Primary Progressive Aphasia: Advances in Diagnosis, Prognosis, & Treatment

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I. Objectives

A. Review *clinical syndromes* of PPA that (1) reflect area of brain most affected by pathology; and (2) *grossly* correspond to a particular pathology

B. Describe advances in diagnosis: recently developed tests & imaging for identifying these variants

C. Describe advances in prognosis: imaging data that may help predict rate of decline

D. Describe advances in treatment: emerging investigational treatment for at least temporarily delaying decline/improving language

II. Definition: Deterioration of language for at least 2 years before decline in other cognitive functions (Mesulam, 1982)

III. Variants

A. The 3 main variants of primary progressive aphasia (PPA) are *clinical syndromes* – collection of symptoms that frequently co-occur

B. Can be subdivided into other variants (e.g. Primary Progressive Apraxia of Speech)

C. The main variants reflect the area of brain most affected by the disease

D. The variants provide clues as to the *most likely* underlying pathology (disease)

E. Underlying disease determines what problems the person *may* develop in the future

F. Main variants of PPA are distinguished by distinct patterns of language performance and supportive patterns of atrophy on imaging. (Gorno-Tempini, et al., 2011)

G. All 3 variants have prominent naming impairment

1. Nonfluent Agrammatic Variant (nfaPPA)

Core features:

a. Effortful, halting speech with inconsistent sound errors ("apraxia of speech") and/or

b. Agrammatic language production (difficulty producing complete, grammatical sentences)

Area of greatest atrophy in nfaPPA: posterior inferior frontal cortex, insula

Pathology of nfaPPA: Usually tau (Corticobasal degeneration, Progressive supranuclear palsy, Frontotemporal lobar degeneration (FTLD-t), Pick's disease; Argyrophilic grain disease)

2. *Semantic Variant PPA (svPPA)*

Core Features of svPPA:

Both of the following core features must be present:

a. Impaired naming of objects (more than actions)

b. Impaired single word comprehension

Area of greatest atrophy in svPPA: anterior and inferior temporal cortex(Left>Right)

Most common pathology in svPPA: Frontotemporal lobar degeneration (FTLD-TDP-43) (Tau DNA Binding Protein- 43 kD)

3. Logopenic variant PPA (lvPPA)

Core features of lvPPA:

Both must be present:

a. Impaired word retrieval in conversation and naming tasks and

b. Impaired repetition of sentences and phrases

Area of greatest atrophy in lvPPA: Posterior inferior parietal & Posterior superior temporal lobe

Most common pathology in lvPPA: Amyloid plaques and neurofibrillary tangles of Alzheimer's Disease (Gorno-Tempini, Hillis, Weintraub, et al., 2011

IV. Advances in Diagnosis:

A. NACC FTLD Module (Knopman et al.; Uniform Dataset 2):Letter Fluency, Word & Sentence reading; Semantic Associates; Sentence Anagram test (syntactic production); Sentence repetition; Noun & verb naming; Benson Complex Figure Memory; Caregiver and examiner scales for observations of key behavioral elements; Neurological examination; Standardized diagnostic checklist for bvFTD and PPA

B. Some limitations of NACC FTLD Battery:

1. Performance on the anagram test correlates with performance on tests of semantic processing ($r=.43$; $p<0.05$) and working memory (repetition; $r=.72$; $p<.05$), as well as disease duration ($r=.44$; $p<.05$).

Ability to produce grammatical sentences with anagrams to match pictures is impaired in all variants of PPA, and does not distinguish among them.

2. Word comprehension test is insensitive to word comprehension deficits early in course (word/picture verification is more sensitive; (Breese & Hillis, 2004)

3. Sentence repetition test is also insensitive to sentence repetition problems early in course

4. Inadequate testing of social cognition & executive function

C. 14-item PPT provide rapid test of nonverbal semantics that:

1. Distinguishes svPPA from healthy controls
2. Distinguishes svPPA from other variants
3. Correlates with anterior temporal & orbitofrontal atrophy
4. Distinguishes FTLD pathology from other pathologies relatively early

D. Eye tracking using word-picture matching with unrelated foils is sensitive to:

1. svPPA (even before individuals meet criteria of impaired spoken word comprehension in off-line tasks)
2. Atrophy in left and right temporal pole

V. Advances in Prognosis:

A. Study showed: rapid decliners and slow decliners among all variants.

1. nfaPPA decline most rapidly in HANA (verb naming);
2. svPPA decline most rapidly in PPT (semantics)
3. lvPPA decline most rapidly in BNT (noun naming)
4. No association between age or education & rate of decline.

B. Progressive decline in specific tests is closely related to progressive atrophy in focal areas, providing further evidence that these areas are critical for the associated tasks. For example: left supramarginal gyrus is critical for working memory; left orbitofrontal gyrus is critical for executive function; left inferior temporal gyrus & other temporal regions are critical for naming nouns; left inferior frontal gyrus & temporal regions are critical for naming verbs

C. The only baseline imaging parameter that significantly correlated with rate of subsequent decline in naming (after correction for multiple comparisons) was the resting state connectivity (functional correlation) between homologous pre-frontal cortices

VI. Advances in Treatment

A. Speech and Language intervention is the mainstay of treatment (McNeil et al., 1995; Henry et al., 2008; Rapp & Glocroft, 2009; Newhart al. 2009; Tsapkini & Hillis, 2013)

B. May be augmented with transcranial direct current stimulation (tDCS; Tsapkini et al., 2014)

C. In recent study of 19 PPA participants: tDCS+spelling intervention was more beneficial than spelling intervention alone; treatment effects are better retained at both 2 weeks and 2 months follow-up with tDCS; tDCS + spelling intervention generalized to untrained items

VII. Conclusions

A. PPA is a group of clinical syndromes, distinguished by language characteristics that reflect different locations of atrophy (and usually distinct pathologies)

B. There are tests being developed & standardized to efficiently identify these variants. Short PPT or eye-tracking with word-picture matching identifies svPPA early in course

C. Rate of decline varies widely across tasks, & individuals in all variants; might be predictable with rsfcMRI

D. Language therapy may slow the rate of decline in some language tasks, and might be augmented by tDCS (but results are preliminary; study is in progress)

A large study of language therapy alone is also in progress (Georgetown + Hopkins)

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