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Diagnostic assessment in primary progressive aphasia: An illustrative case example

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Abstract

Purpose

Diagnosis and classification of primary progressive aphasia (PPA) requires confirmation of specific speech and language symptoms, highlighting the important role of speech-language pathologists (SLPs) in the evaluation process. The purpose of this case report is to inform SLPs regarding current practices for diagnostic assessment in PPA, describing standard approaches as well as complementary, state-of-the-art procedures that may improve diagnostic precision.

Method

We describe the diagnostic evaluation of a 49-year old female with complaints of progressive word-finding difficulty. She completed standard neurological, neuropsychological, and speech-language evaluations, as well as magnetic resonance and positron emission tomography imaging of her brain. In addition, a history of developmental speech, language, and learning abilities was obtained, as well as genetic testing, and assessment of cerebrospinal fluid biomarkers. We discuss the evaluation results in the context of the most current research related to PPA diagnosis.

Conclusion

Detailed behavioral assessment, thorough intake of symptom history and neurodevelopmental differences, multimodal neuroimaging, and comprehensive examination of genes and biomarkers are of paramount importance for detecting and characterizing PPA, with ramifications for early behavioral and/or pharmacological intervention.

Introduction

The diagnosis of primary progressive aphasia (PPA) is made when a patient has a predominant and progressive loss of communication caused by neurodegenerative disease that targets speech and language regions of the brain (Gorno-Tempini et al., 2004; Mesulam, 1982). Diagnosis of PPA requires confirmation of specific speech and language symptoms, highlighting the important contribution of speech-language pathologists (SLPs) during the evaluation process. Approaches to assessment and clinical characterization have evolved along with diagnostic terminology for PPA. Initially, PPA was characterized using a binary classification system with two predominant subtypes: nonfluent PPA (also referred to as progressive nonfluent aphasia, or PNFA; Grossman et al., 1996; Turner et al., 1996; Neary et al., 1998) and fluent PPA (also referred to as semantic dementia, or SD; Snowden, Goulding, & Neary, 1989; Warrington, 1975). As understanding of the clinical manifestations of PPA has grown, a tripartite clinical classification scheme emerged and was formalized in international consensus criteria for diagnosis (Gorno-Tempini et al., 2011). Current consensus criteria delineate clinical, imaging, neuropathological, and genetic features of each of the three variants of PPA.

Contemporary approaches to PPA diagnosis continue to evolve with the discoveries of novel imaging and genetic biomarkers and studies investigating symptom trajectories and neurodevelopmental patterns. Procedures for a multidisciplinary evaluation of typical PPA cases have been previously outlined for a general clinical audience (Marshall et al., 2018) and speech-language assessment procedures were recently summarized (Henry & Grasso, 2018). However, best practices for PPA diagnosis via a comprehensive, multidisciplinary evaluation have yet to be described for a SLP audience. This case report illustrates the application and interpretation of current assessment tools, including MRI, PET imaging, fluid biomarkers, genetic testing,

neurodevelopmental history-taking, and state-of-the-art speech-language and cognitive testing. First, we outline modern diagnostic procedures that may complement standard assessments and improve diagnostic precision, with a particular focus on issues relevant to SLPs. Subsequently, we will apply these diagnostic best practices to an illustrative case of PPA and discuss the clinical decision-making process as well as recommendations for clinical management.

Establishing a PPA diagnosis and clinical phenotpying

According to the international consensus criteria for PPA (Gorno-Tempini et al., 2011), clinical diagnosis is a two-step process: the first step involves determining whether an individual's pattern and trajectory of symptoms meet criteria for PPA, and the second step includes PPA variant classification. The earliest criteria for PPA diagnosis included a decline in speech and/or language that occurred in isolation from other symptoms for at least 2 years after disease onset (Mesulam, 1982, 2001; Mesulam & Weintraub, 1992). However, the "2-year rule" was ultimately thought to hinder diagnosis of PPA at early or mild stages of the disease (Mesulam et al., 2012). Currently, a clinical diagnosis of PPA requires predominant and progressive speech and/or language symptoms during initial stages of the disease, that these deficits are the primary limitation to activities of daily living, and that impairments cannot be better explained by psychiatric, behavioral, or non-degenerative central nervous system disorders.

The second diagnostic step is classification by PPA clinical variant, when possible. The international consensus criteria for PPA define three clinical variants based on core impairments and associated features (see Gorno-Tempini et al., 2011 for more details). The semantic variant (svPPA) is characterized by core impairments in both single-word comprehension and

confrontation naming, and at least three of four associated features: loss of object knowledge (especially for items that are less frequent or less familiar), surface dyslexia or dysgraphia, spared repetition, and spared grammar and motor speech. A diagnosis of logopenic variant (lvPPA) occurs when both core impairments in repetition of sentences/phrases as well as word retrieval in spontaneous speech and confrontation naming are present, as well as at least three of four associated features: phonemic errors in spontaneous speech and naming, spared single-word comprehension and object knowledge, spared motor speech, and absence of frank agrammatism. The nonfluent/agrammatic variant (nfvPPA) is indicated with at least one of two core deficits, either agrammatism in language production or apraxia of speech, and at least two of three associated features: impaired comprehension of syntactically complex sentences, spared single-word comprehension, and spared object knowledge.

Diagnosis by clinical variant has important implications for managing a patient's symptoms. Because each PPA variant is associated with a primary behavioral locus of deficit and neuropathological cause, classification can inform recommendations for appropriate behavioral or pharmacological interventions. In addition, each clinical variant is associated with a unique pattern and trajectory of decline (Brambati, et al., 2015; Faria, et al., 2014; Hsieh, et al., 2012; Rogalski et al., 2011, 2014; Van Langenhove, et al., 2016), and information regarding probable patterns of symptom evolution can help the patient's family prepare for current and future management of the disease.

For each PPA variant, an imaging-supported diagnosis can be established if the clinical symptoms are accompanied by evidence of particular patterns of atrophy, hypoperfusion, or glucose hypometabolism in the brain (Gorno-Tempini, et al., 2011): for svPPA, involvement of

the anterior temporal lobe in the left hemisphere (greater than right); for lvPPA, left posterior perisylvian involvement; and for nfvPPA, left posterior inferior frontal lobe involvement.

Etiology

The etiology of neurodegeneration varies across the three variants of PPA, each of which is linked to different pathological processes. There is a strong association between lvPPA and Alzheimer's Disease (AD) neuropathology (Deramecourt, et al., 2010; Josephs, et al., 2008; Mesulam, et al., 2008; Rohrer, Rosser, & Warren, 2012; Spinelli, et al., 2017). Semantic and nonfluent/agrammatic variants of PPA are considered two of three forms of frontotemporal dementia (FTD), the third being behavioral variant FTD (bvFTD), a non-aphasic phenotype that is characterized by prominent behavioral changes during initial stages of the disease. With respect to the two FTD PPA variants, the majority of svPPA cases have been linked to the transactive response DNA binding protein 43 kDa (TDP-43) type C (Rohrer et al., 2010a; Mackenzie et al., 2011; Hodges et al., 2009; Cairns et al., 2007; Josephs et al., 2011), and less commonly with TDP-43 type B and tauopathies including Pick's disease, and globular glial tauopathy (Spinelli et al., 2017). The neuropathological profile of nfvPPA is the most heterogeneous and includes 4R-tauopathies such as progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) (Chare et al, 2014; Deramecourt et al., 2010, Mesulam et al., 2014; Santos-Santos et al., 2016). Atypical neuropathologies associated with nfvPPA include Pick's Disease (a 3R-tauopathy) and TDP-43 type A (Spinelli, et al., 2017).

Genetic basis

PPA is usually sporadic, but in rare cases, there may be an underlying genetic basis. Although genetic testing is not currently standard procedure in the assessment of PPA, emerging

research in the genetics of PPA has demonstrated it may serve as a complementary tool for diagnosis. In the largest genetic screening study of PPA to-date, 14 of 403 cases (or 3.5%) had gene mutations, primarily in *C9ORF72* and *GRN* (Ramos et al., 2019). In addition, 9 of the 14 genetic cases had a first or second degree relative with a clinical diagnosis of dementia, suggesting most genetic PPA cases present with a family history of dementia. Previous case reports have also reported mutations in *MAPT* (Munoz et al., 2007; Tacik et al., 2017; Villa et al., 2011), including a study with 13 familial cases of PPA (Pickering-Brown et al., 2008). If motor function is affected (e.g., motor speech), pathological abnormalities in the *FUS* gene may be indicative of amyotrophic lateral sclerosis (ALS; Vance et al., 2009). In addition, pathological abnormalities in the *TARDBP* gene have been linked to various FTD phenotypes, including svPPA (Floris et al., 2015; González-Sánchez, et al., 2018).

Due to the association between lvPPA and Alzheimer's Disease (AD) neuropathology, the genetics of AD is also important to consider. *APP*, *PSEN1*, and *PSEN2* are known to cause AD and should be tested in patients with a family history of Alzheimer's dementia (see Loy, et al., 2014 for a review). For sporadic cases of AD, genetic variations of Apolipoprotein E (ApoE) should be examined. While most people have the ApoE E3/E3 genotype, people with E3/E4 and E4/E4 genotypes are three and eight times more likely to develop AD, respectively (Pericak-Vance & Haines, 2002; Karch & Goate, 2015). In contrast, individuals with the ApoE E2/E3 genotype have a 66%, 87%, and 99.6% lower odds ratio of developing AD compared to those with the ApoE E2/E3, ApoE E3/E3, and ApoE E4/E4 genotypes, respectively (Reiman et al., 2019).

Interestingly, some research suggests that unclassifiable PPA cases (where PPA criteria are met, but classification by clinical variant is not possible) or mixed PPA cases (where

classification criteria for two or more clinical variants are met) are more likely to have a genetic basis (Rohrer, 2014). Such unclassifiable and mixed PPA cases have been reported in 10-41% of patients across studies (Gil-Navarro, et al., 2013; Harris, et al., 2013; Mesulam, et al., 2012; Sajjadi, et al., 2012; Utianski et al., 2019).

Overview of Evaluation Procedures

Patient History

In current clinical practice, diagnosis and classification of PPA are determined by a clinician (typically a behavioral neurologist) based on the patient's history of symptoms and family history, a comprehensive evaluation of speech, language, and cognition, and clinical brain imaging. A detailed history helps to establish the symptom pattern at onset and the development of clinical features over time. Obtaining the patient's history usually involves an informal interview with the patient and/or their caregiver as well as medical chart review. The history should include the first symptoms observed; a timeline of symptom progression; how current symptoms impact activities of daily living; any concurrent psychiatric, memory, visuospatial, behavioral, and non-degenerative nervous system disorders; a developmental history with an emphasis on learning differences; and patient and family medical history.

There is great value in obtaining a clinical history directly from the patient, but severity of language and cognitive symptoms should be considered. Less impaired patients may be able to provide thoughtful insight regarding the onset and progression of symptoms. A patient interview also provides an opportunity for the clinician to begin forming impressions of the patient's ability to communicate. The following strategies can be applied when speaking with individuals with suspected PPA:

- Use simple, frequent, and literal words, because patients may have word or object knowledge loss (as in svPPA).
- Use short sentences, because patients may have impaired phonological working memory (as in lvPPA).
- Speak in sentences with canonical word order (e.g., subject-verb-object) and offer encouragement to use multi-modal communication such as writing, typing, or pointing to a picture board, because patients may have difficulty understanding complex grammatical structures and present with motor speech disorders (as in nfvPPA).
- For more severely impaired patients, a comprehensive interview may not be feasible, though the interaction can be shortened and used as an opportunity to build rapport.

During the interview or chart review, obtaining information regarding handedness and developmental history can be useful for the diagnostic team. Information about handedness may be relevant for interpreting imaging findings that deviate from the left-lateralized pattern of involvement typically observed in PPA. Additionally, a greater proportion of non-right-handed individuals with svPPA has been documented compared to the general population (Miller et al., 2013). Notably, a greater prevalence of developmental dyslexia has been observed in individuals with lvPPA relative to other PPA variants, and lvPPA patients with reported learning disabilities have been shown to have a relatively younger age-of-onset and better performance on global cognitive assessments than those without a significant developmental history (Miller et al., 2013, 2019). Since dyslexia is highly heritable (Darki et al., 2012), it may be informative to inquire about possible developmental learning differences in patients' first- and second-degree relatives, especially when the patient's neurodevelopmental history is unclear.

183

184 **Speech-language and neuropsychological assessment**

185 Skilled professionals in speech, language, and cognition, including SLPs and
186 neuropsychologists, should play an integral role in the diagnostic process. Specifically, SLPs'
187 expertise in communication disorders may be especially valuable in the detection and
188 characterization of subtle or complex speech and language features (see Henry & Grasso, 2018
189 for details on comprehensive assessment of speech and language in PPA), which is critical for
190 classifying a patient by PPA variant. For example, SLPs are trained in differentiating between
191 apraxic speech errors and phonemic errors in speech production, and assessing whether word
192 retrieval difficulty stems from degraded semantic, phonological, or motoric processes.

193 The domains examined in a comprehensive speech and language battery are listed in
194 *Table 1*, along with example tasks for assessing each domain and the expected behavioral pattern
195 for each PPA variant. Global assessments of speech and language function, such as the Western
196 Aphasia Battery – Revised (Kertesz, 2007), may help with determining overall severity and
197 identifying patterns of deficits, but should not be the sole instrument used for evaluating speech
198 and language symptoms. Because PPA diagnosis and classification by clinical variant require
199 confirmation of presence and absence of specific features, it is important for examiners to
200 evaluate multiple linguistic domains, including semantic, phonological and syntactic processing,
201 as well as written language and motor speech. The typical evaluation will comprise assessments
202 of spontaneous speech, confrontation naming, repetition, single-word and sentence
203 comprehension, verbal and nonverbal semantic processing, reading/spelling, and also a motor
204 speech battery comprising of tasks of varying articulatory difficulty (i.e., diadochokinesis as well
205 as production of syllables, multisyllabic words, phrases, and sentences).

Examination of cognitive abilities is also standard practice in an evaluation of PPA to rule out other diagnoses or to identify cognitive impairments that may have emerged during the progression of the disease. A cognitive screening tool, such as the Mini Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975), can provide a gross estimation of functional impairment. However, for PPA patients, the MMSE may overestimate the severity of cognitive impairments because the test heavily relies on language comprehension and production abilities. A standard neuropsychological evaluation should also include assessments of memory, learning, calculations, executive function, and visuospatial function (Kramer et al., 2003). In all three PPA variants, cognitive deficits arise during advanced stages of the disease. However, recent research suggests that visuo-executive deficits or dyscalculia may develop earlier in lvPPA (Ramanan, et al., 2019; Rohrer et al., 2010b; Tippett, et al., 2019; Watson, et al., 2018).

Subjective instruments can also be utilized during the evaluation to aid in the interpretation of more objective measures. The Geriatric Depression Scale (GDS; Yesavage, 1982) is a common questionnaire used for assessing mood in older adults, and can be helpful for contextualizing patient symptoms or performance. Clinicians can also use instruments, such as the Clinical Dementia Rating (CDR; Morris, 1993) scale, to characterize and monitor a patient's global level of impairment across multiple cognitive and functional domains. The CDR uses information from semi-structured interviews with the patient and a reliable informant (e.g., caregiver or spouse) to rate the domains of memory, orientation, judgement and problem solving, community affairs, home and hobbies, and personal care.

Brain Imaging

MRI and other types of brain imaging may provide context for behavioral findings and can rule out other neurological causes for observed deficits. MRI is a noninvasive method

commonly used for visualizing cortical and subcortical brain structures. For individuals with PPA, a structural MRI scan would be expected to show left-lateralized atrophy, indicated by cortical thinning and widening of sulci, in the syndrome-specific left hemisphere regions noted above.

Additional neuroimaging techniques may complement clinical evaluations and structural brain scans for a more definitive PPA diagnosis. Arterial spin labeling (ASL) MRI or single-photon emission computed tomography (SPECT) (which is less commonly used) can be used to measure blood flow, or perfusion, in the brain. Hypoperfused areas are indicated by regions of decreased blood flow, whether or not atrophy is observed. Similarly, PET imaging using the radioactive tracer F-18 fluorodeoxyglucose (FDG-PET) can localize regions of hypometabolism, or reduced glucose uptake, indicative of decreased neural function.

Important and emerging clinical applications of PET imaging involve the use of radioactive tracers to detect the presence of β-amyloid plaques and neurofibrillary tau tangle aggregation. For lvPPA, AD is the most common neuropathological finding on autopsy and is characterized by the brain's accumulation of both β-amyloid plaques and tau tangles, which trigger downstream neural dysfunction and atrophy (Chare et al., 2014; Kirshner, 2012; Mesulam et al., 2008; Rohrer, et al., 2012; Santos-Santos et al., 2018; Spinelli et al., 2017). Accumulation of β-amyloid plaques, which may occur decades before an individual develops clinical symptoms, can be detected with PET imaging using nuclear ligand tracers that selectively bind to β-amyloid plaques (i.e., "amyloid-PET" imaging). A "positive" amyloid-PET scan, illustrated by increased tracer uptake in the cortex relative to a reference region, such as the cerebellar cortex, is a strong indication for underlying AD neuropathology only when the individual has cognitive or language symptoms. Across the three PPA variants, high rates of amyloid positivity have been

observed in lvPPA, whereas high rates of amyloid negativity have been reported in svPPA and nfvPPA (Santos-Santos et al., 2018). Amyloid-PET images of asymptomatic individuals should be interpreted with caution because amyloid positivity has also been observed in cognitively healthy people over the age of 50 with no clear relationship between amyloid burden and cognitive abilities (Hedden et al., 2013).

Similar to amyloid-PET, aggregation of tau tangles can also be detected with PET imaging using nuclear ligand tracers that selectively bind to tau tangles (i.e., "tau-PET" imaging). However, unlike amyloid-PET, increased tau-PET tracer uptake in left posterior perisylvian regions has been strongly linked to the cognitive symptoms observed in lvPPA (Josephs et al., 2018; Osseenkoppele et al., 2016). To a lesser extent, tau-PET tracer uptake in left posterior inferior frontal areas has also been associated with symptoms in nfvPPA (Josephs et al., 2018; Tsai et al., 2019; Utianski et al., 2018). For svPPA, the utility of tau-PET imaging remains unclear (Josephs et al., 2018; Whitwell et al., 2019; Tsai et al., 2019).

CSF Biomarkers

Additional neuropathological evidence for AD can also be acquired by inspecting cerebrospinal fluid (CSF) for the 42 amino acid form of the amyloid-β peptide (Aβ42), total tau (t-tau), and phosphorylated tau (p-tau) (Blennow & Hampel, 2003; see Blennow et al., 2010 for a review). AD is indicated with a reduction of CSF Aβ42, a biomarker for Aβ metabolism and the formation of plaques (Fagan et al., 2006; Forsberg et al, 2008; Strozyk et al, 2003; Tapiola et al., 2009). Increased levels of p-tau in CSF is specific to AD pathology (Blennow, 2004), whereas high levels of t-tau in CSF are found in AD and other neurological conditions involving neuronal damage including stroke, traumatic brain injury, and Creutzfeldt-Jakob disease (Hesse et al.,

2001; Öst et al, 2006; Riemenschneider, et al., 2003; Tapiola et al., 2009). Extraction of these biomarkers is conducted by lumbar puncture: an invasive procedure involving the insertion of a needle into the spinal canal to extract CSF, a fluid that flows between the brain and spinal cord. A comprehensive review by Blennow et al. (2015) reported that within AD and prodromal AD, levels of Aβ42, p-tau, and t-tau is respectively half, double, or triple the amount seen in controls. A summary of typical neuropathological and imaging findings for the PPA variants is shown in Table 2.

Genetic testing

When behavioral and imaging findings are unclear, genetic testing is an additional tool that can be used to inform differential diagnosis. Genetic testing requires the patient to provide a biological specimen such as saliva or blood. A typical genetic testing procedure involves a buccal swab, in which cell samples are collected from inside the patient's mouth along their cheek. The chromosomes, proteins, and DNA from the cells are then examined for abnormalities. Genetic testing may be especially informative when findings from behavioral testing and neuroimaging are inconclusive.

In the following case report, we illustrate the components of a comprehensive PPA evaluation, including both standard assessments and state-of-the-art diagnostic procedures. We discuss the case of a 49-year old female patient who presented with progressive deterioration of speech and language that significantly affected activities of daily living and eventually led to her early retirement. She and her husband provided a developmental history, a timeline of symptoms, and information regarding her current functional status. Comprehensive speech, language, and cognitive testing was conducted. In addition, neuroimaging data were acquired which included a

high resolution structural MR brain image and amyloid-PET, tau-PET, and FDG-PET imaging. Finally, CSF biomarkers were obtained, genetic testing was conducted and a family history was gathered to provide additional information to inform diagnostic decision-making.

Case Report

Clinical History

DR was a right-handed, 49-year old retired pediatrician who was seen at the Memory and Aging Center at the University of California, San Francisco (UCSF) with a primary complaint of progressive word-finding difficulty. Onset of current symptoms began approximately five years prior to the evaluation. Her initial symptom was forgetting words during conversations but remembering them later, typically after a long delay. Her husband reported that she compensated for this difficulty by using words with similar meanings or sounds, or by simplifying her language during conversations. Over the next few years, language symptoms began to significantly impact her personal and professional life, and became noticeable to friends and colleagues. For example, she required assistance spelling familiar words, exhibited increasing forgetfulness for names of people and objects, and had difficulty sequencing tasks in a logical manner and following conversations. DR was first seen locally by a neurologist and neuropsychologist, at which time frontotemporal dementia was introduced as a potential diagnosis. However, FDG-PET results indicated reduced glucose uptake in posterior brain regions. Soon after, she was seen at a university hospital where she was given the diagnoses of Alzheimer's Disease (AD) and PPA.

Subsequent to the initial neurological evaluation, DR left her medical practice, and she and her husband both noticed a striking decline in her language over the course of approximately one

year. She spoke even less, used simpler language, began losing track of her own speech in conversations, and experienced greater difficulty with writing. She stopped driving and became more tearful. As the disorder progressed, she described several occasions where she experienced visual hallucinations in the form of shapes, figures, or fictional characters, but was aware they were not actually there. She was prescribed 15mg daily of donepezil and 10mg daily of citalopram, but these medications did not yield any change to her hallucinations. Her husband reported that citalopram, however, did result in slight improvements in mood.

Academic, Family, and Social History

DR's academic performance was reported to have been generally strong, although she mentioned spelling difficulty in childhood and stated that she failed calculus in medical school. She practiced medicine for nearly 20 years and specialized in pediatrics. At the time of her UCSF evaluation, she lived with her husband and two children. DR's family history was significant for several relevant factors. In her immediate family, one of her sons was diagnosed with dyslexia, and her mother reported a history of reading difficulty. Her maternal grandmother had memory loss in her later years, but lived past 100 years of age. Probable psychiatric illness was reported in one maternal relative, and an unspecified mental illness was indicated in one paternal relative.

Clinical Assessment

Throughout DR's evaluation at UCSF, she was loquacious, speaking excessively during and between testing sessions. Her behavior was gregarious and at times overly friendly, but she was interpersonally warm. On several occasions, she remarked that her husband is "good to look

at" and she became tearful when talking about how "the poet inside of [her is]…watching [her] self fade away." She frequently requested repetition of task instructions and auditorily-presented stimuli. In general, she required additional time to complete testing due to difficulty with the tasks and her insistence on finishing tasks as accurately as possible.

During neurological examination, DR struggled with imitating the Luria sequence (a sequence of three hand motions repeated three times), indicating some difficulty with motor sequence learning. On motor examination, no pronator drift was noted, but there was notable parietal/sensory drift upwards in the right upper extremity, indicating potential sensorimotor dysfunction. Muscle tone was normal. Rapid finger tapping was slightly slower on the right compared to the left and reflexes were more brisk on the right compared to the left, both consistent with asymmetric involvement of the left motor system. However, there was no evidence of snout, rooting, jaw-jerk, palmomental, Hoffman's or grasp reflexes, indicating relatively normal involuntary motor responses to sensory stimuli. Hearing was intact to finger rub bilaterally.

Tables 3 and 4 show a detailed summary of scores from neuropsychological and speech-language assessments. On the Geriatric Depression Scale (Sheikh & Yesavage, 1986), she scored 17 out of 30 points, indicating mild depression. On a global test of cognition (Mini-Mental State Examination; MMSE; Folstein, Folstein, & McHugh, 1975), DR earned a score of 19 of 30 points. She lost points on items involving orientation to time and place, verbal memory, and phrase repetition. Digit span forward was 4 and backward was 2. She demonstrated poor immediate and delayed verbal recall of a list of words (California Verbal Learning Test – Short Form; CVLT; Delis et al., 1987); on recognition of a list of words, she identified all words from the list but also selected 10 false positive distractors. Visual memory performance was impaired

and her approach was disorganized. She drew 7 of 17 components of a complex figure 10 minutes after copying it; however, she was able to recognize the correct figure from a field of 4 choices. She was unable to understand the verbal instructions on a test of executive function which required her to alternate between ascending numbers and sequential days of the week (modified Trails B). DR was also unable to do the Stroop inhibition task where she needed to name the ink color for color words while inhibiting reading the word itself (e.g., the word "blue" written in the color red). DR was accurate on only 2 of 5 simple arithmetic problems. Copy of the complex figure was largely accurate, but she performed poorly on the digit location subtest of the Visual Object and Space Perception battery. In summary, impaired performance was observed in memory and learning, executive function, and arithmetic, and results were mixed on assessment of visuospatial abilities.

With regard to speech-language assessment, DR showed impairments across several tasks, including spontaneous speech, auditory verbal comprehension, repetition, and naming. On a general speech-language measure (Western Aphasia Battery – Revised; WAB-R; Kertesz, 2007), her aphasia quotient was 75.3/100. DR spoke at a relatively normal rate and her speech was well-articulated, with no evidence of motoric impairment. Spontaneous speech was tangential and prominent anomia was observed, with frequent pauses, mazes, revisions, phonological errors and paraphasias, and circumlocutions. For example, when asked to describe herself as a student, she said:

> *I am a…I'm...I don't have any siblings. Um I've always been…um…uh an A…student. Um…I've always been…um a science person from you know…My my parents didn't know what to do with that because they…were both more…they're both teachers. And you know…they had not…you know sometimes in the…later stages when you um…uh...you know like…when it's like high school or something like that you can…have different things but…m-my dad…um…was in the…uh um you know in the…the higher up…kind of stuff.*

No apraxia of speech or dysarthria was observed during a motor speech examination. Auditory comprehension was unimpaired for yes/no questions, but comprehension difficulty was noted on multi-step commands. Repetition of simple words and common phrases and sentences was relatively accurate, but she struggled with repeating multi-syllabic words and uncommon and non-meaningful phrases and sentences. Confrontation naming performance was impaired on the Boston Naming Test (Kaplan, Goodglass, & McCabe, 2001), with errors primarily consisting of semantic and phonological paraphasias and circumlocutions. Phonemic cues were beneficial for 6 out of 12 object names. Generative naming of animals (semantic fluency) and words beginning with the letter “d” (phonemic fluency) were also poor, as she was only able to produce four of each within one minute. However, lexical retrieval was less impaired during sentence completion and in response to wh-questions on the WAB-R. Her performance across these tasks indicated an underlying severe verbal short-term memory and lexical retrieval deficits.

With regard to semantic processing, DR made only a few errors on auditory word-to-picture matching tasks (WAB Auditory Word Comprehension, and a shortened version of the Peabody Picture Vocabulary Test; Dunn & Dunn, 1981) as well as a written emotion-to-face matching task. She demonstrated some impairment on a test of semantic associates (Pyramids and Palm Trees, Howard & Patterson, 1992) which involves selecting one of two pictures (e.g., palm tree and pine tree) that is more closely related to a target picture (e.g., pyramid).

Phonological manipulation tasks presented the most striking difficulty for DR across all language assessments. These tasks included deleting or replacing a phoneme from a word/pseudoword to create a new word/pseudoword, and blending three sequential phonemes into a word/pseudoword (Arizona Phonological Battery; Henry et al., 2016; Rapcsak, et al., 2009). Her performance ranged from 20-45% accuracy. DR was impaired on both reading and

spelling tasks (Arizona Reading and Spelling Battery; Beeson, et al., 2010). She exhibited the greatest difficulty on reading and spelling of irregular words (e.g., *consion* for "conscious," *suble* for "subtle" in spelling) as well as spelling pseudowords. Passage reading was slow due to frequent pauses and numerous attempts at self-correcting phonemic paralexias. Performance on syntax comprehension (auditory sentence-to-picture matching; Wilson, et al., 2010) was relatively better than syntax production (shortened version of the Northwestern Anagram Test; Thompson, Weintraub, & Mesulam, 2011), but both scores indicated some impairment. For syntax comprehension, complex or long sentences were particularly difficult for her. It should be noted that the syntax production task required her to order word cards to create a sentence that matched a picture. Given the executive demands of this task, DR's poor performance is consistent with her difficulty with executive function tasks from the neuropsychological assessment.

Imaging and CSF Results

The neurologist's review of the structural MRI scan noted the presence of bilateral temporoparietal atrophy dorsally and posteriorly, with greater involvement of the left hemisphere than the right. Mild atrophy was also noted in bilateral hippocampi and anterior temporal lobes. *Figure 1* shows the structural MRI scan with representative axial and coronal slices. In addition to the clinical review of the MRI scan, results from a single-subject voxel-based morphometry (VBM) analysis[1] compared DR's brain to those of a control group of N=534 neurologically healthy adults (age range 44-99 years of age, Mean±SD: 68.7±9.1; 302 Females; see

[1] Quantitative analysis of a structural MRI is not standard practice in routine clinical settings, but is sometimes employed in academic medical settings to supplement the neurologist or radiologist's impression with a data-driven analysis.

supplementary methods for more details). *Figure 2* shows statistically significant differences between DR's brain and a control group using a standardized W-score (similar to a Z-score, but regresses out effects of age, gender, total intracranial volume, and scanner type; Ossenkoppele, et al., 2015). VBM results demonstrated the greatest reduction in gray matter relative to controls in the left inferior parietal lobe, including bilateral angular and supramarginal gyri, with extension into the left postcentral gyrus anteriorly and left superior parietal lobe dorsally. Significant reductions in gray matter volume were also identified in left middle and inferior temporal gyri, extending posteriorly to fusiform and inferior occipital gyri. Atrophy was also noted in left superior frontal gyrus, insula, heschl's gyrus, superior temporal gyrus, and middle cingulum cortex. Significantly atrophic right hemisphere regions included the rolandic operculum, superior temporal gyrus, and supramarginal gyrus.

Amyloid-PET imaging was positive, as indicated by high standardized uptake value ratios (SUVR) across the cortex (see *Figure 3 left panel* with results from a 64 year-old cognitively-normal female for comparison). The SUVR measure indicates the tracer's binding to β-amyloid plaques in the cortex relative to the radiotracer's binding in the cerebellum, typically devoid of β-amyloid plaques until very late stages in AD. In a cognitively healthy individual, one would expect limbic and heteromodal cortices (regions affected in AD) to show lack of the tracer's binding, i.e., present a clear contrast between gray and white matter (Dickerson et al., 2009; La Joie et al., 2012; Landau et al., 2009). However, *Figure 3* (*top row, left panel*) demonstrates that DR's amyloid-PET scan was diffusely positive in the cortical gray matter, with SUVR greater than 2.5 in some frontal regions, and a general loss of gray-white matter contrast.

Tau-PET results showed very elevated binding in fronto-temporo-parietal regions bilaterally and also in the posterior cingulate and precuneus. These findings were consistent with the

neurologist's assessment of the structural MRI scan. For tau-PET, the SUVR indicates the tracer's binding to neurofibrillary tau tangles aggregates in the cortex relative to uptake in the inferior cerebellum. Again, higher than normal SUVR values were observed in the tau-PET scan (*Figure 3, middle panel* with results from the same 64 year-old cognitively-normal female for comparison).

Evaluation of the FDG-PET images primarily revealed hypometabolic areas in temporal, parietal and frontal regions, findings which were greater in the left than the right hemisphere (*Figure 3, right panel* with results from an age-matched, 49 year-old cognitively-normal female for comparison). FDG-PET SUVR values indicate brain glucose utilization as compared to glucose uptake in the pons. The brain was more hypometabolic dorsally and posteriorly in comparison to ventral and anterior areas. Details regarding methodology for MRI and PET imaging and analyses can be found in supplementary methods.

CSF biomarkers indicated that the level of Aβ42 peptide in the CSF was approximately half of that seen in controls. While the level of p-tau was nearly three times greater than the control level, the level of t-tau was almost six times greater. These results were consistent with probable AD neuropathology.

Genetic Testing Results

DR was tested for common pathogenic variants of gene mutations known to cause dementia. She was negative for pathogenic variants associated with AD including *APP*, *PSEN1*, and *PSEN2*, as well as negative for those associated with FTD including *C9ORF72*, *GRN*, and *MAPT*. Results showed she was ApoE 3/3, a finding which is not associated with dementia.

Lastly, findings were also negative for *TARDP* and *FUS*, both of which are associated with FTD and ALS.

Discussion

This case report illustrates a comprehensive and multidisciplinary evaluation conducted with a 49-year old female with complaints of progressive word-finding difficulty. Taken together, the assessments revealed a complex early-onset, non-genetic case of probable AD with an initial lvPPA syndrome. The following discussion will elaborate on the interpretation of findings from DR's comprehensive evaluation and examine how they relate to her PPA diagnosis.

The first step in the diagnostic process was determining whether DR met diagnostic criteria for PPA. Her most prominent clinical feature and primary complaint were her difficulties with speech and language, specifically, pervasive word-finding difficulty. At symptom onset, she and her caregiver reported behaviors consistent with word-finding difficulty in conversation including semantic and phonemic paraphasias and circumlocution. Importantly, aphasia was the most prominent symptom in her clinical presentation at onset and her speech and language symptoms worsened to the point where she struggled in socializing and completing everyday work responsibilities. The clinical team determined that this patient satisfied the diagnostic inclusion criteria for PPA.

Ruling out exclusionary factors for PPA required careful consideration. This is often the case when a patient is assessed several years post-onset and the diagnostic team must tease apart symptoms that were likely predominant at disease onset from symptoms that arose during the evolution of the disease. DR's medical history and clinical presentation did not indicate a non-

degenerative nervous system or medical disorder, nor a prominent initial behavioral disturbance, and psychiatric status was assessed to be within normal limits. To establish that the patient's speech-language symptoms were isolated enough to meet PPA criteria, the diagnostic team needed to discern whether the patient had prominent initial episodic memory, visual memory, and visuo-perceptual impairments, given her poor performance on tests of verbal memory and learning, executive function, arithmetic, and visuospatial abilities. In individuals with PPA and probable or definite AD pathology, episodic and visual memory impairments typically emerge with progression of the disease (Rohrer, Rosser, & Warren, 2012). Findings from recent studies also suggest that visuo-executive deficits are prevalent in the logopenic variant of PPA rather than a symptom of disease progression (Ramanan, et al., 2019; Tippett, et al., 2019; Watson, et al., 2018). Similarly, dyscalculia is frequently observed in the logopenic variant of PPA and typically present in other parietal lobe syndromes (Rohrer et al., 2010b). Considering DR's overall history and pattern of symptoms, the diagnostic team ultimately concluded that her cognitive impairments were not exclusionary and agreed that she satisfied criteria for PPA.

With regard to classification by clinical variant, the diagnostic team was confident that DR did not meet core criteria for nfvPPA. This diagnosis requires the presence of either agrammatic language production or effortful/halting speech with inconsistent speech sound errors and distortions (apraxia of speech). Examination of her spontaneous speech revealed intelligible, grammatical speech disrupted by frequent word-finding difficulty. In addition, the motor speech exam was unremarkable.

We considered the remaining two PPA variants, each of which presents with prominent anomia but with a different underlying cause of impairment. In DR's case, the underlying deficit appeared to be more phonological than semantic. Lexical retrieval errors and phonological

paraphasias in spontaneous speech and confrontation naming were pervasive and prominent, and her repetition impairment followed a classic pattern typically seen in logopenic variant PPA. It was relatively easier for her to repeat long, overlearned phrases on the Bayles Repetition Test (Bayles et al., 1996) (*That must have…costed…cost…ugh…it must have been a pretty penny* for "That must have cost a pretty penny") as compared to non-meaningful phrases that were either short (*Cracked emanel enam emmanual I can't get that word* for "Cracked enamel surface") or long (*Something about um…* for "Loud ambassadors freeze stable waves"). Generally, repetition is relatively preserved in semantic variant PPA. DR also demonstrated difficulty carrying out sequential commands, a very reduced digit span, and impaired performance on the comprehension of long, complex sentences as well as phonological manipulation tasks. This pattern is consistent with phonological working memory impairment.

On the Arizona Battery of Reading and Spelling, DR demonstrated a pattern of overregularization errors (/pɪnt/ for *pint*) and phonologically implausible errors (temenant for *tenement*). However, her developmental and family history raised the possibility of an undiagnosed developmental reading disability, making it difficult to fully interpret the nature of these errors. Developmental learning disorders such as dyslexia are more prevalent in the logopenic variant of PPA compared to other variants (Miller et al., 2013; 2018). Although DR also presented with some evidence of semantic deficits, these impairments were much less pronounced. She made a few errors on the WAB Auditory Word Recognition subtest and shortened version of the PPVT-R, and several errors on the Pyramids and Palm Trees test. However, it is possible that impaired executive functioning affected her ability to complete these tasks, which required selecting a target from an array of distractors. Participants with executive function deficits may fail to inhibit distractors, or may have difficulty orienting to the task for

non-semantic reasons. The latter was observed on the Pyramids and Palm Trees test, as DR required frequent verbal reminders to select which of the two pictures on the bottom "goes best" with the one on top.

The neuroimaging and CSF results provided additional helpful information to inform DR's diagnosis. Positive amyloid-PET and tau-PET scans, reduced levels of Aβ42, and elevated levels of total tau and phosphorylated tau indicated probable underlying AD pathology, which is most associated with lvPPA. A common pattern of results across the structural MRI and FDG-PET images showed neurodegeneration in bilateral posterior temporoparietal cortices typically affected by the disease, with both FDG-PET and VBM results showing more pronounced neurodegeneration in the left posterior parietal cortex compared to the right. Asymmetry in the FDG-PET and VBM results were consistent with a similar asymmetry observed on tau-PET, which showed left greater than right binding in temporoparietal regions. The VBM analysis and FDG-PET results also showed that the left inferior occipital gyrus was affected, which may be linked to DR's visual hallucinations (Holroyd, et al., 2000).

Results from DR's genetic testing were unremarkable, but did rule out a clear genetic contribution to her disease. Her clinical and neuroimaging results strongly indicated early-onset AD (EOAD; younger than age 65), and her genetic testing results demonstrated that her syndrome was not caused by dominantly inherited genes associated with the disease (e.g., Chartier-Harlin, et al., 1991; van Duijin et al., 1994). She had the typical ApoE E3/E3 genotype, and was negative for any other dementia-related genetic mutations including *TARDBP*, *C9ORF72*, *GRN*, *MAPT*, *FUS*, *APP*, *PSEN1*, and *PSEN2*. Together with findings from the clinical evaluation, the diagnostic team determined that DR's current presentation of symptoms

was consistent with an initial lvPPA syndrome and EOAD pathology with predominant language symptoms, followed by the emergence of executive and memory difficulties.

Following DR's diagnosis, we provided the patient and family with several recommendations to facilitate and promote communication, which continued to be her most prominent area of difficulty. We encouraged DR's caregiver to monitor her hearing ability since degraded auditory input will exacerbate auditory comprehension difficulties. We advised that communication partners speak to DR in short sentences no longer than 4-5 words, as this was her maximum forward digit span. We suggested that she continue participating in her local AD support group and dementia advocacy support group as these social activities can enrich patients' daily lives with community and purpose, and may alleviate some depressive symptoms. We also recommended that she increase her dosage of citalopram to 20mg daily to target mood and daytime fatigue. Finally, she and her husband decided to enroll in our restitutive speech-language treatment research program aimed at improving object naming in svPPA and lvPPA (see Henry et al., 2019 for details on lexical retrieval treatment). Briefly, the 10 week treatment included twice weekly sessions with an SLP augmented by daily homework which, together, provided guided, structured and functional lexical retrieval practice. The benefit of treatment was demonstrated in improved confrontation naming accuracy for trained and untrained words at post-treatment: she improved from 25% to 90% accuracy for trained object names, and modestly improved from 33% to 50% accuracy for untrained objects. Subjectively, she endorsed decreased word-finding difficulties and reduced frustration on a post-treatment survey.

Conclusion

In summary, this report outlined a comprehensive PPA evaluation using an illustrative case of a patient with suspected PPA. We have highlighted the critical diagnostic procedures and complex points of discussion that contributed to DR's diagnosis. Advances in clinical research and diagnostic procedures are of paramount importance for detecting PPA as early as possible and for identifying the likely pathological basis, particularly in cases that are behaviorally complex or mixed in their speech-language presentation. Neural and genetic biomarkers provide objective measures that can significantly contribute to clinical diagnosis, affording opportunities for beneficial treatments. As this case highlights, evidence-based treatment of PPA can have positive effects in mild to moderate cases (e.g., Beeson et al., 2011; Henry et al., 2018; Henry et al., 2019; Jokel et al., 2016), and this underscores the importance of early and accurate diagnosis and timely speech-language intervention.

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Supplemental Material

Supplementary document: The authors provided detailed methods of the MRI and PET acquisition and analyses.

Figure Captions

Figure 1: Arrows highlight the neurologist's review of the DR's structural MRI brain scan. The doctor indicated greater atrophy in the left hemisphere compared to the right. The left and middle images shows parietal atrophy on axial and coronal views, respectively. The right image highlights anterior temporal lobe (top arrows) and hippocampal atrophy (bottom arrows).

Figure 2: Single-subject voxel-based morphometry analysis of DR compared to a group of neurologically healthy adults. More negative W-score indicates more difference from control group after regressing out for age, years of education, and scanner type.

Figure 3: Amyloid-, Tau- and FDG-PET results from DR (top row), amyloid- and tau-PET results from a 64-year old cognitively-normal female control participant (bottom row, left and middle panels) and FDG-PET from an age-matched (49-year old) female control participant (bottom, right panel).

Figure 1.

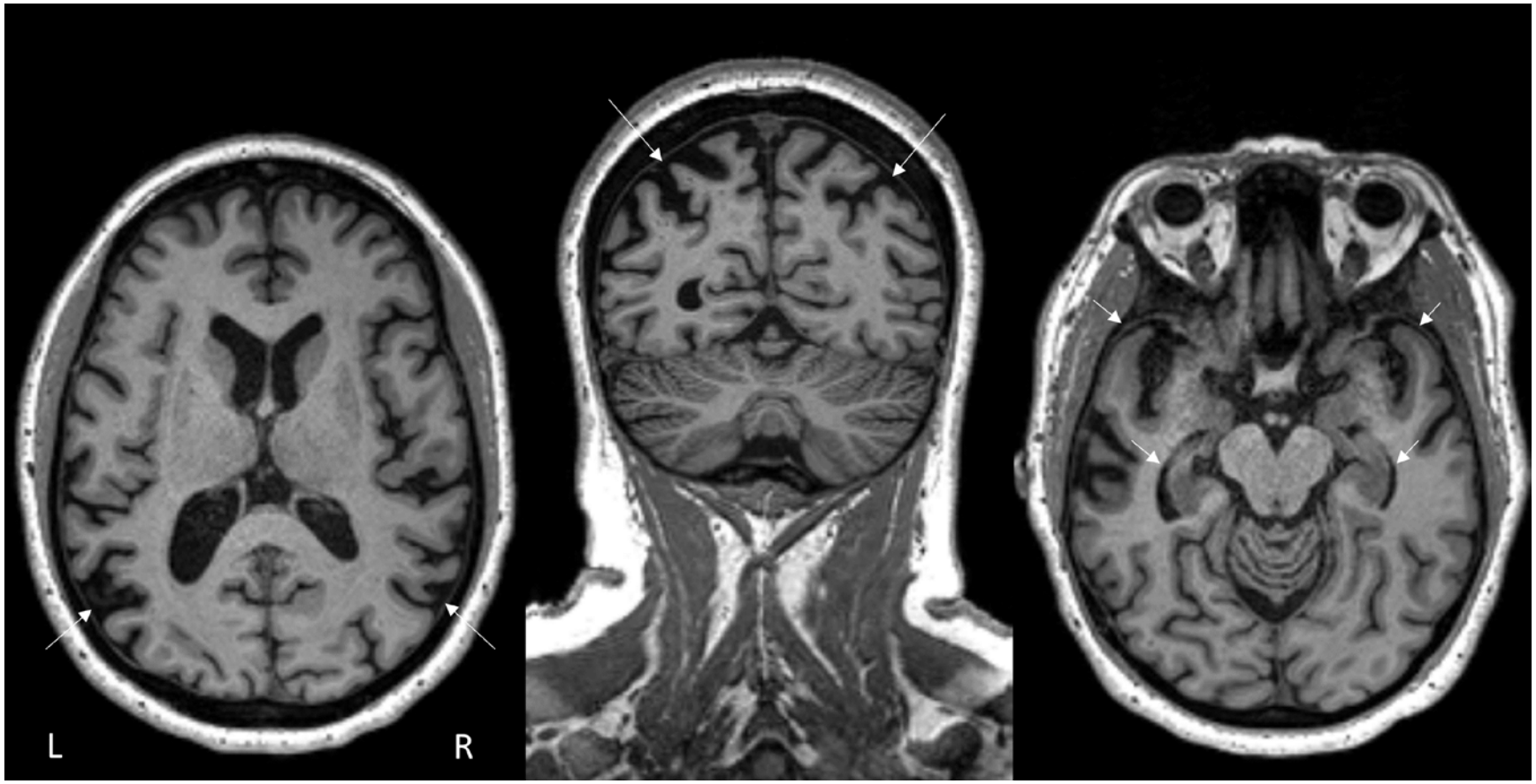


Figure 2.

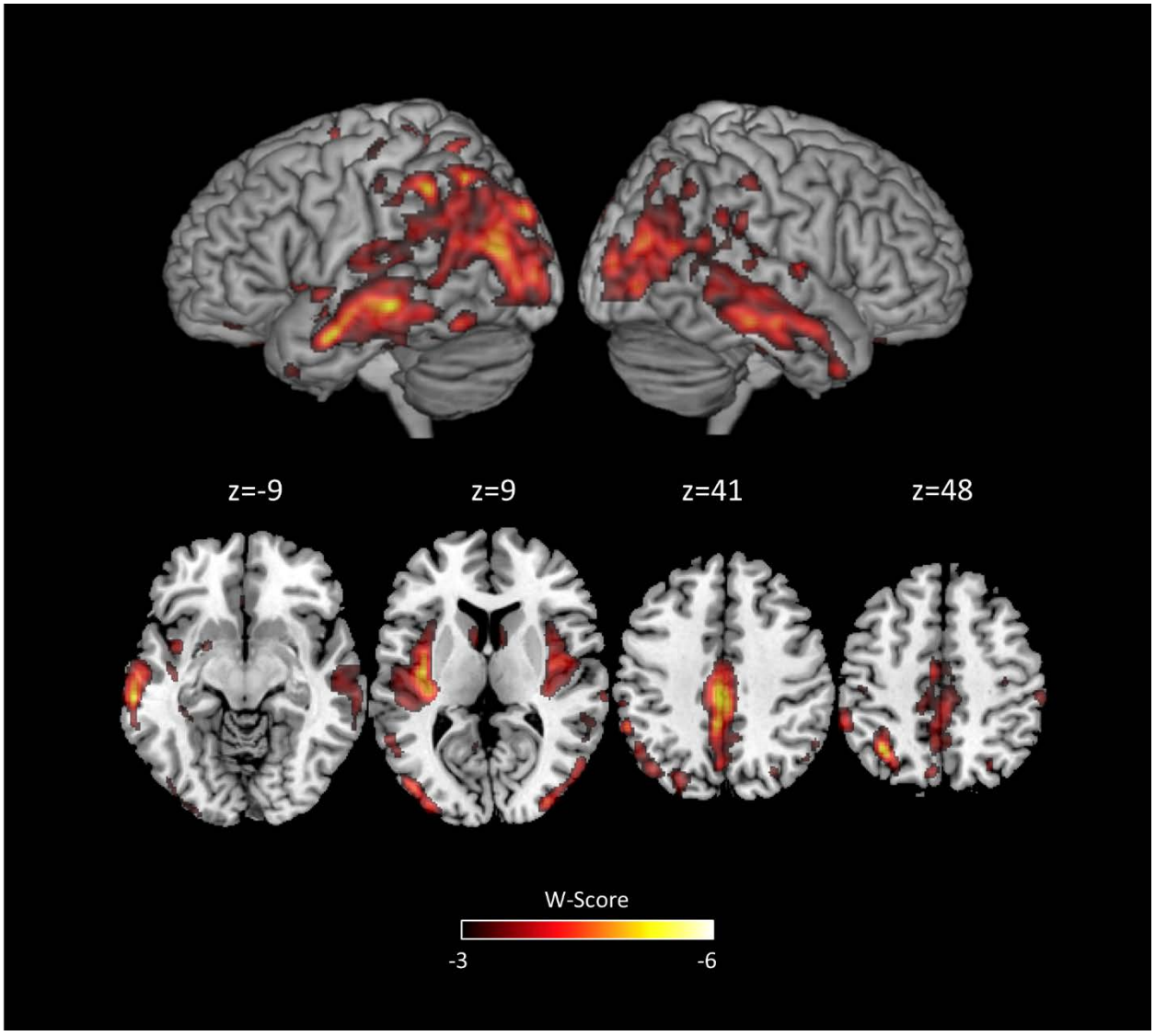
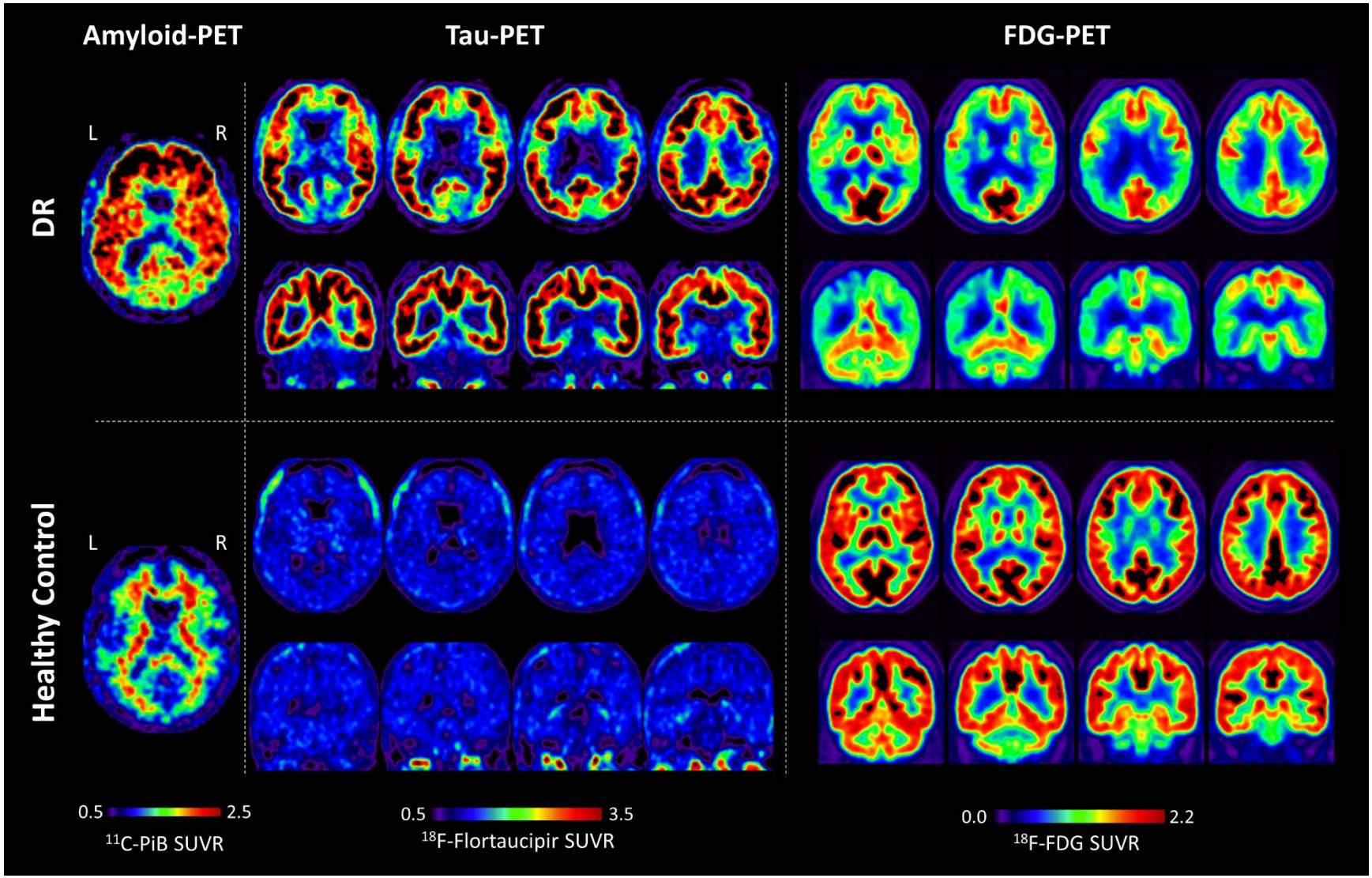


Figure 3.


Amyloid-PET
Tau-PET
FDG-PET
DR
Healthy Control
L
R
L
R
0.5
2.5
11C-PiB SUVR
0.5
3.5
18F-Flortaucipir SUVR
0.0
2.2
18F-FDG SUVR