Neural Networks for Spoken and Written Language: Evidence from Primary Progressive Aphasia

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1 Sie

Slany

Arnold Pick (1851 - 1924)









ARNOLD PICK

On the relationship between senile cerebral atrophy and aphasia*1

1892

Translated by D. M. GIRLING and G. E. BERRIOS

Classic Text No. 29

On the symptomatology of left-sided temporal lobe atrophy¹

> 1904 Prof. A. PICK, Prague

Translated and annotated by D. M. GIRLING and G. E. BERRIOS²

- Progressive fluent aphasia, with impaired comprehension and naming
- Preserved motor speech and repetition
- Language profile similar to transcortical sensory aphasia (Wernicke/Lichtheim)
- "...pronounced atrophy of the gyri of the left hemisphere, particularly of the left temporal lobe...the origin of the disturbance is in the second and third left temporal gyri."
- "...it seems right to state that a more or less sharply *circumscribed* type of aphasia may exist at a particular point in time and be related to *circumscribed*, perhaps simple atrophic, brain changes."

Semantic Dementia or Semantic Variant of Primary Progressive Aphasia (PPA-S)



Primary Progressive Aphasia (PPA) (Mesulam, 2013)

- Neurodegeneration that primarily targets the left-hemisphere language network
- Insidious onset and gradual progression of language impairment affecting speech production/comprehension, reading/spelling
- Aphasia is the initial and most salient cognitive deficit and the main cause of disability for the patient
- Diagnostic tests provide confirmation of a neurodegenerative process as the underlying cause

Primary Progressive Aphasia (PPA)

- Different clinical subtypes or phenotypes can be identified reflecting the distribution of the neuropathological process within the language network
- PPA subtype/language phenotype provides important clues about the location and nature of the underlying disease process
- Histopathology
 - Frontotemporal Lobar Degeneration with Tauopathy (FTLD-TAU) 30%
 - Frontotemporal Lobar Degeneration with TDP-43 (FTLD-TDP) 30%
 - Alzheimer pathology with β amyloid plaques and NF tangles 40%
- Accurate diagnosis may have important therapeutic implications

Primary Progressive Aphasia (PPA)

- Age of onset: 50s or 60s, considerably younger than AOS for typical amnestic presentation of Alzheimer's disease (AD)
- Male = Female
- Usually sporadic, but can be familial and associated with gene mutations (MAPT, GRN, C9orf72, PS1)
- Unlike amnestic AD, APOE4 carrier status is not a significant risk factor
- Higher incidence of learning disability, developmental language disorders/dyslexia – genetic vulnerability of the language network?

PPA Risk Factors



Mesulam, 2013

PPA: Clinical Subtypes

- Non-fluent/agrammatic variant (PPA-NF)
- Semantic variant (PPA-S)
- Logopenic variant (PPA-LP)
- Diagnosis and clinical classification based on assessment of
 - Speech production/comprehension
 - Repetition
 - Naming
 - Reading/Spelling

and supported by

 Neuroradiological studies demonstrating focal atrophy/hypometabolism involving the language network

Diagnostic Criteria: Non-Fluent/Agrammatic Variant PPA

At least one of the following core features must be present:

- Agrammatism in language production
- Effortful, halting speech with inconsistent speech sound errors and distortions (apraxia of speech)

At least 2 of the 3 following other features must be present:

- Impaired comprehension of syntactically complex sentences
- Spared single-word comprehension
- Spared object knowledge

Imaging must show one or more of the following:

- Predominant left posterior fronto-insular atrophy on MRI
- Predominant left posterior fronto-insular hypoperfusion/hypometabolism on SPECT or PET

Gorno-Tempini et al., 2011

Non-Fluent/Agrammatic PPA: Neuroimaging

Structural MRI





Wilson et al., 2009

VBM/Cortical Thickness



Left



Wilson et al., 2010

Mesulam, 2013

Dickerson, 2011

Non-Fluent/Agrammatic PPA: Neuroimaging

FDG PET





Josephs et al., 2010

Non-Fluent/Agrammatic PPA: Lesion-Deficit Correlations



Fluency

Rogalski et al. 2011





Dominant AOS



Josephs et al. 2013

Wilson et al. 2011

Non-Fluent/Agrammatic PPA: Neuropathology

- FTLD-TAU (60-70%)
 - Pick's Disease (PiD)
 - Corticobasal Degeneration (CBD)
 - Asymmetrical rigidity, limb apraxia, alien hand, dystonia, myoclonus
 - Progressive Supranuclear Palsy (PSP)
 - Vertical gaze palsy, axial rigidity, frequent falls
 - Strong association between apraxia of speech and extrapyramidal disorders (CBD and PSP)

FTLD-TDP

- Agrammatism without apraxia/motor speech disorder
- Association with motor neuron disease (ALS)
 - Muscle weakness, wasting, fasciculations, bulbar symptoms, upper motor neuron signs



AD neuropathology

Grossman, 2012



Josephs, 2008

Diagnostic Criteria: Semantic Variant PPA

At least one of the following core features must be present:

- Impaired confrontation naming
- Impaired single word comprehension

At least 3 of the following other features must be present:

- Impaired object knowledge, particularly for low-frequency items
- Surface dyslexia or dysgraphia (choir "quire", sew "soo")
- Spared repetition
- Spared speech production (grammar and motor speech)

Imaging must show one or more of the following:

- Predominant anterior temporal lobe atrophy on MRI
- Predominant anterior temporal hypoperfusion or hypometabolism on SPECT or PET

Gorno-Tempini et al., 2011

Semantic Variant PPA: Impaired Word Comprehension and Object/Person Knowledge



Semantic Variant PPA: Neuroimaging



Structural MRI



VBM/Cortical Thickness



Mesulam et al., 2009



Henry et al., 2011

Semantic Variant PPA: Neuroimaging

FDG PET



Semantic Variant PPA: Lesion-Deficit Correlations Verbal Tasks: Left ATL



Word Comprehension Rogalski et al., 2011

S2

S4

Right

Left







64-item naming







S1

Naming Mesulam et al., 2013

Semantic Variant PPA: Lesion-Deficit Correlations Object/Face Knowledge: Bilateral ATL

B NUFFACE naming correlations in PPA



C NUFFACE recognition correlations in PPA





Rapcsak, 2013











Semantic Variant PPA: Neuropathology

FTLD-TDP43 (70-80)% FTD-TAU AD





Hodges & Patterson, 2007/Hodges et al., 2010

Diagnostic Criteria: Logopenic Variant PPA

Both of the following core features must be present:

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

At least 3 of the following other features must be present:

- Speech (phonologic) errors in spontaneous speech and naming
- Spared single-word comprehension and object knowledge
- Spared motor speech
- Absence of frank agrammatism

Imaging must show at least one of the following results:

- Predominant left posterior perisylvian or parietal atrophy on MRI
- Predominant left posterior perisylvian or parietal hypoperfusion or hypometabolism on SPECT or PET

Gorno-Tempini et al., 2011

Logopenic Variant PPA: Neuroimaging



Structural MRI



Gorno-Tempini et al., 2008

Rohrer et al., 2009

Mesulam, 2013

PPA-L

C



Dickerson, 2011

VBM/Cortical Thickness



Wilson et al., 2010

Logopenic Variant PPA: Neuroimaging





U 0 z-score (bw) L -5 z-score (bw) 0 z-score (bw)

U D z-score (be L -5 z-score (be

Logopenic Variant PPA: Lesion-Deficit Correlations

Sentence Repetition



Rogalski et al., 2011



Digit Span

Repetition

Baldo et al., 2012



Buchsbaum et al., 2011

Logopenic PPA: Neuropathology

AD Pathology (70-80%) β amyloid plaques/NFT FTLD-TAU FTLD-TDP





Mesulam, 2013





PPA-L

AD

PPA Subtypes and the Language Network





Gorno-Tempini et al., 2004



Grossman, 2010

10 Henry, Wilson & Rapcsak, 2013

Mesulam, 2013

PPA Subtypes and the Language Network



Dorsal Pathway: Phonology, Motor Speech Production, Syntax

Non-Fluent/Agrammatic PPA Logopenic PPA

Ventral Pathway: Lexical-Semantics Speech Comprehension Object/Person Knowledge

Semantic Variant PPA

Hickock & Poeppel, 2007

Neural Substrates of Sublexical vs. Lexical Reading/Spelling in PPA Voxel-Based Morphometry (VBM)/Cortical Thickness



Hot: correlation with nonword read/spell Cool: correlation with irregular word read/spell Henry et al., 2012



SING	r=-0.337, p=0.023
Orb	r=-0.387, p=0.020



Exceptional Word Spelling Erro	
TP	r=-0.371, p=0.026
FG	r=-0.434, p=0.008

r=-0.401. p=0.015

r=-0.358, p=0.033

ateral view

Shim et al., 2012

Tri

Operc



Brambati et al., 2009

Correlation between L-ATL Atrophy and Irregular Word Reading in PPA-S (n=24)



Henry et al., 2011

Written Language in PPA



Dorsal Pathway: Poor nonword reading/spelling or phonological alexia/agraphia

Non-Fluent/Agrammatic PPA Logopenic PPA

Ventral Pathway: Poor reading/ spelling of irregular words or surface alexia/agraphia

Semantic Variant PPA

Hickock & Poeppel, 2007

Dual-Pathway Model of Written Language Processing



Progressive Alexia: Dysfunctional Visual Word-Form Processing



Figure 2 Reading time increased as a function of word length in Patient J, a pattern that is characteristic of letter-by-letter reading.



Control 1 (72M)



False font > Fix VWFA (Words > False font) Control 2 (74M)



VWFA (Words > False font)



se font > Fix VWFA (Words > False font) Control 3 (77M)

	100 March 1	
1.7	t	
Words/I	False for	t > Fb
3.8	1	1



False font > Fix VWFA (Words > False font) Progressive alexic patient 1: Patient J (71M)



False font > Fix

Wilson et al., 2013



Molecular Imaging in PPA: Amyloid PET



LPA (Case 3)

SD (Case 2)



PPA in the Age of Biomarkers and Disease-Modifying Agents





Aphasia Research Project

Collaborators:

Pelagie Beeson Maya Henry Esther Kim Stephen Wilson Andrew Tesla DeMarco Kindle Rising Sarah Andersen Hyesuk Cho

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