

Clinical & Neuroimaging Features of Prodromal PPA

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1/17/2015



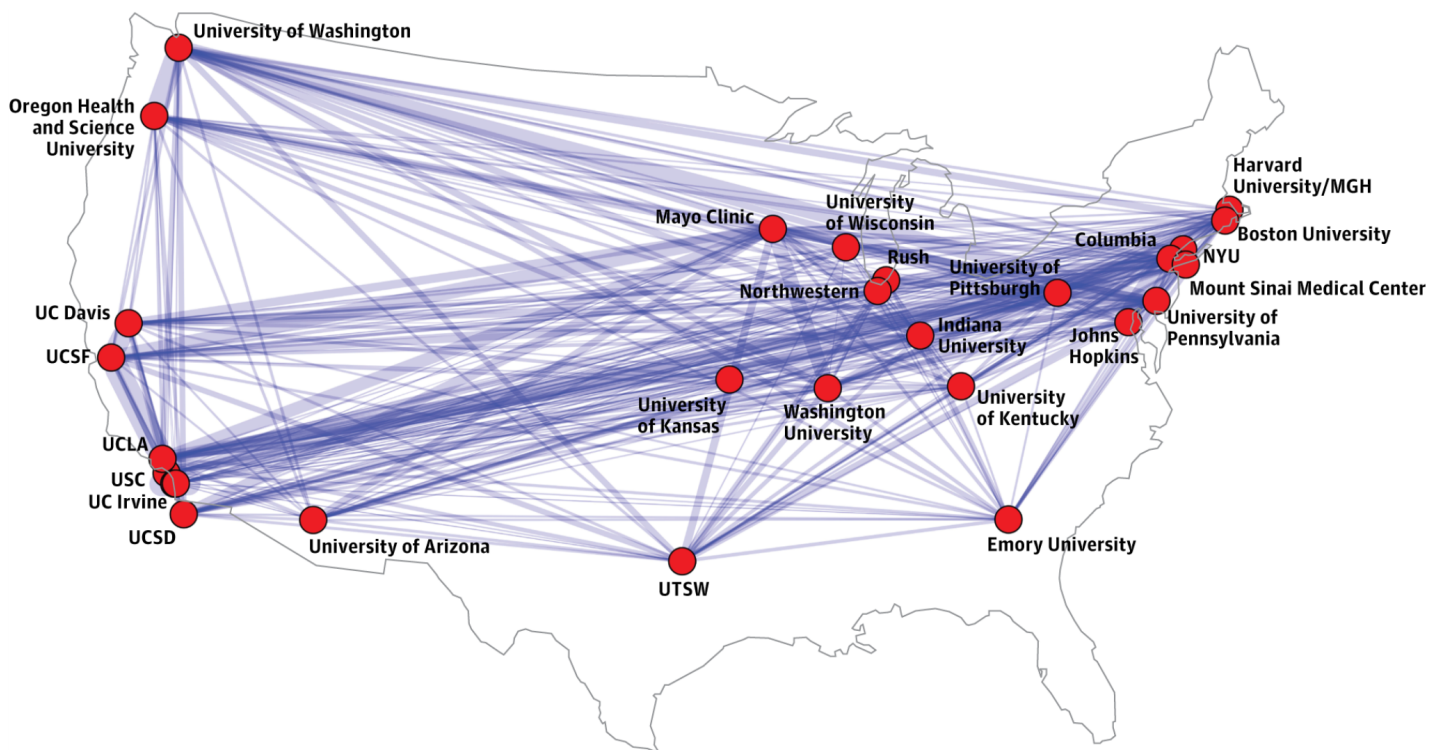
Northwestern University Feinberg School of Medicine

Cognitive Neurology and
Alzheimer's Disease Center

The Northwestern AD Center is Part of a National Network

Funded by the National Institute on Aging

Collect | Collaborate | Translate

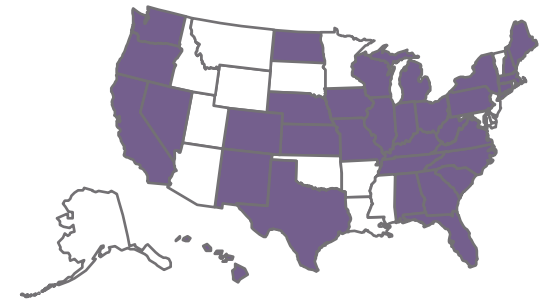


Clinical Dementia Syndromes



Northwestern PPA Research

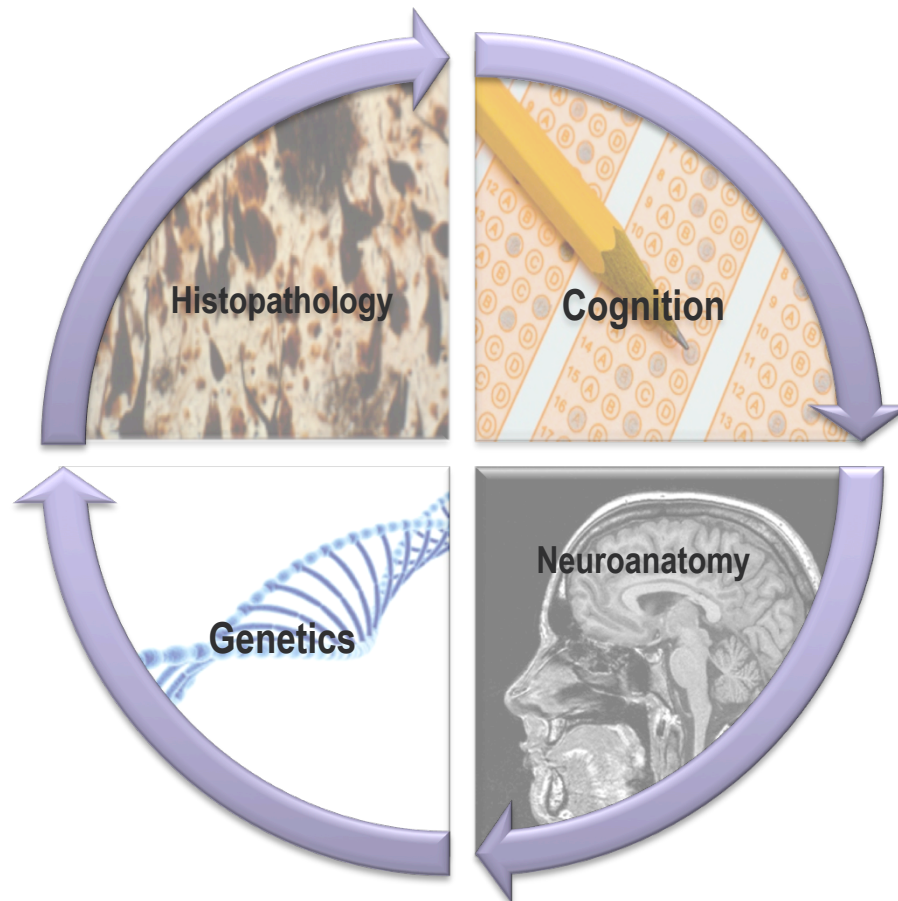
2007-2014



126 patients

48 autopsies

50+ publications



Primary

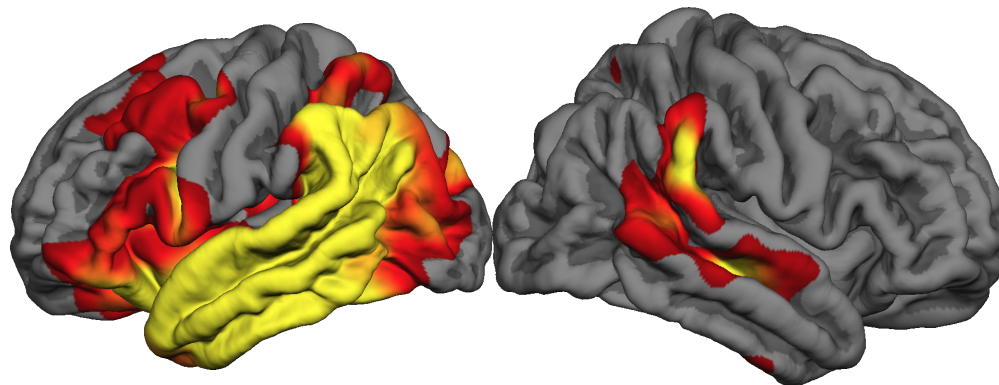
Impairment is prominent in a single domain (language) with relative sparing of other domains early on (e.g., memory, personality and perception)

Progressive

The impairment will get worse over time, since its caused by a neurodegenerative disease

Aphasia

a language impairment

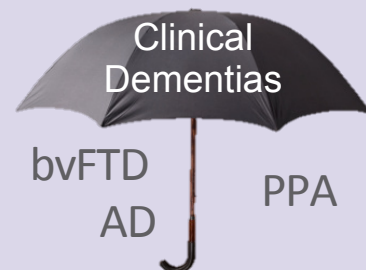


Early PPA Literature

Clinical Syndrome

Identify
unique
Type

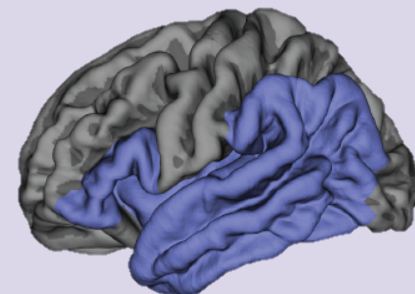
that was
Alzheimer's
by stroke



Neuroanatomic Features

Establish
the le

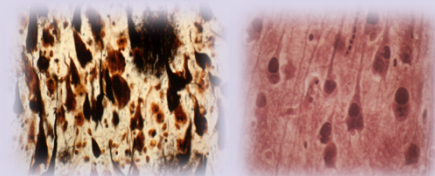
of PPA for
the network



Neuropathologic
Features

Identify
asso

tures

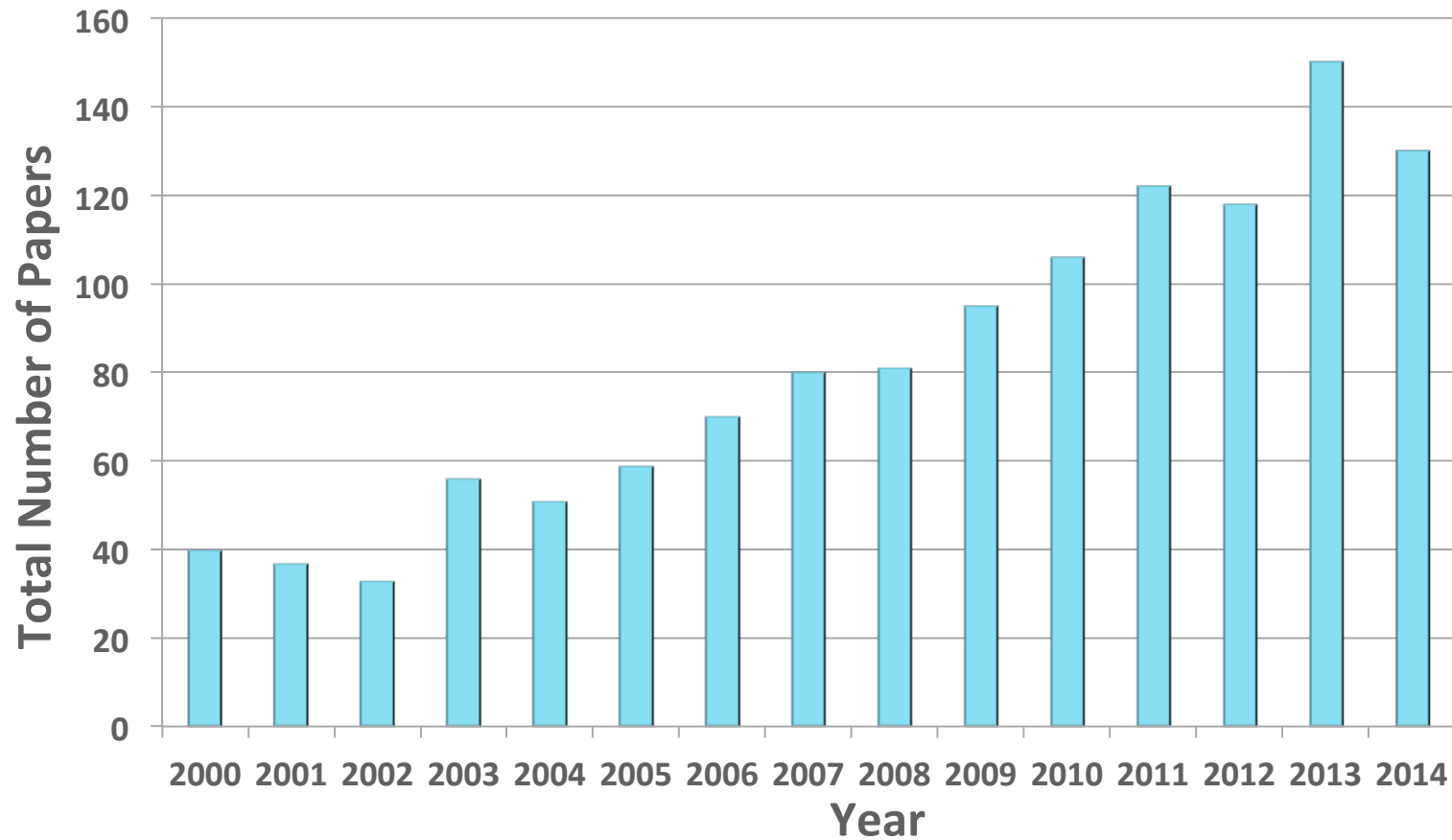


FAST



FORWARD

Research on PPA is growing



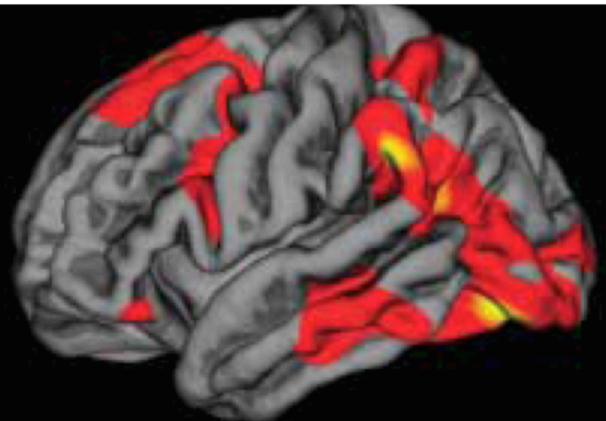
Aphasia comes in different flavors



PPA phenotypes

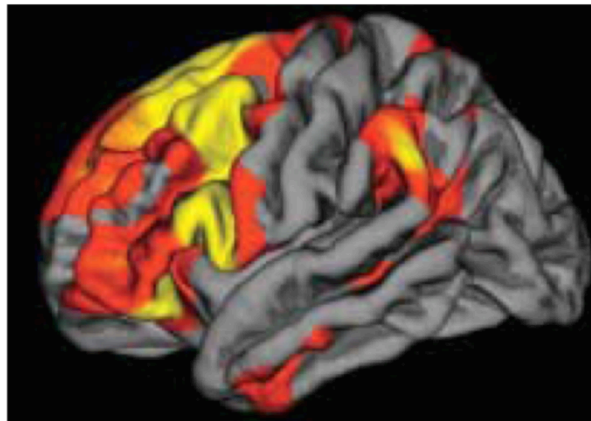
PPA-L (logopenic)

Preserved Grammar
Preserved Word Comprehension
Impaired word-finding
Impaired repetition*



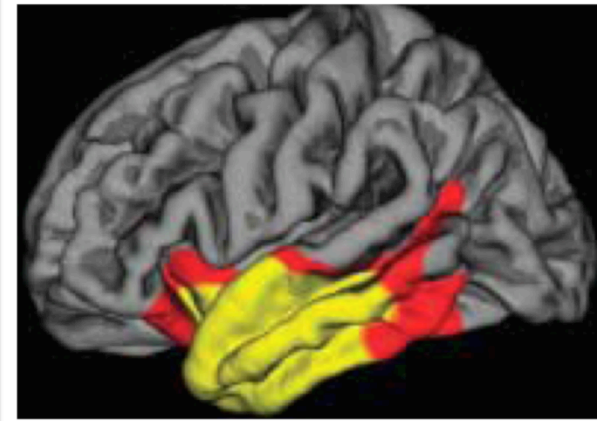
PPA-G (agrammatic)

Impaired Grammar
Preserved Word Comprehension
Impaired word-finding



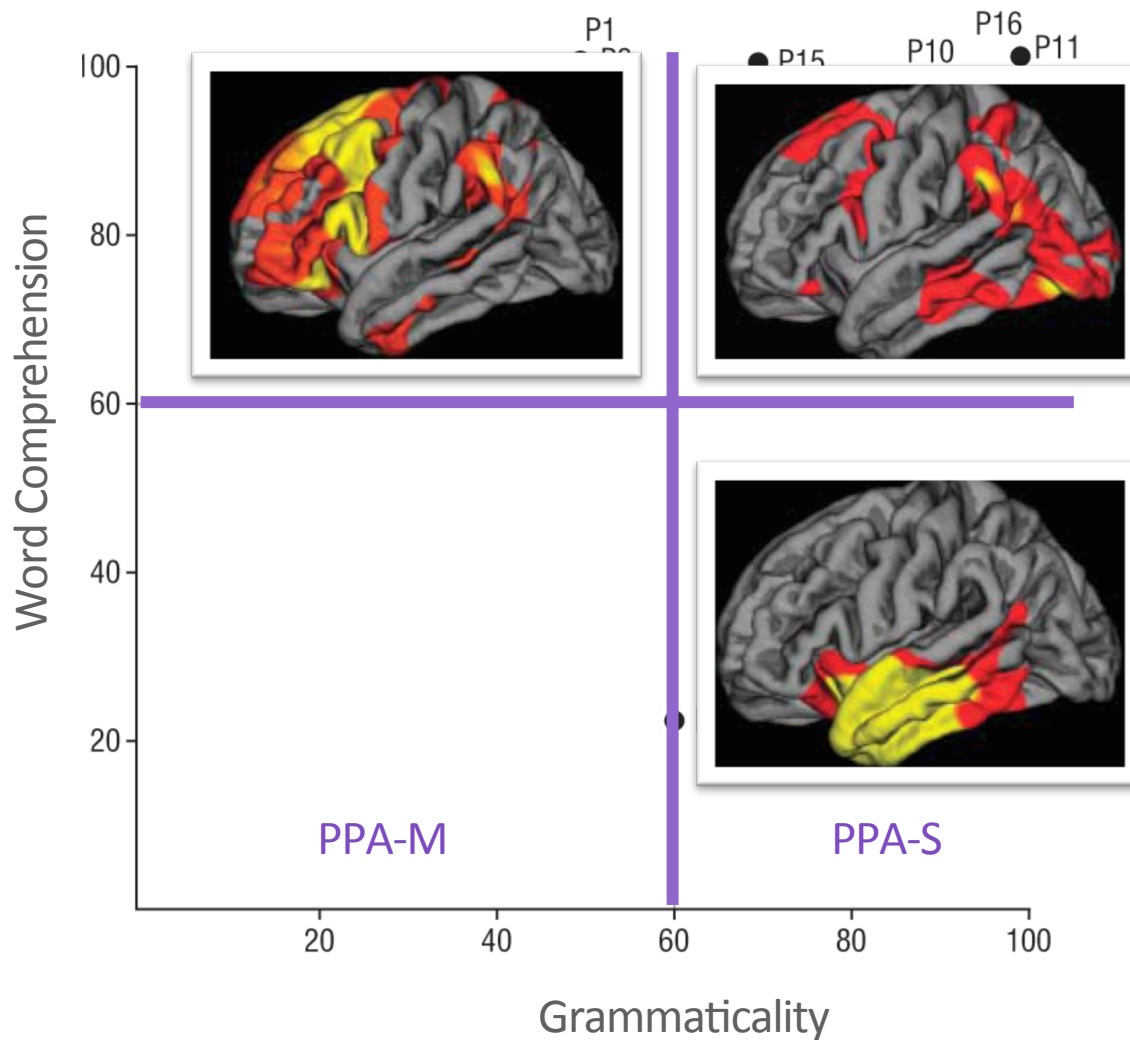
PPA-S (semantic)

Preserved Grammar
Impaired Word Comprehension
Impaired word-finding



Template approach to classification

Mesulam 2009



Clinico-pathological correlations in PPA

Clinical
Syndrome

Progressive language
impairment

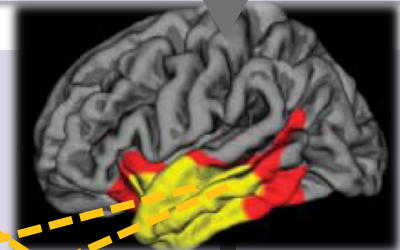
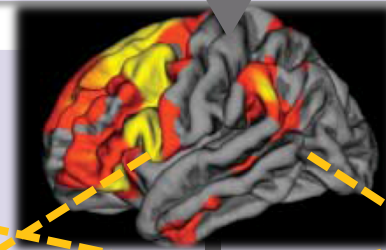
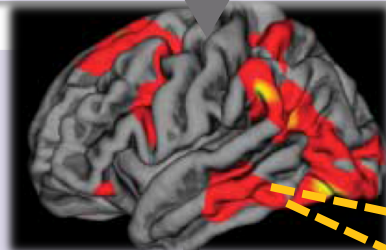
Clinical
Subtypes

PPA-L

PPA-G

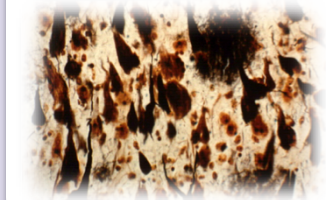
PPA-S

Anatomy

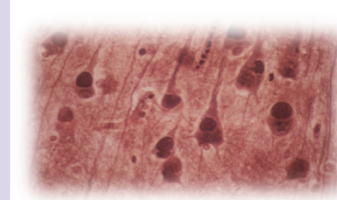


Pathology

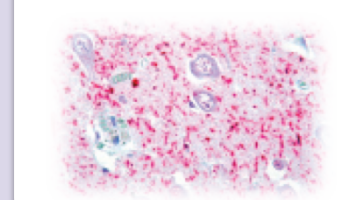
AD



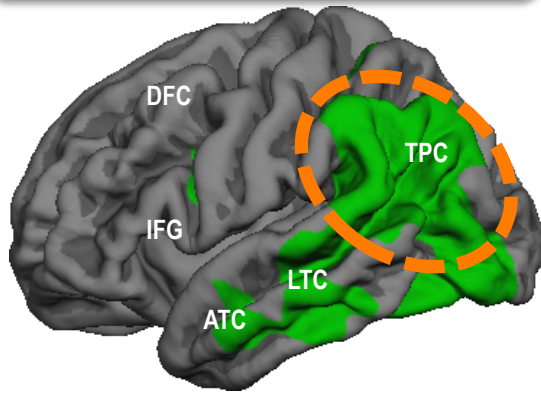
FTLD-T



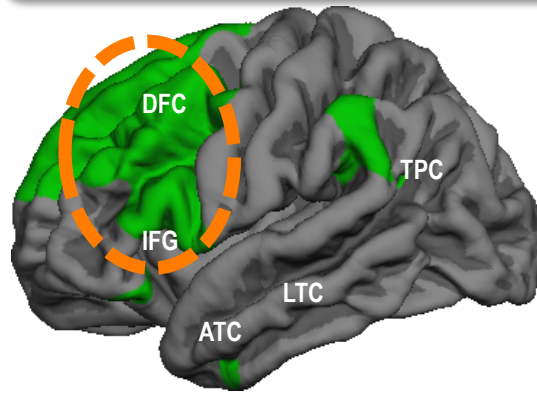
TDP-43



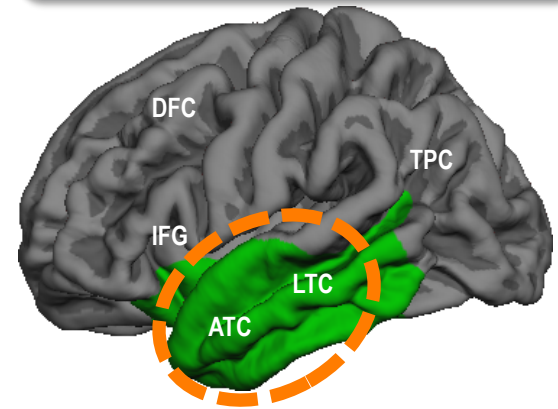
PPA-L (logopenic)



PPA-G (agrammatic)



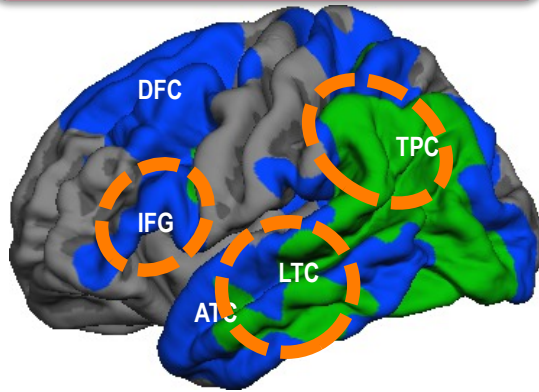
PPA-S (semantic)



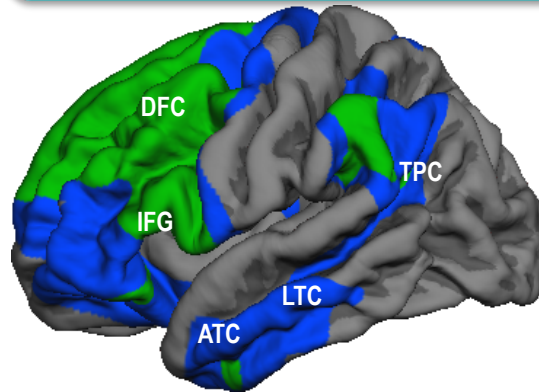
Visit 1 

- At **Visit 1** there are distinct patterns of atrophy for each subtype.

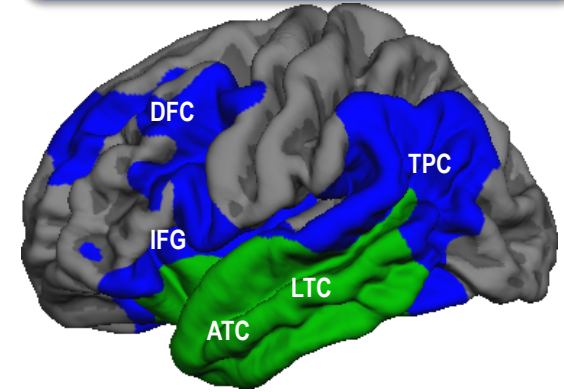
PPA-L (logopenic)



PPA-G (agrammatic)



PPA-S (semantic)



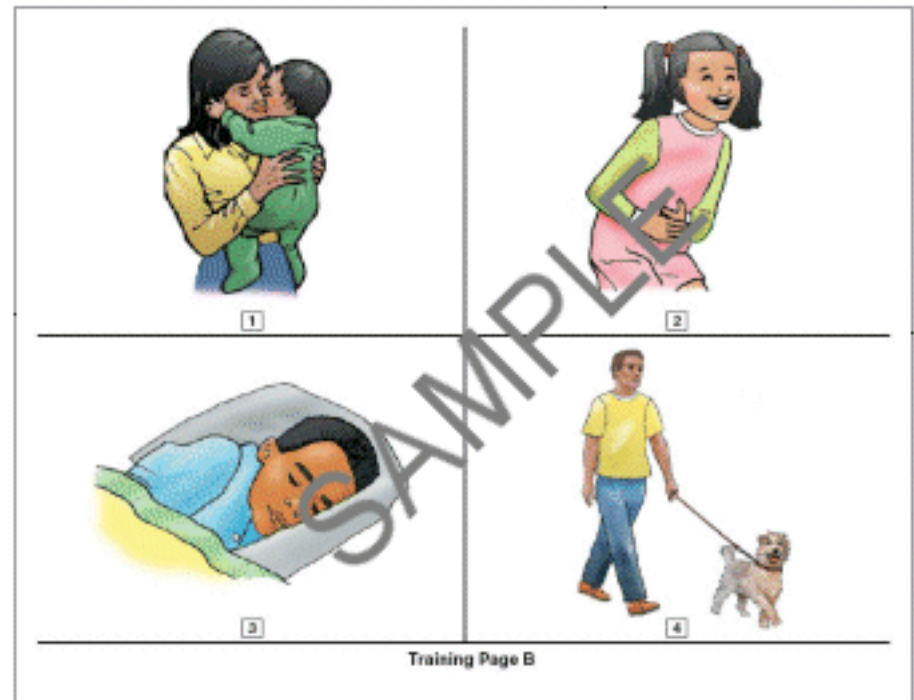
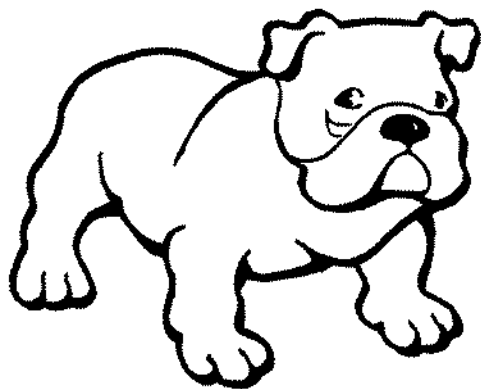
Visit 1  Visit 2 

- At **visit 2** peak atrophy sites spread beyond the **initial** distinctive locations that characterized each of the three subtypes and...
- Displayed a more convergent distribution encompassing all three major components of the language network:
 - 1) **inferior frontal gyrus**
 - 2) **temporoparietal junction**
 - 3) **lateral temporal cortex**



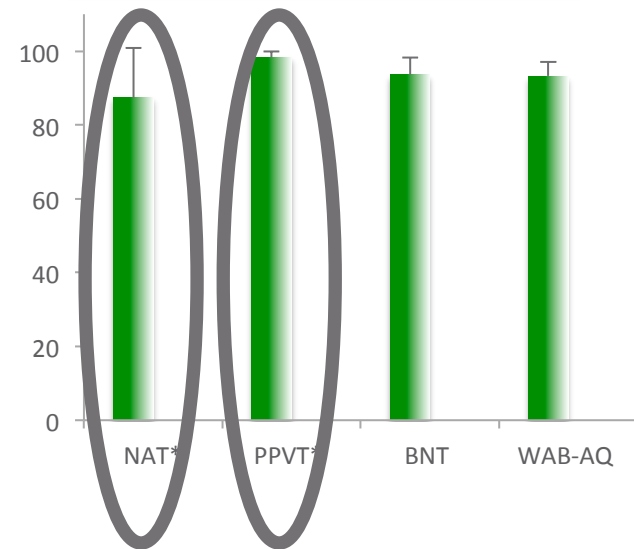
tickle

The girl is tickling the boy

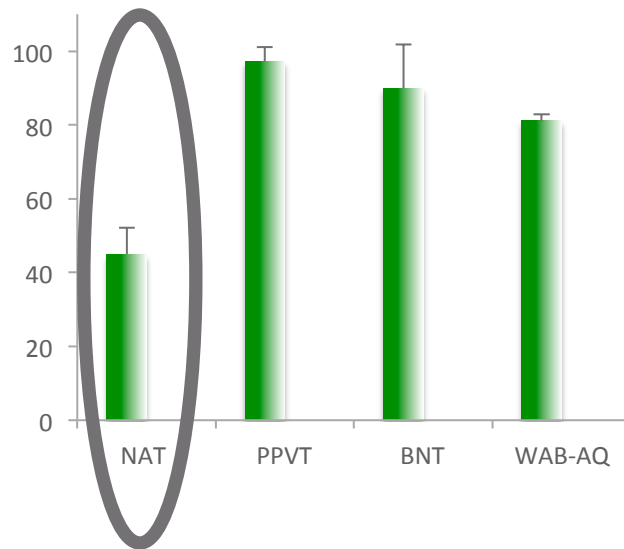


Neuropsychological Performance: Visit 1

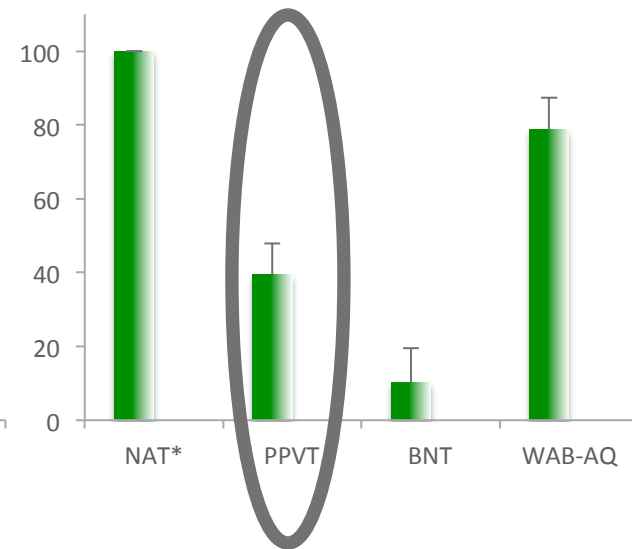
PPA-L (logopenic)



PPA-G (agrammatic)

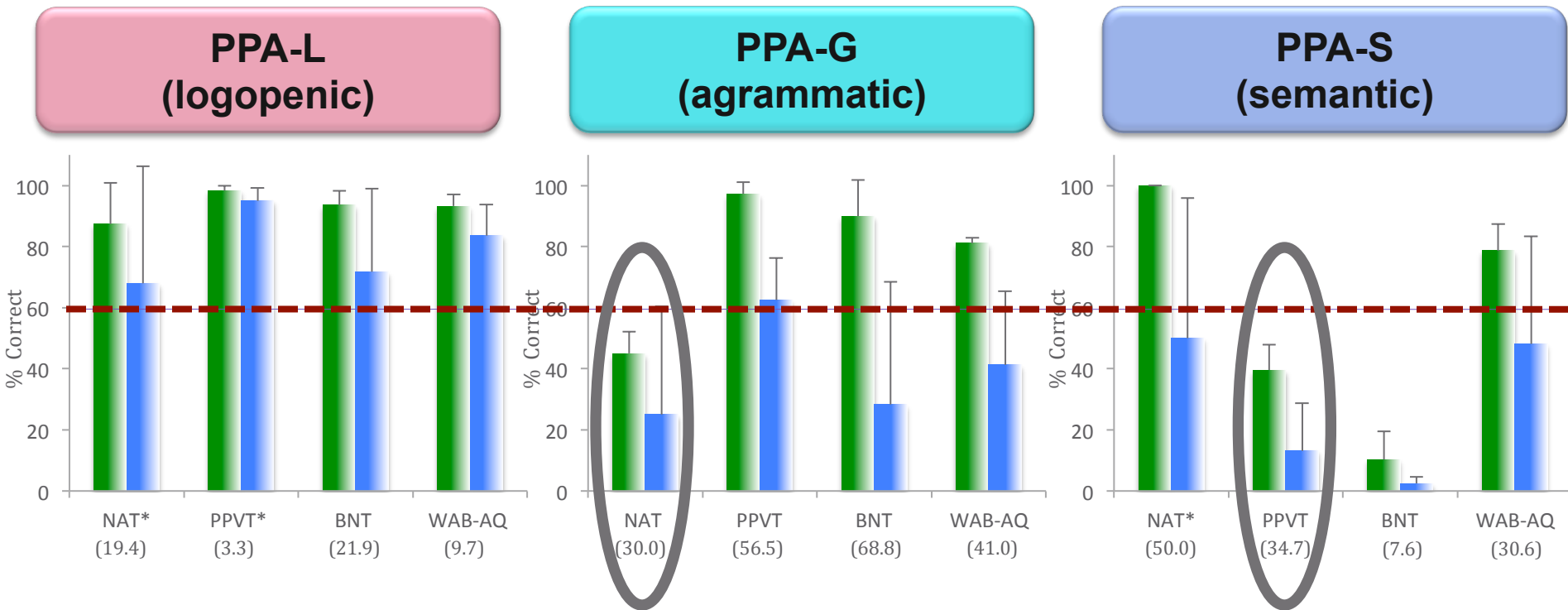


PPA-S (semantic)



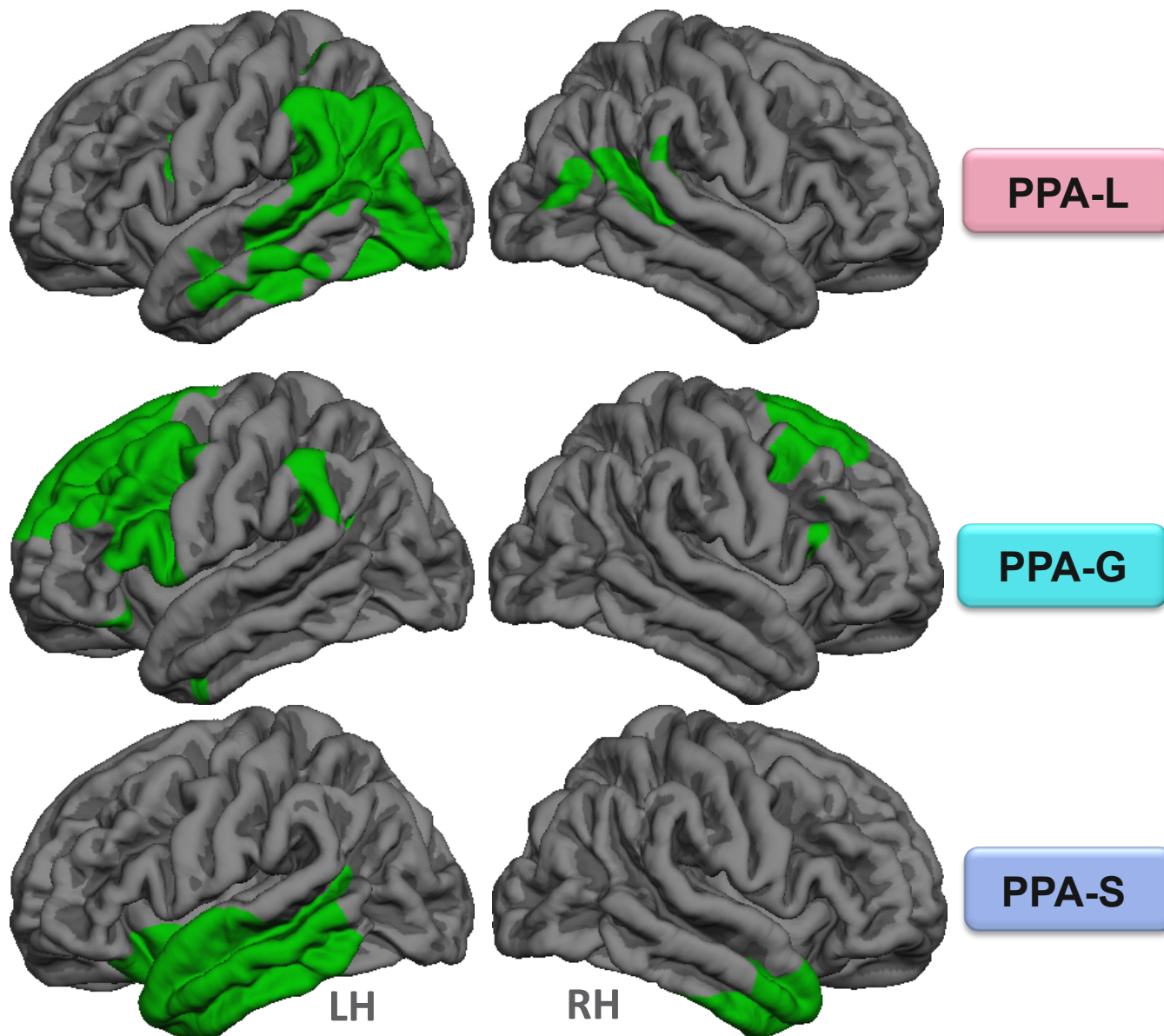
- Distinct patterns of performance for each subtype.

Neuropsychological Performance: Visit 2

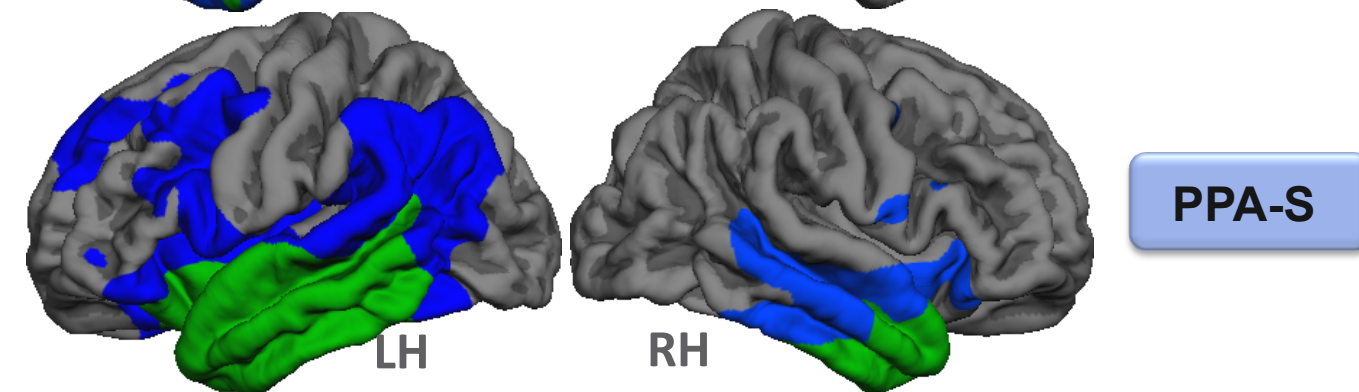
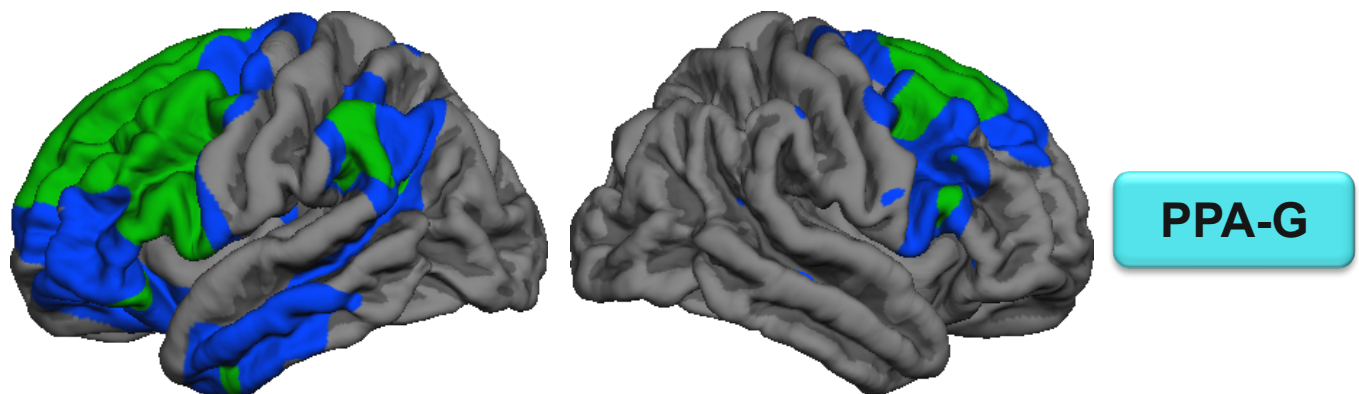
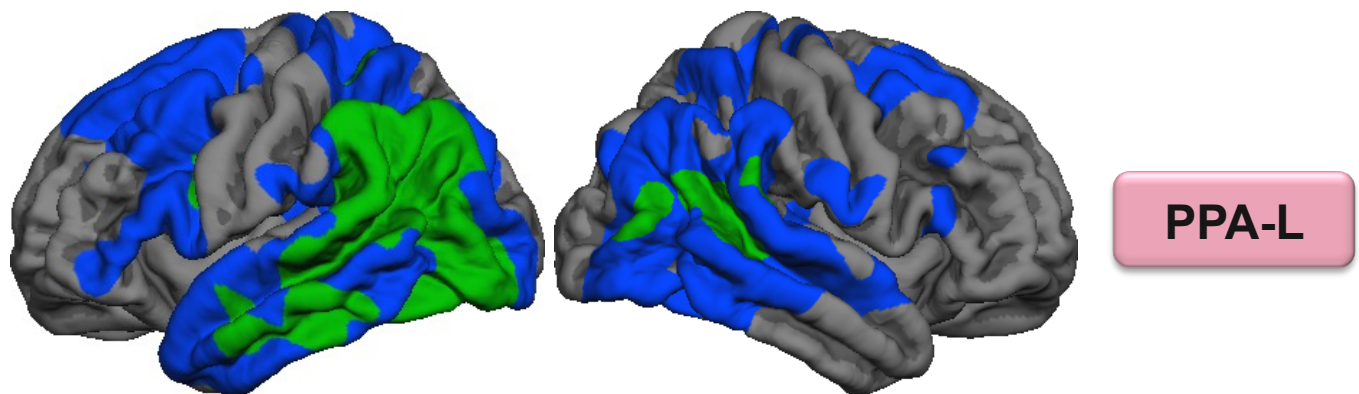


- Neuropsychological language performance patterns lost the sharp distinctions that differentiated one PPA variant from another.
- Nonetheless, the subtype-specific differential impairment of word comprehension versus grammatical processing was largely maintained.

Distribution Brain atrophy over 2 years



Brain atrophy remains LH dominant over 2 years





PPA +

- Prominent impairment in an additional domain (e.g. memory, behavior, or motor),
ADL severely compromised



PPA

- Prominent language difficulty is the most salient feature and the major cause of compromised ADL



Prodromal/Early Stage

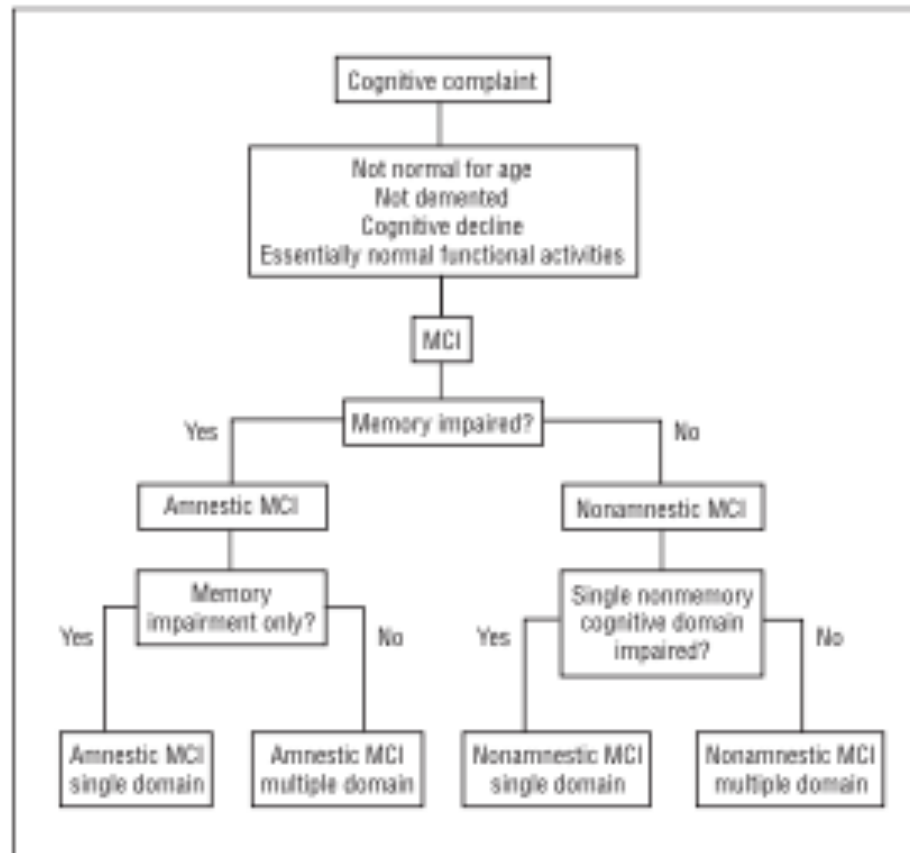
- Subjective, transient or mild language disturbance without compromise of ADL



Quantitative classification of mild PPA

- 2 main goals
 - Identify qualitatively and quantitatively the early and mild stages of PPA
 - How well do the consensus criteria work in the early/mild stages of PPA?

Defining “early/mild” PPA



Defining “early/mild” PPA

- Study Criteria
 - Met diagnostic criteria for PPA
 - Western Aphasia Battery Quotient (WAB-AQ): > 85 (max score =100)
- 100 consecutive patients surveyed → 25 met criteria for PPA and had sufficient data for study
 - Age at research visit: 65 ± 7.9
 - Age at onset:
 - 50's (n= 9)
 - 60's (n=10)
 - 70's (n=6)
 - Gender: 13 Males; 12 Females
 - Education: 16 ± 2.1
- 13 patients were within 2 years of symptom onset

Characteristics of “early/mild” PPA

General features of the group

- **Initial Symptoms** (as reported by patient/informant):
 - Impaired word-finding (n=23)
 - Abnormal spelling (n=9)
 - Other early changes:
 - Speech abnormalities (slurring/mispronunciation) (n=8); Word comprehension errors (n=6); Misuse of words (semantic paraphasias) (n=2); Difficulty with arithmetic (n=3)
- **Global functioning:**
 - CDR: median=1; MMSE: mean =27.5 (+/-2.1)
 - Informant reports confirmed relatively preserved ADLs
 - many patients continued to work, participated in social/recreational activities and a few engaged in new complex hobbies
- **Imaging** (at the time of the initial medical consultation):
 - MRI/CT: Negative or non-focal atrophy (n=19)
 - PET scans: 5 cases showed characteristic asymmetric LH hypometabolism

Quantitative classification of mild PPA

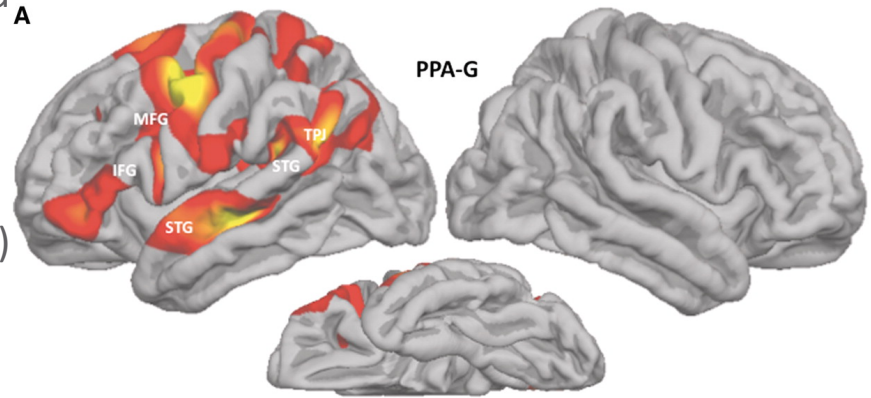
- 2 main goals
 - Identify qualitatively and quantitatively the early and mild stages of PPA
 - How well do the consensus criteria work in the early/mild stages of PPA?

How well do the 2011 consensus criteria work in the early/mild stages of PPA?

Non-fluent/agrammatic PPA
(PPA-G) (Gorno-Tempini et al., 2011)

• N=10*

- At least 1 core feature
 1. Agrammatism in language production.
 2. Effortful, halting speech with inconsistent speech sound errors and distortions (apraxia of speech).
- 2/3 ancillary features required
 1. Impaired comprehension of syntactically complex (non-canonical) sentences.
 2. Spared single-word comprehension.
 3. Spared object knowledge.



How well do the 2011 consensus criteria work in the early/mild stages of PPA?

Semantic PPA

• N=4

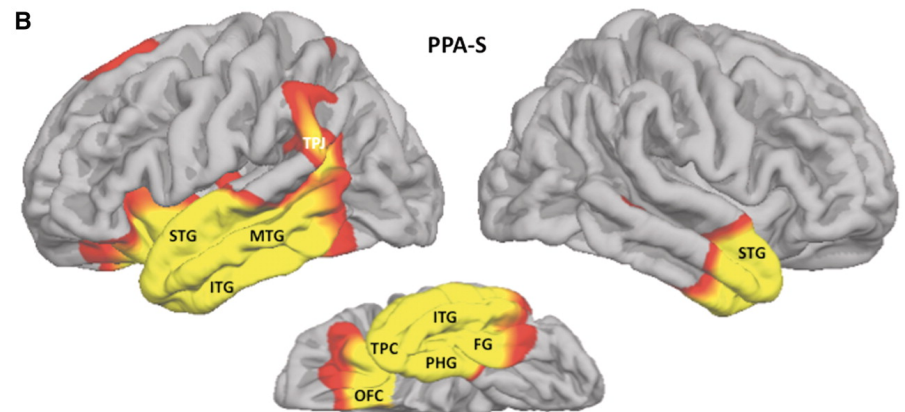
(PPA-S) (Gorno-Tempini et al., 2011)

- 2 required core features:

1. Impaired object naming.
2. Impaired single-word comprehension.

- 3 ancillary features required.

1. Impaired object knowledge, particularly for low-frequency or low-familiarity items.
2. Surface dyslexia or dysgraphia.
3. Spared repetition.
4. Spared grammaticality and motor aspects of speech.



How well do the 2011 consensus criteria work in the early/mild stages of PPA?

Logopenic PPA

(PPA-L) (Gorno-Tempini et al., 2011)

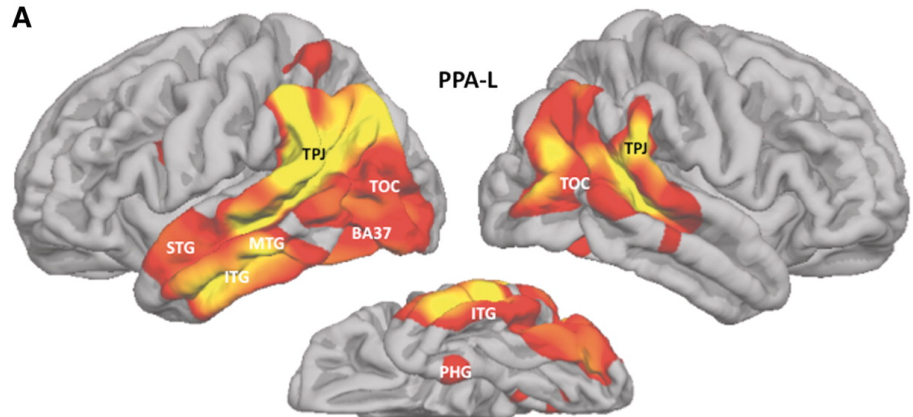
• N=6

- 2 Core features required:

1. Impaired single-word retrieval in spontaneous speech and naming.
2. Impaired repetition of phrases and sentences.

- 3 ancillary features required.

1. Phonological errors (phonemic paraphasias) in spontaneous speech or naming. 2. Spared single-word comprehension and object knowledge.
2. Spared motor speech.
3. Absence of frank agrammatism.



Ambiguity in the PPA-G vs. PPA-L designation

Non-fluent/agrammatic

(PPA-G) (Gorno-Tempini et al., 2011)

- At least 1 core feature
 1. Agrammatism in language production.
 2. Effortful, halting speech with inconsistent speech sound errors and distortions (apraxia of speech).
- 2/3 ancillary features required
 1. Impaired comprehension of syntactically complex (non-canonical) sentences.
 2. Spared single-word comprehension.
 3. Spared object knowledge.

Logopenic

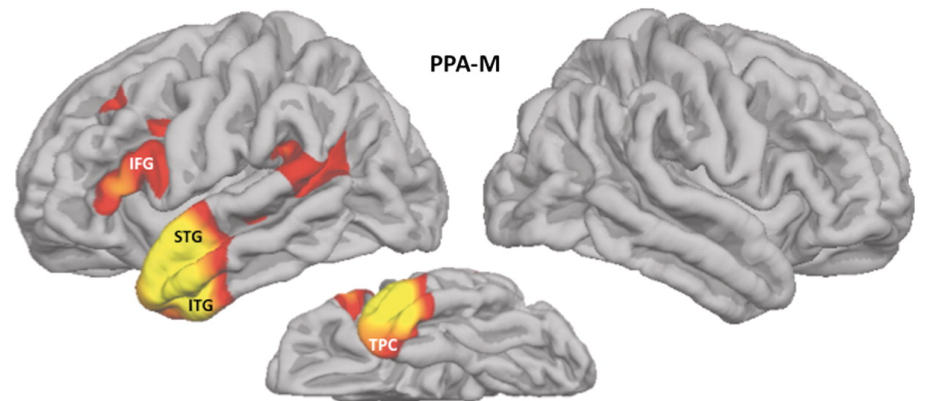
(PPA-L) (Gorno-Tempini et al., 2011)

- 2 Core features required:
 1. Impaired single-word retrieval in spontaneous speech and naming.
 2. Impaired repetition of phrases and sentences.
- 3 ancillary features required.
 1. Phonological errors (phonemic paraphasias) in spontaneous speech or naming.
 2. Spared single-word comprehension and object knowledge.
 3. Spared motor speech.
- Absence of frank agrammatism.

Other PPA phenotypes

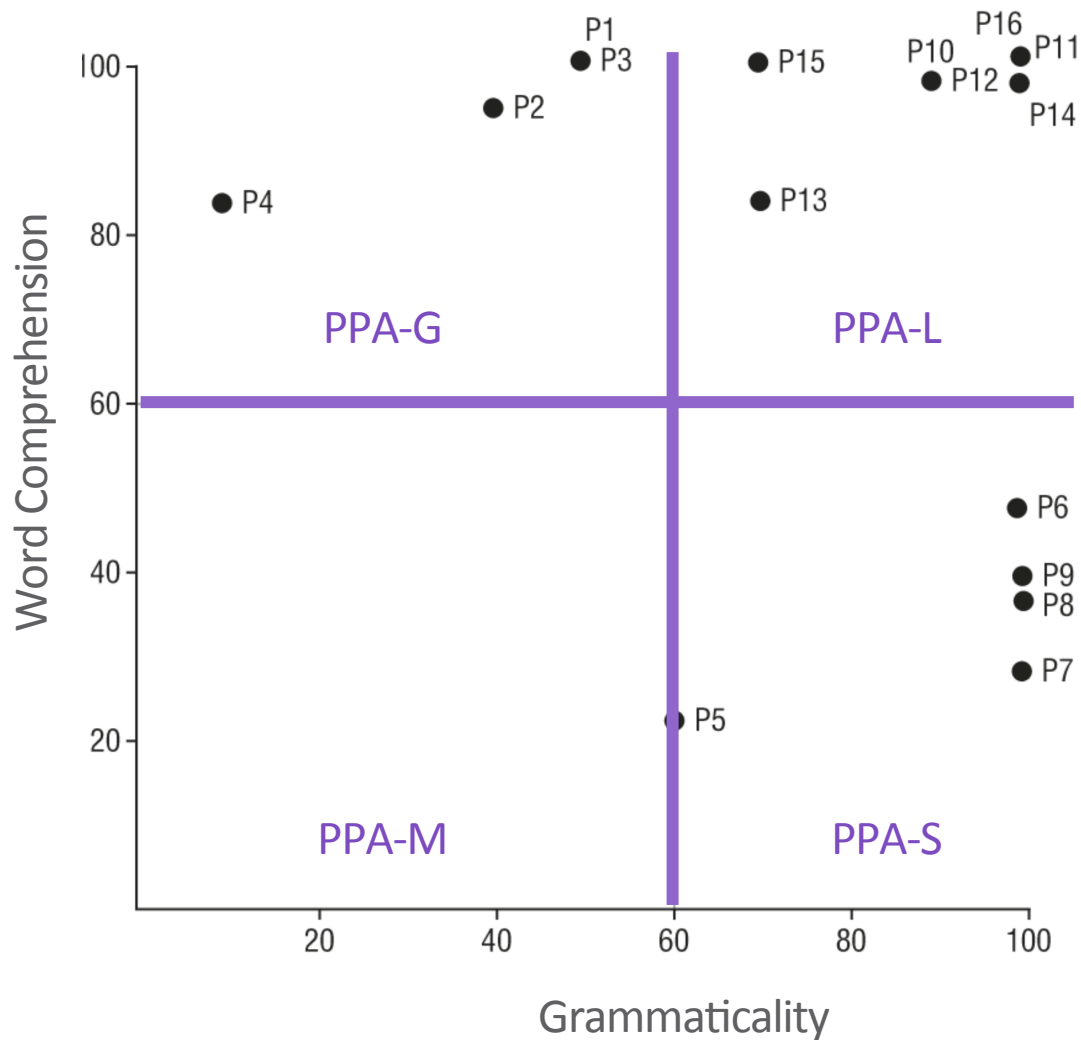
- Mixed variant (PPA-M)
(Mesulam et al., 2009)
- N=2
- 2 Core features required
 1. Agrammatism in language production.
 2. Word comprehension impairments.

B

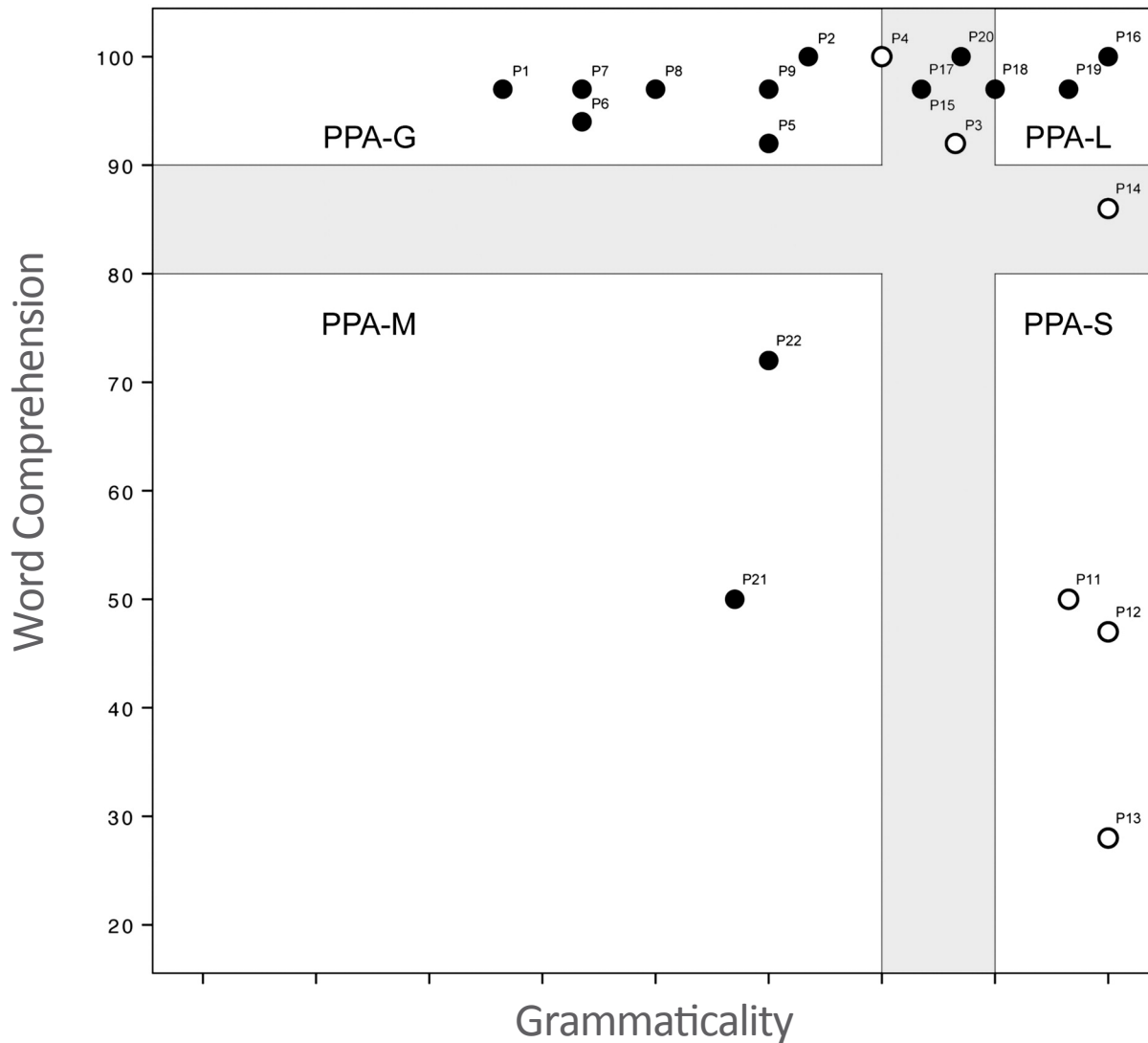


Template approach to classification

Mesulam 2009



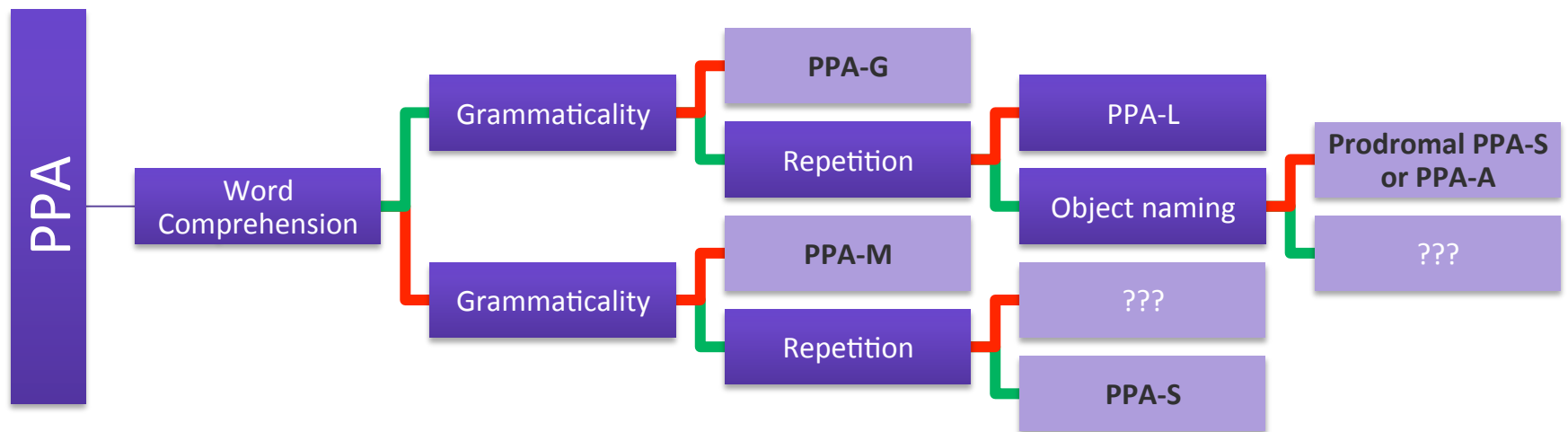
Template classification of mild PPA



Conclusions / Insights

- Flexibility in the “2-year rule”
- Consensus criteria are able to classify 80% of patients with mild/early PPA.
 - Classification improves to 90% if the PPA-M phenotype is used
 - Current consensus criteria lead to some ambiguity in differentiating PPA-G from PPA-L
 - The PPA-mixed phenotype is possible even in the early/mild stages of PPA
- Early/mild PPA cases showed phenotypically concordant patterns of cortical atrophy.

Road Map for subtyping in PPA



Acknowledgments

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