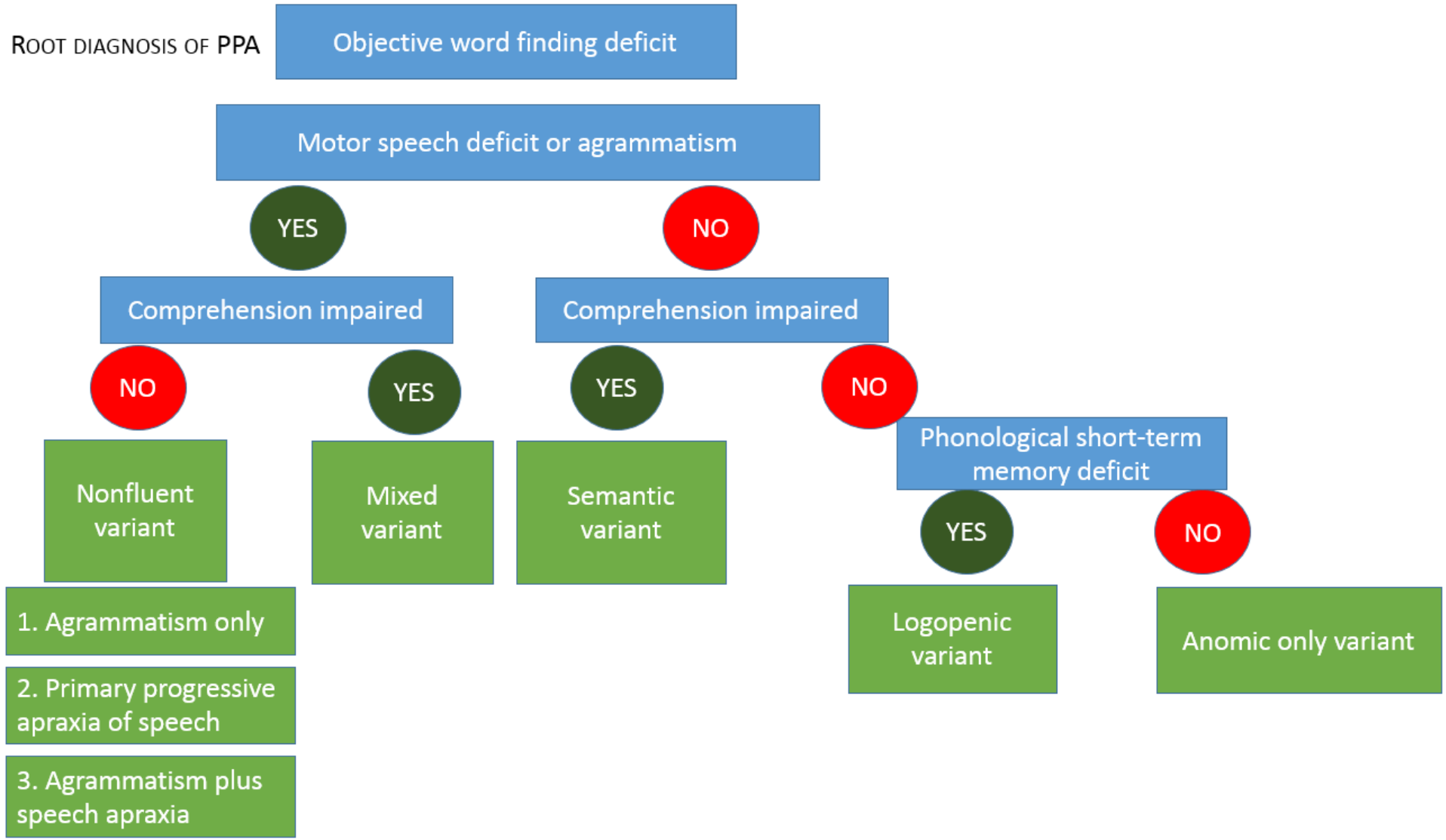
Logopenic variant



Vandenberghe R, Alzheimer's Research and Therapy, 2016

Controversies in PPA subtyping

- Patients who do not neatly fall within one of the three subtypes
  - Word comprehension problems together with speech apraxia or agrammatism
- Logopenic variant of progressive aphasia in AD most frequently expands to a more generalized impairment of different language and other cognitive domains



Vandenberghe R, Alzheimer's Research and Therapy, 2016

Conclusion

- Language difficulties can be easily overlooked or misinterpreted during history taking
- A restricted set of tests allows for reliable subtyping
- Biomarker use is needed to get to an etiological diagnosis

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