Primary Progressive Aphasia
Part 1

Cynthia K. Thompson
Departments of Communication Sciences and Disorders
Cognitive Neurology and Alzheimer’s Disease Center
NORTHWESTERN UNIVERSITY
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Overview of Frontotemporal Disorders/Dementias
- Behavioral/cognitive deficits and neuropathology
- PPA Subtypes
  - Language deficit patterns
  - Regions of cortical atrophy
- Classifying PPA by Subtype

FRONTOTEMPORAL DISORDERS/DEMENTIAS (FTD)

Progressive Behavior Change
Progressive Language Change
Progressive Motor Change

bvFTD: Behavioral variant (FTD)
tvFTD: Temporal/Frontal FTD
‘Pick’s Disease’

Primary Progressive Aphasia (PPA)
- Agrammatic (PPA-G)
- Logopenic (PPA-L)
- Semantic (PPA-S)

Corticobasal Syndrome (CBS)
Progressive Supranuclear Palsy (PSP)
FTD + Parkinsonism
FTD - Motor Neuron Disease

Dementia Diagnosis
Primary Symptoms

Personality Behavioral Δ
Language Δ

Behavioral variant (bvFTD)
Primary Progressive Aphasia (PPA)

BV(FTD)
Progressive Comportmental/Executive Dysfunction

Early Stage Symptoms
1. Change in personality OR exaggeration of prior traits
2. Poor judgment
3. Social-interpersonal skills deteriorate, e.g. politeness, hygiene
4. Emotional reactions: absent or changed
5. Executive functions: planning, persistence, multi-tasking
6. Behavioral symptoms: mental rigidity, distractibility, perseverative behaviors, obsessive-compulsive symptoms, decreased motivation/initiative, disinhibition
7. Unaware of symptoms, indifferent

Late Stage Symptoms
1. Severe behavioral/executive deficits
2. Agitation, irritability, combative behaviors, extreme behavior
3. Severe lack of motivation, aka “abulia”
4. Inability to initiate activities
5. Aphasia
6. Memory loss
Dementia Diagnosis

Primary Symptoms

- Personality
- Behavioral
- Language
- Memory Loss

(bvFTD) (PPA) Alzheimer’s Disease

Language Deficits in the Dementias

- bvFTD
  - Abnormalities in discourse (cohesion problems)
  - Reduced verbal initiation
- CBD, PSP, MND-FTD
  - Features of agrammatism (in some patients)
  - Articulatory difficulties, hesitant speech (Dysarthria)
- Alzheimer’s disease
  - Naming deficit in early course of the disease
  - Difficulties in comprehension usually arise later
- Presence of progressive decline in language does not necessarily mean PPA

Primary Progressive Aphasia (PPA)

- Reported in 19th century
  - Pick (1892), Pick (1904), Franceschi (1908), Rosenfeld (1909), Mangazzini (1914)
- Gained attention in late 20th century
  - Mesulam (1982): 6 cases of “Slowly Progressive Aphasia”
  - Mesulam (1987): “Primary Progressive Aphasia”
- Adult onset
- Language impairment is the most salient symptom (primary)
- Caused by a neurodegenerative disease (progressive)
- No evidence of stroke or other neurological disease
- Language/cognitive deficits consistent with aphasia (aphasia)
- Hundreds of cases now reported in literature

Primary Language Deficit

Vascular pathology

Symptoms acute; potential for improvement

Symptoms progressive, no acute onset; declination

Stroke Aphasia vs. Primary Progressive Aphasia (PPA)

Early Stage Symptoms:

1. Language difficulties
   - Word-finding difficulty
   - Sentence production
   - Comprehension difficulty
   - Reading/writing difficulty
2. Other functions are normal or relatively preserved
3. Daily living activities are affected mostly by aphasia; short term memory and personality are intact
4. Awareness of symptoms may lead to depression
5. Symptoms progress over time and other problems develop

Late Stage Symptoms:

1. Mutism
2. Severe comprehension deficits
3. Personality changes
4. Memory loss
5. Daily living activities severely limited
Early PPA versus bvFTD

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>PPA</th>
<th>FTD-bv</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aphasia</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Memory Loss</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Visual Disorder</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Personality Change</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Concentration Problem</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Social-Interpersonal</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

Motor symptoms may be present in both

Late PPA versus bvFTD

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>PPA</th>
<th>FTD-bv</th>
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<tbody>
<tr>
<td>Aphasia</td>
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<td>+/-</td>
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<td>Social-Interpersonal</td>
<td>+/-</td>
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</tr>
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</table>

Motor symptoms may be present in both

Awareness of PPA

- Despite a growing body of research, general awareness of PPA is poor
- Individuals with PPA incorrectly diagnosed with
  - Alzheimer’s Disease (AD)
  - Psychopathology

PPA Demographics and other Information

- Age of onset → 40-80 years (average 60)
- More males than females → 2:1 ratio
- Family history of dementia
  - 50% (parent or sibling)
  - Possible genetic component
- Variable language decline
  - 2 – 11 years
  - Eventually nonverbal (unable to comprehend or produce language)
- Episodic memory unimpaired (in early stages)

Risk Factors

- Male gender (?) (Mesulam & Weintraub, 1992)
- Learning Disability (self, family) (Mesulam & Weintraub, 1992; Rogalski et al, 2008)
- Genetic factors
  - ApoE € 4 allele NOT a risk factor for PPA, even in those with AD pathology at death (Rogalski et al, 2011)
  - Heterozygosity of Met/Val at codon 129 of prion protein (Li et al, 2003)
  - Over-representation of HTTH haplotype (also in PSP, CBD) (Geschwind et al, 2004)
  - Two PPA families with PGRN mutation (Mesulam et al, 2006)

Etiology of PPA

- Unknown
- Progressive neuronal loss (= atrophy)
  - In grey matter
  - White matter remains mostly intact
- Neural loss related to abnormal accumulation of material (proteins, plaques, neurofibrillary tangles)
- Atrophy is clearly asymmetric in right-handed (left>right)
  - As opposed to Alzheimer’s disease (left + right)
Neuroimaging in PPA

- Magnetic Resonance Imaging (MRI)
  - Exclusion of other causes of language deficit
    - i.e., stroke, tumor
  - Left-lateralized atrophy

- Positron Emission Topography (PET)
  - Decreased blood flow in the left hemisphere
  - Helpful when MRI is within normal limits

Tissue Diagnosis on Autopsy

- Dementia of the Alzheimer Type
  - AD: ~ 90%
  - Other: 10%

- bvFTD
  - FTLD: 80%
  - Tauopathy, TDP-43
  - Proteinopathy, FUS-opathy
  - Other: 20%

- PPA
  - FTLD: 70%
  - Tau, TDP-43
  - AD: 30%

  - Frontotemporal lobar degeneration (FTLD)
  - Alzheimer’s disease (AD)

Alzheimer and frontotemporal pathology in subsets of primary progressive aphasia

Logopenic: n=11 (7 AD; 4 FTLD)
Agrammatic: n=6 (5 FTLD-T; none with AD pathology)
PPA Cognitive Deficit Pattern

**Impaired**
- Language
- Memory and orientation
- Facial recognition
- Reasoning
- Attention
- Ability to learn
- Activities of daily living
  - With the exception of those requiring language

**Unimpaired**
- Language
- Memory and orientation
- Facial recognition
- Reasoning
- Attention
- Ability to learn
- Activities of daily living

Criteria for PPA Diagnosis

**Table 1. Inclusion and Exclusion Criteria for the Diagnosis of Primary Progressive Aphasia (modified from Mesulam, 2003) (paraphrased for this presentation)**

**INCLUSION: 1-3 are necessary**
1. Language deficits are most prominent (word-finding deficits, paraphasias, effortful speech, grammatical and/or comprehension deficits).
2. Aphasia is the principal cause of impairments in ADLs which could otherwise be normal.
3. Aphasia is most prominent deficit at onset and for the initial phases of the disease.

**EXCLUSIONARY**
1. Other diseases that account for deficits (e.g., neoplasm, cerebrovascular disease, hypothymidism, etc.)
2. Psychiatric diagnosis present that accounts for deficits
3. Prominent initial episodic memory, visual memory and visuo-perceptual impairments (e.g., inability to copy simple line drawings)
4. Prominent initial behavioral disturbance (e.g., marked disinhibition, emotional detachment, hyperactivity or repetitive/compulsive behaviors)

PPA Subtypes; Language Deficits

<table>
<thead>
<tr>
<th>Agrammatic (PPA-G)</th>
<th>Logopenic (PPA-L)</th>
<th>Semantic (PPA-S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grammatical Impairments</td>
<td>Word Impaired</td>
<td>Non-grammatical Impairments</td>
</tr>
<tr>
<td>Naming Impaired</td>
<td>Naming Impaired</td>
<td>Naming Severely Impaired</td>
</tr>
<tr>
<td>Word Comprehension Unimpaired</td>
<td>Word Comprehension Unimpaired</td>
<td>Word Comprehension Unimpaired</td>
</tr>
<tr>
<td>Repetition Impaired</td>
<td>Repetition Impaired</td>
<td>Repetition Impaired</td>
</tr>
</tbody>
</table>

Coding Analysis

Cinderella stories
- Transcribed
- Segmented into utterances
  - Syntactic
  - Semantic
  - Pragmatic

Coding
- Utterance Level
  - Sentence or non-sentence
  - Grammaticality
- Lexical Level
  - Grammatical class
  - Open class, closed class
- Bound Morpheme Level
  - Inflectional morphemes

Thompson, Cho, Hsu, Wiencke, Redemaker, Witner, Mesulam & Weintraub (2012); Thompson, Ballard, Tait, Weintraub, & Mesulam (1997)

Gorno-Tempini et al., 2004; Hils et al., 2004; Hodges & Patterson, 1996; Mesulam et al., 2009; Thompson et al., 1997, 2012; Weintraub et al., 2008; Wilson et al., 2010

NEUROPSYCHOLOGY OF PPA

**Percent Change in Test Scores Over 2 Years**

<table>
<thead>
<tr>
<th>Language and Related Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1, Weintraub et al., 1990</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Non Language Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 3, Weintraub et al., 1990</td>
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</tbody>
</table>

PPA subtypes

(From: Gorno-Tempini et al., 2011)
Speech Sample: PPA-G (Thompson et al., 2011)

“She made a (pumpkinpen pumpkined) pumpkin (in a to a inste uh ins) 0:03 into (a) a, stage coach.
(And uh) and she maked four mices into (uh) horses.”

- Effortful, halting speech
- Reduced speech rate and phrase length
- Agrammatic production patterns
- Word retrieval difficulty
- Motor speech errors (apraxia of speech)

Speech Sample: PPA-L (Thompson et al., 2011)

“Cinderella (and her) and the (uh uh) good fairy.
And they took a pumpkin and (uh) made it into the (uh) carriage.
And the (houses house uh) horses were (uh uh) from the mice.”

- Absence of agrammatic production errors
- Word retrieval difficulty
- Nouns more impaired than verbs
- No motor speech errors

Speech Sample: PPA-S (Thompson et al., 2011)

“I think that’s where she came with this other … type of person.
And that’s where she changed the clothes and stuff.
And then that’s when she got the other type of shoes things on.”

- Absence of agrammatic production errors
- Word retrieval difficulty
- Nouns more impaired than verbs
- Overuse of pronouns
- Overuse of high frequency nouns
- No motor speech errors

Fluency and Grammaticality
Thompson, Ballard, Taal, Weintraub, Mesulam (1997)

Fluency Measures
MLU- Words

Ratio of Open Class to Closed Class Words

Fluency Measures: WPM and MLU-W across Participant Groups

<table>
<thead>
<tr>
<th>Participants</th>
<th>Years Post-onset (M)</th>
<th>Age (yr)</th>
<th>Education (yr)</th>
<th>WAB AQ (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPA-G</td>
<td>11</td>
<td>3.66</td>
<td>63.27</td>
<td>16.82</td>
</tr>
<tr>
<td>PPA-L</td>
<td>20</td>
<td>3.78</td>
<td>65.90</td>
<td>15.85</td>
</tr>
<tr>
<td>PPA-S</td>
<td>6</td>
<td>2.67</td>
<td>56.3</td>
<td>16.0</td>
</tr>
<tr>
<td>StrAg</td>
<td>8</td>
<td>4.53</td>
<td>52.8</td>
<td>16.3</td>
</tr>
<tr>
<td>Age-Matched Controls</td>
<td>13</td>
<td>63.23</td>
<td>16.31</td>
<td>99.82</td>
</tr>
</tbody>
</table>

Thompson, Cho, Hsu, Wieneke, Rademaker, Witner, Mesulam & Weintraub (2012)

<table>
<thead>
<tr>
<th>Fluency Measures</th>
<th>Grammatical measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>WPM</td>
<td>Proportion of grammatical sentences</td>
</tr>
<tr>
<td></td>
<td>Noun to verb ratio</td>
</tr>
<tr>
<td></td>
<td>Proportion of correctly inflected verbs</td>
</tr>
</tbody>
</table>

WPM
PP-A: Mean = 50 - 60
PPA-L: Mean = 80 - 100
PPA-S: Mean = 115 - 135

(ml controls M: 130-150)
Fluency by PPA Subtype

Fluency based on WPM. Nonfluent = at or below 113.4 WPM cut-off (control mean minus 1 SD)

Fluency and Grammaticality

Dissociation between fluency and grammaticality in primary progressive aphasia

Cynthia K. Thompson, M.D., Anna Chiu, Chun-Ju Ho, Christina Wieneke, M.A., Harry Bahamu, M.D., and Soojin Cho, Ph.D.

Aphasia and Neuropsychiatry Laboratory, Northwestern University, Evanston, IL, USA

Published in Aphasiology (2012)

Classification of PPA by Subtype

Quantitative Template for Subtyping Primary Progressive Aphasia

Marcel Heudelen, MD; Christina Wieneke, BA; Bing Bing Wei, MD; Emily Rogalski, PhD; and Sandra Weintraub, PhD

Archives of Neurology (2009)

Summary: Fluency and Grammaticality

1. Different regions of atrophy are associated with reduced fluency and reduced grammatical processing in PPA

2. Impairments of fluency and grammar do not always go together

Primary Language Measures

- Western Aphasia Battery (WAB; Karlson, 2006)
- Boston Naming Test (BNT; Kaplan et al., 1983)
- Northwestern Naming Battery (Thompson & Weintraub, experimental version)
- Peabody Picture Vocabulary Test (PPVT; Dunn & Dunn, 2006)
- Northwestern Assessment of Verbs and Sentences (Thompson, 2011)
- Northwestern Anagram Test (NAT; Thompson, Weintraub, & Mesulam, 2012)

Diagnostically Salient Measures:

Word Comprehension (PPVT)
Sentence Grammaticality (NAT)
Deficit/Atrophy Patterns in Mild PPA

Quantitative classification of primary progressive aphasia at early and mild impairment stages

M.-M. Mesulam, C. Wienieke, C. Thompson, E. Rogalski, and L. Weintraub

Brain (2012)

Language Patterns in Mild PPA

Table 2. Diagnostic features for the NONINFLUENTIAL/AGRAMMATIC variant PPA (aka PPA-G)

1. Clinical Diagnosis
   - At least one of the following core features must be present:
     1. Agrammatism in language production
     2. Effortful, halting speech, "speech of speech"
     3. 2 of the following other features must be present:
        1. Impaired comprehension of syntactically complex sentences
        2. Spared single word comprehension
        3. Spared object knowledge
   - Imaging-Supported Diagnosis of AgrammaticNonfluent: Both must be present:
     1. Clinical diagnosis of noninfluential/agrammatic variant PPA
     2. Imaging must show one or more of the following results:
        a. Predominant left posterior fronto-insular atrophy on MRI
        b. Predominant left posterior frontal hypoactivation or hypometabolism (PET, SPECT)

2. Noninfluential/agrammatic variant PPA with Definite Pathology:
   - Criterion 1 must be present and either 2 or 3 must be present:
     1. Clinical diagnosis of noninfluential/agrammatic variant PPA
     2. Neuropathological evidence of a specific pathology (e.g., FTLD-tau, FTLD-TDP, AD, other)
     3. Presence of a known pathogenic mutation

Patterns of Neural Atrophy PPA Subtypes

Mesulam, Wienieke, Rogalski, Cobia, Thompson, and Weintraub (2009). Archives of Neurology

Atrophy Patterns in Mild PPA

Mesulam, Wienieke, Thompson, Rogalski, & Weintraub (2012). Brain.
In frequency than the unrelated stimuli, we first examined the each SOA for each participant group. Because we were unable to

\[ \text{Table 3. Diagnostic Criteria for the Semantic Variant PPA (PPA-S)} \]

<table>
<thead>
<tr>
<th>Diagnostic Criteria for the Semantic Variant PPA (PPA-S)</th>
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<tbody>
<tr>
<td>1. Clinical Diagnosis of semantic variant PPA:</td>
</tr>
<tr>
<td>a. Poor confrontation naming (of pictures or objects, especially low frequency/familiarity)</td>
</tr>
<tr>
<td>b. Impaired single-word comprehension</td>
</tr>
<tr>
<td>c. At least three of the following other diagnostic features must be present:</td>
</tr>
<tr>
<td>1. Poor object knowledge, particularly for low frequency or low familiarity items</td>
</tr>
<tr>
<td>2. Surface dyslexia and/or dysgraphia</td>
</tr>
<tr>
<td>3. Sparing of past objects, personal names, and proper names</td>
</tr>
<tr>
<td>2. Imaging-Supported semantic variant PPA Diagnosis:</td>
</tr>
<tr>
<td>a. Clinical diagnosis of semantic variant PPA</td>
</tr>
<tr>
<td>b. Imaging must show one or more of the following results:</td>
</tr>
<tr>
<td>1. Prominent anterior temporal lobe atrophy</td>
</tr>
<tr>
<td>2. Prominent posterior temporal hyperperfusion or hypometabolism (SPECT, PET)</td>
</tr>
<tr>
<td>3. Presence of a known pathogenic mutation</td>
</tr>
</tbody>
</table>

\[ \text{Table 4. Diagnostic criteria for logopenic variant PPA (aka PPA-L)} \]

<table>
<thead>
<tr>
<th>Diagnostic Criteria for the Logopenic Variant PPA:</th>
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<tbody>
<tr>
<td>1. Clinical Diagnosis of Logopenic Variant PPA:</td>
</tr>
<tr>
<td>a. Poor confrontation naming (of pictures or objects, especially low frequency/familiarity)</td>
</tr>
<tr>
<td>b. Impaired single-word comprehension</td>
</tr>
<tr>
<td>c. At least three of the following other diagnostic features must be present:</td>
</tr>
<tr>
<td>1. Speech (phonological) errors in spontaneous speech and naming</td>
</tr>
<tr>
<td>2. Sparing of single-word comprehension and object knowledge</td>
</tr>
<tr>
<td>3. Absence of formalized aphasia</td>
</tr>
<tr>
<td>d. Absence of frank dysarthria</td>
</tr>
</tbody>
</table>

Challenges in Classification

- Some patients difficult to classify
  - Mixed-PPA
  - Semantic processing deficits found in PPA-G and PPA-L
    - Not just PPA-S
    - Phonological processing deficits found in PPA-G and PPA-L
      - Not just PPA-L

PPA-G and PPA-L show Abnormal Semantic Interference at SOA -1000 ms

- Slowed picture naming in the presence of a semantically-related distractor presented 1000 ms before the picture (not seen in controls)

Word Interference Paradigm: Phonological Facilitation

SOAs (between interfering stimulus and picture)

\[ \text{SOA} = 1000, 500, 0, -100, -500, -1000 \text{ ms} \]

- +500 ms
- +300 ms
- +100 ms
- 0 ms

Mack, Cho-Reyes, Kluit, Weintraub, Mesulam, & Thompson, 2013

Cognitive Neuropsychology

ISHA 2015, Indianapolis, IN (C.K. Thompson)
PPA-G and PPA-L show Abnormal Phonological Facilitation

• PPA-G: Protracted phonological facilitation effects
  • Faster picture naming at +300 ms when phonologically-related distractor present
• PPA-L: Weak phonological facilitation effects
  • Significant effects only at 0 ms when phonologically-related distractor present

Mack, Cho-Reyes, Kloet, Weintraub, Mesulam, & Thompson, 2012

Summary

• Several types of dementia
  o Dementia of the Alzheimer’s type
  o Frontotemporal dementias
    • bvFTD
    • PPA
• Three PPA subtypes (PPA-G, PPA-L, PPA-S)
  o Language deficit patterns
  o Atrophy patterns
  o Challenges in classification

Aphasia and Neurolinguistics Research Laboratory
Northwestern University

Collaborators
Roelien Basdwaan
David Caplan
Audrey Holland
Swathi Kiran
M. Marsel Mesulam
Todd Parrish
Brenda Rapp
Emily Rogalski
Dorothy Saur
Lewis P. Shapiro
David Swinney
Sandra Weintraub
Masaya Yoshida

Doctordal Students
Kerrie Ballard
JungWan (Janet) Chey
Eddie Eduardo
Naomi Hashimoto
Chien Hsu
Beverly Jacobs
Mikyong Kim
Jadwana Lukic
Swathi Kiran
Jiyoon Lee
Elynn Riley
Sandra Schneider
Yasmeen Faroqi-Shah

Post Doctoral Fellows
Elena Barbarisi
Borna Bonakdarpour
Dirk den Ouden
Michael Walsh Dickey
Stephen Fox
Rob Hurley
Aneta Kielar
Melissa Lee
Jennifer Mack
Aya Meibuz-Auscher
Aaron Meyer
Lisa Milman
Michaela Nerantzis

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