PRIMARY PROGRESSIVE APHASIAS

Stefano F. Cappa

University Institute of Advanced Studies

and Mondino Foundation

Pavia, Italy

stefano.cappa@iusspavia.it

Disclosure

- None

Learning objectives

- The learner will be able to:
  - Diagnose primary progressive aphasia (PPA) on the basis of a clinical examination

  - Request the appropriate tests to support the diagnosis

  - Diagnose the subtype of PPA and the most likely pathological cause

  - Propose a management plan to patient and family

Key message

- PPAs are a group of phenotypic presentations of different neurodegenerative disorders

- PPA is not rare in cognitive/behavioural neurology practice

- A correct diagnosis has prognostic and management relevance

VIEWS & REVIEWS

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, MD*
J.R. Hodges, MD*
M.M. Mesulam, MD*
M. Grossman, MD*

Address correspondence and reprint requests to Dr. Maria Luisa Gorno-Tempini, Memory and Aging Center, Department of Neurology, UCSF, 350 Parnassus Avenue, Suite 905, San Francisco, CA 94143-1207
marilu@memory.ucsf.edu

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 renamed primary progressive aphasia (PPA).[4] Warrington[5] described a progressive disorder of semantic memory in 1975. This condition was also described by Snowden et al.[6] as semantic dementia. In the early 1990s, Hodges and colleagues[7] provided a comprehensive characterization of semantic dementia. Subsequently, Grossman et al.[8] described a different form of progressive language disorder, termed progressive nonfluent aphasia. A consensus meeting attempted to develop criteria for these conditions in relation to frontotemporal lobar degeneration.[9] For about 2 decades, cases of PPA were generally categorized as semantic dementia or progressive nonfluent aphasia, or in some studies as "fluent" vs "nonfluent." However, there

When to suspect a PPA? (Mesulam 2003 criteria, modified)

- Inclusion
  - Most prominent clinical feature is a language impairment (aphasia)
  - This impairment is the only determinant of difficulties in the activities of daily living
  - Aphasia is the most prominent disorder at onset and in the early phase of disease
- Exclusion
  - Aphasia can be due to non neurodegenerative or other medical causes
  - Aphasia can be attributed to a psychiatric disorder
  - Prominent early episodic memory or visuo-spatial disorders
  - Prominent early behavioural disturbances

How to diagnose a PPA?

- Quantitative/qualitative analysis of connected speech

- Naming and comprehension of single words

- Repetition

- Comprehension of grammatically complex sentences

The analysis of connected speech
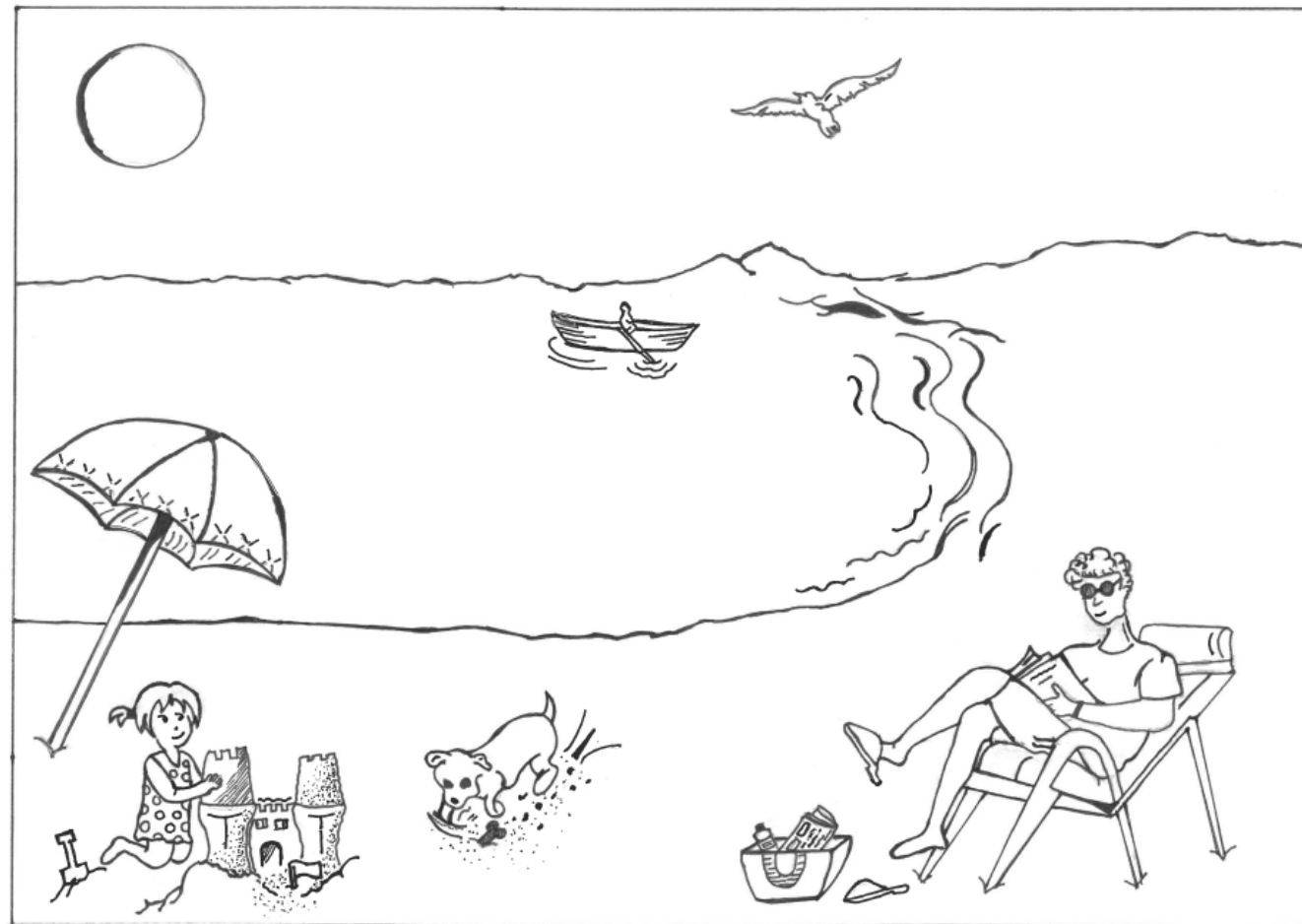
What to look for?

- Motor speech production
- Other disorders of fluency (pauses and repetitions)
- Lexical/semantic errors
- Grammar (morphology, syntax)

How to diagnose a PPA?

- Quantitative/qualitative analysis of extended production

- Naming and comprehension of single words

- Repetition

- Comprehension of syntactically complex sentences

A comprehensive semantic memory test

- Picture naming
- Naming from verbal description
- Word-picture matching
- Picture sorting
- Feature generation and verification

Naming from verbal description

"It is a fruit, it is yellow, with the shape of a half-moon. Monkeys like them very much»

Picture naming

Word-picture matching

Sorting

Feature generation and verification
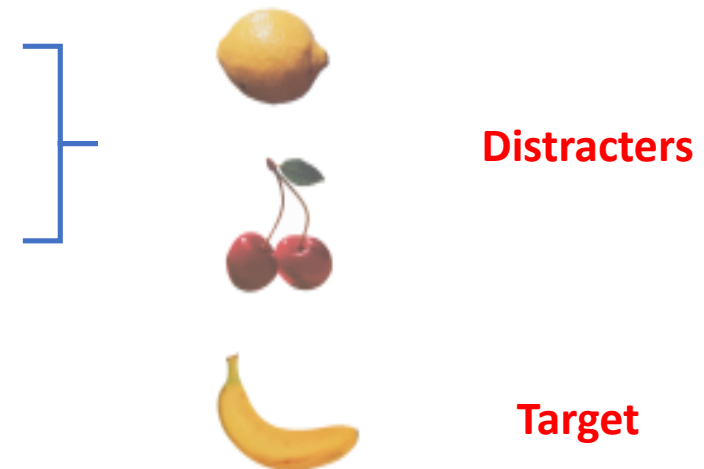
Distracters

Target

How to diagnose a PPA?

• Quantitative/qualitative analysis of extended production

• Naming and comprehension of single words

• Repetition

• Comprehension of syntactically complex sentences

A comprehensive assessment of repetition

- Vowels and syllables
- Digits
- Words
- Pseudowords
- Sentences of increasing length

A "core" assessment procedure

- Quantitative/qualitative analysis of extended production

- Naming and comprehension of single words

- Repetition

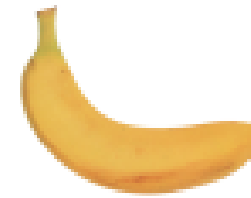- Comprehension of syntactically complex sentences

The boy and the dog are being followed by the girl
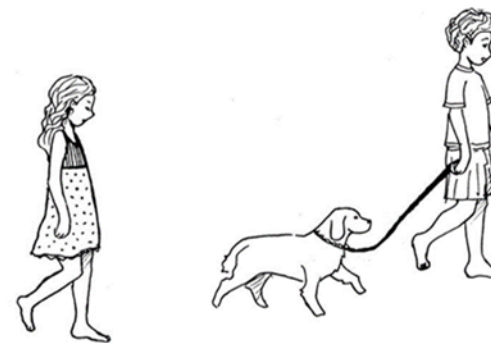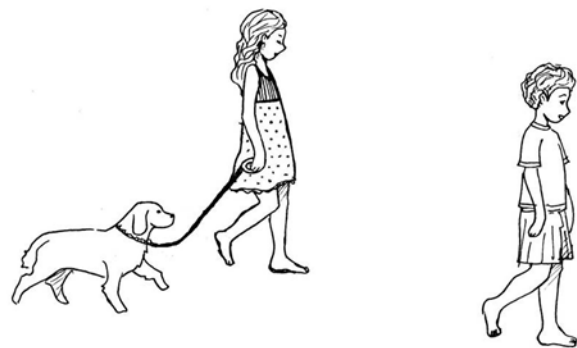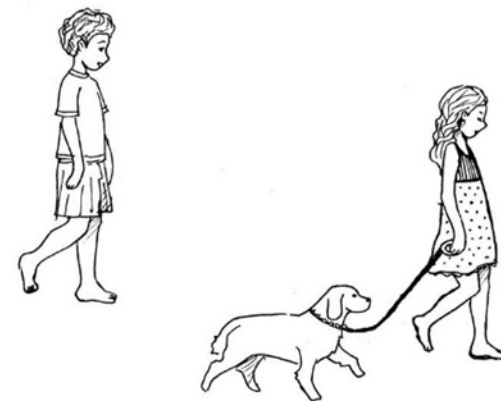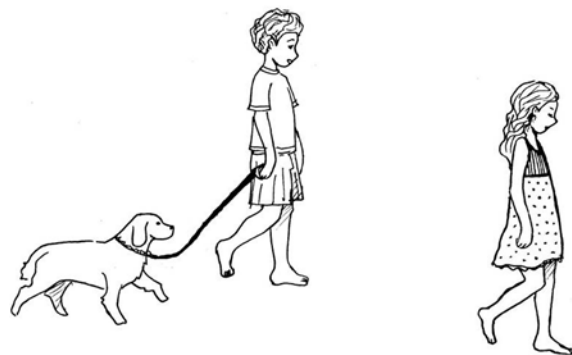
The new screening battery for aphasia

Italian version

SAND: a Screening for Aphasia in NeuroDegeneration. Development and normative data

Eleonora Catricalà[1] · Elena Gobbi[2] · Petronilla Battista[1,3,4] · Antonio Miozzo[5] · Cristina Polito[6] · Veronica Boschi[1] · Valentina Esposito[2] · Sofia Cuoco[7] · Paolo Barone[7] · Sandro Sorbi[4] · Stefano F. Cappa[1,8] · Peter Garrard[9]

1. Picture naming (14)

2. Sentence comprehension (8)

3. Single word comprehension (12)

4. Repetition (6 words, 4 nwds)

5. Repetition of sentence (6)

6. Reading (16)

7. Written description (1)

8. Semantic knowledge (pictures) (4)

9. Connected speech (1)

10-15 min

Test Materials:

User's Manual

Norms Guide

Scoring Template

Clinical variants

- Non fluent/agrammatic

- Semantic

- Logopenic/phonological

- Other variants

Semantic variant

- Fluent speech, with anomias and semantic paraphasias
- **Naming and single word comprehension impairment**
- **Impaired nonverbal semantics**

Case S.P. ♂ 63 years old, 13 years of education, svPPA (GRN +)

Figure 2. Axial T1-weighted MRI images at the diagnosis (A) and at a 18-month follow up (B)

A

B
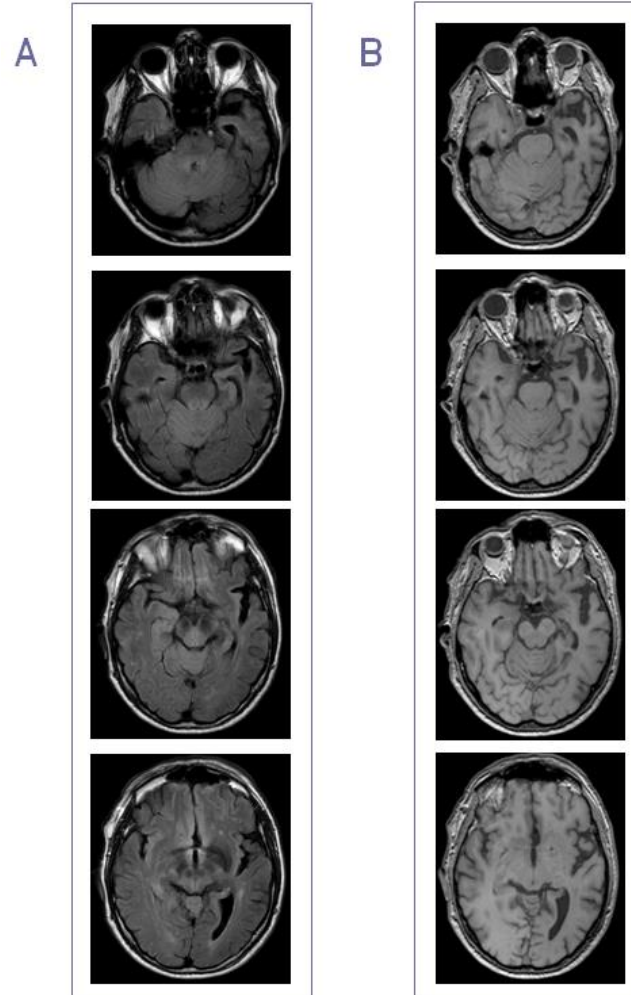
Figure 3. SPM-T map of hypometabolism (SPM5; http://www.fil.ion.ucl.ac.uk/spm/software/spm5/) of the single-patient [^{18}F]FDG-PET scan compared to 112 normal scans and displayed at a voxel-wise corrected threshold (p=0.05, FWE) with a minimum cluster size of 100 voxels

C
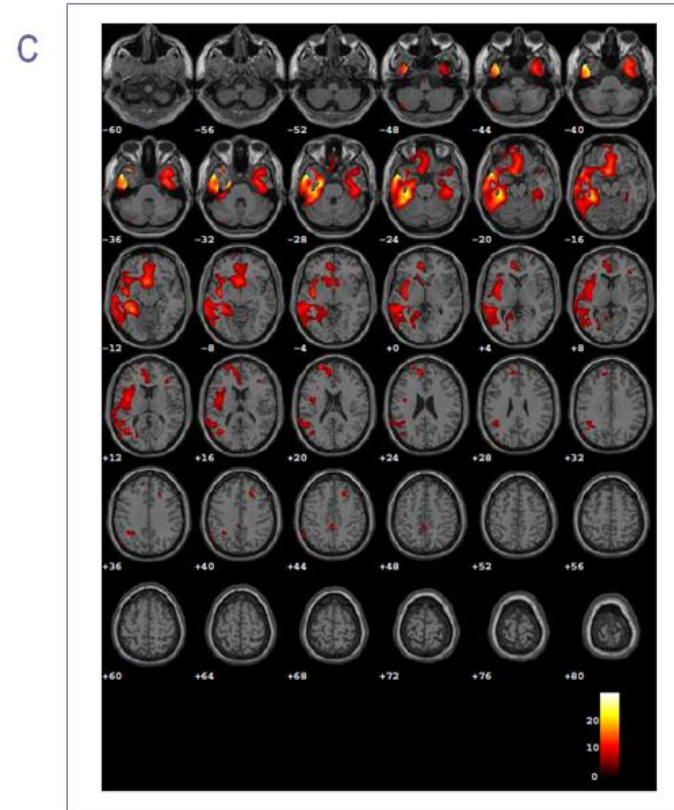
Non fluent/agrammatic variant

- **Nonfluent production with articulation impairment and agrammatism**

- Naming moderately impaired

- Preserved single word comprehension

- Defective comprehension of syntactically complex sentences

Case M.G. ♀ 62 years old, 17 years education

SPM-T map of hypometabolism of the single patient [^{18}F]FDG-PET scan compared to 112 HC (FWE)

❏ **Neuropsychological Evaluation** Language assessment

AREA INDAGATA	TEST	P. GREZZO	P. CORRETTO	P. EQUIVALENTE
LINGUAGGIO: denominazione orale nomi comprensione nomi (*word picture matching* test).........	CAGI:	48/48 48/48	48 48	4 4
comprensione di ordini complessi..............	Token Test..............	33/36	30.50	2
Comprensione grammaticale uditiva......	BADA:	58/60	Cut off: 58	Al limite
Comprensione grammaticale visiva.........		42/45	Cut off: 43	Deficitario
Accesso al lessico...................	Fluenza semantica...... Fluenza fonemica.........	24 10	22 5	0 0
Memoria semantica.........	Test Palma Piramide	48/52	45.77	Nella norma
Ripetizione	AAT: Suoni Parole Parole straniere Parole composte e sintagmi Frasi TOTALE	28/30 30/30 30/30 29/30 30/30 147/150	-	Nessun deficit
Lettura......................... Scrittura sotto dettato......	AAT:	30/30 30/30	- -	Nessun deficit Nessun deficit
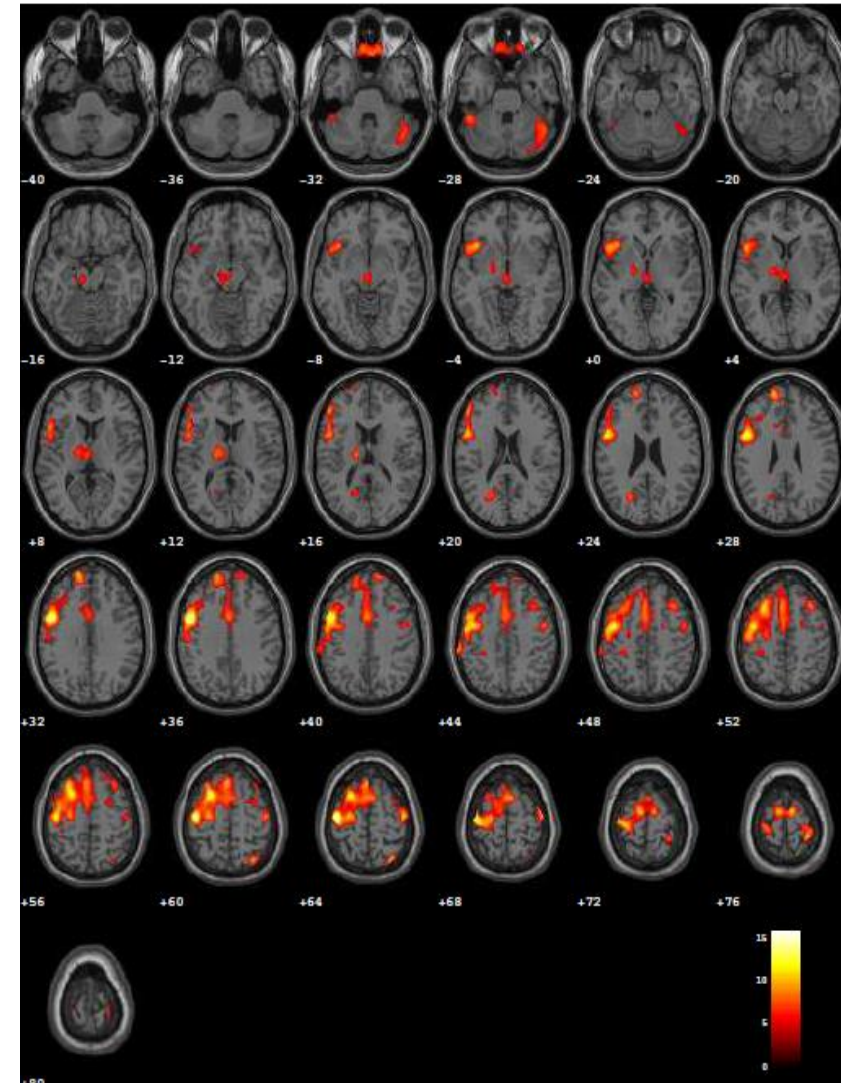
Logopenic/phonological variant (original definition)

- Dysfluent speech, with anomic pauses, hesitations and phonogical errors, but normal articulation and grammar

- Preserved single word comprehension

- Defective repetition and auditory verbal short-term memory

- Defective sentence comprehension

Case E.M. ♀ 77 years old, 10 years schooling, suspected PPA

❑ **<u>Instrumental Evaluations</u>**

SPM-T map of hypometabolism of the single patient [^{18}F]FDG-PET scan compared to 112 HC (FWE)

CSF Aβ42 and Tau measures

LCR-BETA AMILOIDE (I-42)	269	ng/L	> 500 ←
LCR-PROTEINA TAU	322	ng/L	0.0 - 500.0
LCR-PROTEINA TAU FOSFORILATA	74	ng/L	0.00 - 61.00 ←
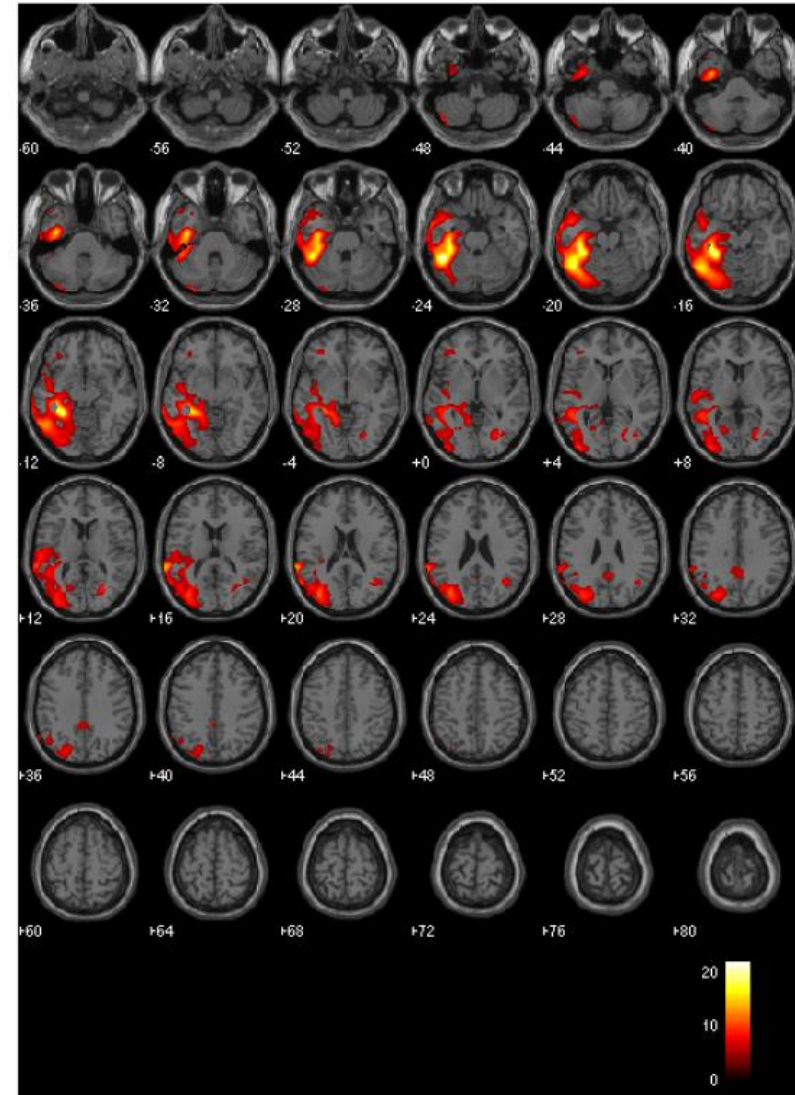
	NF/Av	Sv	L/Phv
Motor speech	Impaired (apraxia of speech)	normal	pauses, hesitations, phonological errors
Grammar	impaired	normal	preserved
Word-finding	mildly impaired	impaired, semantic errors	Impaired, anomias, phonemic paraphasias
Word comprehension	preserved	impaired early	preserved
Sentence repetition	motor impairment	preserved	impaired
Sentence comprehension	Impaired (grammatically complex sentences)	preserved	Impaired (long sentences)

Pathology
(Spinelli et al., 2017)

- Nf/Av
  - FTLD Tau 88%
- Sv
  - TDP-C 83%
- L/Phv
  - AD 100%

Management

- Advice and support
- Symptomatic treatment: depression, behavioural disorders
- Speech and language therapy
- Neuromodulation

References

- Ash, S., Evans, E., O'Shea, J., Powers, J., Boller, A., Weinberg, D., . . . Grossman, M. (2013). Differentiating primary progressive aphasias in a brief sample of connected speech. Neurology, 81(4), 329-336

- Battista, P., Catricalà, E., Piccininni, M., Copetti, M., Esposito, V., Polito, C., ... & Picillo, M. (2018). Screening for Aphasia in NeuroDegeneration for the Diagnosis of Patients with Primary Progressive Aphasia: Clinical Validity and Psychometric Properties. Dementia and Geriatric Cognitive Disorders, 46(3-4), 243-252.

- Boschi, V., Catricalà, E., Consonni, M., Chesi, C., Moro, A., & Cappa, S. F. (2017). Connected speech in neurodegenerative language disorders: a review, 8, 269.

- Caffarra, P., Gardini, S., Cappa, S., Dieci, F., Concari, L., Barocco, F., . . . Prati, G. D. (2013). Degenerative jargon aphasia: unusual progression of logopenic/phonological progressive aphasia? Behav Neurol, 26(1-2), 89-93.

- Cappa, S.F., Cerami, C. (2016). Primary Progressive Aphasia. In Dickerson, B.C. (ed.) Hodges' Frontotemporal Dementia, Cambridge University Press

- Catani, M., Mesulam, M. M., Jakobsen, E., Malik, F., Martersteck, A., Wieneke, C., . . . Rogalski, E. (2013). A novel frontal pathway underlies verbal fluency in primary progressive aphasia. Brain, 136(Pt 8), 2619-2628.

- Catricalà, E., Gobbi, E., Battista, P., Miozzo, A., Polito, C., Boschi, V., ... & Cappa, S. F. (2017). SAND: a Screening for Aphasia in NeuroDegeneration. Development and normative data. Neurological Sciences, 38(8), 1469-1483.

- Cotelli, M., Borroni, B., Manenti, R., Alberici, A., Calabria, M., Agosti, C., . . . Cappa, S. F. (2006). Action and object naming in frontotemporal dementia, progressive supranuclear palsy, and corticobasal degeneration. Neuropsychology, 20(5), 558-565.

- Gorno-Tempini, M. L., Brambati, S. M., Ginex, V., Ogar, J., Dronkers, N. F., Marcone, A., . . . Miller, B. L. (2008). The logopenic/phonological variant of primary progressive aphasia. Neurology, 71(16), 1227-1234.

- Gorno-Tempini, M. L., Hillis, A. E., Weintraub, S., Kertesz, A., Mendez, M., Cappa, S. F., . . . Grossman, M. (2011). Classification of primary progressive aphasia and its variants. Neurology, 76(11), 1006-1014.

- Iaccarino, L., Crespi, C., Della Rosa, P. A., Catricala, E., Guidi, L., Marcone, A., . . . Perani, D. (2015). The semantic variant of primary progressive aphasia: clinical and neuroimaging evidence in single subjects. PLoS One, 10(3), e0120197.

- Mesulam, M. (2013). Primary progressive aphasia: A dementia of the language network. Dement Neuropsychol, 7(1), 2-9.

- Mesulam, M., Wicklund, A., Johnson, N., Rogalski, E., Léger, G. C., Rademaker, A., . . . Bigio, E. H. (2008). Alzheimer and frontotemporal pathology in subsets of primary progressive aphasia. Ann Neurol, 63(709-19).

- Mesulam, M. M., Rogalski, E. J., Wieneke, C., Hurley, R. S., Geula, C., Bigio, E. H., . . . Weintraub, S. (2014). Primary progressive aphasia and the evolving neurology of the language network. Nat Rev Neurol, 10(10), 554-569.

- Mesulam, M. M., Thompson, C. K., Weintraub, S., & Rogalski, E. J. (2015). The Wernicke conundrum and the anatomy of language comprehension in primary progressive aphasia. Brain, 138(Pt 8), 2423-2437.

- Montembeault, M., Brambati, S. M., Gorno-Tempini, M. L., & Migliaccio, R. (2018). Clinical, anatomical, and pathological features in the three variants of primary progressive aphasia: a review. Frontiers in neurology, 9.

- Rohrer, J. D., Ridgway, G. R., Crutch, S. J., Hailstone, J., Goll, J. C., Clarkson, M. J., . . . Warren, J. D. (2010). Progressive logopenic/phonological aphasia: erosion of the language network. Neuroimage, 49(1), 984-993.

- Spinelli, E. G., Mandelli, M. L., Miller, Z. A., Santos-Santos, M. A., Wilson, S. M., Agosta, F., ... & Henry, M. L. (2017). Typical and atypical pathology in primary progressive aphasia variants. *Annals of neurology*, *81*(3), 430-443.

- Teichmann, M., Kas, A., Boutet, C., Ferrieux, S., Nogues, M., Samri, D., . . . Migliaccio, R. (2013). Deciphering logopenic primary progressive aphasia: a clinical, imaging and biomarker investigation. Brain, 136(Pt 11), 3474-3488.

- Wilson, S. M., Henry, M. L., Besbris, M., Ogar, J. M., Dronkers, N. F., Jarrold, W., . . . Gorno-Tempini, M. L. (2010). Connected speech production in three variants of primary progressive aphasia. Brain, 133(Pt 7), 2069-2088.