Universitat Autònoma de Barcelona

# Clinicopathologic correlations and neuroimaging biomarkers in primary progressive aphasia

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**CERTIFICATE OF DIRECTION**

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**CERTIFY:**

That the thesis titled "Clinicopathologic correlations and neuroimaging biomarkers in primary progressive aphasia" was carried out under our supervision and meets all the requirements necessary for the doctoral candidate to proceed to its defense before the corresponding tribunal.


| Maria Luisa Gorno-Tempini | Juan Fortea Ormaechea | Antonio Escartín Siquer |
|---|---|---|
| *Memory and Aging Center, University of California San Francisco* | *Memory Unit, Hospital de la Santa Creu i Sant Pau* | *Professor of Neurology, Hospital de la Santa Creu i Sant Pau* |


June 27th, 2017

*To the patients and families whose amazing effort and patience made this research possible*

*A mi familia, a mis dos princesitas*

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## GLOSSARY OF ABBREVIATIONS

**AD** Alzheimer's disease

**APOE** apolipoprotein E gene

**CBD** corticobasal degeneration

**CSF** cerebral spinal fluid

**[$^{18}$F]AV45** florbetapir compound

**FTLD** frontotemporal lobar degeneration

**FUS** fused-in-sarcoma (FUS) protein

**GM** grey matter (brain)

**lvPPA** logopenic variant primary progressive aphasia

**nfvPPA** non-fluent/agrammatic variant primary progressive aphasia

**PPA** primary progressive aphasia

**PET** Positron Emission Tomography

**PIB or [$^{11}$C]PIB** Pittsburgh compound B

**PSP** progressive supranuclear palsy

**SUVr** standardized uptake value ratios

**svPPA** semantic variant primary progressive aphasia

**TDP-43** TAR DNA-binding protein of 43 kDa

**VBM** Voxel based morphometry

**WM** white matter (brain)

# III. INTRODUCTION

# INTRODUCTION

## A. DEFINITION & HISTORY

Primary progressive aphasia (PPA) is a clinical entity differentiated from other forms of neurodegenerative disease in that language difficulty is the most prominent clinical feature as well as the primary cause of functional impairment at onset and during the first years of disease. It is caused by degeneration of the language network and recent neuroimaging studies have established the association between particular patterns of neuroanatomic damage and clinical presentation (Gorno-Tempini, Dronkers, et al., 2004).

The term aphasia denotes a heterogeneous clinical disorder characterized by impaired language function due to lesions of the brain. The neural network responsible for language function is composed of different areas whose dysfunction results in differentiable behavioral manifestations. These differences have been extensively studied since Paul Broca's first description in the 1890s of a patient who could understand language but couldn't speak due to a lesion in the inferior part of his left frontal lobe caused by a stroke. Clinical aphasiology has progressed greatly in this last century, primarily from the study of stroke patients as neurovascular disease is the most common cause of aphasia. Our knowledge of the biology of language has evolved alongside clinical aphasiology, and, as a result, is biased towards explaining the mechanisms of the symptoms presented by "stroke aphasics." Aphasia due to neurodegenerative disease appears gradually and then advances progressively in contrast to a strokes abrupt onset, maximum initial impairment, and later recovery. The pathological mechanisms at work in degenerative disease are not determined by the anatomy of the neurovascular system and thus injure other areas of the language network, resulting in different clinical presentations.

Arnold Pick published the first case of a progressive disorder of language associated to atrophy of the left frontal and temporal lobes in the 1890s (Pick, 1892), but these forms of progressive aphasia did not attract much scientific attention until Mesulam published his landmark paper in 1982 "Slowly progressive aphasia without generalized dementia (M. Mesulam, 1982)." In the ensuing years various reports appeared (Kirshner, Tanridag, Thurman, & Whetsell, 1987) describing cases of progressive language impairment associated to an "unspecific" neurodegenerative process with distinct pathological features than those seen in Alzheimer's Disease (AD). Warrington was the first to describe a patient with progressive loss of semantic knowledge in 1975 (Warrington, 1975) but it was Snowden et al (J. S. Snowden, Goulding, & Neary, 1989) who coined the term "semantic dementia" in 1989 to describe a progressive disorder of semantic memory that manifested as a "fluent" aphasia. A "non-fluent" form of progressive aphasia characterized mainly by a disorder of expressive grammar was described by Grossman et al in 1996 (M Grossman, Mickanin, Onishi, & al, 1996). For many years the cases of what became known as "Primary progressive aphasia" (M M Mesulam & Weintraub, 1992) were classified as semantic dementia or progressive non fluent aphasia or more generally as fluent vs non fluent aphasia and, as knowledge of clinicopathological correlations progressed, both forms of PPA were included in the 1998 consensus FTLD clinical diagnostic criteria (Neary et al., 1998) with the aim of improving the ability to discriminate AD and non-AD neurodegeneration during life. However, in the following years it became evident that a substantial proportion of cases of semantic dementia and non-fluent aphasia presented AD at autopsy (Galton, Patterson, Xuereb, & Hodges, 2000; Kertesz & Munoz, 2003; Kramer & Miller, 2000; Li et al., 2000) and that the fluent vs non-fluent scheme did not adequately describe all cases of PPA. In 2004, a third form of PPA was delineated and named logopenic variant (lvPPA) (Gorno-Tempini, Dronkers, et al., 2004). Speech production in lvPPA was characterized by frequent word-finding pauses along with segments of normal speech thus falling in

between the previous fluent vs non-fluent divide and phonological short-term memory impairment was the main cause of repetition and comprehension difficulties. The posterior pattern of atrophy, and early biomarker and pathological studies suggested that lvPPA might be primarily caused by AD (M. Mesulam et al., 2008; Gil D. Rabinovici et al., 2008).

Currently, there are 3 commonly recognized clinical phenotypes of PPA though other less frequent forms of presentation have been described (Perez et al., 2013). Patients with the nonfluent/agrammatic form (nfvPPA) typically show atrophy in the left posterior frontal and insular regions, those with the semantic variant (svPPA) display bilateral anterior temporal lobe volume loss with a typical asymmetrical predominance, and left temporal-parietal regions show the most atrophy in the logopenic variant (lvPPA) (see Figure-3.1). The classification of PPA cases into these clinical-anatomical phenotypes is of great importance because they are linked to different prevalence of underlying pathology.

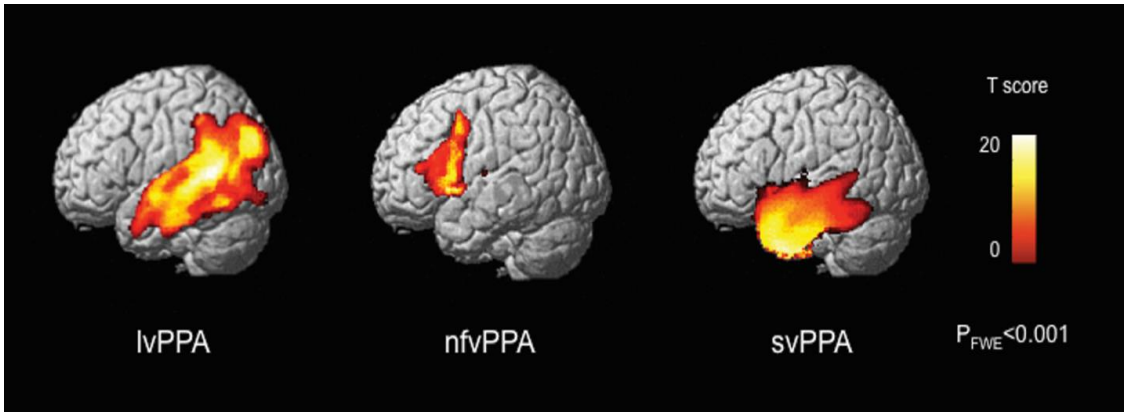



***Figure-3.1: Pattern of atrophy in Primary Progressive Aphasia Variants versus Controls***
*Statistical parametric maps show patterns of gray matter atrophy in lvPPA (n = 24), nfvPPA (n = 40), and svPPA (n = 58) compared to their relative healthy control groups*

*matched for age, gender, scan, and sample size. Voxel based morphometry results are thresholded at $P_{FWE} < 0.001$.*

**B. PATHOPHYSIOLOGY, GENETICS, AND EPIDEMIOLOGY.**

The correlation between the clinical presentation and anatomic area of damage is more reliable than the clinical-anatomic presentation's correlation to the underlying pathology. Most cases of PPA at autopsy display Frontotemporal Lobar Degeneration-type (FTLD) or Alzheimer's disease (AD) pathology (M M Mesulam, Grossman, Hillis, Kertesz, & Weintraub, 2003). FTLD refers to a heterogeneous group of pathological disorders which can be classified according to the cellular inclusions present. In recent years FTLD has been shown to classify into 3 major groups, those with tau-positive (FTLD-tau), TAR DNA-binding protein of 43 kDa (TDP-43) positive (FTLD-TDP), and fused-in-sarcoma (FUS) protein positive inclusions (Mackenzie et al., 2010). These 3 pathologic groups underlie the various syndromes that constitute the clinical FTD-spectrum. Recent studies generally agree on the preferential association of each clinical variant to a particular underlying pathology: FTLD-tau in nfvPPA, FTLD-TDP in svPPA, and AD pathology as well as in vivo biomarkers suggestive of AD (PET-PIB positivity and decreased AB42 and increased tau in cerebral spinal fluid [CSF]) in lvPPA (Murray Grossman, 2010; Josephs et al., 2011; Leyton et al., 2011; M. Mesulam et al., 2008; Gil D. Rabinovici et al., 2008); however, no study has ever established a direct correspondence of a clinical presentation to any pathology indicating that the correspondence between clinical syndrome and pathology is not absolute. Future work may refine this relationship, however, this also suggests that certain neural networks may display only relative vulnerability for different pathologies (Seeley, Crawford, Zhou, Miller, & Greicius, 2009).

PPA is primarily a sporadic disease but cases due to dominantly inherited genetic mutations also exist. The explosion of knowledge in FTLD genetics of the last decade has sparked great interest in characterizing the clinical phenotype and neuroimaging features of genetically inherited PPA. Most of these cases are due to a mutation on chromosome 17 in the Progranulin (GRN) gene or in the microtubule associated protein tau (MAPT) gene (M. Mesulam et al., 2007; J. S. Snowden et al., 2006; van Swieten & Spillantini, 2007). Similar to the clinical presentation's probabilistic relationship to pathology, its relation to genetics is also unclear. In fact, the same dominantly inherited mutations can cause different clinical syndromes in the same family (M. Mesulam et al., 2007; Simon-Sanchez et al., 2012; J. S. Snowden et al., 2006). These genetic cases generally exhibit a more global form of aphasia and it is not clear how they will fit in the recently established diagnostic criteria. The search for factors responsible for the language network's selective vulnerability to disease is a burgeoning topic. Other non FTLD genes, such as Apolipoprotein E gene (ApoE) and forkhead box P2 gene (FOXP2) are being studied because they might confer increased risk of developing PPA (Premi et al., 2012; E. J. Rogalski et al., 2011). Non genetic risk factors such as the presence of childhood learning disabilities have also been linked to PPA (E. Rogalski, Weintraub, & Mesulam, 2013). A recent study has detailed that a history of developmental learning disability is specific to the logopenic variant, whereas there was an increased prevalence of non-right-handedness in the semantic variant population and a decreased prevalence of non-right-handedness in the nonfluent/agrammatic variant. Together these findings have suggested that there may be differential neurodevelopmental trajectories towards disorders of the language network (Miller, Mandelli, et al., 2013). Further, another study also showed an association with non-thyroid autoimmune disorders within the semantic variant PPA suggesting a potential role for chronic inflammation as a risk factor for developing this condition (Miller, Rankin, et al., 2013).

Epidemiologic data on PPA are scarce; however, an estimate may be inferred by considering studies on frontotemporal dementia for which a prevalence of about 15 cases per 100,000 people has been calculated (Onyike & Diehl-Schmid, 2013). According to various clinicopathologic studies describing case series of FTLD, around 45% of FTLD present as PPA, about half of which are of the non-fluent variant (Josephs et al., 2011; J D Rohrer et al., 2011). The PPA cases associated to Alzheimer's disease pathology must be added for a more complete estimate of prevalence. PPA is listed as a "rare disease" by the Office of Rare Diseases (ORD) of the National Institutes of Health. There is some evidence suggesting that demographic characteristics may vary according to clinical phenotype. One study of 353 FTLD cases found svPPA to have an earlier onset (mean age, 59.3 years) and affect men more frequently (66.7%) while nfvPPA started at a later age (mean age, 63.0 years) and affected more women (Johnson et al., 2005) but this finding has not been confirmed in more recent studies (Ioannidis, Konstantinopoulou, Maiovis, & Karacostas, 2012). What seems clear is that PPA generally appears at a younger age than the most frequent amnestic form of Alzheimer's disease (Gao, Hendrie, Hall, & Hui, 1998).

**C. DIAGNOSTIC CRITERIA.**

In 2011, an international consortium of investigators established the classification scheme for the three most common variants of PPA (Gorno-Tempini et al., 2011). These guidelines reflected the accumulated knowledge of the patterns of cognitive impairment, brain atrophy and underlying pathology typically associated to each clinical variant and represented a collective effort to increase comparability between studies and eventually improve the ability to predict the underlying pathology. Since their redaction, numerous investigations have been carried out within each of the three main

PPA variants greatly advancing knowledge of the neurobiology of language and clinicopathological relationships in neurodegenerative disease.

International diagnostic guidelines have been established recently and are summarized in table-3.1. Diagnosis requires an initial diagnosis of PPA and subsequent classification into one of the clinical variants. An insidious onset and a gradually progressive and relatively isolated impairment of language functions are required for a diagnosis of PPA. Once a PPA diagnosis is established, the relative presence or absence of salient speech and language features should be considered to classify PPA variants. Classification of PPA into one of the variants may occur at one of three levels: clinical, imaging-supported, or definite pathological diagnosis. Clinical diagnosis occurs when a case presents with speech and language features that are characteristic of a specific variant. At least one of the "core features" should be present for nfvPPA while both must be present for the semantic and logopenic variants. Patients who do not meet criteria for any of the three variants are classified as PPA "unclassifiable". For an "imaging-supported" diagnosis, evidence of a specific pattern of neuroimaging changes (structural or functional imaging) is required. The third level, a "definite pathology" diagnosis, requires fulfillment of the clinical criteria (with or without neuroimaging evidence) along with pathologic evidence or presence of a genetic mutation known to be associated with FTLD spectrum, AD or other disease pathology.

***Table-3.1: 2011 International consensus PPA diagnostic criteria.***

| General PPA criteria |
| --- |
| **I. Inclusion criteria:**<br>1. Most prominent clinical feature is difficulty with language.<br>2. Language deficit is the cause of impaired activities.<br>3. Aphasia is the prominent deficit at symptom onset and for the initial phases of the disease. |

**II. Exclusion citeria:**
1. Presence of other medical diagnosis that can cause symptoms.
2. Presence of other psychiatric diagnosis that can cause symptoms.
3. Prominent initial episodic memory, visual memory and visuo-perceptual impairments .
4. Prominent, initial behavioral disturbance.

| Semantic Variant PPA | Nonfluent Variant PPA | Logopenic Variant PPA |
|---|---|---|
| **I. Core Criteria** (both must be present):<br>1. Poor confrontation naming;<br>2. Impaired single-word comprehension | **I. Core Criteria** (one must be present):<br>1. Agrammatism;<br>2. Effortful, halting speech production with speech sound errors (consistent with apraxia of speech) | **I. Core Criteria** (both must be present):<br>1. Poor single-word retrieval;<br>2. Impaired repetition of sentences |
| **II. Supportive Features** (at least three must be present):<br>1. Poor object/face knowledge;<br>2. Surface dyslexia/dysgraphia;<br>3. Spared repetition;<br>4. Spared motor speech and grammar | **II. Supportive Features** (two of three must be present):<br>1. Impaired syntactic comprehension;<br>2. Spared single-word comprehension;<br>3. Spared object knowledge | **II. Supportive Features** (at least three must be present):<br>1. Phonological errors;<br>2. Spared single word comprehension and semantics;<br>3. Spared motor speech;<br>4. Absence of frank agrammatism |
| **III. Imaging-supported** (both must be present):<br>1. Clinical diagnosis of svPPA;<br>2. anterior temporal lobe atrophy on MRI and/or hypometabolism/hypoperfusion | **III. Imaging-supported** (both must be present):<br>1. Clinical diagnosis of NFV;<br>2. left posterior fronto-insular atrophy on MRI and/or hypometabolism/hypoperfusion | **III. Imaging-supported** (both must be present):<br>1. Clinical diagnosis of lvPPA;<br>2. Posteriori perysilvian atrophy on MRI and/or hypometabolism/hypoperfusion |

## D. CLINICAL CHARACTERIZATION OF THE THREE MOST COMMON VARIANTS.

### A. Semantic variant PPA (svPPA) (Also known as Semantic Dementia)

The most frequent initial complaint of patients with semantic variant PPA is difficulty finding words, anomia, in spontaneous speech and writing. Patients frequently describe this symptom as loss of memory for words. Anomia is a relatively frequent and unspecific symptom across different syndromes of cognitive impairment and can arise by breakdown of many cognitive processes involved in language production. However, the anomia experienced by svPPA patients is particular, because it is caused by a deficit in semantic memory with multimodal loss of conceptual knowledge of the object or person that needs to be named (Hodges, Patterson, Oxbury, & Funnell, 1992). Anomia is

particularly severe in these patients and performance in confrontation naming tasks is usually not improved by any type of cue. Single word comprehension, or word meaning, is also impaired though patients are usually less aware of their comprehension problems. Performance on naming, comprehension and other semantic memory tasks is very sensitive to the familiarity and typicality of the stimuli. Less frequent or atypical items are lost first and rare exemplars of a certain category (such as camel) usually trigger paraphasic errors such as the supraordinate (animal) or a more typical item (horse). Surface dyslexia and dysgraphia, a selective deficit in reading and spelling words with atypical spelling-to-sound correspondence, are now also considered a symptom of semantic loss, as knowledge of atypical spelling patterns are a form of stored, long-term memory (Woollams, Ralph, Plaut, & Patterson, 2007). Atypical words will often be "regularized" (the word PINT may be read as if it rhymed with MINT) or pronounced as they are spelled due to impaired word semantics but preserved phonologic reading.

In the early stages of svPPA, the stricking loss of naming and comprehension abilities contrasts with preservation of motor speech, phonological and grammatical skills, producing a clinical syndrome that was unknown in stroke aphasia: well-articulated and grammatically correct speech in which missing content words are replaced by more frequent and less specific words, such as "thing". In the initial stages of disease, no abnormalities may be apparent when engaged in simple conversations (which predominate the majority of a person's encounters) or reading simple texts. However, family and friends often report a dwindling capacity to maintain longer meaningful conversations and a shift from reading books to simple newspaper or magazine articles. During examination, when patients are confronted with an out-of-context, low frequency word, or object, comprehension deficits become apparent.

Difficulty recognizing objects and famous faces, as well as difficulty using objects correctly are also features of their multimodal semantic memory loss. This deficit is

often noticed later than the word finding difficulties because it is also influenced by the familiarity effect and families generally only see the patient interacting with common objects that are used every day; similar to what happens to words, it is the less familiar objects and less popular people that are difficult to use and/or recognize in the early stages of the disease. It is of note that, while early reports called the right temporal syndrome "progressive prosopagnosia" (Evans, Heggs, Antoun, & Hodges, 1995), the loss of knowledge for famous people is multimodal and involves proper names as well (G Gainotti, 2007, 2010; G Gainotti, Barbier, & Marra, 2003).

Changes in behavior constitute the other major group of symptoms manifested by patients with svPPA. In fact, in cases of predominant right temporal atrophy, changes in behavior might be noted before symptoms of semantic loss that can be limited to famous people (Edwards-Lee et al., 1997; Gorno-Tempini, Rankin, et al., 2004; Henry, Wilson, et al., 2012). These patients are often misdiagnosed with psychiatric disorders for this reason. Semantic loss for words and objects instead usually dominates the early clinical picture of cases with predominant left temporal atrophy, but behavioral changes invariably manifest at later stages, probably in relation to spreading of atrophy to the right temporal lobe and orbitofrontal regions. One study describes an early behavioral syndrome characterized by emotional detachment, irritability, and disruption of physiologic drives (sleep, appetite, libido) and an ensuing stage 5 to 7 years from onset when disinhibition, compulsions, impaired people knowledge, and altered food preferences emerge (Seeley et al., 2005).

B. Non fluent / Agrammatic variant PPA (nfvPPA)

Slower and effortful speech output is typically the first complaint of patients with nfvPPA. Two main factors are thought to underlie this symptom. The first is an articulation planning deficit known as Apraxia of Speech (AOS) and the other is the omission or inappropriate use of grammatical morphemes such as articles, prepositions,

and auxiliary verbs, which is known as “agrammatism.”. Patients typically present decreased speech rate and dysarthric errors are also common (J. M. Ogar, Dronkers, Brambati, Miller, & Gorno-Tempini, 2007). Their speech rate is slower than patients with other PPA syndromes even when word pauses are controlled for (Ash et al., 2009) and is characterized by inconsistent sound errors comprising distortions, deletions, insertions, and substitutions (J. M. Ogar et al., 2007). Prosody is frequently impaired as well. Observers may perceive uncoordinated “groping” mouth movements while these patients try to articulate. Agrammatism in speech will manifest as a decreased mean length of utterance, simplification of grammatical forms, and presence of frank grammatical errors or omissions of determiners, auxiliaries, and verbal inflections (Ash et al., 2009; Gunawardena et al., 2010; S. M. Wilson, Henry, et al., 2010). Difficulty comprehending (written +/- auditorily presented) grammatically complex sentences can also be a feature of the initial clinical picture, though it usually arises after the early speech problems.

Other cognitive symptoms that frequently emerge are difficulty concentrating, multitasking, and planning/organizing. Extrapyramidal parkinson-like symptoms such as limb rigidity and slower less agile hand movements can also occur during disease course but should not be a prominent early feature, otherwise the diagnosis of PPA does not apply. These symptoms reflect the prominent degeneration of the posterior frontal lobe and its subcortical connections. As the disease progresses, speech becomes progressively less fluent and AOS increasingly severe and patients can develop selective mutism when other congnitve and motor abilities are still relative spared. Difficulty concentrating and multitasking can also progress and errors in judgment become more frequent. Finally, disinhibited or compulsive behaviors can also occur in advanced stages of disease. The clinical picture of many nfvPPA patients will evolve into one with more generalized cognitive and motor problems compatible with a diagnosis of cortical basal

syndrome (CBS) or progressive supranuclear palsy (PSP) (Gorno-Tempini, Murray, Rankin, Weiner, & Miller, 2004; Josephs et al., 2006; Nestor et al., 2007).

C. Logopenic variant PPA (lvPPA)

One of the prominent early complaints of patients with logopenic variant PPA is word-finding difficulty in spontaneous speech. Besides frequent difficulty in naming, spontaneous speech is characterized by its slow rate due to frequent word-finding pauses. While speech rate is often decreased, confrontation naming is less impaired than in svPPA patients, as the defective cognitive mechanism is difficulty with word-retrieval without severe semantic memory loss. In between word-finding pauses, however, their language production improves as articulation deficits are typically absent. A proportion of lvPPA patients exhibit phonological paraphasias, or speech sound errors, which are phonological in nature but can nevertheless be difficult to distinguish form AOS errors (Croot, Ballard, Leyton, & Hodges, 2012). Sentences are typically shorter and there is absence of frank grammatical errors and omissions which also differentiates them from nfvPPA (S. M. Wilson, Henry, et al., 2010). Paragramatic errors (Goodglass, Christiansen, & Gallagher, 1994; B. Wilson, 2011), however, can occur in lvPPA patients, typically later in the disease course, resulting in erroneous word order, word usage, and argument structures. The other prominent difficulty these patients typically experience as disease progresses is difficulty comprehending spoken language, particularly long or unfamiliar sentences. A deficit of phonological short-term memory (or phonological loop) is thought to be the cause of this difficulty in comprehension and can be detected by sentence repetition tests. Accordingly, single word comprehension is relatively spared and increasing sentence length, more than grammatical complexity, worsens their comprehension. Losing track of what they say and particular difficulty with phone conversations are typical lvPPA complaints due to their difficulty processing phonologic aspects of language. Complaints of increasing difficulty reading and spelling are also typical as the disease progresses and reflect impaired phonology. Problems with

calculations, visuospatial symptoms, praxis, and memory have been found to occasionally occur concomitantly to the language difficulties but usually develop afterwards (Gorno-Tempini et al., 2008; J D Rohrer, Ridgway, et al., 2010; Jonathan D Rohrer et al., 2013).

## D. NEUROANATOMY OF COGNITIVE SYMPTOMS IN PRIMARY PROGRESSIVE APHASIA.

### A. Semantic variant PPA (svPPA) (Also known as Semantic Dementia)

Patients with semantic variant PPA have a primary impairment in semantic memory and therefore their symptoms transcend an isolated language dysfunction. The majority of evidence accrued over the years indicates that this deficit is multimodal in nature which explains their difficulties in semantic tests involving different modalities of input such as language, vision, sounds, smells, and tactile sensation (Bozeat, Lambon Ralph, Patterson, Garrard, & Hodges, 2000; Luzzi et al., 2007). The reasons responsible for the early and prominent impairment in language are still matter of debate. Some authors defend an early dysfunction of a verbal semantic system that supports word knowledge and subsequent dysfunction of a separate system responsible for non-verbal object knowledge (Guido Gainotti, 2012; M M Mesulam et al., 2013); other authors defend the existence of a unitary semantic knowledge system and cite the inherent difference between the arbitrary phonologic relationship that words have with the meaning of an object and the systematic relationship between the structure of an object and its meaning as the reason for the initial and predominant deficit in language compared to the other modalities (M A Lambon Ralph, McClelland, Patterson, Galton, & Hodges, 2001; M A Lambon Ralph, Sage, Jones, & Mayberry, 2010). The neuroanatomy and physiology underlying semantic knowledge is also matter of ongoing discussion and study. The association of svPPA's predominant deficit in semantic memory alongside their brain atrophy, principally involving the bilateral anterior temporal lobes (ATL),

constitutes the longest standing evidence for this region's involvement in semantic memory (Chan et al., 2001; Mummery et al., 2000). Other studies using functional neuroimaging in svPPA such as PET also support the ATL's involvement in semantic cognition (Desgranges et al., 2007; Diehl-Schmid et al., 2006). More recent studies have focused on strengthening and refining this relationship using novel techniques. Binney et al., used transcranial magnetic stimulation (rTMS) and functional MRI (fMRI) in healthy participants and identified specific regions within the ATL that are responsible for semantic cognition (Binney, Embleton, Jefferies, Parker, & Ralph, 2010). Subsequent work using fMRI in healthy participants (Visser, Jefferies, Embleton, & Lambon Ralph, 2012; Visser & Lambon Ralph, 2011) and FDG PET in svPPA (Mion et al., 2010) has gone on to examine the specific roles that different ATL sub-regions play in semantics. The study by Mion et al which correlated resting glucose metabolism with performance in semantic tasks found left anterior fusiform function predicted performance on two verbal semantic tasks, while right anterior fusiform metabolism predicted performance on a non-verbal task. While different interpretations for these findings exist, the authors of the study defend the existence of a single bilaterally represented semantic system and that differential task performance according to laterality reflects greater connectivity of the left ATL region to left dominant language systems. The study of svPPA has been the primary inspiration of the "hub and spoke" model of semantic cognition which posits that the anterior temporal lobes act as a semantic amodal hub (Patterson, Nestor, & Rogers, 2007) operating as a convergence zone (Damasio, 1989; Meyer & Damasio, 2009) where inputs from a network of functionally connected upstream modality-specific regions are elaborated into higher order concepts. There are recent studies using novel neuroimaging methods measuring structural (Binney, Parker, & Lambon Ralph, 2012) and functional (Guo et al., 2013) connectivity that provide architectural and physiological evidence in support of this model.

Recent multimodal neuroimaging studies have provided a neuroanatomical framework for many of the symptoms of language dysfunction in PPA. A recent multimodal (Difusion tensor imaging [DTI] and functional magnetic resonance imaging [fMRI]) neuroimaging study analyzing svPPA patients suggested that fluent speech and relative preservation of grammar and phonology is thought to reflect the relative structural and functional sparing of the dorsal language pathway, the fronto-parietal superior longitudinal fasciculus; while impairment in single word comprehension and object knowledge is thought to be associated with anatomical damage to the major superior and inferior temporal white matter connections of the left hemisphere likely involved in semantic and lexical processes (Agosta et al., 2010) (see figure-3.2).

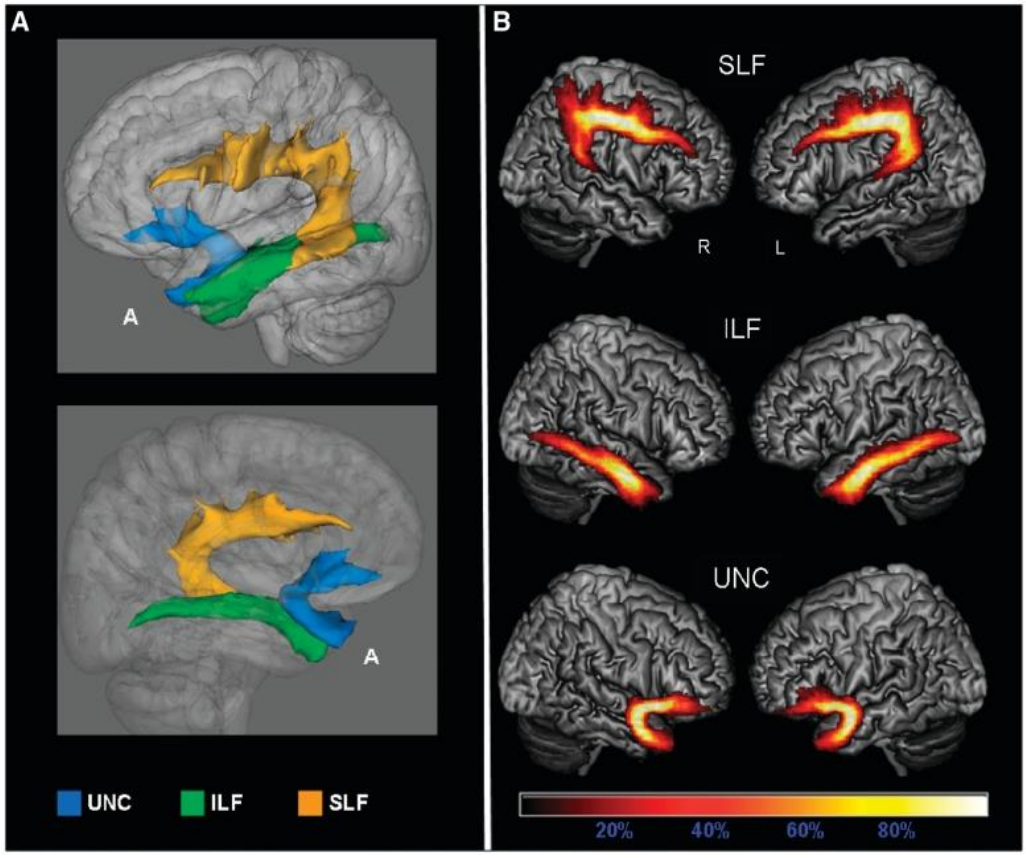


***Figure-3.2: Probabilistic maps of the language-related tracts from 48 subjects****:* non-fluent (*n* = 9); semantic (*n* = 9); logopenic (*n* = 9); and normal controls (*n* = 21). The tracts are overlaid on a 3D rendering of the MNI standard brain. Only voxels present in at least 10% of the subjects are shown. (**A**) 3D reconstruction of all-subjects probability maps of left superior longitudinal fasciculus (SLF), inferior longitudinal fasciculus (ILF) and uncinate fasciculus (UNC) seen from left (*top*) and right (*bottom*). (**B**) All-subjects probability maps of bilateral SLF, inferior longitudinal fasciculus and uncinate fasciculus. The colour scale indicates the degree of overlap among subjects. Figure from (Galantucci et al., 2011).

svPPA has served as a precious model to understand the neural basis of reading processes. A few noteworthy studies have been able to integrate evidence from svPPA with task fMRI in healthy participants. One study showed how reading of irregular or exception words elicited activity in the left anterior middle temporal gyrus in a healthy control, a region observed to be atrophic in a patient with svPPA (M. A. Wilson et al., 2012). An earlier study identified an area in the left inferior parietal sulcus that was associated with reading pseudowords and low-frequency regular words but not exception words in healthy controls; in svPPA patients, however, this area was activated by reading exception words, especially when making regularization errors, suggesting that this area is involved in subword reading processes that are differentially recruited in svPPA patients who have lost word-specific information (S. M. Wilson et al., 2009). Another voxel based morphometry (VBM) study (Binney et al., 2016) comparing reading performance between left predominant and right predominant svPPA patients found the L-svPPA group to be more impaired in exception word reading. Furthermore, this impairment correlated with atrophy in the lateral left ATL leading the authors to hypothesize that the role of the lateral left ATL in irregular word reading is related to representations supporting lexical-semantics and that the lateralization of this role is due to proximity of these regions to the left lateralized speech production network. The study of svPPA is also proving to be crucial for understanding the temporal lobe's role in sentence level processing. While various PET and fMRI studies have shown increased

ATL activation in response to sentences compared with lists of words (Humphries, Binder, Medler, & Liebenthal, 2006; Pallier, Devauchelle, & Dehaene, 2011; Vandenberghe, Nobre, & Price, 2002), svPPA patients present near normal syntactic function despite their profound bilateral ATL atrophy (S. M. Wilson, Galantucci, Tartaglia, & Gorno-Tempini, 2012). This apparent paradox has led to the hypothesis that the ATL's role in sentence level processing primarily involves combinatorial semantic processes instead of syntactic parsing. A recent study that combines structural and functional task MRI in svPPA and healthy controls provides novel evidence supporting this hypothesis (S. M. Wilson et al., 2014).

There are fewer studies addressing the functional relationship between behavioral symptoms and neuroanatomic damage in svPPA and those that exist rely solely on structural neuroimaging analysis. There is growing evidence that links these symptoms to grey matter volume loss in the ventromedial frontal, insular, and bilateral infero-posterior temporal regions (Seeley et al., 2005). One study found the most common abnormal behaviors in svPPA were irritability, disinhibition, depression and abnormal appetite. Via voxel based morphometry (VBM), greater atrophy of the right lateral orbitofrontal cortex (OFC) was associated to anxiety, apathy, irritability/lability and abnormal appetite/eating disorders while greater atrophy of left OFC and left anterior superior and medial temporal lobe was associated with disinhibition (J D Rohrer & Warren, 2010). Even more recent VBM studies provide evidence of the right temporal and right frontal lobe's predominant role in the socioemotional cognitive defecits observed in svPPA such as deficits in self-awareness of empathic concern, insight, and theory of mind (Irish, Hodges, & Piguet, 2014; Shany-Ur et al., 2014; Sollberger et al., 2014).

<u>B. Non fluent / Agrammatic variant PPA (nfvPPA)</u>

Apraxia of speech (AOS) and agrammatism are the core deficits behind the language production difficulties present in nfvPPA. In recent years, multiple studies using different neuroimaging methods have addressed the relationship between anatomical damage/dysfunction and impaired grammar processing in non-fluent PPA. One VBM study found that comprehension of multiclausal relative sentences significantly correlated with voxels in the dorsal portion of the left inferior and middle frontal gyri (Amici et al., 2007) and showed overlap with a digits backward task (a nonsyntactic verbal working memory task) in the dorsolateral left frontal region, supporting a single source of verbal working memory for syntactic and nonsyntactic tasks. The following structural and fMRI study was able to nicely combine findings in nfvPPA and healthy controls to arrive at an integrated model of grammar comprehension. The authors used a syntax comprehension task to show that the posterior inferior frontal cortex is not only atrophied, but also displays abnormal functionality (S. M. Wilson, Dronkers, et al., 2010). In nfvPPA patients, this area did not show the expected modulation by syntactic complexity that was seen in healthy controls, i.e. greater activity with increasingly complex grammatical stimuli. Recent work has focused on the relationship between white matter tract lesions and language symptoms in PPA. One study, using diffusion tensor imaging (DTI), showed how microstructural damage to the left hemisphere dorsal language tracts (the superior longitudinal fasciculus including the arcuate component) was strongly associated with deficits in syntax comprehension and production; and subsequently confirmed, with fMRI, that these white matter tracts connected regions modulated by syntactic processing (S. M. Wilson et al., 2011). Another study that also examined white matter tract integrity in non-fluent PPA found a correlation between a reduced proportion of grammatically well-formed utterances and damage to dorsal (arcuate fasciculus) and ventral (inferior frontal-occipital and uncinate fasciculus) language tracts (M Grossman et al., 2012). Recent work has focused on determining which specific syntactic structures are impaired in nfvPPA. One such study found that, while all PPA variants showed impairment comprehending sentences containing center-

embedded subordinate clauses, only nfvPPA patients demonstrated specific impairment understanding cleft sentence structures (Charles et al., 2014). Using structural imaging techniques (VBM and DTI), atrophy of left anterior superior temporal regions and damage to the left inferior frontal occipital tract as well as the anterior corpus callosum and corona radiata were implicated in this specific deficit comprehending cleft sentences. The authors relate these findings to previous work (M Grossman et al., 2012) that suggests these structures are part of ventral white matter projection stream important for processing grammatical information in nfvPPA and mention the need for confirmation of these imaging results in future studies using a larger number of patients.

Apraxia of speech (AOS) is a somewhat controversial syndrome but is usually defined as a disorder of speech motor planning that is distinguishable from aphasia and dysarthria (J. Duffy, 1995). Even though the method of measuring AOS varies and is often subjective, a number of studies have analyzed AOS's clinical profile and structural neuroimaging correlates in PPA patients. These studies agree with general findings from studies in stroke aphasics (Borovsky, Saygin, Bates, & Dronkers, 2007; Dronkers, 1996; J. Ogar et al., 2006) and functional MRI in healthy normals (Eickhoff, Heim, Zilles, & Amunts, 2009; Price, 2012) outlining the fundamental role of a left fronto-insular cortico-subcortical network for speech production. One such study performed a detailed analysis of motor speech errors in 18 patients with nfvPPA and investigated their neural correlates using VBM on magnetic resonance imaging scans. Patients with AOS-only and AOS plus dysarthria showed atrophy in the left posterior frontal, anterior insular, and basal ganglia regions when compared with controls (J. M. Ogar et al., 2007). Another clinicopathologic study of 17 nfvPPA patients used VBM to show that premotor and supplemental motor cortices were the main cortical regions associated with AOS, while the anterior peri-sylvian region was associated with non-fluent aphasia (Josephs et al., 2006). Yet another study that analyzed speech samples from 50 PPA patients showed that speech distortions (a characteristic of AOS) occurred consistently only in nfvPPA

and correlated with volume loss in the white matter underlying left frontal cortex, especially the superior longitudinal fasciculus, and a smaller homologous region in the right (S. M. Wilson, Henry, et al., 2010). Recent studies are exploring the connections between white matter (WM) tract damage and speech production deficits in nfvPPA (Catani et al., 2013; Mandelli et al., 2014). The more recent of these studies found significant WM damage in tracts connecting left premotor, inferior frontal, supplemental motor area, and the striatum in nfvPPA only and went on to show correlations between the integrity of these tracts and different aspects of motor speech. Specifically, they showed that the left posterior connections between SMA and ventral premotor cortex correlated only with the number of distortions while the more anterior connections between posterior Broca's (BA44) and anterior SMA (preSMA), correlated with number of distortions, rate of speech and syntax production indicating this anterior tracts fundamental role in higher level cognitive aspects of speech production. Currently, a lot of attention is being put into refining the clinical features and neuroimaging correlates of AOS because of its potential for improving differential diagnosis between PPA variants as well as clinical-pathologic correlation in the nfvPPA variant (Croot et al., 2012; J R Duffy & Josephs, 2012). Some authors propose that patients presenting with AOS predominantly and no aphasia, should be classified into a separate clinical syndrome called "progressive apraxia of speech" because of their different clinical and neuroimaging features (Josephs et al., 2012, 2013). These authors find that patients with only AOS or predominant AOS (versus agrammatism) show focal imaging abnormalities in premotor cortex, whereas patients with predominant agrammatism show a more widespread involvement affecting premotor, prefrontal, temporal and parietal lobes, caudate, and insula.

C. Logopenic variant PPA (lvPPA)

A primary phonological deficit characterizes the lvPPA neuropsychological profile. Sentence repetition is impaired, particularly for low probability sentences. A tendency

to provide semantically appropriate but shorter renditions of repeated sentences is frequently observed and reflects preserved semantics (Henry & Gorno-Tempini, 2010). A sentence comprehension deficit influenced primarily by length and not grammatical complexity can also be observed. Single word comprehension or word meaning and syntax production, on the other hand, are relatively preserved in accordance with the relative preservation of the semantic and grammar systems. Other measures that reflect phonologic loop integrity such as digit span, letter span, and word span also show deficits (Gorno-Tempini et al., 2008). Repetition of pseudowords is particularly difficult for lvPPA patients because they cannot benefit from their relatively spared understanding of the word's meaning. In contrast to svPPA patients, they show a length effect typical of phonologic deficits. Written language processing also reflects impaired phonology as they demonstrate a reading pattern consistent with phonological alexia, a selective deficit in pseudoword reading (Brambati, Ogar, Neuhaus, Miller, & Gorno-Tempini, 2009; J D Rohrer, Ridgway, et al., 2010). Recent studies have identified mixed mechanisms (impaired access to lexical representations and defective phonology to orthography conversion) underlying spelling mistakes in lvPPA (Sepelyak et al., 2011; Shim, Hurley, Rogalski, & Mesulam, 2012).

Various neuroimaging studies in logopenic PPA patients using volumetric analyses of structural MRI and FDG-PET images have consistently shown a pattern of atrophy and hypometabolism primarily affecting the left posterior superior and middle temporal gyri and inferior parietal lobule (Gorno-Tempini, Dronkers, et al., 2004; Gil D. Rabinovici et al., 2008). There is considerable lesion and fMRI data suggesting that verbal working memory depends on the posterior superior temporal and inferior parietal cortical areas and the white matter tracts that originate from them (Buchsbaum et al., 2011). Likewise, numerous fMRI studies in stroke aphasics and healthy normals throughout recent years consistently point towards this area's fundamental role in all tasks that require phonologic processing (Price, 2012). However, there are only a few studies

directly correlating performance on phonologic tasks and neuroimaging in lvPPA and most are structural in nature. One VBM study found a correlation between the digits backwards scores (a test of verbal working memory) and dorsolateral prefrontal and inferior parietal volumes in 58 patients with neurodegenerative disease (Amici et al., 2007). Another VBM study also found a direct correlation between phonologic errors in spontaneous speech, which is typical though not specific of lvPPA patients, and atrophy of the posterior temporal cortical region (S. M. Wilson, Henry, et al., 2010). An increased interest in using phonologic tasks to improve clinical diagnosis between PPA variants, in particular concerning lvPPA and nfvPPA, has propelled a series of studies focused on phonology and PPA in last couple of years (Croot et al., 2012; Leyton, Ballard, Piguet, & Hodges, 2014). One such study administered a comprehensive language battery to a group of PPA which included all 3 variants and found overall performance on phonologic tasks correlated with atrophy in a perisylvian network which included the inferior frontal gyrus, precentral gyrus, rolandic operculum, insula, supramarginal gyrus, and superior temporal gyrus while performance in semantic tasks correlated with an extrasylvian network which included the left temporal lobe and angular gyrus (Henry, Beeson, Alexander, & Rapcsak, 2012). Henry et al followed this work with another study constituting what is probably the most comprehensive evaluation of phonologic ability in PPA to date. They administered an extensive battery of phonological tasks to a large group of PPA patients and healthy controls and found a significant correlation between the integrity of left hemisphere cortical frontal and temporo-parietal regions and phonological ability confirming that structures from the “dorsal stream” language pathway are critical for phonological processing (Henry et al., n.d.). lvPPA patients have also been part of various DTI studies. One of these showed white matter tract damage in the temporo-parietal component of the arcuate fasciculus (Galantucci et al., 2011). Another DTI study (Mahoney et al., 2013) reported damage to both dorsal (Superior longitudinal fasciculus and Cingulum bundle) and ventral (Inferior longitudinal fasciculus and uncinate) tracts (also predominating in the left posterior temporo-parietal

components) compared to healthy controls and suggested that damage in the dorsal white matter tracts are likely responsible for the phonologic working memory impairment while damage to the ventral language tracts could relate to their word-finding difficulties as lexical-retrieval has been found to correlate with atrophy of anterior and inferior temporal regions. In general, white matter changes in lvPPA patients are less prominent than in the other two PPA syndromes, reflecting their likely underlying AD pathology.

**E. CLINICOPATHOLOGICAL CORRELATION IN PRIMARY PROGRESSIVE APHASIA.**

svPPA demonstrates a very robust clinical-pathologic relationship to FTLD TDP-43 type C pathology (Hodges et al., 2010; Josephs et al., 2011; J D Rohrer et al., 2011); however FTLD-tau (usually Picks disease) and AD can be found at autopsy in about 10% of cases. A recent study analyzed a cohort of 100 svPPA cases, 24 of which had autopsy data. They reported only 3 cases with FTLD-tau (Picks disease) and another 3 with AD pathology (Hodges et al., 2010). nfvPPA is preferentially associated to FTLD-tau pathology (about 70%) according to recent studies summarizing large clinical pathological series (Murray Grossman, 2010; Josephs et al., 2011; J D Rohrer et al., 2011). FTLD-TDP 43 and AD are the other pathologies most frequently found at autopsy (Knibb, Xuereb, Patterson, & Hodges, 2006; J. Snowden, Neary, & Mann, 2007) however one must take into account that many patients with progressive non-fluent aphasia could possibly be reclassified into lvPPA when using current 2011 PPA diagnostic criteria. AD pathology and in vivo biomarkers (PET-PIB positivity and decreased AB42 and increased tau in CSF) are most frequently associated to the lvPPA syndrome (M. Mesulam et al., 2008; Gil D. Rabinovici et al., 2008; J D Rohrer, Ridgway, et al., 2010; J D Rohrer, Rossor, & Warren, 2012). However, cases of individuals with lvPPA and non-AD pathology have been reported (M Grossman et al., 2008; M. Mesulam et al., 2008). It is

important to note that widespread adoption of the 2011 PPA diagnostic criteria has the potential to significantly alter clinicopathologic correlation in PPA, in theory due to improved ability of identifying cases caused by AD pathology by delineation of the logopenic syndrome. This, in fact, is one of the main questions addressed by this thesis.

# IV. JUSTIFICATION, HYPOTHESES, OBJECTIVES & OUTLINE

## JUSTIFICATION

One of the overarching aims of the research conducted for this thesis is to advance the knowledge of clinicopathologic correlations in neurodegenerative disease to improve the ability of predicting the underlying pathologic molecule in-vivo. Future disease modifying agents will most likely target the underlying pathology and the ability to modify the accumulation of these pathologic proteins by means of a targeted treatment could result in slowing of disease progression or a complete cure. A necessary prerequisite is knowing which pathologic protein or proteins are present in the brain of the (living) patient in front of us, and thus the crucial importance of reliable clinicopathologic correlation for the success of future treatments against neurodegenerative disease. The 2011 consensus primary progressive aphasia diagnostic criteria describe the three most common clinical variants and were established in an effort to improve the reliability of clinicopathologic correlations compared to the previous semantic dementia and progressive non-fluent aphasia criteria included in the 1998 consensus FTLD clinical diagnostic criteria. Since their publication, a few studies have reported amyloid imaging and pathological results in PPA (Chare et al., 2014; Harris et al., 2013; Leyton et al., 2011; M M Mesulam et al., 2014). However, most of these studies are retrospective in nature and the prevalence of FTLD and Alzheimer's disease pathological findings or biomarkers in each variant has been inconsistent across the literature (svPPA 0-16% Alzheimer's disease; nfvPPA 13-31%; lvPPA 54-92%), therefore prospective validation with biomarker and autopsy data remains scarce and highly necessary.

Similarly, the distribution of amyloid deposition and its relationship to atrophy in PPA is rarely reported and the few studies that have, show inconsistent results, some finding asymmetric amyloid in the left hemisphere (Frings et al., 2015; Martersteck et al., 2016), whereas others report relatively symmetric amyloid deposition at autopsy (Gefen et al.,

2012) and on PET (Jung et al., 2015; Lehmann et al., 2013; Leyton et al., 2011). A better understanding of the links between amyloid and neurodegenerative phenotype has important implications for our understanding of Alzheimer's disease pathophysiology and drug development.

## HYPOTHESES

1. Prospective classification according to the current primary progressive aphasia consensus diagnostic criteria will demonstrate significant improvements with respect to previous criteria, in particular in their ability to identify patient groups with largely homogeneous biomarker and pathologic features.

2. Refinement of clinical and neuroimaging phenotypes may aid in the in-vivo prediction of underlying pathology in patients with non-fluent/agrammatic primary progressive aphasia (nfvPPA) which is the most pathologically heterogeneous of the three most common primary progressive aphasia variants. In particular, patients who present progressive supranuclear palsy (PSP) or corticobasal degeneration (CBD) at autopsy may show differences in clinical and/or neuroimaging features that could aid in the in-vivo prediction of underlying pathology.

3. Non-language clinical features neuroimaging features may be useful for predicting amyloid status and thus hold potential to improve current criteria. These features might be captured by data driven classification methods aiming to predict amyloid-PET biomarker status in patients with primary progressive aphasia.

4. Even in patients with primary progressive aphasia presumably due to underlying Alzheimer´s disease pathology (patients with logopenic variant), amyloid deposition will not correlate with clinical symptoms or brain atrophy.

**OBJECTIVES**

1. To analyze the clinical, structural MRI, amyloid-PET, and pathological features associated with each primary progressive aphasia (PPA) subtype according to the current (2011) consensus diagnostic criteria and to compare them with the previous diagnostic criteria in a large cohort of PPA patients.

2. To identify clinical and neuroimaging features that could help for the in vivo prediction of underlying pathology in patients with non-fluent/agrammatic primary progressive aphasia (nfvPPA) patients who present progressive supranuclear palsy (PSP) or corticobasal degeneration (CBD) at autopsy.

3. To determine the ability of data driven methods for predicting PET-PIB amyloid status in patients with primary progressive aphasia.

    a. To study and quantify the ability of different cognitive tests including non-language measures to predict PET-PIB amyloid status.

    b. To study the ability of automated imaging analysis techniques to predict PET-PIB amyloid status.

4. To study the topography of amyloid deposition in the brain measured by PET-PIB and its relationship to clinical symptoms and atrophy in patients with primary progressive aphasia presumably due to underlying Alzheimer´s disease pathology (patients with logopenic variant)

**OUTLINE**

In this line, the objective of the first study included in this thesis was to evaluate the current (2011) PPA consensus diagnostic criteria. First, we wanted to test if classification according to the current criteria results in groups with largely homogeneous biomarker and pathologic features. We also wanted to characterize cases with "discordant" amyloid biomarker status (amyloid positive svPPA and nfvPPA, and amyloid negative lvPPA) and mixed cases (cases with core features of more than one variant) in search of features that could aid in their identification.

The second study aimed to identify clinical and neuroimaging features that could help for the in vivo prediction of underlying pathology in patients with non-fluent/agrammatic primary progressive aphasia (nfvPPA) patients who present progressive supranuclear palsy (PSP) or corticobasal degeneration (CBD) at autopsy. This objective fits in a larger goal of our lab of improving clinicopathologic correlations in the nfvPPA which is the most pathologically heterogeneous of the three common variants. The majority of cases of nfvPPA in the MAC UCSF cohort have either PSP (6 out of 25) or CBD (12 out of 25) (Spinelli et al., 2017).

The third study used data driven methodology to quantify and determine which clinical and neuroimaging measures were the best predictors of amyloid imaging biomarker status. We were specifically interested in the predictive ability of non-language clinical measures and their potential to improve diagnosis in patients with primary progressive aphasia. In this study we also analyzed the topography of amyloid deposition and its relationship to symptoms and atrophy in lvPPA..

# V. MATERIALS & METHODS

## MATERIALS & METHODS

This section will give a general overview of the methodologies relevant to the investigations included in this thesis. Detailed descriptions can be found in the corresponding methods section of each study included in the results section.

### PATIENT COHORT CHARACTERIZATION

Patients were recruited at the University of California (UCSF) Memory and Aging Center (MAC). Primary progressive aphasia is a rare disease but we were able to recruit an unusually large cohort taking advantage of multiple ongoing studies carried out at the UCSF MAC that focus on specific patient populations: the UCSF FTD program project grant (focused on FTD and early-onset AD), the UCSF Alzheimer's Disease Research Center grant (any variant of AD), the UCSF Neuroimaging Initiative on Frontotemporal Dementia project (PPA and bvFTD), the UCSF 4 Repeat Tauopathy Neuroimaging Initiative (PSP and CBD).

As part of the research evaluation, all participants underwent a history and physical examination by a neurologist, a structured caregiver interview by a nurse, a battery of neuropsychological tests, multimodal brain imaging scans, as well as an extensive battery of language tests. After initial evaluation, a syndromic diagnosis was reached by consensus between the multi-disciplinary evaluation team. Initial diagnosis was based on all neurologic, cognitive, language, and structural MRI data collected.

Healthy controls were recruited from the San Francisco aging cohort study. All controls had a Clinical Dementia Rating Scale sum of boxes (CDR-SB) score of 0, a normal neurologic examination, and no cognitive complaints. All study participants underwent informed consent and signed consent forms approved by the UCSF, UC Berkeley and Lawrence Berkeley National Laboratory human research committees.

**CLINICAL AND COGNITIVE EVALUATION**

Clinical: All participants underwent a history and physical examination by a neurologist who subsequently filled out structured forms collecting clinical symptoms, clinical signs, and presence of features included in the diagnostic criteria of the relevant neurodegenerative disease syndromes. The Unified Parkinsons Disease Rating Scale (UPDRS) was used to collect presence and severity of parkinsonian symptoms. All participants underwent a structures interview by a nurse who subsequently completed scales evaluating clinical severity of disease (Clinical Dementia Rating scale, CDR) and behavioral symptoms (Neuropsychiatric Inventory, NPI).

Cognitive: All participants underwent the UCSF neuropsychological battery (Kramer et al., 2003). Verbal episodic memory was evaluated with the the California Verbal Learning Test– Short Form (CVLT-SF) and visual episodic memory by 10-minute delayed drawing of the modified Rey-Osterrieth figure. Different areas of executive function were evaluated: fluency (verbal fluency- number of words beginning with the letter “d” in one minute; design fluency- number of designs in one minute (Delis, Kaplan, & Kramer, 2001)), working memory (backward digit span), and cognitive flexibility (Modified trail making test). Visuospatial abilities were assessed by a simplified Rey–Osterrieth figure copy, the Number Location sub-test from the Visual Object Space Perception Battery , and the facial matching subtest of the Comprehensive Affect Testing System.

Language: Motor speech was evaluated with the Motor Speech Evaluation (MSE) (Wertz, LaPointe, & Rosenbek, 1984) in which the examiner elicits different speech samples through a variety of oral tasks. Videotaped MSEs were reviewed by a certified speech pathologist to rate presence and severity apraxia of speech (AOS) and dysarthria in each patient on a 0-7 scale. Briefly, AOS is defined as a disorder of articulatory planning resulting in slow speech rate, effortful articulation, sequencing errors and

frequent consonant distortions (J. Duffy, 1995). Dysarthria is instead defined as a primary motor deficit of the musculature involved in speech and is characterized mostly by consistent and predictable errors in comparison to AOS (Wertz et al., 1984). Buccofacial apraxia was also evaluated and defined as one's ability to move oral musculature on command for non-speech purposes, such as puckering the lips, licking, or coughing. Connected speech and syntactic production were evaluated using the spontaneous speech section from the Western Aphasia Battery (SS-WAB) (Shewan & Kertesz, 1980). Verbal repetition was evaluated by the repetition sub-test of the WAB and confrontation naming was tested with the 15-item Boston Naming test. Sentence comprehension and receptive grammar were tested with the Sequential commands sub-test of the WAB and one of the two following tests: the Curtiss-Yamada Comprehensive Language Evaluation-Receptive (CYCLE-R) (Curtiss & Yamada, 1988) or the UCSF grammar comprehension test (S. M. Wilson, Dronkers, et al., 2010). The two latter tests systemically vary sentence length and syntactic complexity to take into account the effect of verbal working memory load on syntactic comprehension.

**NEUROIMAGING**

Structural magnetic resonance imaging: *Acquisition*- All patients and controls underwent whole-brain structural MRI using a 1.5T (Gorno-Tempini, Dronkers, et al., 2004; Mormino et al., 2011), 3T (Bettcher et al., 2012), or 4T (Zhang et al., 2011) scanner as previously described. *Image processing*- performed with Statistical Parametric Mapping (SPM12) software using the Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) toolbox according to standard procedures (Ashburner, 2007; Ashburner & Friston, 2005). *Voxel based morphometry (VBM)*- is a technique used for detection of differences in brain structure between groups of subjects by performing voxel-wise comparisons of structural MRI data (Ashburner & Friston, 2000). After specific image pre-processing steps (spatial normalization,

segmentation, modulation, and smoothing), the segmented, normalized, modulated, and smoothed grey or white matter images of each subject are entered into a statistical general linear model and different analysis can be performed to investigate regional differences in grey or white matter between groups of subjects.

Positron Emission Tomography: *Radiochemistry and Acquisition*- [$^{11}$C]PIB was synthesized at the Lawrence Berkeley National Laboratory's Biomedical Isotope Facility using a previously published protocol (G D Rabinovici et al., 2007). [$^{18}$F]AV45 (florbetapir) was provided by Avid Radiopharmaceuticals. PET scans were performed at Lawrence Berkeley National Laboratory using a Siemens ECAT EXACT HR PET scanner and Siemens Biograph Truepoint PET/CT scanner in 3D acquisition mode. 15 mCI of [$^{11C}$C] PIB or 10 mCi of [$^{18}$F] AV45 were injected intravenously. Images for all subjects were acquired at least over a 50-70 min post-injection. *Image processing*- All PET data were reconstructed using an OSEM 3D iterative algorithm with weighted attenuation. In addition, [$^{11}$C]PIB was smoothed with a 4mm Gaussian kernel and the [$^{18}$F]AV45 was smoothed with a 3mm Gaussian kernel. Both had scatter correction and were evaluated for motion correction. A mean image of frames 50-70-minute post injection was created for both [$^{11}$C]PIB and [$^{18}$F]AV45. This mean image was normalized by the grey cerebellum (for PIB) to create native space standardized uptake value ratios (SUVRs). *Visual inspection*- Visual reads of native space PIB or AV45 SUVR images were performed by experienced investigators blinded to clinical data (G.D.R, H.J.R or W.J.J) using published criteria (Clark et al., 2012; G D Rabinovici et al., 2011).

**NEUROPATHOLOGY**

Autopsies were performed at UCSF, University of Pennsylvania (n=3), and Vancouver General Hospital (n=1). UCSF pathological assessments were performed using institution-specific protocols (Villeneuve et al., 2015) and included tissue sampling in

regions relevant to the differential diagnosis of dementia based on published consensus criteria (Hyman et al., 2012; Mackenzie et al., 2010).

# VI. RESULTS

The analyses included in section “VIa. Rates and significance of amyloid imaging positivity in a prospective cohort of primary progressive aphasia” correspond to hypothesis one and objective one. These analysis are also included in a journal article format that is currently under review in JAMA Neurology included as annex number one.

The analyses included in section “VIb. Cross-sectional and longitudinal features of non-fluent/agrammatic primary progressive aphasia with underlying corticobasal degeneration or progressive supranuclear palsy pathology” correspond to hypothesis two and objective two. These analyses are also included in a journal article format that was publishd in JAMA Neurology included as annex number two.

The analyses included in section “VIc. Clinical and neuroanatomical features predictive of amyloid imaging status in primary progressive aphasia” correspond to hypothesis three and four and objectives three and four. These analyses are being prepared for submission to a scientific journal.

## VIa RATES AND SIGNIFICANCE OF AMYLOID IMAGING POSITIVITY IN A PROSPECTIVE COHORT OF PRIMARY PROGRESSIVE APHASIA

**A. Introduction**

**B. Participant selection and characterization**

**C. Demographic, genetic, and clinical data**

**D. Amyloid PET and autopsy data**

**E. PPA with discordant (amyloid positive svPPA and nfvPPA, and amyloid negative lvPPA) amyloid status**

**F. PPA mixed**

## A. INTRODUCTION:

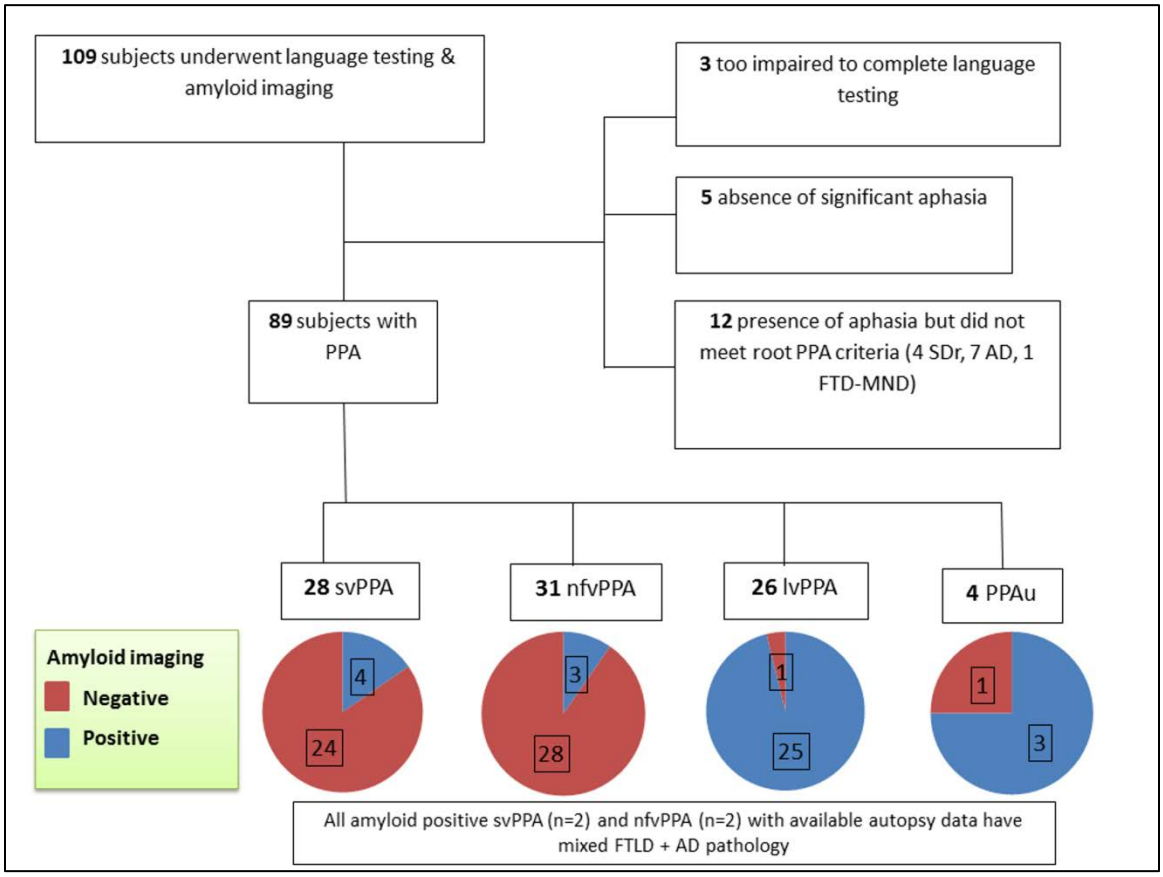
We studied amyloid brain imaging in a large cohort of prospectively diagnosed PPA patients to test the hypothesis that classification according to the current criteria in well-characterized patients with language and MRI imaging evaluations will result in groups with largely homogeneous biomarker features. A second objective was to analyze amyloid "discordant" (amyloid positive svPPA and nfvPPA, and amyloid negative lvPPA) and mixed cases (PPAm) in search of characteristics that may aid in their identification.

## B. PARTICIPANT SELECTION AND CHARACTERIZATION:

We recruited participants that presented prospectively to the University of California San Francisco (UCSF) Memory and Aging Center (MAC) between the years 2002-2015 as part of an ongoing PPA research project. We included patients that met the following criteria: clinical diagnosis of PPA, availability of complete speech, language, and cognitive testing, MRI performed within six months of the cognitive evaluation, and PET PiB or AV45 brain scan results. As part of the research evaluation, all participants underwent a history and physical examination by a neurologist, a structured caregiver interview by a nurse, a battery of neuropsychological tests, multimodal brain imaging scans, as well as an extensive battery of language tests. After initial evaluation, a syndromic diagnosis was reached by consensus between the multi-disciplinary evaluation team. Initial diagnosis was based on clinical judgment after considering all available neurologic, cognitive, language, and structural MRI data. We are reporting these prospective, consensus, PPA clinical variant diagnoses made at presentation. Amyloid imaging results were not available for any participant at the time of initial diagnosis. Since 2002, the UCSF MAC PPA research project has used essentially the same features for classification, as reported in previous publications (Gorno-Tempini, Dronkers, et al., 2004; G D Rabinovici et al., 2008), which are analogous to current criteria (Gorno-Tempini et al., 2011). When it was not possible to identify a predominant

area of language impairment or more than one area was impaired (for example motor speech and repetition difficulties) a diagnosis of PPA mixed (PPAm) was made.

***Figure-6.1.1: Study cohort flow chart.***




*SDr= semantic dementia right temporal predominant. AD= Alzheimer's disease. FTD-MND= frontotemporal dementia with motor neuron disease. svPPA, nfvPPA, lvPPA, PPAu= semantic, non-fluent/agrammatic, logopenic variant, mixed PPA. FTLD= frontotemporal lobar pathology.*

One hundred and nine patients (figure-6.1.1) were referred to the UCSF MAC for evaluation of language symptoms and underwent amyloid imaging between 2002 -2015. Out of these, three subjects were excluded because of inability to complete the language evaluation due to advanced severity of disease, five for absence of significant aphasia, and twelve for presenting with significant initial symptoms outside of the language domain and consequently not meeting root PPA criteria (table-6.1.1). This left a cohort of 89 PPA subjects [28 svPPA, 31 nfvPPA, and 26 lvPPA and 4 PPA mixed (PPAm)].

***Table-6.1.1: Excluded patients that did not meet root PPA criteria.***

| **Exclusion criterion** | Clinical diagnoses | Language syndrome | Amyloid imaging | Pathology |
|---|---|---|---|---|
| Initial behavioral symptoms predominated (n=4) | semantic dementia -right temporal predominant (4) | svPPA (4) | negative (4) | tdp-b with MND (1) |
| Initial memory and/or visuospatial impairment predominated (n=7) | AD language (5), early onset alzheimer's disease (1), AD frontal (1) | lvPPA (6), PPAm (1) | positive (7) | n/a |
| Initial motor neuron signs (n=1) | progressive spastic dysarthria (1) | nfvPPA (1) | negative (1) | tdp-b with MND (1) |
| Absence of significant aphasia (n=5) | amnestic MCI (1), executive MCI (3), conversion disorder (1) | no aphasia | positive (1) / negative (4) | n/a |
| Too impaired to complete language testing (n=3) | lvPPA (1), nfvPPA (1), Global aphasia (1) | n/a | positive (2) / negative (1) | AD (1), PiD (1) |

**C. DEMOGRAPHC, GENETIC, AND CLINICAL DATA:**

Clinical data: Demographic and cognitive data were compared between PPA variants using one-way analysis of variance followed by post hoc comparisons of continuous variables with Bonferroni adjustments. Chi squared test was used for dichotomous variables (table-6.1.2).

Voxel-based morphometry analysis: *Comparison of PPA variants and healthy controls:* We included svPPA (n=28), nfvPPA (n=31), and lvPPA (n=26), and healthy controls (n=84). Whole brain analyses of differences in GM were investigated using an analysis of variance (ANOVA) test across groups, including age, gender, total intracranial volume, total grey matter volume, and scanner type as nuisance variables. Results are displayed at a Family-Wise Error (FWE) corrected threshold of $p<0.05$ (figure-6.1.3).

Comparison of demographic characteristics (table-3) between variants revealed significantly older age at symptom onset in nfvPPA than svPPA or lvPPA. A significantly higher proportion of lvPPA subjects had at least one apoliporotein E e4 allele (44%) compared to nfvPPA (11%). No mutations of microtubule associated protein tau (MAPT) (0/80), TAR DNA-binding protein (TARDBP) (0/74), Granulin (GRN) (0/84), or chromosome 9 open reading frame 72 (0/78) were found despite testing of the majority of subjects.

As a group, nfvPPA patients were less impaired on MMSE and Clinical Dementia Rating Sum-of-Boxes (table-3). All variants showed relatively preserved figure copying. SvPPA showed preserved working memory and executive functions but more behavioral impairment than both nfvPPA and lvPPA. LvPPA patients performed worse on the number location and calculation tests than svPPA and nfvPPA respectively. Both lvPPA and svPPA scored worse than nfvPPA on free recall of a list of learned words but only lvPPA scored worse on recall of the Benson figure.

Language testing revealed expected group differences based on the criteria for PPA subtyping (table-3). svPPA scored significantly worse than both nfvPPA and lvPPA on tests of verbal semantic knowledge and semantic association of pictures (PPTp). Greater presence of apraxia of speech, dysarthria, and decreased fluency scores differentiated nfvPPA from both lvPPA and svPPA. lvPPA scored significantly worse than svPPA on sentence repetition.

VBM analysis of PPA subgroups versus controls also revealed the expected patterns of atrophy associated with each variant (figure-6.1.3), bilateral predominantly left anterior temporal lobe in svPPA, left posterior frontal lobe in nfvPPA, and left mid-posterior temporal and inferior parietal lobes in lvPPA.

***Table-6.1.2: Demographics, amyloid imaging, genetic and clinical data in svPPA, nfvPPA, lvPPA, and PPAm.***

| | svPPA | | | | | nfvPPA | | | | lvPPA | | PPAm | | | | Controls |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **DEMOGRAPHICS/ GENE/ PATH** | amyloid – (n=24) | amyloid + (n=4) | | | | amyloid – (n=28) | amyloid + (n=3) | | | amyloid + (n=25) | amyloid - (n=1) | amyloid + (n=2) | | amyloid – (n=2) | | amyloid na (n=10) |
| **Patient identifier** | | A | B | C | D | | E | F | G | | H | W | X | Y | Z | |
| **Age at symptom onset, y** | 59 (7)b | 72 | 57 | 61 | 71 | 64 (8)ac | 63 | 62 | 72 | 58 (8)b | 67 | 55 | 61 | 66 | 58 | na |
| **Age at initial evaluation, y** | 63 (7)b | 75 | 59 | 63 | 74 | 68 (8)a | 66 | 67 | 74 | 63 (8)b | 70 | 57 | 66 | 70 | 61 | 69.5 (8.1) |
| **Gender (M/F)** | 14;10 | M | F | F | F | 9; 19 | F | F | F | 9;16 | F | F | F | F | M | 7;3 |
| **Handedness (R/L/A)** | 19;2;3 | L | R | R | R | 25;2;1 | R | R | R | 20;4;1 | R | R | R | R | R | 10;0 |
| **Education, y** | 17 (3) | 17 | 16 | 12 | 12 | 17 (3) | 14 | 14 | 12 | 17 (3) | 12 | 20 | 12 | 13 | 20 | 16.9 (2) |
| **Age at PET** | 63 (7) | 75 | 62 | 63 | 74 | 68 (8) | 67 | 70 | 74 | 63 (8) | 70 | 57 | 66 | 70 | 61 | na |
| **PET SUVR** | 1.1 (0.1)c | 1.23 | 2.4 | 2.01 | 2.28 | 1.2 (0.1)c | 1.36 | 1.72 | 2.33 | 2.2 (0.3) | 1.3 | 2.22 | 2.33 | 2.25 | 1.05 | na |
| **ApoE e4 copies (0; ≥1)** | 15; 9 | E3/E4 | E3/E3 | E3/E4 | E3/E4 | 25;3c | E3/E4 | E3/E3 | E3/E3 | 13;11b | E3/E3 | E3/E3 | E3/E3 | E3/E3 | E3/E3 | na |
| **TAU Haplotype (H1/H1; other)** | 16; 7 | H1/H1 | H1/H1 | H1/H2 | H1/H1 | 21;6 | H1/H1 | H1/H1 | H1/H1 | 14;9 | H1/H2 | H1/H1 | H1/H1 | H1/H1 | H1/H2 | na |
| **Pathologic Diagnosis** | table-2 | ? | TDP-C + AD | TDP-C + AD | ? | table-2 | CBD +AD +TDP-A | PiD + AD | ? | table-2 | ? | ? | ? | ? | PiD | na |
| **GENERAL COGNITION** | amyloid – svPPA | A | B | C | D | amyloid – nfvPPA | E | F | G | amyloid + lvPPA | H | W | X | Y | Z | |
| **CDR total** | 0.7 (0.4)b | 0.5 | 0.5 | 1 | 1 | 0.5 (0.3)a | 0.5 | 0 | 0.5 | 0.6 (0.2) | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0 |
| **CDR sum of boxes** | 3.9 (2.3)b | 3.5 | 1 | 6 | 5 | 1.9 (1.5)ac | 2 | 0 | 2 | 3.3 (1.8)b | 3 | 1.5 | 4 | 3 | 3 | 0 |
| **MMSE** | 23 (7.3) | 22 | 29 | 26 | 14* | 26 (3.7)c | 27 | 25 | 25 | 22 (6.2)b | 22 | 28 (-3.9) | 19 (-24) | 27 (-6.1) | 13 (-37.5) | 29.7 (0.7) |
| **NPI total** | 32.3 (18.7)bc | 7 | 16 | 24 | 36 | 17.3 (14.5)a | 25 | 0 | 0 | 10 (8.4)a | 8 | 16 | 3 | 4 | 5 | na |
| **UPDRS** | 2 (2.4)b | 6* | 0 | 0 | 0 | 13 (12)ac | 0 | 13 | 2 | 5.7 (9.1)b | 2 | 1 | 10 | 1 | 21 | na |
| **Benson figure copy ( /17)** | 15.1 (1.3) | 16 | 17 | 16 | 16 | 14.9 (1.9) | 16 | 15 | 16 | 13.8 (3.6) | 14 | 15 (-0.9) | 0 (-13.9) | 12 (-3.5) | 12 (-3.5) | 15.7 (1.4) |
| **VOSP Number Location ( /10)** | 8.9 (1.3)c | 7* | 10 | 10 | 10 | 8.5 (1.5) | 2*** | 8 | 9 | 7.3 (2.5)a | 10 | 9 (-1.1) | 1 (-16.7) | 6 (-7) | 6 (-7) | 9.4 (1.1) |
| **Facial matching ( /12)** | 11.8 (0.7) | 11* | 12 | 9*** | 12 | 11.3 (1.4) | m | 12 | 12 | 11 (3.1) | 12 | 12 (0.4) | 12 (0.4) | 12 (0.4) | 10 (-5.5) | 11.9 (0.3) |
| **Calculations ( /5)** | 3.9 (2.3)c | 5 | 5 | 4 | 3 | 4.4 (0.8)c | 5 | 5 | 5 | 3.2 (1.1)ab | 4 | 3 (-2.8) | 2 (-4.5) | 5 (0.5) | 0 (-7.8) | 4.8 (0.4) |
| **CVLT-MS Total recall** | 17 (8.3) | 15 | 18 | 17 | 11 | 22.4 (6.2)c | 31 | 28 | 25 | 17.4 (7.5)b | 5* | 23 (-3.8) | 9 (-10.4) | 32 (0.4) | 17 (-6.6) | 30.9 (3.1) |

VIa. Rates and significance of amyloid imaging positivity in a prospective cohort of primary progressive aphasia

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CVLT-MS 10m free | 2.5 (2.5)b | 0 | 3 | 0 | 0 | 5.5 (2.6)ac | 7 | 9 | 8 | 3.3 (2.9)b | 2 | 6 (-1.5) | 2 (-4.6) | 9 (0.8) | 0 (6.2) | 8.1 (1.3) |
| Benson figure recall ( /17) | 7.9 (4.6) | 8 | 7 | 10 | 0* | 10.1 (3.6)c | 4* | 10 | 7 | 6.3 (3.6)b | 6 | 6 (-2.3) | 0 (-4.4) | 5 (-2.7) | 7 (-2) | 12.7 (3.3) |
| Digits Forward | 6.3 (1.8)bc | 7 | 7 | 6 | 7 | 4.6 (1.1)a | 3* | 5 | 5 | 4.2 (1.2)b | 4 | 4 (-4.4) | 4 (-4.4) | 6 (-1.9) | 5 (3.1) | 7 (1.2) |
| Digits Backward | 4.4 (1.3)bc | 5 | 6 | 5 | 5 | 3.4 (1.2)a | 2* | 5 | 3 | 2.8 (1.1)b | 3 | 3 (-1.8) | 2 (-2.6) | 4 (-1) | 0 (-4.2) | 4.8 (1.1) |
| Modified trails (lines | 21.3 (12.5)bc | 1.5* | 15.8 | 16.2 | 5.5* | 13.4 (8.6)a | 1.5* | 17.5 | 3.5* | 8.8 (8.8)b | 1 | 24 (-1.1) | 1.5 (-3.7) | 5.5 (-3.3) | u | 29.7 (8.1) |
| Design fluency | 8.4 (2.4) | 15 | 11 | 9 | 4* | 6.3 (3.4) | 7 | 6 | 5 | 6.7 (3.7) | 7 | 9 (-1) | 1 (-3.8) | 9 (-1) | u | 11.8 (2.9) |
| Stroop interference | 38.7 (18.7)bc | 27 | 42 | 38 | u | 22.8 (11)a | 32 | 21 | 20 | 16.1 (11.1)b | 16 | 20 (-2.5) | 5 (-3.7) | 22 (-2.3) | u | 52 (12.8) |
| **LANGUAGE** | **amyloid – svPPA** | **A** | **B** | **C** | **D** | **amyloid – nfvPPA** | **E** | **F** | **G** | **amyloid + lvPPA** | **H** | **W** | **X** | **Y** | **Z** | |
| Boston Naming Test ( BNT, 15) | 4.6 (3.2)bc | 1* | 3 | 3 | 0* | 12.1 (2.8)a | 12 | 9* | 13 | 9.9 (4.1)a | 4* | 14 (-0.9) | 13 (-2.1) | 8 (-8.4) | 5 (12.2) | 14.8 (0.4) |
| Speech fluency (WAB, 10) | 9 (0.5)b | 10 | 9 | 8 | 8* | 7.1 (2)ac | 4* | 2** | 9 | 8.5 (1.4)b | 8 | 9 | 9 | 9 | 9 | na |
| Information content (WAB, 10) | 9.1 (1) | 9 | 9 | 10 | 8* | 9 (0.9) | 9 | 8* | 8* | 8.9 (1.7) | 6* | 8 | 9 | 9 | 9 | na |
| Semantic fluency (animals) | 7.3 (4.4) | 2* | 5 | 5 | 1* | 10.3 (5.3) | 9 | 9 | 13 | 9.9 (4.1) | 5* | 12 (-2.8) | 9 (-3.5) | 12 (-2.8) | 0 (-5.4) | 24 (6.4) |
| Phonemic fluency (D | 7 (4.3) | 8 | 8 | 5 | 3 | 5.6 (2.6) | 3* | 5 | 6 | 7.5 (4) | 2* | 16 (-0.3) | 4 (-2.7) | 17 (-0.1) | 0 (-3.6) | 18.3 (3.4) |
| AOS (MSE, 7) | 0b | 0 | 0 | 0 | 0 | 2.4 (2)ac | 2 | 6* | 4 | 0b | 0 | 4 | 2 | 0 | 0 | 0 |
| Dysarthria rating (MSE, 7) | 0b | 0 | 0 | 0 | 0 | 1.8 (2.1)ac | 0 | 2 | 1 | 0b | 0 | 3 | 0 | 0 | 0 | 0 |
| PPVT total ( /16) | 8.1 (3.8)bc | 9 | 11 | 5 | 2* | 14.5 (2)a | 12* | 15 | 13 | 13.9 (2)a | 9** | 15 (-1.4) | 16 | 11 (-8) | 8 (-13) | 15.3 (0.7) |
| PPTp total ( /52) | 40 (7.2)bc | 42 | 49 | 32* | 30* | 48.1 (5.1)a | 49 | 49 | m | 48.5 (2.8)a | 46 | 50 (-1.8) | m | 41 (-12.4) | 45 (-7.6) | 51.5 (0.8) |
| Sequential commands (WAB, | 74.5 (11.6) | 59* | 80 | 70 | 54* | 70.3 (12.7) | 57* | 80 | 72 | 66.8 (14.3) | 58 | 70 (-5.5) | 70 (-5.5) | 72 (-4.3) | 65 (-8.4) | 79.2 (1.7) |
| Grammar comprehension^ (%) | 93.1 (10.6) | 87 | 100 | 87 | 90 | 87.9 (11.3) | 60** | 94 | 83 | 84.5 (12.7) | m | 85 (-5.1) | 90 (-3.2) | 88 (-3.9) | 74 (-9.3) | 98.4 (2.6) |
| Repetition (WAB, 100) | 87.6 (15.6)c | 89 | 100 | 84 | 81 | 83.9 (15) | 72 | 67* | 90 | 73.9 (16)a | 54* | 84 (-10.9) | 79 (-14.4) | 84 (-10.9) | 81 (-13) | 99.2 (1.4) |

**For svPPA, nfvPPA, and lvPPA:** Scores expressed as mean (standard deviation); [a]significantly different than svPPA; [b]significantly different than nfvPPA; [c]significantly different than lvPPA; *>1 standard deviation worse than group with typical amyloid status; **>2 standard deviations worse than group with typical amyloid status; ***>3 standard deviations worse than group with typical amyloid status. **For PPAm:** Patient scores followed by (z-score) with respect to control group mean.

m= missing; u= unable to perform; na= not applicable; AD: alzheimer's disease; AOS: apraxia of speech; CBD: Corticobasal degeneration; CDR: Clinical dementia rating scale; CVLT: California verbal learning test; MMSE: mini mental state examination; MSE: motor speech exam; NPI: neuropsychiatric inventory; PiD: Pick's disease; PPVT: Peabody's picture vocabulary test; PPTp: pyramids and palm trees picture version; SUVR: standardized uptake value ratio; UPDRS: unified parkinsons disease rating scale; TDP: transactive response DNA binding protein; VOSP: visual object & space perception battery; WAB: western aphasia battery. ^Grammar comprehension tests used were either the Curtiss Yamada Comprehensive Language Evaluation receptive language test (CYCLE-R) and the UCSF grammar comprehension test and their scores are expressed as percentage correct.

**D. AMYLOID PET AND AUTOPSY DATA:**

Mean (standard deviation) time between first diagnosis-PET and PET-autopsy was 244 (337) and 1641 (926) days respectively. Overall prevalence of amyloid PET positivity in our PPA cohort was 35/89 (39.3%). Twenty-four of 28 svPPA (85.7%) and 28/31 nfvPPA (90.3%) patients were amyloid PET negative, whereas 25/26 (96.1%) patients with lvPPA were amyloid positive. For comparison, the rates of amyloid PET-positivity in svPPA and nfvPPA were similar to those reported in cognitively normal individuals at a similar age (15%-20% in individuals aged 60-65 (Jansen et al., 2015)), whereas the rate in lvPPA was much higher than expected for age. Of the 4 mixed PPA (PPAm), 3 were amyloid positive and 1 negative. LvPPA had significantly greater PiB standardized uptake value ratios (SUVR) than nfvPPA and svPPA (figure-4, table-3). Although they were considered positive for the purposes of this study, one svPPA and another nfvPPA received "equivocally positive" amyloid PET reads. These patients showed evidence of focal tracer uptake in regions of early amyloid positivity (e.g. precuneus/posterior cingulate cortex, dorsomedial and dorsolateral prefrontal cortex, in contrast to the widespread binding patterns across large regions of association cortex that are typical in full-blown Alzheimer's disease (Villeneuve et al., 2015)). Accordingly, both cases had global SUVRs consistent with early positivity (1.23 and 1.36 respectively), but lower than the conservative threshold used in our group to "rule-in" Alzheimer's disease-like levels of binding (global SUVR ≥ 1.40).

Autopsy diagnoses were available for 20 patients (table-6.1.3). Overall, patients with positive amyloid scans all had intermediate-to-high Alzheimer's disease Neuropathological Changes (ADNC). When the PPA phenotype was lvPPA positive amyloid PET was associated with primary Alzheimer's disease, whereas when the PPA phenotype was nfvPPA or svPPA the primary causative neuropathology was FTLD, with Alzheimer's disease present as a contributing co-pathology. Conversely, all patients with

negative amyloid imaging had absent to low ADNC, with FTLD as the primary causative neuropathology.

***Figure-6.1.2: Scatter plot depicting PET PIB standardized uptake value ratios (SUVr) across PPA variants (A).***

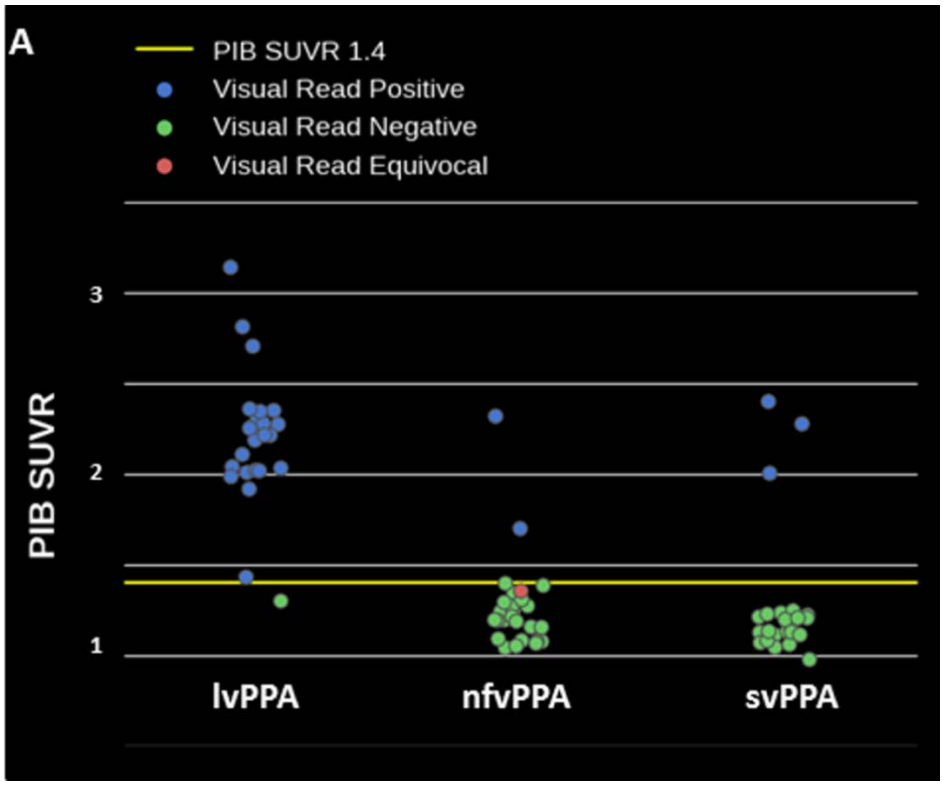


***Table-6.1.3: Pathological diagnoses and amyloid imaging for all PPA.***

| | | Primary pathologic diagnosis | Contributing pathologic diagnosis | Incidental pathologic diagnosis | Alzheimer's disease neuropathological change (ADNC) | Amyloid imaging | PIB SUVR |
|---|---|---|---|---|---|---|---|
| svPPA | 1 | FTLD-TDP-C | PSP | | *Braak 1, CERAD 0 | - | 1.12 |
| | 2 | FTLD-TDP-C | FTLD-tau unclassifiable | mild Ascl | Low ADNC (A1, B1, C0) | - | 1.21 |
| | 3 | FTLD-PiD | | | *Braak 1, CERAD moderate | - | 0.98 |
| | 4[B] | FTLD-TDP-C | AD | mild Ascl; VID, mild CAA | Intermediate ADNC (A3, B1, C2) | + | 2.40 |
| | 5[C] | FTLD-TDP-C | AD | AGD, mild Ascl; severe CAA | High ADNC (A3, B3, C3) | + | 2.01 |
| nfvPPA | 1[F] | FTLD-PiD | AD | moderate CAA & Ascl | *Braak 5, CERAD frequent | + | 1.72 |
| | 2 | FTLD-PSP | | AGD; LBD | No ADNC (A0, B1, C0) | - | n/a |
| | 3 | FTLD-PiD | | mild Ascl | No ADNC (A0, B0, C0) | - | 1.08 |
| | 4 | FTLD-PSP | | | No ADNC (A0, B1, C0) | - | 1.20 |
| | 5 | FTLD-CBD | FTLD-TDP unclassifiable; AGD; LBD | mild Ascl, AD | Low ADNC (A1, B2, C0) | - | 1.08 |
| | 6 | FTLD-CBD | VID; moderate Ascl | LBD; AD | Low ADNC (A1, B1, C1) | - | 1.16 |
| | 7[E] | FTLD-CBD | AD; FTLD-TDP-A | mild Ascl | Intermediate ADNC (A2, B2, C3) | + | 1.36 |
| | 8 | FTLD-CBD | | mild Ascl; AD | Low ADNC (A1, B3, C0) | | 1.07 |
| | 9 | FTLD-PiD | | mild Ascl; AD | Low ADNC (A1, B1, C0) | - | 1.08 |
| | 10 | FTLD-CBD | VID | mild Ascl; AD | Low ADNC (A1, B0, C0) | - | 1.16 |
| | 11 | FTLD-CBD | | mild Ascl | No ADNC (A0, B1, C0) | - | 1.19 |
| | 12 | FTLD-CBD | LBD | | No ADNC (A0, B1, C0) | - | 1.31 |
| lvPPA | 1 | AD | | VID; mild Ascl; moderate CAA | High ADNC (A3, B3, C3) | + | 2.01 |
| | 2 | AD | | mild Ascl; mild CAA | High ADNC (A3, B3, C3) | + | 2.33 |
| | 3 | AD | | Mild CAA; limbic AGD | High ADNC (A3, B3, C3) | + | 2.25 |
| PPAm | 1[Z] | FTLD-PiD | | LBD; AD | Low ADNC (A1, B0, C0) | - | 1.04 |

VIa. Rates and significance of amyloid imaging positivity in a prospective cohort of primary progressive aphasia

[B, C, E, F, Z] Patient identifiers corresponding with table-1. *Complete ADNC score not available; SvPPA, nfvPPA, lvPPPA, PPAm: semantic, nonfluent/agrammatic, logopenic, and mixed PPA variants; AD: Alzheimer's disease; AGD: Argyrophilic grain disease; Ascl: arteriolosclerosis; CAA: Cerebral amyloid angiopathy; CBD: Corticobasal degeneration; FTLD: frtontotemporal lobar degeneration; LBD: Lewy body disease;; PiD: Pick's disease; PSP: progressive supranuclear palsy; SUVR= standardized uptake value ratio; TDP: transactive response DNA binding protein; VID: vascular ischemic disease;

**E. PPA WITH DISCORDANT (AMYLOID POSITIVE SVPPA AND NFVPPA & AMYLOID NEGATIVE LVPPA) AMYLOID STATUS:**

Clinical data: To identify factors that may help identify PPA cases with discordant amyloid imaging within each PPA variant, we converted the raw cognitive test scores of amyloid discordant PPA cases into z-scores with respect to the mean score of the group with typical amyloid imaging status (table-6.1.2).

Voxel-based morphometry analysis: *Single subject VBMs:* We compared each PPA case with discordant amyloid imaging status (amyloid positive svPPA and nfvPPA, and amyloid negative lvPPA) and each PPAm (n=4) to the same group of 84 healthy controls. Whole brain analyses of differences in GM were investigated using a t-test, including age, gender, total intracranial volume, and scanner type as nuisance variables. Results are displayed at a voxelwise threshold of $p<0.01$ (figure-6.1.3).

Amyloid positive svPPA [patients A-D]: All amyloid positive svPPA patients (A-D) had PIB SUVRs above 2.0 except patient A, who displayed significant amyloid binding only in the right frontal lobe and received an “equivocally positive” radiologic read. Autopsy data were available for patients B and C who received a mixed pathological diagnosis, FTLD-TDP type C as the primary with Alzheimer’s disease contributing. Despite having the highest PIB SUVR, patient B only showed intermediate ADNC (Braak stage 2 and moderate [CERAD] neuritic but frequent diffuse plaques). Three out of four had one ApoE4 allele. All patients showed the typical svPPA cognitive profile and atrophy pattern.

Amyloid positive nfvPPA [patients E-G]: All patients had PIB SUVRs above 2.0 except patient E whose scan was read as “equivocally positive” and had an SUVR of 1.36. Patient E had three contributing pathologies, FTLD-CBD, Alzheimer’s disease (Braak 4, CERAD frequent), and FTLD-TDP type A. Patient F (previously described in (Caso et al.,

2013)) had a dual pathological diagnosis, FTLD-PiD and Alzheimer's disease (Braak 5, CERAD frequent). Language testing revealed varying degrees of motor speech impairment and agrammatism with spared verbal and visual semantics in all three amyloid positive nfvPPA cases. All cases showed atrophy in the left posterior frontal lobe with different areas of accompanying atrophy.

Amyloid negative lvPPA [patient H]: The case of amyloid negative lvPPA had an SUVR of 1.3 and autopsy data was not available. Her prominent impairment was in sentence repetition but also had worse single word comprehension than the amyloid positive group. VBM revealed a fronto-temporal pattern of atrophy.

**F. PPA MIXED:**

Clinical data: To highlight the pattern of impaired and relatively preserved cognitive functions in PPA mixed (PPAm), we calculated z-scores with respect to the healthy control group (table-6.1.2).

Voxel-based morphometry analysis: *Single subject VBMs:* see previous section (figure-6.1.4).

Three out four PPA mixed (patients W, X, and Y) were amyloid positive and the SUVR was greater than 2.2 in all three. The only patient that came to autopsy (patient Z) had FTLD-PiD. All patients showed word finding difficulties. At presentation, both patient W and X showed impaired motor speech (AOS and dysarthria), sentence repetition and grammar comprehension. Patient Y presented with impaired semantics, sentence repetition, and grammar comprehension. Patient Z showed impaired grammar, semantics, sentence repetition and grammar comprehension. Consistent with their clinical presentation, these patients did not show the typical patterns of atrophy seen in the three main variants (figure-6.1.4).

***Figure-6.1.3: Voxel-based morphometry of grey matter atrophy patterns for amyloid negative svPPA, amyloid negative nfvPPA, and amyloid positive lvPPA groups.*** Single subject VBM of amyloid discordant patients. A, B, C, D: amyloid positive svPPA. E, F, G: amyloid positive nfvPPA. H: amyloid negative lvPPA. L= left, R= right.

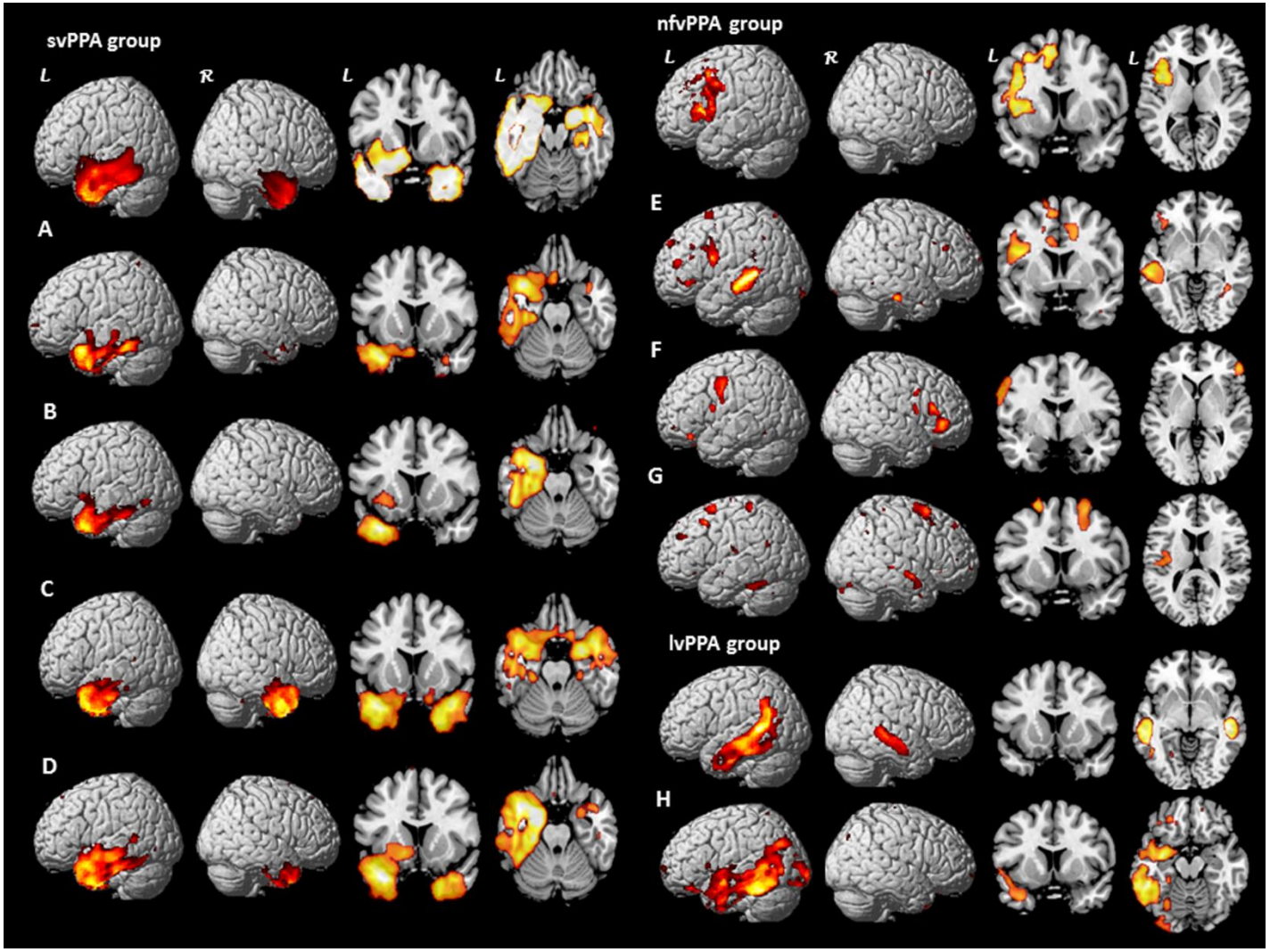
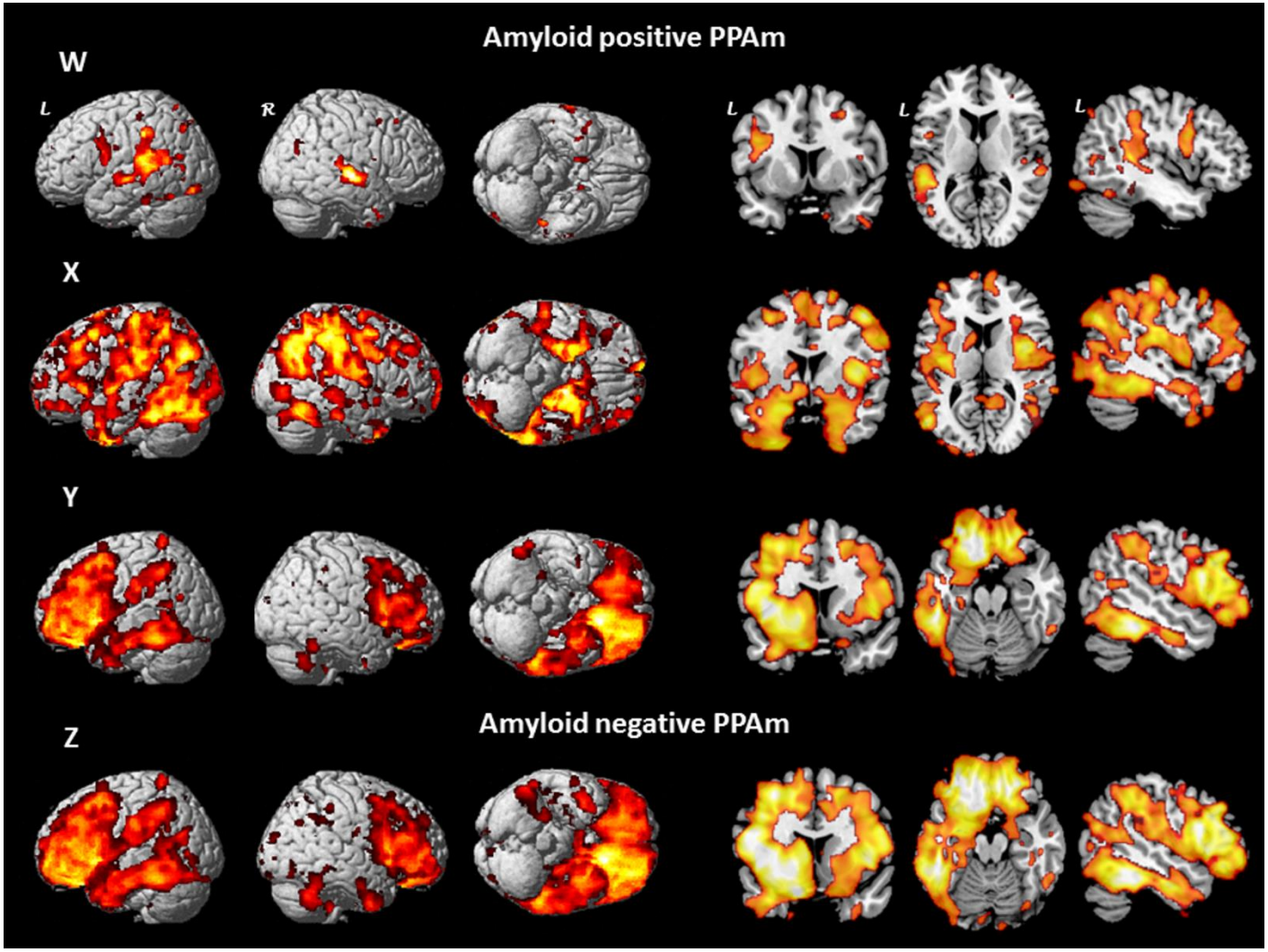


***Figure-6.1.4: Voxel-based morphometry of grey matter atrophy patterns for PPA mixed (PPAm):*** W, X, Y: amyloid positive (PPAm). Z: amyloid negative PPAm. L= left, R= right.



## VIb. CROSS-SECTIONAL AND LONGITUDINAL FEATURES OF NON-FLUENT/AGRAMMATIC PRIMARY PROGRESSIVE APHASIA WITH UNDERLYING CORTICOBASAL DEGENERATION OR PROGRESSIVE SUPRANUCLEAR PALSY PATHOLOGY

A. **Introduction**
B. **Participant selection and characterization**
C. **Demographic, general cognitive, language and neurological data**
D. **Cross-sectional neuroimaging analysis at initial evaluation**
E. **Longitudinal neuroimaging analysis**

VIb. Cross-sectional and longitudinal features of non-fluent/agrammatic primary progressive aphasia with underlying corticobasal degeneration or progressive supranuclear palsy pathology.

**INTRODUCTION:**

The purpose of this study was to characterize the early features and longitudinal trajectories of neurological, cognitive and neuroimaging impairment in patients with sporadic nfvPPA and autopsy confirmed PSP or CBD pathology.

**PARTICIPANT SELECTION AND CHARACTERIZATION:**

Subjects were evaluated at the University of California San Francisco (UCSF) Memory and Aging Center (MAC) as part of a prospective, longitudinal research study between the years 2002-2014. Inclusion criteria: clinical diagnosis of nfvPPA according to current criteria (Gorno-Tempini et al., 2011), availability of speech, language, and cognitive testing for at least one evaluation, magnetic resonance imaging (MRI) within 6 months of initial evaluation, and a postmortem pathological diagnosis of FTLD-4R-tau. This resulted in a cohort of 15 patients: 5 with pathologically confirmed PSP, 9 with CBD, and one with an unclassifiable 4R tauopathy. Tau immunohistochemistry demonstrated evidence of globose tangles and tufted astrocytes (Yamada, McGeer, & McGeer, 1992) in all PSP and astrocytic plaques (Feany & Dickson, 1995) and thread-like inclusions in all CBD. Genetic screening for mutations in MAPT and Progranulin genes were negative in all subjects. Since our primary objective was to characterize and contrast features of nfvPPA-PSP and nfvPPA-CBD, the unclassifiable case of 4R tauopathy was excluded. Subjects were followed for 2.9 (± 1.6) years. The criteria used for the syndromic diagnosis of probable PSP and CBD were published previously (Boxer et al., 2006): Probable PSP- (1) a gradually progressive disorder with onset at the age of 40 years or later and (2) vertical supranuclear gaze palsy and prominent postural instability. Probable CBD- (1) a slowly progressive course, (2) asymmetric limb or axial rigidity, present without reinforcement, (3) aphasia, visuospatial impairment or neglect, or apraxia, and (4) dystonia, myoclonus, cortical sensory loss, or alien limb phenomenon. It was possible for one subject to meet both sets of diagnostic criteria.

**DEMOGRAPHIC, GENERAL COGNITIVE & LANGUAGE, AND NEUROLOGICAL DATA:**

We compared cognitive test scores between nfvPPA-PSP (n=5), nfvPPA-CBD (n=9), and controls (n=10) at initial evaluation and 1 year follow-up (PSP=4; CBD=6). Mann-Whitney U and Kruskal –Wallis tests were used for two and three group comparisons respectively. For analysis of longitudinal cognitive data, we performed a paired Wilcoxon test to compare performance at initial evaluation and follow-up within each group. Presence of clinical symptoms and neurological signs were compared between groups at presentation (PSP n=5; CBD n=9), at 1 year follow-up (PSP n=5; CBD n=6), and follow-up closest to time of death (PSP n=4; CBD n=5) using the Chi-squared test.

**Demographic data:**

PSP and CBD did not differ significantly in age of symptom onset or age at initial evaluation. However, four out of five PSP and only 2 out of 9 CBD cases presented after the age of 65. PSP showed a trend ($p = 0.058$) towards longer survival following onset of first symptom.

**General Cognitive and Language data:**

At initial evaluation (Table-6.2.1)**:** In nfvPPA-4R-tau, tests of general cognition (MMSE), memory, and executive function were significantly worse than controls. Speech and language measures showed impairment in measures of motor speech, verbal fluency, naming, and sentence comprehension.

nfvPPA-PSP was significantly more depressed than nfvPPA-CBD, and only nfvPPA-CBD was significantly worse than controls in a test of working memory (digits backward). All 14 patients showed AOS. Mixed hypokinetic and spastic dysarthria was present and rated as more severe than AOS in all of the nfvPPA-PSP cases. In CBD, dysarthria was present in only 4 out 9 cases. Dysarthria was significantly more severe in nfvPPA-PSP. Only nfvPPA-CBD was significantly worse than controls in both measures of sentence comprehension and showed a trend for lower scores compared to nfvPPA-PSP in these

measures. No significant differences were found when directly comparing patient groups in the measures derived from the recorded speech sample. However, both groups scored significantly worse than controls in words per minute, distortions per hundred words, proportion of syntactical errors, and proportion of words in sentences. Only nfvPPA-CBD produced significantly fewer narrative words than controls.

At 1-year follow-up (Table-6.2.2)**:** In nfvPPA-4R-tau, MMSE scores showed significant decline, while visuospatial and visual memory tests were still not significantly impaired compared to controls. Digits backward remained impaired but did not decline significantly. All speech and language measures declined significantly except phonemic fluency, sequential commands, and dysarthria (which only showed a trend towards significant decline).

At follow-up, cross-sectional comparisons did not show significant differences between patient groups in any cognitive measure. Accordingly, nfvPPA-CBD showed higher dysarthria scores and nfvPPA-PSP performed worse on grammar comprehension than before. However, longitudinal change in these measures was not significant. In nfvPPA-CBD longitudinal analysis showed significant decline in MMSE, AOS, speech fluency, and auditory word recognition (although patients continued to be relatively preserved in this single word comprehension task, as they missed only one out 60 items). nfvPPA-PSP showed significant decline in semantic fluency only. Both groups showed a trend towards significant decline in grammar comprehension.

***Table-6.2.1: Demographic and cognitive data in nfvPPA-PSP, nfvPPA-CBD, and controls at initial visit.***

| Demographic Data | All 4R tau | PSP (n=5) | CBD (n=9) | control (n=10) |
|---|---|---|---|---|
| Gender (M/F) | 4/10 | 1/4 | 3/6 | 3/7 |
| Handedness (R/L) | 13/1 | 4/1 | 9/0 | 10/0 |
| Education, y | 17 (12-21) | 16.4 ± 3.9 | 18 (12-20) | 17 (14-20) |
| Age at symptom onset, y | 62.5 (51-79) | 15 (12-21) | 61 (51-79) | n/a |
| Age at initial evaluation, y | 66.5 (54-81) | 70 (62-72) | 65.3 ± 9.1 | 71.5 (57-78) |

VIb. Cross-sectional and longitudinal features of non-fluent/agrammatic primary progressive aphasia with underlying corticobasal degeneration or progressive supranuclear palsy pathology.

| | | | | |
|---|---|---|---|---|
| Survival, y | 7.23 (4.4-11.6) | ***9.6 (6.4-11.6)*** [c] | ***6.4 (4.4-10.3)*** [c] | n/a |
| **General Cognitive Data** | | | | |
| MMSE | 27 (20-30) [a] | 28 (24-30) [a] | 27 (20-29) [a] | 30 (28-30) |
| CDR sum of boxes | 2 (0-4.5) | 1.5 (0-2.5) | 2 (1-4.5) | n/a |
| GDS total | 5 (0-28) [a] | **19 (3-28)** [ab] | 4 (0-16) | 3.5 (0-13) |
| NPI total | 10.5 (1-50) | 16.5 (8-50) | 10.5 (1-38) | n/a |
| Digits Backward | 3 (2-6) [a] | 3 (2-6) | 3 (2-4) [a] | 5 (3-7) |
| Modified trails (lines per min) | 9.3 (0.5-32.3) [a] | 2 (0.5-32.3) [a] | 10.1 (4-26.3) [a] | 30 (14-40) |
| Calculation | 5 (2-5) | 5 (2-5) | 5 (3-5) | 5 (4-5) |
| Benson figure copy | 15 (13-17) | 15 (13-16) | 15 (13-17) | 16 (13-17) |
| Benson figure recall | 11.5 (3-17) | 10 (3-13) | 12 (9-17) | 14 (7-17) |
| CVLT-MS Total recall | 25 (16-34) [a] | 26 (16-28) [a] | 23.5 (17-34) [a] | 32 (26-35) |
| CVLT-MS 10min free recall | 6 (4-8) [a] | 7 (4-8) [a] | 6 (5-8) [a] | 8.5 (5-9) |
| **Language Cognitive test** | | | | |
| AOS rating (MSE, 7) | 2 (1-4) | 1 (1-4) | 2 (1-4) | n/a |
| Dysarthria rating (MSE, 7) | 2 (0-7) | **4 (2-7)** [b] | **0 (0-4)** [b] | n/a |
| Speech fluency (WAB, 10) | 9 (4-10) | 9 (6-9) | 9 (4-10) | n/a |
| Information content (WAB, 10) | 10 (5-10) | 10 (5-10) | 10 (9-10) | n/a |
| Sequential commands (WAB, 80) | 73.5 (49-80) [a] | ***80 (69-80)*** [c] | ***68 (49-80)*** [ac] | 80 (76-80) |
| Grammar comprehension (%) | 81 (65-100) [a] | ***98 (80-100)*** [c] | ***81 (65-98)*** [ac] | 100 (92-100) |
| Repetition (WAB, 100) | 91.5 (52-100) [a] | 95 (52-100) [a] | 88 (64-100) [a] | 100 (96-100) |
| Word recognition (WAB, 60) | 60 (55-60) | 60 (59-60) | 60 (55-60) | 60 (60-60) |
| Boston Naming Test (BNT, 15) | 13.5 (11-15) [a] | 12 (11-15) [a] | 14 (11-15) [a] | 15 (14-15) |
| Phonemic fluency (D words) | 4.5 (0-13) [a] | 5 (2-13) [a] | 4 (0-6) [a] | 17 (14-24) |
| Semantic fluency (animals) | 9 (4-22) [a] | 9 (6-22) [a] | 9 (4-13) [a] | 26 (14-33) |
| **Spontaneous Speech sample analysis (Picnic** | | | | |
| Total narrative words | 66.5 (9-452) [a] | 69 (9-452) | 64 (14-131) [a] | 140 (89-238) |
| Words per minute | 55.5 (11-90.5) | 65.9 (18.8-90.5) | 54.8 (10.7-70.4) | 154.7 (112-198) |
| Proportion of syntactic errors | 4 (0-35) [a] | 3.3 (0-11.11) [a] | 4.8 (0-35) [a] | 0 (0-1.02) |
| Proportion of words in sentences | 0.91 (0-1) [a] | 0.9 (0.6-1) [a] | 0.83 (0-1) [a] | 1 (0.88-1) |
| Proportion of distortions (per 100wrds) | 6.3 (0-33.3) [a] | 10.7 (1.5-33.3) | 4 (0-31.25) [a] | 0 (0-1.33) |

[a] p< 0.05 vs controls; **[b]p< 0.05 PSP vs CBD**; ***[c] Italicized= trend p≤0.10 PSP vs CBD.***
Kruskal-Wallis and post-hoc Mann-Whitney U tests performed. MMSE: minimental state examination. CDR: clinical dementia rating scale. GDS: geriatric depression scale. NPI: neuropsychiatric inventory. CVLT: California verbal learning test. AOS: apraxia of speech.

***Table 6.2.2: Cognitive data at baseline and 1 year follow-up evaluation.***

| | All 4R tau (n=12) | | PSP (n=5) | | CBD (n=7) | |
|---|---|---|---|---|---|---|
| | Baseline | Follow-up | Baseline | Follow-up | Baseline | Follow-up |
| MMSE | 27 (23-30) | ***23 (15-29)***[1 x] | 28 (24-30) | *23 (18-29)*[y] | 27 (23-29) | ***23.5 (15-26)***[1x] |
| Digits Backward | 3 (2-6) | *3 (0-6)*[1] | 3 (2-6) | 3 (0-6) | 3 (3-4) | *3 (0-3)*[1] |
| Benson figure copy | 15 (13-17) | 16 (9-17)[3] | 15 (13-16) | 16 (9-17) | 15 (13-17) | 15.5 (14-17)[3] |
| Benson figure recall | 11.5 (3-17) | 9 (5-16)[3] | 10 (3-13) | 8 (5-13) | 12 (9-17) | 9.5 (7-16)[3] |
| AOS (MSE, 7) | 2 (1-4) | **4 (1-7)**[3x] | 1 (1-4) | 4.5 (1-7)[1] | 2 (1-4) | **4 (3-7)**[2x] |
| Dysarthria (MSE, 7) | 2 (0-7) | 5 (0-7)[3y] | 4 (2-7) | 5.5 (2-7)[1] | 1 (0-4) | 2 (0-7)[2] |
| Speech fluency (WAB, 10) | 9 (5-10) | **5 (1-9)**[2x] | 9 (6-9) | 5.5 (1-9)[1] | 9 (5-10) | **4.5 (2-9)**[1x] |
| Information content (WAB, 10) | 10 (5-10) | **8 (4-10)**[2x] | 10 (5-10) | 5.5 (4-10)[1] | 10 (9-10) | **9 (5-9)**[1x] |
| Sequential commands (WAB, 80) | 75.5 (61-80) | *78 (54-80)*[2] | 80 (69-80) | *78 (66-80)*[1] | 72 (61-80) | *77.5 (54-80)*[1] |
| Grammar comprehension (%) | 86.5 (74-100) | ***73 (58-98)***[2x] | 98 (80-100) | *80 (73-94)*[1y] | 81 (74-98) | *71 (58-98)*[1y] |
| Repetition (WAB, 100) | 88 (52-100) | ***70.5 (12-98)***[2x] | 95 (52-100) | *58 (23-98)*[1y] | 88 (64-100) | *71 (12-98)*[1] |
| Word recognition (WAB, 60) | 60 (59-60) | ***59 (58-60)***[2x] | 60 (59-60) | *59 (58-60)*[1] | 60 (60-60) | ***59 (58-60)***[1x] |
| BNT (15) | 13.5 (11-15) | ***12 (7-15)***[1x] | 12 (11-15) | *12 (10-15)* | 14 (11-15) | *11.5 (7-14)*[1] |
| Phonemic fluency | 5 (2-13) | *3.5 (1-13)*[2] | 5 (2-13) | *5 (1-13)* | 5 (3-6) | *3 (2-9)*[2] |
| Semantic fluency | 10 (6-22) | ***6.5 (1-20)***[2x] | 9 (6-22) | ***8 (1-20)***[x] | 11 (6-13) | ***5 (2-10)***[2x] |

[1] missing one case, [2] missing two cases, [3] missing three cases.

Longitudinal within group comparison: [x] **Baseline vs Follow-up significant at p<0.05;** [y] Baseline vs Follow-up trend at p<0.10**;**

Cross-sectional comparison between groups at time-point 2: *Italicized* = p<0.05 vs Controls at follow-up**.** PSP and CBD did not differ significantly in any measure at time-point 2 when compared directly. Kruskal-Wallis and post-hoc Mann-Whitney U tests performed.

**Neurological symptoms and signs at initial and follow up evaluations** (table-6.3.3)**:**
At presentation, all cases reported difficulty with speech production as their initial and main complaint as well as the primary cause of impaired daily function. A significantly greater proportion of nfvPPA-PSP cases reported sensation of reduced balance and presence of at least 2 falls in the previous year. Also at presentation, a significantly greater proportion of nfvPPA-PSP cases showed buccofacial apraxia and mild axial rigidity in the neurological exam. At 1-year follow-up, more patients with nfvPPA-PSP complained of some swallowing difficulties and showed slower or lower amplitude of vertical than horizontal eye movements on neurologic exam. nfvPPA-CBD patients showed a trend for greater impulsive and obsessive-compulsive behaviors that were nevertheless present in both groups at follow-up.

***Table-6.3.3: Neurological symptoms and signs at presentation, 1 year, >1 year follow-up evaluations and overall****. Number of cases that reported or presented each symptom or sign. Percentages in parenthesis.*

| SYMPTOMS | Presentation | | 1yr follow-up | | >1yr follow-up | |
|---|---|---|---|---|---|---|
| | psp (n=5) | cbd (n=9) | psp (n=5) | cbd (n=6) | psp (n=4) | cbd (n=5) |
| Swallowing complaints | 3 (60) | 1 (11) | **5 (100)** [a] | 1 (17) | 4 (100) | 4 (80) |
| Reduced manual dexterity | 2 (40) | 2 (22) | 4 (80) | 2 (33) | 4 (100) | 3 (60) |
| Gait / Balance | **3 (60)** [a] | 0 (0) | 3 (60) | 1 (17) | 4 (100) | 3 (60) |
| Falls | **2 (40)**[a] | 0 (0) | 3 (60) | 0 (0) | 4 (100) | 2 (40) |
| Incontinence | 0 (0) | 0 (0) | 2 (40) | 0 (0) | 3 (80) | 1 (20) |
| Impulsive | 1 (20) | 4 (44) | 2 (40) | 5 (83) | 2 (40) | 5 (100) |
| Obsessive/ Compulsive | 1 (20) | 2 (22) | 1 (20) | 2 (33) | 1 (20) | 3 (60) |
| **SIGNS** | | | | | | |
| Ocular movements* | 2 (40) | 1 (11) | **5 (100)** [a] | 1 (17) | 4 (100) | 4 (80) |
| -Vertical movements worse^ | 1 (20) | 0 (0) | **4 (80)** [a] | 1 (17) | 4 (100) | 2 (40) |
| Buccofacial apraxia | **4 (80)** [a] | 0 (0) | 5 (100) | 3 (50) | 4 (100) | 3 (60) |
| Asymmetric limb rigidity | 2 (40) | 2 (22) | 4 (80) | 2 (33) | 4 (100) | 3 (60) |
| Axial rigidity | **3 (60)** [a] | 0 (0) | 3 (60) | 2 (33) | 4 (100) | 3 (60) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Limb Dystonia | 0 (0) | 2 (22) | 3 (60) | 1 (16) | 3 (75) | 3 (60) |
| Limb Apraxia | 3 (60) | 3 (33) | 3 (60) | 2 (33) | 4 (100) | 3 (60) |
| Postural instability | 1 (20) | 0 (0) | 2 (40) | 1 (17) | 4 (100) | 2 (40) |
| Cortical sensory/neglect | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 2 (40) |
| Met probable PSP-S criteria | 0 (0) | 0 (0) | 1 (20) | 0 (0) | 2 (50) | 0 (0) |
| Met probable CBD-S criteria | 0 (0) | 0 (0) | 3 (60) | 1 (16) | 4 (100) | 3 (60) |

*Chi squared test performed* ***[a] p< 0.05 PSP vs CBD.*** **Includes mild abnormalities such as decreased initiation, velocity, or amplitude of saccades. ^Indicates vertical movements were more impaired than horizontal movements (only one PSP case presented clear vertical supranuclear gaze palsy at 1yr follow-up and thus met PSP-S criteria). PSP-S, CBD-S: PSP, CBD, syndrome (It was possible for one subject to meet both sets of diagnostic criteria).*

**CROSS-SECTIONAL NEUROIMAGING ANALYSIS AT INITIAL EVALUATION:**

We compared nfvPPA-PSP (n=5) and nfvPPA-CBD (n=9) groups to each other and to healthy controls (n=80) (figure-6.2.1). Image processing was performed using the unified segmentation procedure and the DARTEL toolbox implemented in SPM12 according to standard procedures described elsewhere (Ashburner, 2007; Ashburner & Friston, 2005). Whole brain analyses of differences in grey matter (GM) and white matter (WM) and differences in annual rate of volume change were investigated using an analysis of variance (ANOVA) test across groups, including age, gender, total intracranial volume (TIV), and scanner type as nuisance variables. For the figures, we depicted t-maps at a $p<0.001$ uncorrected threshold for better visualization of differences and similarities between groups. SPM Anatomy toolbox version 2.0 (Eickhoff et al., 2005) was used for reporting of GM coordinates (table-6.2.4).

**Grey Matter:** nfvPPA-4R-tau showed atrophy primarily in a left posterior frontal insular-basal ganglia and superior medial frontal network. The most significant atrophy peaks

were located in left precentral, middle and inferior frontal gyri, left medial supplemental motor area (SMA), left putamen, and left insula.

nfvPPA-CBD showed significant GM atrophy compared to controls in all regions mentioned above, while nfvPPA-PSP only showed small areas of significant GM atrophy in left SMA, precentral and middle frontal gyri, and right cerebellum. Direct group comparison showed greater GM atrophy in nfvPPA-CBD primarily in the left insula and putamen.

**White Matter:** nfvPPA-4R-tau showed extensive left frontal involvement predominantly affecting the WM between the striatum, premotor and prefrontal regions. Other smaller areas of significant atrophy were found in mid corpus callosum, underlying right premotor cortex, and in the midbrain-diencephalic junction.

Both pathological groups showed predominant WM atrophy beneath the left precentral gyrus and SMA and less significant atrophy in mid corpus callosum, right frontal, and left midbrain-diencephalic regions. As shown in figure-6.2.1, in nfvPPA-CBD atrophy extended considerably more anteriorly affecting WM underlying left frontal middle and inferior gyri. The relative proportion of GM to WM damage was strikingly different between patient groups, with PSP showing more WM than GM atrophy. Direct comparison of patient groups showed small regions of greater left prefrontal WM atrophy in nfvPPA-CBD.

**LONGITUDINAL NEUROIMAGING ANALYSIS:**

Only subjects with two MRI scans performed on consecutive years and on the same scanner were included (5 nfvPPA-PSP, 5 nfvPPA-CBD, and 42 controls) (figure-6.2.2). Differences in annual rate of grey and white matter volume change were investigated using an analysis of variance (ANOVA) test across groups, including age, gender, total intracranial volume (TIV), and scanner type as nuisance variables. Image processing was

performed using the unified segmentation procedure, DARTEL toolbox, and Pairwise Longitudinal Registration toolbox (Ashburner & Ridgway, 2012) implemented in SPM12.

**Grey Matter:** The area that showed greatest annual rate of change in nfvPPA-4R-tau included left precentral, middle frontal, and inferior frontal cortex. A homotopic area in the right hemisphere showed the second greatest rate of change followed by contiguous regions of bilateral SMA and middle cingulate cortex.
Both patient groups displayed significant longitudinal atrophy compared to controls in left precentral gyrus and SMA. nfvPPA- PSP showed more areas of significant GM longitudinal change including bilateral precentral, dorsal midbrain and right cerebellar regions. nfvPPA-CBD showed significant change in more anterior parts of left prefrontal cortex. Direct comparison did not reveal any significant differences.

**White Matter:** The area showing greatest rate of change in nfvPPA-4R-tau compared to controls was located underlying the left premotor region and extending anteriorly beneath prefrontal cortex and downwards through the corona radiata, posterior limb of the internal capsule, midbrain-diencephalic junction, left cerebral peduncle, and pons. Another less significant area of contraction was located in right frontal WM.
nfvPPA-CBD only showed significant longitudinal atrophy in one WM cluster underlying left precentral and middle frontal gyrus which extended farther anterior than in nfvPPA-PSP. In nfvPPA-PSP, the greatest rate of annual change included WM in the left half of the midbrain and pons and extended bilaterally into the cerebellar peduncles. Large areas of significant WM change were also visible underlying left and right precentral gyri. Direct comparison did not reveal any significant differences

***Figure-6.2.1: Cross-sectional VBM at presentation of nfvPPA: 4R tau (n=14), PSP (n=5), and CBD (n=9).*** p<0.001 uncorrected for multiple comparisons; 3 group anova (PSP=5, CBD=9, controls= 80). 4 covariates (age, scanner, tiv, gender). Color bar indicates t-values (min: 0, max: 6). Images are in neurological view (left=left).

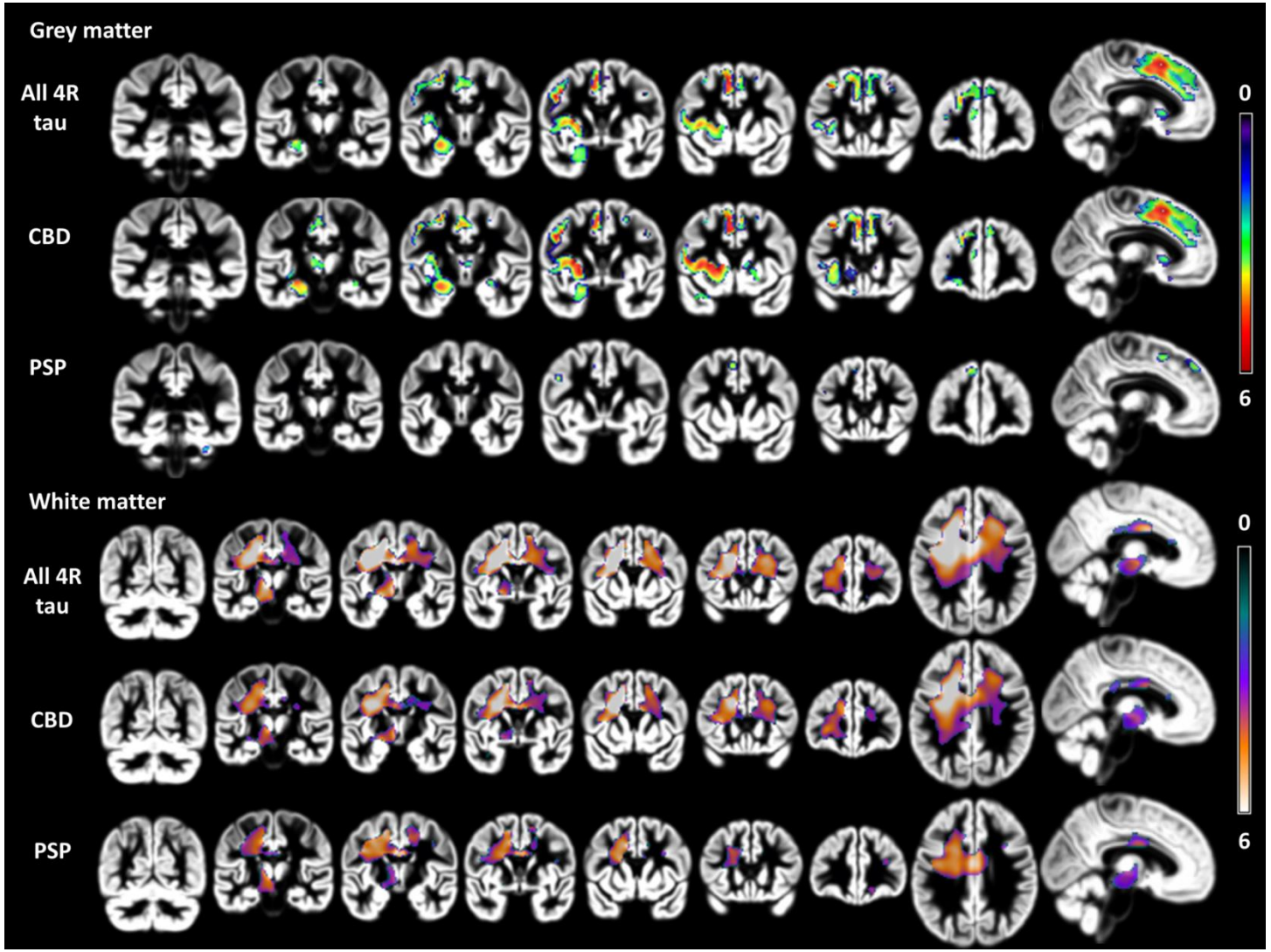


***Figure-6.2.2: Longitudinal VBM of nfvPPA: 4R tau (n=10), PSP (n=5), and CBD (n=5).*** p<0.001 uncorrected for multiple comparisons; 3 group anova (PSP=5, CBD=5, controls= 42). 4 covariates (age, scanner, tiv, gender). Color bar indicates t-values (min: 0, max: 6). Images are in neurological view (left=left).

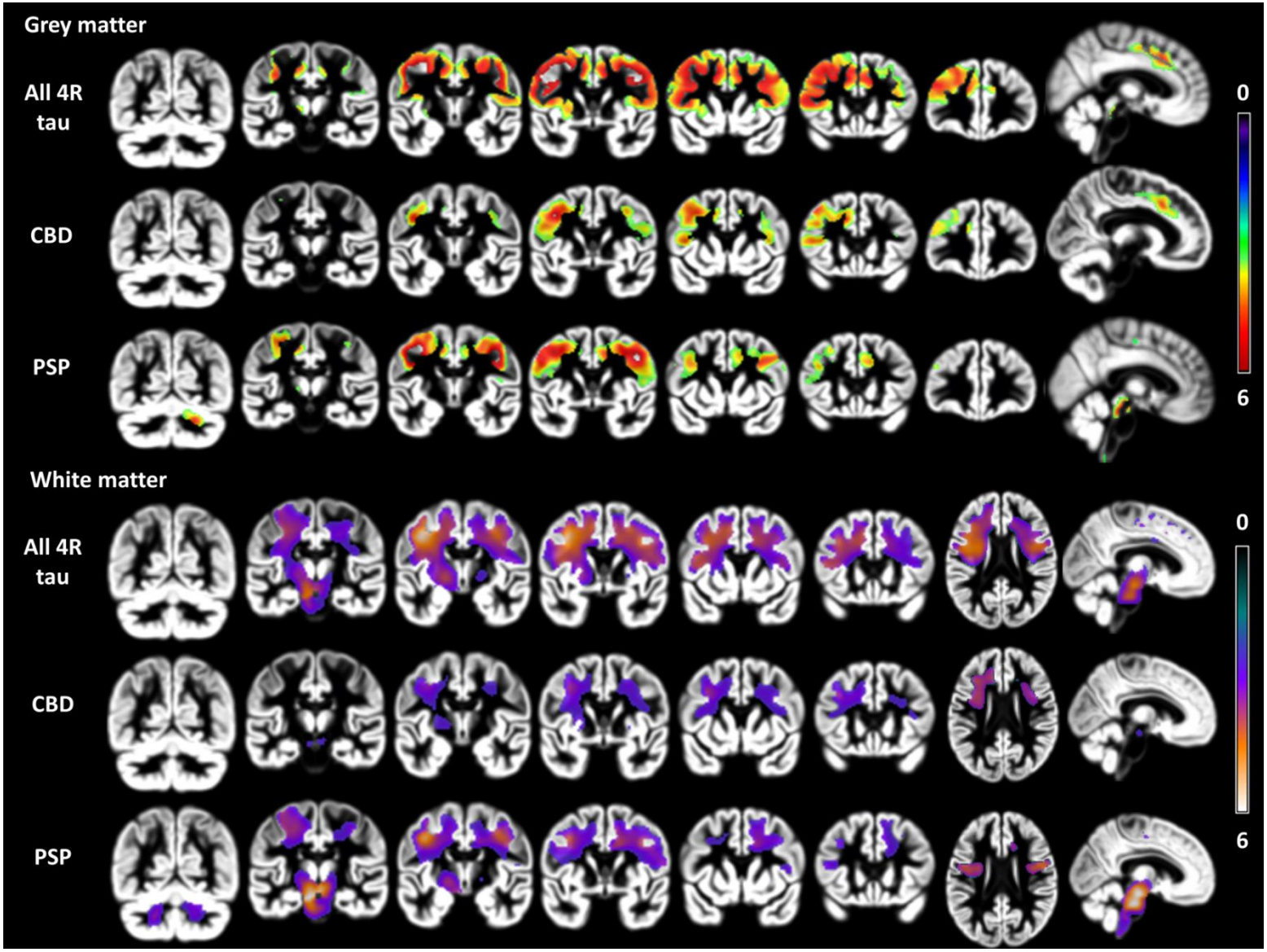


***Table-6.2.4: MNI coordinates of the cross-sectional voxel based morphometry (VBM) analysis.*** SPM Anatomy toolbox version 2.0 used for localization of grey matter coordinates. Effect size= contrast estimate (beta) ± 90% confidence interval. L/R: left/right; SMA: supplementary motor area; IFG: inferior frontal gyrus.

| Cross-sectional VBM - Grey Matter | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **CBD (n=9) < Controls (n=80) [p<0.001 uncorrected threshold]** | | | | | | | | |
| | **x** | **y** | **z** | **t-value** | **p fwe-corr** | **p uncorr** | **Effect size (contrast estimate)** | **Region** |
| Cluster 1 (28288 vox) | | | | | | | | |
| maximum 1 | -42 | 12 | 32 | 6.28 | 0.000 | 0.000 | 0.2 ± 0.04 | L Precentral Gyrus |
| maximum 2 | -48 | -4 | 38 | 7.00 | 0.000 | 0.000 | 0.11 ± 0.03 | L Insula Lobe |
| maximum 3 | -21 | 6 | 6 | 6.17 | 0.000 | 0.000 | 0.09 ± 0.02 | L Putamen |
| maximum 4 | -8 | 15 | 52 | 6.05 | 0.000 | 0.000 | 0.12 ± 0.03 | L posterior-medial frontal |
| maximum 5 | -9 | 14 | 44 | 5.85 | 0.001 | 0.000 | 0.11 ± 0.03 | L MCC |
| maximum 6 | -22 | -3 | 52 | 5.82 | 0.001 | 0.000 | 0.15 ± 0.04 | L Superior Frontal Gyrus |
| maximum 7 | -51 | 9 | 18 | 5.71 | 0.001 | 0.000 | 0.16 ± 0.04 | L IFG (p. Opercularis) |
| Cluster 2 (1144 vox) | | | | | | | | |
| maximum 1 | 18 | 0 | 20 | 4.14 | 0.257 | 0.000 | 0.07 ± 0.03 | R Caudate Nucleus |
| maximum 2 | 27 | -10 | -14 | 3.89 | 0.463 | 0.000 | 0.05 ± 0.02 | R Hippocampus |
| maximum 3 | 21 | 6 | -3 | 3.77 | 0.578 | 0.000 | 0.06 ± 0.03 | R Putamen |
| Cluster 3 (641 vox) | | | | | | | | |
| maximum 1 | 46 | 8 | 40 | 5.02 | 0.016 | 0.000 | 0.13 ± 0.04 | RPrecentral Gyrus |
| maximum 2 | 40 | 2 | 56 | 3.28 | 0.956 | 0.001 | 0.1 ± 0.05 | R Middle Frontal Gyrus |
| Cluster 4 (230 vox) | | | | | | | | |
| maximum 1 | -12 | -15 | 9 | 3.90 | 0.443 | 0.000 | 0.09 ± 0.04 | L Thalamus: prefrontal |
| maximum 2 | -2 | -15 | 6 | 3.33 | 0.935 | 0.001 | 0.1 ± 0.05 | L Thalamus: temporal |
| maximum 3 | 6 | -6 | 9 | 3.40 | 0.901 | 0.001 | 0.06 ± 0.03 | R Thalamus: temporal |
| Cluster 5 (170 vox) | | | | | | | | |
| maximum 1 | -10 | 22 | -24 | 3.79 | 0.561 | 0.000 | 0.06 ± 0.03 | L Superior Orbital Gyrus |
| Cluster 6 (113 vox) | | | | | | | | |
| maximum 1 | 30 | 28 | 45 | 3.74 | 0.607 | 0.000 | 0.1 ± 0.04 | R Middle Frontal Gyrus |
| **PSP (n=5) < Controls (n=80) [p<0.001 uncorrected threshold]** | | | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Cluster 1 (180 vox) | | | | | | | | |
| maximum 1 | -12 | 40 | 51 | 3.86 | 0.494 | 0.000 | 0.07 ± 0.03 | L Superior Frontal Gyrus |
| Cluster 2 (122 vox) | | | | | | | | |
| maximum 1 | -8 | 12 | 54 | 3.69 | 0.664 | 0.000 | 0.09 ± 0.04 | L posterior-medial frontal |
| maximum 2 | -12 | 22 | 52 | 3.41 | 0.868 | 0.000 | 0.07 ± 0.03 | L Superior Frontal Gyrus |
| Cluster 3 (94 vox) | | | | | | | | |
| maximum 1 | -46 | 2 | 38 | 3.85 | 0.503 | 0.000 | 0.12 ± 0.05 | L Precentral Gyrus |
| Cluster 4 (40 vox) | | | | | | | | |
| maximum 1 | 34 | -34 | -33 | 3.50 | 0.832 | 0.000 | 0.07 ± 0.03 | R Cerebelum (VI) |
| **CBD (n=9) < PSP (n=5) [p<0.01 uncorrected voxelwise threshold; 100 voxel clusterwise threshold]** | | | | | | | | |
| Cluster 1 (1511 vox) | | | | | | | | |
| maximum 1 | -20 | 8 | 4 | 3.15 | 0.985 | 0.001 | 0.07 ± 0.03 | L Putamen |
| maximum 2 | -34 | 21 | -10 | 3.00 | 0.997 | 0.002 | 0.11 ± 0.06 | L Insula Lobe |
| Cluster 2 (485 vox) | | | | | | | | |
| maximum 1 | 63 | 0 | -24 | 3.48 | 0.848 | 0.000 | 0.1 ± 0.05 | R Middle Temporal Gyrus |
| maximum 2 | 64 | -16 | -27 | 2.89 | 0.999 | 0.002 | 0.09 ± 0.05 | R Inferior Temporal Gyrus |
| Cluster 3 (410 vox) | | | | | | | | |
| maximum 1 | -21 | -18 | -14 | 3.36 | 0.920 | 0.001 | 0.06 ± 0.03 | L Hippocampus |
| maximum 2 | -34 | -16 | -8 | 2.88 | 0.997 | 0.002 | 0.05 ± 0.03 | L Putamen |
| Cluster 4 (304 vox) | | | | | | | | |
| maximum 1 | 28 | -72 | 40 | 2.93 | 0.999 | 0.002 | 0.1 ± 0.06 | R Superior Occipital Gyrus |
| maximum 2 | 32 | -66 | 36 | 2.56 | 1.000 | 0.006 | 0.16 ± 0.1 | R Middle Occipital Gyrus |
| Cluster 5 (271 vox) | | | | | | | | |
| maximum 1 | -10 | -18 | 6 | 2.83 | 1.000 | 0.003 | 0.1 ± 0.06 | L Thalamus |
| Cluster 6 (145 vox) | | | | | | | | |
| maximum 1 | 18 | 0 | 20 | 3.44 | 0.877 | 0.000 | 0.09 ± 0.04 | R Caudate Nucleus |
| **PSP (n=5) < CBD (n=9) [p<0.01 uncorrected voxelwise threshold; 100 voxel clusterwise threshold]** | | | | | | | | |
| Cluster 1 (104 vox) | 58 | -50 | 42 | 3.05 | 0.995 | 0.002 | 0.1 ± 0.05 | R Angular gyrus |

## VIc. CLINICAL AND NEUROANATOMICAL FEATURES PREDICTIVE OF AMYLOID IMAGING STAUTS IN PRIMARY PROGRESSIVE APHASIA

**A. Introduction**

**B. Participant selection and characterization**

**C. Clinical and neuroanatomical features predictive of amyloid imaging status in primary progressive aphasia**

**D. Amyloid deposition and grey matter asymmetry in lvPPA**

## INTRODUCTION

We studied amyloid brain imaging in a large cohort of prospectively diagnosed PPA patients to investigate which clinical and neuroanatomical features were the most predictive of amyloid positivity. To study the topography of PIB deposition and its relationship to atrophy in lvPPA we extracted PIB uptake and grey matter volumes in selected regions of interest and calculated asymmetry indexes for both amyloid deposition and cortical atrophy.

## PARTICIPANT SELECTION AND CHARACTERIZATION

See section 4.1.A “participant selection and characterization.”

## CLINICAL AND NEUROANATOMICAL FEATURES PREDICTING AMYLOID STATUS IN PRIMARY PROGRESSIVE APHASIA

We used a data driven approach unbiased by PPA variant diagnosis to classify patients according to their amyloid imaging status and to infer which cognitive measures were the best predictors of amyloid status by entering all test scores and the amyloid imaging result for each patient in a discriminant analysis (PPA variant diagnosis was not entered). Statistical analyses were conducted in SPSS statistical package

Discriminant analysis using raw scores of the cognitive measures in table-6.3.1 produced a function that correctly classified 96% (52 out of 54) of the amyloid negative and 86% (29 out of 35) of the amyloid positive cases. Of the misclassified amyloid + cases, two were svPPA (one with mixed FTLD-AD pathology), two nfvPPA (one with mixed FTLD-AD pathology), and two were lvPPA. The misclassified amyloid negative cases were one lvPPA and one nfvPPA. As seen in table-3, the five measures with the highest function coefficients, and therefore highest explanatory power were Benson figure recall, motor speech, phonemic fluency, sentence repetition, and the neuropsychiatric inventory.

Discriminant analysis employing only language measures successfully classified 47 out of 54 amyloid negative and 25 out of 35 amyloid positive patients. In this case the measures with the highest function coefficients were sentence repetition (0.85), single word comprehension [PPVT] (0.69), motor speech (0.64), category fluency [animals](0.62), and phonemic fluency [D-words] (0.57).

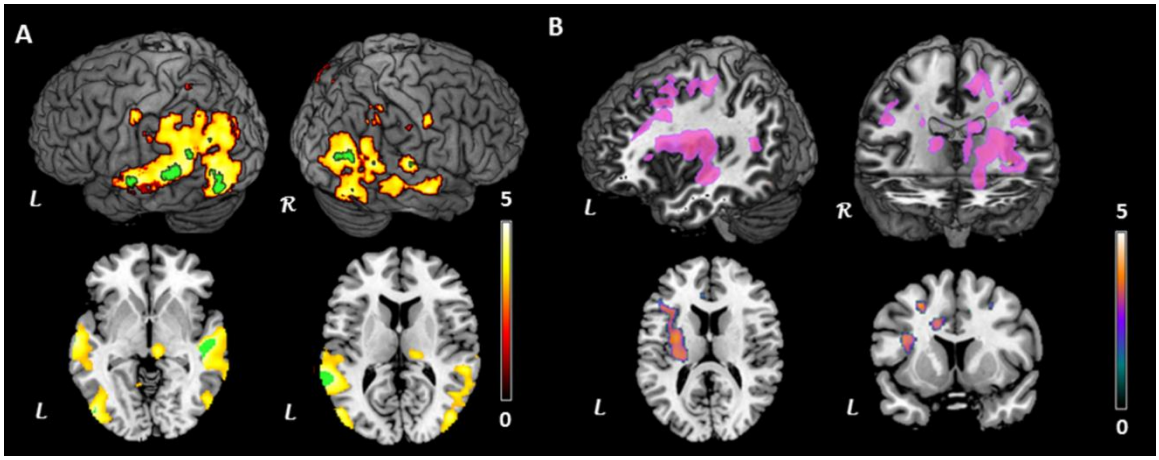
***Table-6.3.1: Clinical features discriminating amyloid status in PPA.***

| GENERAL COGNITION | Standardized discriminant function coefficient |
|---|---|
| GDS | 0.26 |
| NPI | 0.54* |
| UPDRS | 0.27 |
| Benson figure copy (/17) | 0.14 |
| Calculations (/5) | 0.00 |
| CVLT-MS Total recall | 0.43 |
| CVLT-MS 10m free recall | 0.18 |
| Benson figure recall | 0.66* |
| Digits Backward | 0.12 |
| Modified trails (lines per min) | 0.35 |
| LANGUAGE | |
| Boston Naming Test (BNT, 15) | 0.22 |
| Semantic fluency (animals) | 0.38 |
| Phonemic fluency (D words) | 0.60* |
| Speech fluency (WAB, 10) | 0.13 |
| Information content (WAB, 10) | 0.1 |
| Motor speech (AOS+dysarthria) | 0.55* |
| PPVT | 0.36 |
| PPTp | 0.29 |
| Sentence comprehension (%) | 0.11 |
| Repetition (WAB, 100) | 0.54* |

**Features discriminating amyloid status statistically (Wilks' Lambda = 0.462; p<0.0001). NPI: neuropsychiatric inventory. UPDRS: unified parkinsons disease rating scale. CVLT: California verbal learning test. AOS: apraxia of speech. PPVT: Peabody's picture vocabulary test. PPTp: pyramids and palm trees picture version.*

In the whole-brain voxel-wise regression analysis (figure-6.3.1), grey matter atrophy in the bilateral posterior temporal and inferior parietal lobes predicted amyloid positivity at p< 0.05 FWE corrected for multiple comparisons. Left frontal, temporal, and diencephalic white matter volume loss predicted amyloid negativity.

***Figure-6.3.1: Neuroanatomical features predictive of amyloid-PET status*.**




***A**. Voxels in which reduced grey matter volume predicted amyloid positivity in PPA (n=89 PPA subjects). Results shown at a family wise error corrected threshold of p<0.05 (green) and at an uncorrected threshold of p< 0.001 (hot color). **B**. Voxels in which reduced white matter volume predicted amyloid negativity. Results shown at an uncorrected threshold of p< 0.001 (n=89 PPA subjects).*

**AMYLOID DEPOSITION AND GREY MATTER ASYMMETRY IN LVPPA**

First we extracted PIB deposition and grey matter volume values in each region of interest and then calculated an asymmetry index percentage for PIB deposition and grey matter for each subject in each ROI. For all participants who underwent PIB-PET, a

global PIB SUVR was extracted in template space representing mean SUVR values in cortical regions prone to amyloid deposition [for details see (Ossenkoppele et al., 2016)]. In lvPPA only, mean [$^{11}$C]PIB SUVR and GM values were extracted for FreeSurfer-defined ROIs in native space: frontal (superior and middle gyri, pars opercularis, triangularis, and orbitalis, orbitofrontal, precentral, paracentral, and frontal pole), superior temporal (superior temporal sulcus, bank of the superior temporal sulcus, transverse temporal), middle temporal, inferior temporal, precuneus, superior parietal, inferior parietal, supramarginal, anterior cingulate (rostral anterior, caudal anterior), posterior cingulate (isthmus, posterior), and occipital (lateral, lingual, cuneus). We calculated PIB and GM asymmetry indexes for each region of interest using the formula AI [%] = 200 (R-L)/ (R + L). Thus, negative percentages indicate left lateralized asymmetry (Frings et al., 2015; Ossenkoppele et al., 2016). To evaluate the presence of significant asymmetry in each ROI we used a one sample t-test (i.e. distribution of AI percentage significantly different from 0). To study the relationship between [$^{11}$C] PIB deposition and atrophy in each ROI, we used Spearman partial correlation. Age, gender, total intracranial volume (TIV), and GM/TIV (as a measure of disease severity) were included as nuisance variables in both statistical comparisons and the Bonferroni method was used to correct for multiple comparisons.

The PIB asymmetry index (AI) was significantly left asymmetric in the anterior cingulate ROI only whereas the GM AI was significantly left asymmetric in frontal, occipital, all three parietal (superior, inferior, supramarginal), and all three temporal (superior, middle, inferior) ROIs. Neither the PIB and GM AIs nor their raw values were significantly correlated in any of the ROIs (tables-6.3.2&3, figure-6.3.2).

***Table-6.3.2: PIB and GM asymmetry indexes in amyloid positive lvPPA.***

| Region of interest | mean PIB AI (SD) | one sample t-test p-value | mean GM AI (SD) | one sample t-test p-value | Spearman correlation coefficient (p-value) |
|---|---|---|---|---|---|
| ACC | -4 (5.6) | 0.035* | 1.1 (19.1) | 1 | -0.08 (1) |
| PCC | 1.2 (5.7) | 1 | -1.2 (13.6) | 1 | 0.02 (1) |
| frontal | -0.9 (2.8) | 1 | -4.9 (5) | 0.002* | -0.29 (1) |
| occipital | -1.7 (8.4) | 1 | -11.8 (7.4) | 0.000* | 0.03 (1) |
| parietal_inferior | 3.2 (5.7) | 0.171 | -32.1 (11.8) | 0.000* | -0.17 (1) |
| parietal_superior | -2.8 (5.7) | 0.356 | -8.5 (10) | 0.007* | -0.1 (1) |
| precuneus | -2.2 (3.8) | 0.132 | -14.2 (10.6) | 0.000* | -0.06 (1) |
| supramarginal | -2.9 (6.7) | 0.623 | -6.9 (10) | 0.042* | 0.24 (1) |
| temporal_inferior | 0.7 (21.7) | 1 | -16.5 (13.5) | 0.000* | 0.14 (1) |
| temporal_middle | 0.3 (9.7) | 1 | -25.5 (13.5) | 0.000* | 0.05 (1) |
| temporal_superior | -3.5 (6.8) | 0.268 | -9.1 (9.3) | 0.002* | 0.1 (1) |

*Mean (standard deviation) of PIB and GM volume asymmetry index (AI) percentages; one-sample t-test assessing whether PIB and GM AI percentages were significantly different than 0 in each region of interest; Spearman partial correlation between PIB and GM AI (covariates: age, gender, total intracranial volume (TIV), and TIV/GM [as a proxy of disease severity]).*

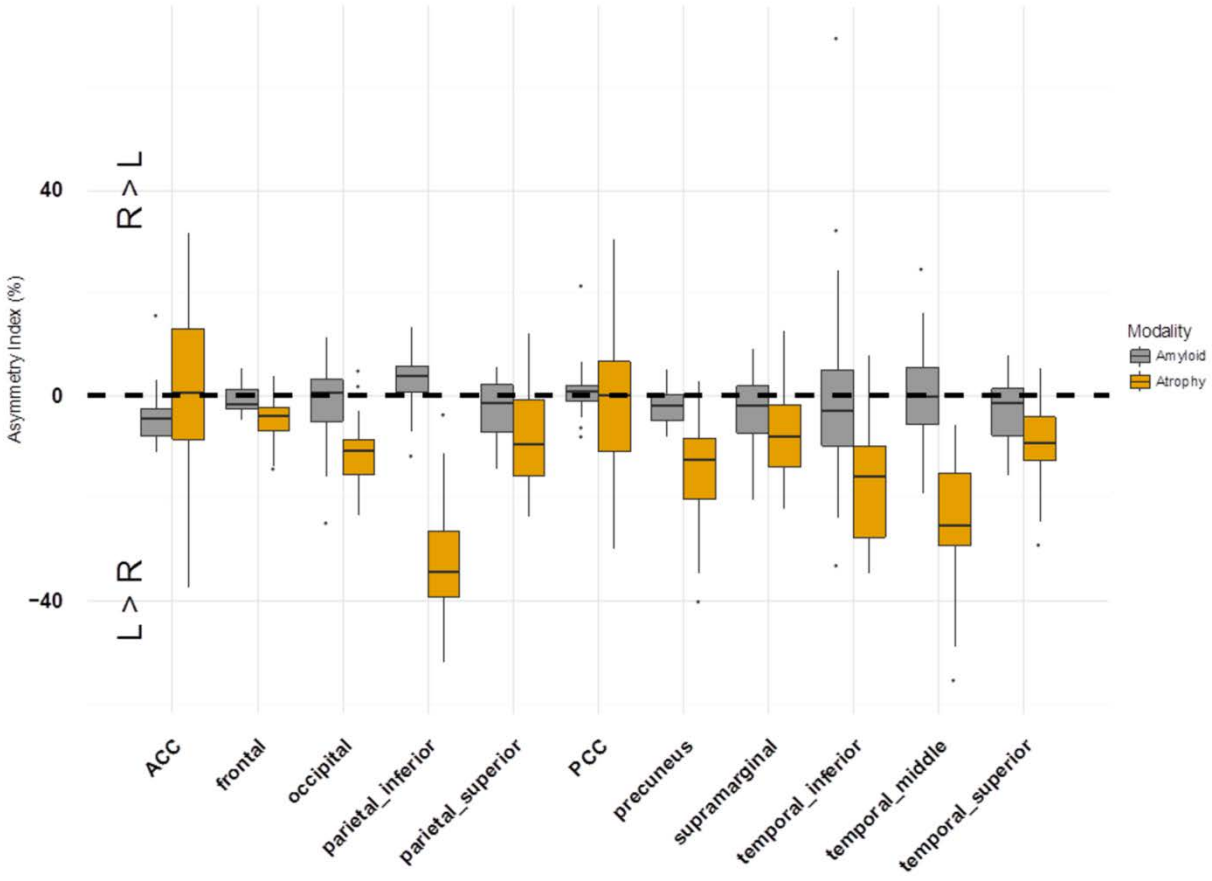
***Table-6.3.3: PIB and GM raw values correlation in amyloid positive lvPPA.***

| Left hemisphere region of interest | Spearman correlation coefficient (p-value) | Right hemisphere region of interest | Spearman correlation coefficient (p-value) |
|---|---|---|---|
| LH_ACC | 0.256 (1) | RH_ACC | -0.136 (1) |
| LH_PCC | 0.055 (1) | RH_PCC | -0.377 (1) |
| LH_frontal | 0.006 (1) | RH_frontal | -0.433 (1) |
| LH_occipital | 0.261 (1) | RH_occipital | 0.237 (1) |
| LH_parietal_inferior | 0.454 (1) | RH_parietal_inferior | 0.275 (1) |
| LH_parietal_superior | 0.194 (1) | RH_parietal_superior | 0.151 (1) |
| LH_precuneus | 0.381 (1) | RH_precuneus | 0.065 (1) |

| | | | |
|---|---|---|---|
| LH_supramarginal | 0.293 (1) | RH_supramarginal | 0.207 (1) |
| LH_temporal_inferior | 0.205 (1) | RH_temporal_inferior | -0.462 (1) |
| LH_temporal_middle | 0.248 (1) | RH_temporal_middle | 0.077 (1) |
| LH_temporal_superior | 0.201 (1) | RH_temporal_superior | 0.223 (1) |

*Spearman partial correlation between PIB and GM raw values (covariates: age, gender, total intracranial volume (TIV), and TIV/GM [as a proxy of disease severity]. Bonferroni corrected for multiple comparisons). L/RH: left/right hemisphere. ACC: anterior cingulate cortex. PCC: posterior cingulate cortex.*

***Figure-6.3.2: Box plot depicting relationship between PIB and grey matter volume asymmetry indexes.*** *Grey= PIB asymmetry index; yellow= atrophy asymmetry index.*



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# VII. DISCUSSION

## DISCUSSION

The studies included in this thesis addressed the issue of clinico-pathologic correlation in neurodegenerative disease and more specifically in primary progressive aphasia. In the first study we analyzed rates of amyloid PET positivity to test the hypothesis that classification according to the recently established consensus PPA variant diagnostic criteria would result in groups with largely homogeneous amyloid biomarker profiles. We found that the current classification scheme was highly predictive of amyloid biomarker status with lvPPA being associated to amyloid positivity in more than 95% of cases. Furthermore, the amyloid biomarker discordant cases (amyloid positive svPPA and nfvPPA) that had available autopsy data received a primary pathologic diagnosis of FTLD with presence of contributing AD pathology, suggesting that cases of amyloid biomarker positive svPPA and nvfPPA might be more indicative of mixed FTLD – AD pathology than primary AD.

In the second study we identified clinical and neuroimaging features that may help predict underlying pathology in nfvPPA which is the most pathologically heterogeneous of the PPA clinical variants. Greater dysarthria and relative predominance of white-matter atrophy at presentation and greater rate of brainstem atrophy and appearance of brainstem clinical signs at follow-up were characteristic of underlying nfvPPA-PSP. nfvPPA-CBD showed more impairment in sentence comprehension, verbal working memory, and greater grey matter atrophy at presentation along with spread of atrophy to anterior cortical structures and greater presence of behavioral symptoms at follow-up.

The third study quantified and evaluated the ability of different cognitive and neuroimaging measures to predict which primary progressive aphasia patients have presumptive Alzheimer's disease pathology (using amyloid-PET as a surrogate marker).

A data-driven analysis was able to correctly classify 96% amyloid negative and 86% amyloid positive cases. We found that measures of visual memory and behavioral impairment show similar ability to predict amyloid-PET status as the best performing language measures, which were motor speech and sentence repetition suggesting non-language measures hold potential value for improving differential diagnosis.

Finally, the last study also investigated the relationship between amyloid deposition measured by PET-PiB imaging and brain atrophy. We found that, within lvPPA, grey-matter volume loss was highly asymmetric and predominant in language regions whereas amyloid deposition was diffuse throughout association cortices and symmetric between hemispheres suggesting another factor different from amyloid deposition is driving progression of brain atrophy.

**PPA variant classification according to 2011 consensus diagnostic criteria improves reliability of clinico-pathologic correlations**

In our cohort of 89 PPA patients, 85% of svPPA and 90% nvfPPA were amyloid negative whereas 96% of lvPPA were amyloid positive. Furthermore, all of the amyloid discordant cases with available autopsy data (two svPPA and two nfvPPA) had primary FTLD and secondary Alzheimer's disease pathological diagnoses. These results mark an important improvement in the reliability of clinico-pathologic correlation in primary progressive aphasia compared to previously when diagnosis was established according to the 1998 consensus frontotemporal clinical diagnostic criteria (Neary) criteria (Neary et al., 1998) which included criteria for semantic dementia, progressive non-fluent aphasia, and frontotemporal dementia. The majority of this improvement stems from the enhanced ability to detect underlying AD, especially in patients presenting progressive non-fluent aphasia which was much more pathologically heterogeneous than semantic dementia. With the appearance of the 2011 PPA variant criteria, many patients who would have received a diagnosis of progressive non-fluent aphasia, are diagnosed instead with lvPPA

which is predominantly associated with AD pathology. In a recent retrospective clinico-pathologic study by (Chare et al., 2014), all FTLD cases from the Cambridge and Sydney databases are reviewed and new clinical and pathologic diagnoses are established and compared with previous ones. They report 55% (18/33) of old progressive non-fluent aphasia and 6% (2/31) old semantic dementia cases received a lvPPA diagnosis and that the lvPPA group was 77% AD pathologically. This marked improvement in AD discrimination is partly tainted because the new nfvPPA group was still 3% AD at autopsy, thus continuing to be the most pathologically heterogeneous of the three PPA variants. Furthermore, other recent studies investigating clinico-pathologic correlations with current PPA criteria vary significantly in the prevalence of AD pathology in each variant, particularly in nfvPPA and lvPPA (svPPA 0-16% Alzheimer's disease; nfvPPA 0-31%; lvPPA 54-100%).

What are the possible reasons for this? A probable factor is presence of significant differences between the patient cohorts included. For example our cohort did not include PPA cases with genetic mutations whereas other studies did. Carriers of progranulin mutations can present with a mixed logopenic-like syndrome [33,34] and are associated to TDP-43 pathology, not AD. Another possible factor could be the retrospective nature of some studies. Many cases possibly lacked the targeted cognitive evaluations required for proper application of current criteria, not to mention the intrinsic difficulty of distinguishing bewtween motor apraxic and phonologic speech errors without audio/video-taped speech samples. Retrospective studies report AD in 0-16% svPPA, 3-31% nfvPPA, and 54-77% lvPPA (Chare et al., 2014; Harris & Jones, 2014; M M Mesulam et al., 2014); whereas prospective studies report 0-5% svPPA, 0-25% nfvPPA, and 92-00% lvPPA (Botha et al., 2015; Gil-Navarro et al., 2013; Leyton et al., 2011). Finally, variability in the application of current diagnostic criteria across centers is also a possible factor affecting the rates of AD pathology in each variant. Some examples of probable causes of variability in the application of current diagnostic criteria across

centers will be discussed later under the section titled “Issues regarding classification according to current PPA consensus criteria.”

**Characteristics of PPA with “discordant” (amyloid positive svPPA and nfvPPA, and amyloid negative lvPPA) amyloid status**

We did not find any demographic, genetic, cognitive, or neuroimaging features that reliably distinguished amyloid positive svPPA or nfvPPA from their primarily amyloid-negative counterparts. Carrying an apoE4 allele was a risk factor for amyloid positivity even within just svPPA and nfvPPA (OR 5.6; 95% CI .-29.; p=0.04). No genetic mutations were found in any of these cases. All four amyloid positive svPPA patients showed the typical profile of predominant semantic impairment with relatively preserved motor speech and phonologic processing associated to an asymmetric predominantly left anterior temporal lobe atrophy pattern suggesting FTLD may be the primary pathologic diagnosis in all four patients. Three patients scored outside of the amyloid negative group’s interquartile range on all tests requiring sentence processing and two patients showed highly impaired set shifting in the Modified trails test which is unusual for typical svPPA and may reflect an Alzheimer’s disease contribution to the clinical picture (Pa et al., 2010). Even though our data suggest that all four amyloid positive svPPA patients in our cohort have mixed FTLD-AD pathology, we recognize cases of pathologically confirmed semantic dementia have been described (Alladi et al., 2007; Davies et al., 2005). A recent study showed that some of these cases would be reclassified as lvPPA (two out of 31, 6%) when using current PPA diagnostic criteria, however five of 27 (6%) of svPPA cases were still found to have AD at autopsy (Chare et al., 2014). The authors found that phonologic parafasias were more frequent in svPPA due to AD and disinhibition in svPPA due to FTLD. In my opinion the retrospective nature of the diagnoses and differences in disease severity at the moment of evaluation (it is known that disease severity can affects the extent of semantic deficits in AD (Matthew A Lambon Ralph, Patterson, Graham, Dawson, & Hodges, 2003; Rogers,

Ivanoiu, Patterson, & Hodges, 2006)) between patients could be significant factors in the unusually high prevalence of AD pathology reported in this study.

All amyloid positive nfvPPA subjects also showed the typical cognitive profile of predominant impairment in speech fluency with varying degrees of motor speech impairment and agrammatism on language testing and predominant executive impairment with milder impairments in memory and visuospatial functions on general cognitive testing. Single subject vbm also revealed a common area of atrophy in the left posterior frontal lobe, though each case presented different areas of accompanying atrophy perhaps reflecting the heterogeneous pathologic diagnoses that are known to be associated with nfvPPA. Case F had accompanying right posterior frontal lobe atrophy which may explain her severe AOS compared to the other cases. Subject G showed significant volume loss in the right medial temporal region which may explain her low score on the visual memory test. Finally, subject E showed significant volume loss in the left middle-superior temporal and posterior frontal regions (both ends of the arcuate fasciculus) which may explain her severely impaired phonologic working memory (measured by digits forward span) (Leyton, Piguet, Savage, Burrell, & Hodges, 2012) and sentence comprehension (Amici et al., 2007; S. M. Wilson, Dronkers, et al., 2010) compared to the amyloid negative nfvPPA group.

The amyloid negative lvPPA case in our cohort showed more semantic impairment and her pattern of left temporal atrophy was more anterior and left asymmetric than the amyloid positive lvPPA group. Recent studies have also reported a trend towards worse semantics (J D Rohrer, Ridgway, et al., 2010) and greater left asymmetric anterior temporal atrophy and/or hypometabolism (Matías-Guiu et al., 2015; Whitwell et al., 2015) in amyloid negative lvPPA. According to current genetic and pathological data, the majority of amyloid negative lvPPA cases are associated with a mutation in the *GRN*

gene (J D Rohrer, Crutch, et al., 2010; Whitwell et al., 2015) or sporadic TDP-A pathology (Chare et al., 2014; Harris et al., 2013; M M Mesulam et al., 2014).

**Characteristics of patients with mixed-PPA syndrome**

All four mixed-PPA (PPAm) patients in our cohort presented core features of more than one variant which were thought to contribute equally to the clinical picture. Patients W and X showed significantly impaired word finding in spontaneous speech, defective phonologic processing (evident in sentence repetition and comprehension scores), and AOS in the motor speech exam. Patient W's pattern of atrophy affected the left mid-posterior temporal and posterior frontal regions in accordance with her symptoms. Patient X presented at a more advanced stage of disease as evidenced by her low scores on the MMSE, memory, and visuospatial function tests along with the global pattern of atrophy. The other two PPAm patients, patients Y and Z, presented with a mixed picture of impaired phonologic processing along with impaired scores on both verbal and visual semantic association tests. Both patients presented strikingly similar atrophy patterns affecting left frontal, temporal and inferior parietal lobes. Furthermore, patient Z was found to have PiD pathology at autopsy. Even before knowing the result of the amyloid imaging, AD was the predicted pathology in both patients with mixed phonologic and motor speech impairment due to the relative predominance of phonologic impairment, posterior vs frontal atrophy, and presence of impaired memory neuropsychological scores. However, the frontal, temporal, and inferior parietal atrophy seen in patients Y and Z is similar to the PiD atrophy pattern previously demonstrated by Rohrer et al (Rohrer et al., 2011) and raises the possibility that patient Y's positive amyloid result reflects another case of mixed PiD-AD pathology. In a recent study carried out in parallel to the work in this thesis we described the entire UCSF MAC PPA pathological cohort (Spinelli et al., 2017) and found that PiD presented as any PPA variant except lvPPA and constituted 50% of the PPAm cases supporting the hypothesis that PiD presents with a variable frontotemporal pattern of atrophy, leading to different clinical correlates within

the spectrum of frontotemporal degeneration disorders (J D Rohrer et al., 2011). If this is true, it is possible that the majority of Picks Disease cases could present a mixed-PPA clinical phenotype if they present to evaluation further enough into their disease course such that frontal, temporal, and anterior parietal regions are affected. We did not find any patient that presented with another previously described mixed PPA phenotype of equally impaired grammatical production and verbal semantics (M. Marsel Mesulam, Wieneke, Thompson, Rogalski, & Weintraub, 2012). Further studies including larger numbers of mixed cases are needed to determine if these present with consistent clinical syndromes and pathologic associations.

**Language profiles were predictive of AD biomarker status in patients that did not meet root PPA criteria**

In our cohort, 20 subjects showed significant aphasia that could be classified into one of the PPA variants however they were excluded because they presented with significant symptoms outside of the language domain and thus did not meet root PPA criteria. Four patients diagnosed as right temporal predominant semantic dementia, six Alzheimer's disease, and one progressive spastic dysarthria presented language symptoms compatible with svPPA, lvPPA, and nfvPPA respectively. These patients showed homogeneous amyloid biomarker status similar to the PPA variants that met root PPA criteria, therefore supporting the use of language profiles for predicting pathology despite not meeting root PPA criteria. This situation has been reported by other authors (Harris et al., 2013) that argue that the requirement that language difficulty be the most prominent impairment during the initial phases of disease can lead to confusion when diagnosing and predicting the underlying pathology in patients with right temporal variant frontotemporal lobar degeneration and early-onset Alzheimer's disease which present similar clinical profiles as svPPA and lvPPA. Ultimately, a consensus should be reached regarding the exact boundaries, the usefulness, and the continued use of these syndromes in clinical and research settings.

**Issues regarding classification according to current PPA consensus criteria**

Similar to other recent studies (Chare et al., 2014; Harris et al., 2013; Leyton et al., 2011), we were able to identify the initial predominantly impaired language domain and classify almost all (85 out of 89) subjects that met root PPA criteria. However, some studies report inability to classify a higher proportion of subjects, especially when attempting data-driven vs clinical classification methods (Sajjadi, Patterson, Arnold, Watson, & Nestor, 2012; Wicklund et al., 2014). What can be causing these discrepancies? Previous reports describe two main issues: that a significant number of subjects present with a mix of core language impairments thus meeting criteria for more than one variant while other subjects present only with anomia and thus do not meet criteria for any variant (Botha et al., 2015; M M Mesulam et al., 2014). It is inevitable that real differences in patient populations will be a source of variability due to referral bias. For example, a possible factor in the absence of patients presenting only anomia in our cohort could be that the aphasia tended to be further evolved prior to referral to our specialty center. The UCSF Memory and Aging Center is a highly specialized center and most of our patients are 3$^{rd}$ or 4$^{th}$ referrals originating from any region of the USA and even other countries. Similarly, the low proportion of mixed cases could be due in part to the absence of progranulin mutation carriers in our cohort, who have been shown to present with a logopenic-like mixed PPA syndrome (J D Rohrer, Crutch, et al., 2010). While both of these issues can definitely cause variability in the proportion of classified cases, their effect is magnified by methodological differences in the application of current diagnostic criteria across centers.

One methodological difference is the use of cut-off scores in specific cognitive tests to determine a binary score of presence/absence of a specific clinical feature instead of using clinical judgment to focus on which cognitive mechanisms are impaired or relatively spared and then establishing a PPA variant diagnosis. This is relevant when

determining the presence of grammatical impairment based on scores in syntax production tests such as the Northwestern agrammatism test (NAT). In our experience many lvPPA patients will score poorly on syntax production and comprehension tests primarily due to impaired executive function instead of a core grammatical impairment. Similarly, significantly impaired word-finding can lead to presence of grammatical errors in connected speech as notably shown by Wilson et al (S. M. Wilson, Henry, et al., 2010). The authors transcribed spontaneous speech samples and quantitated various indexes of grammatical competency and found presence of syntax errors in all PPA variants. Crucially, these errors were of a different form across variants. In lvPPA, grammatical errors were generally of a paragramatic nature (unacceptable juxtapositions of phrases and misuse of words (Goodglass et al., 1994) or substitution errors typical of fluent aphasias (B. Wilson, 2011)), whereas nfvPPA errors were agrammatic (frank omissions of functional words or morphemes). Consequently, many lvPPA patients could be considered agrammatic and diagnosed as nfvPPA or mPPA if one were to focus on this instead of their predominant word-finding and sentence repetition impairment due to a primarily impaired phonologic language system. The use of cut-off scores to determine sentence repetition impairment, a core feature of lvPPA, can also lead to misclassification. In lvPPA, impaired sentence repetition should not primarily be due to impaired motor speech or a general deficit of executive function, but to an impaired phonologic loop (or verbal working memory) which is the cognitive mechanism that localizes to the posterior superior temporal gyrus and is predominantly atrophied in lvPPA. Therefore, in our opinion it is critical for the clinician to judge what cognitive mechanism(s) are causing low scores to effectively apply the diagnostic criteria.

Another methodological difference is the use of non-language data to aid in diagnosis and establish an “imaging confirmed” variant diagnosis as described in current criteria. For example, neuroimaging was not available for the majority of cases described in publications reporting retrospective PPA variant diagnosis. Also, the use of non-

language cognitive data such as memory and visuospatial tests is useful for differentiating between variants however their use has not been operationalized yet which can lead to variability in their application to diagnosis across centers. Some centers may prefer a "pure" language oriented approach to diagnosis whereas others readily incorporate all available data.

A few research groups have proposed modifications to the current criteria to address problems they have encountered such as that many patients present only with anomia and do not meet any criteria, that others present a mix of core language impairments and meet multiple criteria, the heterogeneity of clinicopathologic correlations across centers, and the requirement of absence of non-language symptoms during the initial phases of disease. Undoubtedly there is room for improvement and the current criteria will have to be modified to accommodate future advances; however, as researchers in the field of primary progressive aphasia, we should concentrate efforts on standardizing evaluation methodologies before modifying current clinical criteria. If not, we risk encountering similar problems of discrepant results across centers when applying future diagnostic criteria.

**Advances in clinicopathologic correlation in nfvPPA**

A significant portion of the work included in this thesis focused on clinico-pathologic correlation in the nfvPPA syndrome. As discussed earlier, this is still the most pathologically heterogeneous PPA syndrome despite the clear improvement in the accuracy of AD pathology prediction brought on by the re-classification of cases with progressive non-fluent aphasia to lvPPA when using 20 consensus PPA diagnostic criteria (Chare et al., 2014). Recent work from our lab has recently described the complete UCSF MAC pathologically-proven nfvPPA cohort. 4R-tauopathy (CBD 44%, PSP 24%, unclassifiable 4R-tauopathy 4%, mixed CBD-AD 4%) was the most frequent pathology whereas PiD (6%) and TDP-A (8%) accounted for the remaining cases (Spinelli et al.,

2017). All but 2 patients presented with greater motor speech than agrammatism impairment. Presence of hypokinetic dysarthria, earlier appearance of parkinsonian features, and greater white-matter atrophy distinguished nfvPPA-tau from nfvPPA-TDP-A in which dysarthria was primarily spastic and generalized motor symptoms were less severe and appeared only in late disease stages (Caso et al., 2014). Greater dysarthria and a relative predominance of white vs grey matter atrophy at presentation and greater rate of brainstem atrophy and appearance of brainstem clinical signs at follow-up distinguished nfvPPA-PSP from nvfPPA-CBD which showed a tendency towards greater sentence comprehension impairment presentation and greater rate of anterior frontal atrophy and behavioral signs at follow-up (Santos-Santos et al., 2016). No consistent clinical or neuroimaging features that distinguished nfvPPA-PiD were found.

These results report a stronger association of nfvPPA with FTLD-tau than other previous studies. The differences in prevalence of TDP across cohorts of nfvPPA can result from a combination of reasons. As previously mentioned, differences in patient populations across centers due to various factors such as case selection, referral bias, or different proportion of known or unknown gene mutation carriers could account for part of this variability. Also pathological diagnostic criteria differed across centers before widespread adoption of FTLD consensus criteria in 200 (Mackenzie et al., 2010). Early involvement of white matter structures as measured by VBM or DTI stands out as a promising in-vivo biomarker for differentiating between FTLD-tau and FTLD-tdp (Caso et al., 2014). The finding of prominent apraxia of speech in all cases contrasts with previous studies that suggested that apraxia of speech may be a specific marker of nfvPPA-tau (Josephs et al., 2006) and that predominant agrammatic vs motor speech impairment is typical of nfvPPA-TDP (Deramecourt et al., 2010). This is not to say that further refinement and identification of different motor (apraxia and dysarthria) speech impairment profiles will not prove useful for differentiating between pathologies. In fact, our data suggest that different dysarthria profiles are useful for predicting

underlying pathology as described in the previous paragraph. To improve research into the pathological correlates of apraxia of speech, progress needs to be made in defining its constitutive elements as well the ability to detect and measure them reliably. This is a promising area of future investigation that will hopefully benefit from current research focused on improving reliability of measurement (Haley, Jacks, de Riesthal, Abou-Khalil, & Roth, 2012; Strand, Duffy, Clark, & Josephs, 2014) and/or incorporating new technologies (Ballard et al., 2014; Brodtmann, Pemberton, Darby, & Vogel, 2016; Joseph R Duffy et al., 2017) to the evaluation of motor speech.

A related issue is the recent introduction of the term primary progressive apraxia of speech (PPAOS) to describe patients presenting with isolated apraxia of speech and absence of impairment in other language or cognitive domains. In our cohort, all nfvPPA patients presented with apraxia of speech +/- dysarthria and agrammatism was not detected in only two patients that developed it at the subsequent visit. In our experience, motor speech impairment usually predominates initially whereas agrammatism is less evident and its detection depends significantly on the difficulty of the tests used. As the disease progresses, agrammatism and other signs of aphasia become more evident and are usually present in all cases. Thus, technically, all patients could possibly meet PPAOS criteria and it is unclear if it represents another disease process or just different stages of the same disease. Nonetheless, we recognize that nfvPPA patients can clearly show heterogeneity in the relative intensity of motor speech vs grammar impairment, and that these differences may help predict the underlying pathology. In our cohort nfvPPA-PSP presented greater dysarthria whereas nfvPPA-CBD showed a tendency towards greater sentence comprehension and executive function impairment. It appears that that nfvPPA-PSP present with a similar language and atrophy profile as PPAOS, namely greater motor speech (except that greater dysarthria was the crucial factor behind nfvPPA-PSP's greater motor speech impairment) than agrammatism and brainstem atrophy. Thus nfvPPA-PSP and PPAOS may describe similar

patients, which is consistent with the suggestion by Whitwell et al that that PPAOS and PSP syndrome may share common pathophysiological underpinnings (Whitwell et al., 2013). The fact that greater dysarthria has not been described in PPAOS may be due in part to methodological differences in the motor speech evaluation between centers. Taken together, these finding suggest that standardization in evaluation methodologies of key clinical features such as motor speech and grammatical impairment are necessary for advancement in the clinico-pathological correlates of nvfPPA and, as mentioned before, we think this standardization should be carried out before changing diagnostic criteria.

**Clinical and neuroanatomical characteristics that predict underlying AD pathology**

Discriminant analysis showed that the best language predictors of amyloid status were motor speech, sentence repetition and phonemic fluency and that the non-language measures of visual memory and behavioral impairment quantified by the neuropsychiatric inventory were also significant predictors. Besides supporting the validity of each of the PPA variants' core language deficits as described in the current diagnostic criteria, these results also support the use of a multi-domain evaluation for in-vivo prediction of underlying pathology in PPA. A recent retrospective study also found that sentence repetition was a significant predictor of Alzheimer's disease pathology within a large cohort of patients previously diagnosed with a frontotemporal dementia syndrome (Chare et al., 2014). In the context of previous work analyzing the neuroanatomical signature of Alzheimer's disease pathology within different clinical syndromes such as CBS and bvFTD (Lee et al., 2011; Ossenkoppele et al., 2015; Sha et al., 2015)and white matter damage in PPA (Agosta et al., 2013; Galantucci et al., 2011; M Grossman et al., 2013; Mandelli et al., 2014; Schwindt et al., 2013), we expected posterior temporal and parietal grey matter atrophy would characterize amyloid positive PPA whereas left frontal-temporal white matter atrophy would predict a negative amyloid brain scan. The findings that, within PPA, performance on tests of

visual memory (Butts et al., 2015; Flanagan, Tu, Ahmed, Hodges, & Hornberger, 2014; Foxe, Irish, Hodges, & Piguet, 2013; Ramanan et al., 2016), behavioral impairment (Chare et al., 2014; Halai AD, 2016; Modirrousta, Price, & Dickerson, 2013; Van Langenhove, Leyton, Piguet, & Hodges, 2016), and greater right hemisphere atrophy also predict Alzheimer's disease (Leyton et al., 2014; J D Rohrer et al., 2012; Whitwell et al., 2015) are less known though they also have been reported in other case-series.

Employing raw scores of a combination of widely used general cognitive and language measures, discriminant analysis was able to predict amyloid status in 80 out of 89 cases. If we count the three amyloid positive cases with a primary FTLD pathological diagnosis as correctly classified, the success rate would increase to 83 out 89 or 93%. This rate of success was higher than previously reported in data-driven classification of PPA into clinical subtypes (M M Mesulam, Wieneke, Thompson, Rogalski, & Weintraub, 2012; Sajjadi et al., 2012; Wicklund et al., 2014). One important difference between these previous efforts and this study is that we included non-language cognitive measures. Another difference is that we did not use cognitive test cut-off scores to determine presence of impairment. This method can often lead to inequitable normal-abnormal boundaries given that patients present at different disease stages. Instead, we used the quantitative raw scores of specific cognitive tests enabling the analysis to capture the relationships between performances in different cognitive domains, which better reflects the diagnostic decision process performed by an expert clinician. Despite the high rate of success of the data driven approach, it is noteworthy that consensus diagnosis by a team of experts using current criteria still performed better at achieving biomarker and pathologically homogeneous groups.

**Laterality of amyloid deposition and GM atrophy were not correlated in lvPPA**

Several recent studies have examined the relationship between patterns of amyloid deposition and neurodegeneration. In our lvPPA cohort, amyloid deposition was

significantly asymmetric only in the ACC contrasting with a highly asymmetric pattern of GM atrophy. Furthermore, PIB and GM AIs (and raw values) were not correlated in any of the regions examined. These results are in line with previous studies that did not find significant differences in the pattern of PIB deposition between Alzheimer's disease variants (Lehmann et al., 2013; Leyton et al., 2011). However, other studies have reported greater left asymmetry of AV45 deposition in PPA than in amnestic Alzheimer's disease in the lateral parietal region (Martersteck et al., 2016) and weak but significant negative correlations between PIB deposition and FDG metabolism in relevant cortical regions (Frings et al., 2015). Notably, all of these studies differ in potentially critical methodological factors. Future studies will need to parse out the effects resulting from the different methodologies (PET tracer, partial volume correction, and patient diagnosis and disease stage) to address the current discrepancies. Nonetheless, the mounting evidence across imaging (Ossenkoppele et al., 2016) and pathology (Gefen et al., 2012; M M Mesulam et al., 2014) studies suggests that asymmetry in atrophy and tangle pathology is greater than in amyloid plaque distribution.

**Concluding remarks**

The clinical, imaging and neuropathological correlations found in the work included in this thesis highlight the importance of carefully considering all clinical variables when predicting the underlying neuropathology in PPA and other complex disorders, even when access to AD biomarkers is available. Amyloid PET is a powerful new clinical tool that allows us to detect a key feature of AD molecular pathology during life, and clinicians may be tempted to place too much of an emphasis on amyloid PET results in rendering a diagnosis, in some instances substituting it for "standard of care" diagnostics such as neuropsychological testing and structural brain imaging (Grundman et al., 2013). Our findings suggest that while a negative amyloid PET is very helpful for "ruling-out" AD, interpretation of a positive scan requires a more nuanced approach. When the clinical phenotype is highly suggestive of AD (as in lvPPA), a positive scan

provides important supportive evidence for underlying AD neuropathology. However, when the clinical phenotype is not straightforward or suggests an alternative pathology, clinicians must carefully consider other clinical variables in order to determine whether amyloid is the primary pathology driving the dementia syndrome, or merely a secondary contributing or incidental pathology in a patient whose dementia syndrome is driven by an alternative process.

The studies included in this thesis support a model of neurodegenerative disease in which distinguishable deposits of pathologic molecules reflect distinct pathophysiologic mechanisms that preferentially target and spread through specific large-scale brain networks. Our results also imply that additional refinement of clinical profiles has potential to further improve the accuracy of clinico-pathologic correlations keeping in mind the limitation that these correlations are not absolute but probabilistic relationships. For advances in this area to be made, standardization of evaluation methodologies stands out as a key preliminary step, especially in primary progressive aphasia, in which key clinical features such as motor speech impairment and agrammatism are detected and measured differently across centers. The pathologic heterogeneity of nfvPPA, in theory, justifies the search for sub-syndromes specific for each pathology, and precise clinical phenotyping can potentially help in other areas besides predicting pathology, such as identifying predisposing factors that explain the clinical heterogeneity of a particular pathology (Miller, Mandelli, et al., 2013). However, limitless deep phenotyping could lead to significant confusion if disease terminology were to change with each future identification of a clinically useful sub-syndrome; therefore it is advisable that investigators reach consensus regarding the optimal degree of phenotyping as research advances in the field of neurodegenerative disease.

**Future directions**

The work included in this thesis points towards several important unanswered questions that should be addressed by future research. The first obvious research line is the identification of biomarkers for that could aid in the in-vivo prediction of atypical underlying pathologies in each of the primary progressive aphasia variants. nfvPPA is generally associated to underlying tau pathology but TDP-43 pathology is also found in a minority of cases. As of yet there is no reliable in-vivo biomarker of TDP-43 pathology and the small number of cases with TDP-43 pathology (2/25) in our cohort of nfvPPA with available pathological diagnosis precludes us from finding a definitive answer to this important question. Similarly, lvPPA sometimes is associated with non-Alzheimer's biomarkers or pathology but only one out 26 lvPPA patients in our cohort did not present Alzheimer's disease biomarkers and thus prevented us from effectively addressing this question. As mentioned before, none of the mixed-PPA cases in our cohort presented a mixed PPA language profile described by another group. It is very possible that more mixed profiles will be described in the future and it will be important to determine if these present with consistent clinical-pathologic or genetic associations. As clinicopathologic data and studies accumulate in the future, researchers in the field will have to come to a consensus on whether to modify diagnostic criteria.

Another major unanswered question in the field of neurodegenerative disease is how to determine the clinical relevance of specific pathological deposits, even if they are not considered the primary pathological cause of disease. Four patients in our cohort (two svPPA and two nfvPPA) were found to have mixed pathology, FTLD and AD, at autopsy. Eventhough FTLD was considered the primary causative pathology, it is possible that the AD pathology is also contributing to the generation of clinical symptoms and therefore these patients could also benefit from future treatments directed against AD pathophysiology. The possibility of establishing quantitative relationships between pathologic or in-vivo biomarkers of disease and clinical symptoms is certainly an interesting line for future research. This will probably be even more relevant in

neurodegenerative disease outside of primary progressive aphasia, because the prevalence of mixed and incidental pathologies is much greater in older patients.

The results in the third study align with results from years of research in typical amnestic Alzheimer's disease highlighting the huge gap in our knowledge of Alzheimer's disease pathophysiology. If amyloid deposition is not correlated with clinical symptoms or brain atrophy, then what pathophysiological factors are driving neuronal dysfunction and cell death? Our lab will be addressing this question in primary progressive aphasia by examining the role of tau deposition using novel tau-PET imaging. Other interesting options for future research are examining the role of inflammatory and TDP-43 pathophysiological mechanisms through imaging, cerebrospinal fluid, or blood-based biomarkers.

Finally, what are the factors that determine the selective vulnerability of the phonologic language system in lvPPA? Why does Alzheimer's disease pathophysiology affect the language system to produce a logopenic primary progressive aphasia syndrome? An interesting question to address in future research is that different neurodevelopmental trajectories resulting in adult brain structure variability may affect the way neurodegenerative disease manifests later in life. These last two questions apply to all forms of Alzheimer's disease and neurodegenerative disease in general but primary progressive aphasia serves as an especially valuable model for conducting clinicopathologic studies and for addressing the question of selective vulnerability due to the richness of knowledge, research, and neuropsychological tools provided by the cognitive neuroscience of language.

# VIII. CONCLUSIONS

## CONCLUSIONS

1. Prospective classification according to the current primary progressive aphasia consensus diagnostic criteria demonstrates significant improvements respective of previous criteria.
    a. Classification according to current criteria is able to classify the majority of patients that meet root PPA criteria. Less than 5% of cases that met root primary progressive aphasia criteria did not fit into one of the three described clinical variants and received a “mixed” PPA diagnosis.

    b. The logopenic variant is associated with PIB positivity in more than 95% of cases whereas svPPA and nfvPPA are amyloid negative in the majority of cases (86% and 90% respectively). This is a marked improvement respective of studies using previous criteria that report Alzheimer’s disease pathology in 30-50% of patients with progressive non-fluent aphasia.

    c. Our sub-study in patients with available autopsy data suggests that mixed pathology rather than primary Alzheimer’s disease might be present in amyloid positive svPPA and nfvPPA cases.

    d. PPA clinical variant classification is useful for predicting PIB positivity even in patients with aphasia that do not meet root PPA criteria because they present early symptoms outside of the language domain.

2. Refinement of clinical and neuroimaging endophenotypes is useful for improving the ability to predict underlying pathology in patients with non-fluent/agrammatic primary progressive aphasia (nfvPPA).

a. At presentation, nfvPPA-PSP shows greater dysarthria and relative predominance of white-matter atrophy. nfvPPA-CBD shows greater executive function impairment and a tendency towards greater impairment in receptive grammar.

b. nfvPPA-PSP and nfvPPA-CBD do not show differences in cognitive or language measures at follow-up evaluations possibly due to homogenization of cognitive symptoms as disease progresses through similar motor speech and language production brain networks. However, as disease spreads through non-language brain networks, nfvPPA-PSP show greater rate of brainstem atrophy and brainstem clinical signs, whereas nfvPPA-CBD show greater rate of anterior frontal atrophy and behavioral symptoms.

3. Data driven classification methods employing clinical and/or neuroimaging data are useful for predicting amyloid- PET biomarker status in patients with primary progressive aphasia.
    a. Measures of visual memory and behavioral impairment show similar ability to predict amyloid-PET status as the best performing language measures, which were motor speech and sentence repetition (both are “core clinical features” included in current diagnostic criteria).

    b. Cortical atrophy in bilateral posterior temporal and inferior parietal areas predicts amyloid positivity, whereas left frontal, temporal, and diencephalic white matter volume loss predicted amyloid negativity in patients who meet root primary progressive criteria.

4. Amyloid deposition in primary progressive aphasia due to Alzheimer's disease (lvPPA) does not predict brain atrophy. It shows a diffuse bilateral pattern in contrast to the predominantly left-lateralized pattern of atrophy

# IX. BIBILIOGRAPHY

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# X. ANNEX #1

**Original article**

# Rates and significance of amyloid imaging positivity in a prospective cohort of primary progressive aphasia.

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**KEY POINTS**

**Question**: What are the rates and significance of amyloid imaging positivity in a large cohort of patients with the main variants of primary progressive aphasia (PPA) prospectively diagnosed according to 2011 consensus criteria?

**Findings**: 24/28 (86%) semantic variant PPA and 28/31 (90%) non fluent/agrammatic variant PPA were amyloid PET negative, whereas 25/26 (96%) of logopenic variant and 3/4 (75%) PPA with mixed phenotype were positive. The amyloid positive svPPA and nfvPPA cases with available autopsy data (2/4 and 2/3 respectively) all had a primary Frontotemporal lobar degeneration (FTLD) and secondary Alzheimer's disease pathological diagnoses.

**Meaning**: PPA variant diagnosis according to the current classification scheme is highly predictive of Alzheimer's disease biomarker status. In the presence of a clinical syndrome highly predictive of FTLD pathology, biomarker positivity for Alzheimer's disease may be more predictive of mixed pathology rather than primary Alzheimer's disease.

**ABSTRACT**

**Importance:** The ability to predict the pathology underlying different neurodegenerative syndromes is of critical importance due to the advent of molecule-specific therapies. We report on one of the largest prospectively studied cohorts of primary progressive aphasia (PPA) patients with available amyloid imaging and autopsy data and provide novel evidence that may help for the in-vivo prediction of underlying pathology.

**Objective**: To determine the rates of PET amyloid positivity in the main clinical variants of PPA.

**Design**: Prospective clinical-pathologic case series.

**Setting**: Tertiary research clinic specialized in cognitive disorders.

**Participants**: Subjects were evaluated as part of a prospective, longitudinal research study between the years 2002-2015. Inclusion criteria: clinical diagnosis of PPA, availability of complete speech, language, and cognitive testing, MRI performed within six months of the cognitive evaluation, and PET PiB or AV45 brain scan results.

**Main Outcomes and Measures**: Clinical, cognitive, neuroimaging, and pathology results.

**Results**: 109 patients were referred for evaluation of language symptoms and underwent amyloid imaging. 89 patients met root PPA criteria. Twenty-eight cases were classified as

imaging-supported semantic variant PPA (svPPA), 31 non fluent/agrammatic variant PPA (nfvPPA), 26 logopenic variant PPA (lvPPA), and four PPA mixed (PPAm). 24/28 (86%) svPPA and 28/31 (90%) nfvPPA were amyloid PET negative, while 25/26 (96%) lvPPA and 3/4 (75%) PPAm were positive. The amyloid positive svPPA and nfvPPA cases with available autopsy data (2/4 and 2/3 respectively) all had a primary frontototemporal lobar degeneration (FTLD) and secondary Alzheimer's disease pathological diagnoses, whereas two amyloid PET positive lvPPA patients who came to autopsy were confirmed to have Alzheimer's disease. One amyloid negative PPAm case had Pick's disease at autopsy.

**Conclusion**: PPA variant diagnosis according to the current classification scheme is highly predictive of Alzheimer's disease biomarker status, with the logopenic variant being associated with PIB positivity in more than 95% of cases. Furthermore, in the presence of a clinical syndrome highly predictive of FTLD pathology, biomarker positivity for Alzheimer's disease may be more predictive of mixed pathology rather than primary Alzheimer's disease.

**Keywords:** primary progressive aphasia, amyloid PET, Alzheimer's disease, frontotemporal dementia, biomarker, pathology

## INTRODUCTION

Primary progressive aphasia (PPA) is a clinically and pathologically heterogeneous condition in which language impairment is the predominant cause of functional impairment during the initial phases of disease[1]. In 2011, an international consortium of investigators established a classification scheme for the three most common variants: the semantic (svPPA), non-fluent/agrammatic (nfvPPA), and logopenic (lvPPA) variants of PPA[2]. Classification may occur at one of three levels: clinical, imaging-supported, or definite pathological diagnosis. These guidelines reflected the accumulated knowledge of the patterns of speech and language dysfunction, brain atrophy and underlying pathology typically associated with each clinical variant and represent a collective effort to increase comparability between studies and eventually improve the ability to predict the underlying pathology.

The ability to detect fibrillar amyloid-β plaque depositions using [$^{11}$C]Pittsburgh Compound-B (PIB,[3]) or fluorinated amyloid positron emission tomography (PET) tracers [4] allows in-vivo identification of cases due to putative Alzheimer's disease. A few studies have reported amyloid imaging and pathological results in PPA [5–8]. Taken together, these reports suggest that svPPA and nfvPPA are generally caused by FTLD pathology [9], mainly tau [including Picks disease (PiD), corticobasal degeneration (CBD), progressive supranuclear palsy (PSP)] and TDP-43 proteinopathies, while lvPPA is mostly caused by Alzheimer's disease. However, the prevalence of FTLD and Alzheimer's disease pathological findings or biomarkers in each variant has been inconsistent across the literature (svPPA 0-16% Alzheimer's disease; nfvPPA 13-31%; lvPPA 54-92%). This may be due to the fact that most of these studies are retrospective in nature and may not have had adequate records or appropriate test batteries to apply the current criteria. Therefore prospective validation with biomarker and autopsy data remains scarce and highly necessary.

We studied amyloid brain imaging in a large cohort of prospectively diagnosed PPA patients to test the hypothesis that classification according to the current criteria in well-characterized patients with language and MRI imaging evaluations will result in groups with largely homogeneous biomarker features. A second objective was to analyze amyloid "discordant"

(amyloid positive svPPA and nfvPPA, and amyloid negative lvPPA) and mixed cases (PPAm) in search of characteristics that may aid in their identification.

## METHODS

### A. Participant selection and characterization

Patients: We recruited participants that presented prospectively to the University of California San Francisco (UCSF) Memory and Aging Center (MAC) between the years 2002-2015 as part of an ongoing PPA research project. We included patients that met the following criteria: clinical diagnosis of PPA, availability of complete speech, language, and cognitive testing, MRI performed within six months of the cognitive evaluation, and PET PiB or AV45 brain scan results. As part of the research evaluation, all participants underwent a history and physical examination by a neurologist, a structured caregiver interview by a nurse, a battery of neuropsychological tests, multimodal brain imaging scans, as well as an extensive battery of language tests. After initial evaluation, a syndromic diagnosis was reached by consensus between the multi-disciplinary evaluation team. Initial diagnosis was based on clinical judgment after considering all available neurologic, cognitive, language, and structural MRI data. We are reporting these prospective, consensus, PPA clinical variant diagnoses made at presentation. Amyloid imaging results were not available for any participant at the time of initial diagnosis. Since 2002, the UCSF MAC PPA research project has used essentially the same features for classification, as reported in previous publications [10,11], which are analogous to current criteria [2]. When it was not possible to identify a predominant area of language impairment or more than one area was impaired (for example motor speech and repetition difficulties) a diagnosis of PPA mixed was made.

One hundred and nine patients were referred to the UCSF MAC for evaluation of language symptoms and underwent amyloid imaging between 2002 -2015. Out of these, three subjects were excluded because of inability to complete the language evaluation due to advanced severity of disease, five for absence of significant aphasia, and twelve for presenting with significant initial symptoms outside of the language domain and consequently not meeting root

PPA criteria (supplemental table-1). This left a cohort of 89 PPA subjects [28 svPPA, 31 nfvPPA, and 26 lvPPA and 4 PPA mixed (PPAm)].

Healthy controls: We recruited healthy controls from the San Francisco aging cohort study (matched for age, gender, and scanner type) for the cognitive [n=10; mean (SD) age: 69 (8); %female: 70] and MRI [n=84; mean (SD) age: 64 (8); %female: 60] contrasts with patients. All controls had a Clinical Dementia Rating Scale sum of boxes (CDR-SB) score of 0, a normal neurologic examination, and no cognitive complaints. All subjects underwent informed consent and the study was approved by the UCSF, UC Berkeley and Lawrence Berkeley National Laboratory human research committees.

**B. Cognitive tests**

All patients received the UCSF neuropsychological battery [12] and UCSF speech and language battery (table-1) described extensively in previous publications[13,14]. Briefly, speech and syntactic production were evaluated using the spontaneous speech section from the Western Aphasia Battery (SS-WAB) and a writing sample, motor speech was evaluated using the Motor Speech Evaluation (MSE)[15], single word comprehension was evaluated with items of the Peabody picture vocabulary test-revised (PPVT-R) [16] , repetition by the WAB repetition subtest, and syntactic comprehension abilities were tested using the Sequential Command subtest of the WAB and by one of two experimental syntax comprehension tests that systemically vary sentence length and syntactic complexity to take into account the effect of verbal working memory load on syntactic comprehension (selected subtests of the Curtiss-Yamada Comprehensive Language Evaluation-Receptive (CYCLE-R)[17] or the UCSF grammar comprehension test[18]) (CYCLE-R was administered up until 2010; The score on the two latter tests are summarized into one percentage correct syntax comprehension score in table-1).

**C. Structural magnetic resonance imaging**

All patients and controls underwent whole-brain structural MRI using a 1.5T [10,19], 3T [20], or 4T [21] scanner as previously described. We used voxel based morphometry (VBM) to study grey-matter atrophy patterns of svPPA (n=24), nfvPPA (n=28), and lvPPA (n=25) groups (only including cases

with typical amyloid imaging status) as well as each individual case with discordant amyloid imaging status and each PPAm case (detailed methods in supplementary material).

**D. Positron Emission Tomography**

[$^{11}$C]PIB (n=99) and [$^{18}$F]AV45 (florbetapir) (n=10) PET were performed at Lawrence Berkeley National Laboratory as previously described[22]. Native space standardized uptake value ratios (SUVRs) were created for PIB scans only by normalizing mean images (at 50-70 minute-post-injection) by mean activity in cerebellum gray matter. Visual reads of native space PIB or AV45 SUVR images were performed by experienced investigators blinded to clinical data (G.D.R, H.J.R or W.J.J) using published criteria [23,24]. Visual inspection based on these criteria has been validated previously as a reproducible and reliable estimate of increased tracer uptake when compared with quantitative analysis [23,25].

**F. Neuropathology**

All brain autopsies were performed by the UCSF Neurodegenerative Disease Brain Bank. Pathological assessments were performed using institution-specific protocols [22] and included tissue sampling in regions relevant to the differential diagnosis of dementia based on published consensus criteria (detailed methods in supplementary material) [9,26].

**G. Statistical analysis of clinical and cognitive data**

Demographic and cognitive data were compared between PPA variants using one-way analysis of variance followed by post hoc comparisons of continuous variables with Bonferroni adjustments. Chi squared test was used for dichotomous variables. To identify factors that may help identify PPA cases with discordant amyloid imaging within each PPA variant, we converted the raw cognitive test scores of amyloid discordant PPA cases into z-scores with respect to the mean score of the group with typical amyloid imaging status. To highlight the pattern of impaired and relatively preserved cognitive functions in PPAm, we calculated z-scores with respect to the healthy control group.

## RESULTS

**A. Demographic and genetic data**

Comparison of demographic characteristics (table-1) between variants revealed significantly older age at symptom onset in nfvPPA than svPPA or lvPPA. A significantly higher proportion of lvPPA subjects had at least one apoliporotein E e4 allele (44%) compared to nfvPPA (11%). No mutations of microtubule associated protein tau (MAPT) (0/80), TAR DNA-binding protein (TARDBP) (0/74), Granulin (GRN) (0/84), or chromosome 9 open reading frame 72 (0/78) were found despite testing of the majority of subjects.

**B. Cognitive and MRI comparisons**

As a group, nfvPPA patients were less impaired on MMSE and Clinical Dementia Rating Sum-of-Boxes (table-1). All variants showed relatively preserved figure copying. SvPPA showed preserved working memory and executive functions but more behavioral impairment than both nfvPPA and lvPPA. LvPPA patients performed worse on the number location and calculation tests than svPPA and nfvPPA respectively. Both lvPPA and svPPA scored worse than nfvPPA on free recall of a list of learned words but only lvPPA scored worse on recall of the Benson figure.

Language testing revealed expected group differences based on the criteria for PPA subtyping (table-1). svPPA scored significantly worse than both nfvPPA and lvPPA on tests of verbal semantic knowledge and semantic association of pictures (PPTp). Greater presence of apraxia of speech, dysarthria, and decreased fluency scores differentiated nfvPPA from both lvPPA and svPPA. lvPPA scored significantly worse than svPPA on sentence repetition.

VBM analysis of PPA subgroups versus controls also revealed the expected patterns of atrophy associated with each variant (figure-2), bilateral predominantly left anterior temporal lobe in svPPA, left posterior frontal lobe in nfvPPA, and left mid-posterior temporal and inferior parietal lobes in lvPPA.

**C. Amyloid imaging and autopsy results**

Mean (standard deviation) time between first diagnosis-PET and PET-autopsy was 244 (337) and 1641 (926) days respectively. Overall prevalence of amyloid PET positivity in our PPA cohort was 35/89 (39.3%). Twenty-four of 28 svPPA (85.7%) and 28/31 nfvPPA (90.3%) patients were

amyloid PET negative, whereas 25/26 (96.1%) patients with lvPPA were amyloid positive. For comparison, the rates of amyloid PET-positivity in svPPA and nfvPPA were similar to those reported in cognitively normal individuals at a similar age (15%-20% in individuals aged 60-65 [27]), whereas the rate in lvPPA was much higher than expected for age. Of the 4 mixed PPA (PPAm), 3 were amyloid positive and 1 negative. LvPPA had significantly greater PiB standardized uptake value ratios (SUVR) than nfvPPA and svPPA (figure-1, table-1). Although they were considered positive for the purposes of this study, one svPPA and another nfvPPA received "equivocally positive" amyloid PET reads. These patients showed evidence of focal tracer uptake in regions of early amyloid positivity (e.g. precuneus/posterior cingulate cortex, dorsomedial and dorsolateral prefrontal cortex, in contrast to the widespread binding patterns across large regions of association cortex that are typical in full-blown Alzheimer's disease [22]). Accordingly, both cases had global SUVRs consistent with early positivity (1.23 and 1.36 respectively), but lower than the conservative threshold used in our group to "rule-in" Alzheimer's disease-like levels of binding (global SUVR ≥ 1.40).

Autopsy diagnoses were available for 20 patients (table-2). Overall, patients with positive amyloid scans all had intermediate-to-high Alzheimer's disease Neuropathological Changes (ADNC). When the PPA phenotype was lvPPA positive amyloid PET was associated with primary Alzheimer's disease, whereas when the PPA phenotype was nfvPPA or svPPA the primary causative neuropathology was FTLD, with Alzheimer's disease present as a contributing co-pathology. Conversely, all patients with negative amyloid imaging had absent to low ADNC, with FTLD as the primary causative neuropathology.

**D. PPA with discordant (amyloid positive svPPA and nfvPPA, and amyloid negative lvPPA) amyloid status**

Amyloid positive svPPA [patients A-D]: All amyloid positive svPPA patients (A-D) had PIB SUVRs above 2.0 except patient A, who displayed significant amyloid binding only in the right frontal lobe and received an "equivocally positive" radiologic read. Autopsy data were available for patients B and C who received a mixed pathological diagnosis, FTLD-TDP type C as the primary with Alzheimer's disease contributing. Despite having the highest PIB SUVR, patient B only showed intermediate ADNC (Braak stage 2 and moderate [CERAD] neuritic but frequent diffuse

plaques). Three out of four had one ApoE4 allele. All patients showed the typical svPPA cognitive profile and atrophy pattern (figure-2).

Amyloid positive nfvPPA [patients E-G]: All patients had PIB SUVRs above 2.0 except patient E whose scan was read as "equivocally positive" and had an SUVR of 1.36. Patient E had three contributing pathologies, FTLD-CBD, Alzheimer's disease (Braak 4, CERAD frequent), and FTLD-TDP type A. Patient F (previously described in [28]) had a dual pathological diagnosis, FTLD-PiD and Alzheimer's disease (Braak 5, CERAD frequent). Language testing revealed varying degrees of motor speech impairment and agrammatism with spared verbal and visual semantics in all three amyloid positive nfvPPA cases. All cases showed atrophy in the left posterior frontal lobe with different areas of accompanying atrophy.

Amyloid negative lvPPA [patient H]: The case of amyloid negative lvPPA had an SUVR of 1.3 and autopsy data was not available. Her prominent impairment was in sentence repetition but also had worse single word comprehension than the amyloid positive group. VBM revealed a fronto-temporal pattern of atrophy.

**E. PPA mixed**

Three out four PPA mixed (patients W, X, and Y) were amyloid positive and the SUVR was greater than 2.2 in all three (table-1). The only patient that came to autopsy (patient Z) had FTLD-PiD. All patients showed word finding difficulties. At presentation, both patient W and X showed impaired motor speech (AOS and dysarthria), sentence repetition and grammar comprehension. Patient Y presented with impaired semantics, sentence repetition, and grammar comprehension. Patient Z showed impaired grammar, semantics, sentence repetition and grammar comprehension. Consistent with their clinical presentation, these patients did not show the typical patterns of atrophy seen in the three main variants (figure-3).

## DISCUSSION

We report amyloid brain imaging, cognitive and structural MRI results in the largest PPA cohort prospectively diagnosed using current criteria. Classification according to PPA variant was highly

predictive of Alzheimer's disease biomarker status, with the logopenic variant being associated with PIB deposition in over 95% of our patients with sporadic PPA. Furthermore, we found that most cases with typical svPPA and nfvPPA and an unexpected positive amyloid scan had mixed FTLD and AD pathology. These results suggest that typical clinical and MRI findings in semantic and nonfluent/agrammatic variants are highly predictive of the presence of FTLD pathology, even in the face of discordant molecular AD biomarker results.

***PPA variant classification according to current consensus criteria was highly predictive of amyloid imaging biomarker status***

Four out of 26 (15%) svPPA and three out of 31 (10%) nfvPPA cases had a positive amyloid PET scan. These rates are similar to, if not slightly lower than, the reported prevalence of amyloid positivity in normal individuals at a similar age (15%-20%) [27]. All of the amyloid discordant cases with available autopsy data (two svPPA and two nfvPPA) had primary FTLD and secondary Alzheimer's disease pathological diagnoses. These results are in line with other prospective studies, reporting amyloid positivity in 1/9 svPPA and 2/8 nfvPPA [8] , 0/3 svPPA and 0/11 nfvPPA [29], and 3/ 9 svPPA and 7/ 52 nfvPPA [30] (the last study included patients labeled as primary progressive apraxia of speech). Our results suggest that a substantial proportion of amyloid positive svPPA and nfvPPA patients may have a primary FTLD pathologic diagnosis with amyloid as a contributing or incidental pathology. Clinicopathological studies retrospectively applying current criteria also report increased homogeneity of pathological diagnoses within each PPA variant, however a substantial percentage of cases still receive an Alzheimer's disease pathological diagnosis (0-16% svPPA, 13-31% nfvPPA, and 54-77% lvPPA) [5,7,31]. Although well studied cases of nfvPPA and svPPA with Alzheimer's disease pathology have been reported [32,33], it is possible that the higher percentage of Alzheimer's disease in these studies is due in part to the difficulty of retrospectively assessing key diagnostic features such as apraxia of speech, agrammatism, repetition and semantic impairment. Even today, these key features are evaluated with different instruments across centers and represent a significant hurdle for comparison and generalization of results.

Our finding of only one amyloid negative out of 26 (4%) lvPPA patients is also in line with the rates between 0-20% reported in other prospective PPA cohort studies [8,29,34]. Despite the

general association of lvPPA with Alzheimer's disease, this study and others have reported cases of prospectively [8,34–36] and retrospectively diagnosed lvPPA subjects [5–7,37] without Alzheimer's disease biomarkers or pathology. The studies reporting retrospective diagnoses all report higher rates of non-Alzheimer's disease pathology in lvPPA than the ones reporting prospective diagnoses possibly due to the absence of targeted neuropsychological evaluations that have been implemented more recently. The reasons for discrepancies in the rates of amyloid negative lvPPA are unknown but probably reflect real differences in patient cohorts (such as absence of mutation carriers in our cohort) as well as variability in the application of diagnostic criteria across centers.

***PPA with "discordant" (amyloid positive svPPA and nfvPPA, and amyloid negative lvPPA) amyloid status***

We did not find any demographic, genetic, cognitive, or neuroimaging features that reliably distinguished amyloid positive svPPA or nfvPPA from their primarily amyloid-negative counterparts. Carrying an apoE4 allele was a risk factor for amyloid positivity even within just svPPA and nfvPPA (OR 5.6; 95% CI 1.1-29.1; p=0.04). No genetic mutations were found in any of these cases. All four amyloid positive svPPA patients showed the same language and atrophy profiles as the amyloid typical group concordant with the available autopsy data and suggesting FTLD may be the primary pathologic diagnosis in all four patients. Two patients showed highly impaired set shifting in the Modified trails test which is unusual for typical svPPA and may reflect an Alzheimer's disease contribution to the clinical picture [38]. All amyloid positive nfvPPA subjects also showed the typical language profile and a common area of atrophy in the left posterior frontal lobe, though each case presented different areas of accompanying atrophy perhaps reflecting the heterogeneous pathologic diagnoses that are known to be associated with nfvPPA. The amyloid negative lvPPA case in our cohort showed more semantic impairment and her pattern of left temporal atrophy was more anterior and left asymmetric than the amyloid positive lvPPA group. Recent studies have also reported a trend towards worse semantics [36] and greater left asymmetric anterior temporal atrophy and/or hypometabolism [34,35] in amyloid negative lvPPA. According to current genetic and pathological data, the majority of amyloid negative lvPPA cases are associated with an autosomal dominant *GRN* mutation [34,39] or sporadic TDP-A pathology [5–7].

***Diagnosis according to current PPA consensus criteria was able to classify the majority of subjects***

Similar to other recent studies [6–8], we were able to identify the initial predominantly impaired language domain and classify almost all (85 out of 89) subjects that met root PPA criteria. However, some studies report inability to classify a higher proportion of subjects, especially when attempting data-driven vs clinical classification methods [40,41]. The two main issues described in previous reports are that a significant number of subjects present with both agrammatism and sentence repetition impairment thus meeting criteria for both nfvPPA and lvPPA while other subjects present only with anomia and thus do not meet any criteria [5,30]. Despite the existence of unclear cases that required discussion, in our experience and that of others, application of current criteria and targeted speech and language assessments using clinical judgment to identify the predominantly impaired and relatively spared language domains can resolve many of these cases. Furthermore, visual inspection of MRI images were always used when available to make an imaging-supported diagnosis as defined in the consensus criteria [2]. It is also important to note that the low number of mixed cases in our cohort might be related to the absence of progranulin mutation carriers, who have been shown to present with a logopenic-like mixed PPA syndrome [39]. A possible factor in the absence of patients presenting only anomia in our cohort could be that the aphasia tended to be further evolved prior to referral to our specialty center.

All four PPAm patients in our cohort presented a mix of core features and atrophy typical of more than one variant, which were thought to contribute significantly to the clinical picture. Even before knowing the result of the amyloid imaging, AD was the predicted pathology in both patients with mixed phonological and motor speech impairment due to the relative predominance of phonologic impairment, posterior vs frontal atrophy, and presence of impaired memory neuropsychological scores. No patient presented with another previously described mixed PPA phenotype of equally impaired grammatical production and verbal semantics [42]. Further studies including larger numbers of mixed cases are needed to determine if these present with consistent clinical-pathologic associations.

In summary, PPA variant imaging-confirmed diagnosis according to 2011 consensus classification was highly predictive of Alzheimer's disease biomarker status. Furthermore, our results emphasize that positive amyloid biomarker status does not rule out the possibility of a primary FTLD pathological process driving the clinical syndrome.

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**Table 1: Demographics, amyloid imaging, genes, and cognition in svPPA, nfvPPA, lvPPA, and PPAm.**

| | svPPA | | | | | nfvPPA | | | | lvPPA | | PPAm | | | | Controls |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| DEMOGRAPHICS/ GENE/ PATH | amyloid – (n=24) | amyloid + (n=4) | | | | amyloid – (n=28) | amyloid + (n=3) | | | amyloid + (n=25) | amyloid - (n=1) | amyloid + (n=2) | | amyloid – (n=2) | | amyloid na (n=10) |
| Patient identifier | | A | B | C | D | | E | F | G | | H | W | X | Y | Z | |
| Age at symptom onset, y | 59 (7)b | 72 | 57 | 61 | 71 | 64 (8)ac | 63 | 62 | 72 | 58 (8)b | 67 | 55 | 61 | 66 | 58 | na |
| Age at initial evaluation, y | 63 (7)b | 75 | 59 | 63 | 74 | 68 (8)a | 66 | 67 | 74 | 63 (8)b | 70 | 57 | 66 | 70 | 61 | 69.5 (8.1) |
| Gender (M/F) | 14;10 | M | F | F | F | 9; 19 | F | F | F | 9;16 | F | F | F | F | M | 7;3 |
| Handedness (R/L/A) | 19;2;3 | L | R | R | R | 25;2;1 | R | R | R | 20;4;1 | R | R | R | R | R | 10;0 |
| Education, y | 17 (3) | 17 | 16 | 12 | 12 | 17 (3) | 14 | 14 | 12 | 17 (3) | 12 | 20 | 12 | 13 | 20 | 16.9 (2) |
| Age at PET | 63 (7) | 75 | 62 | 63 | 74 | 68 (8) | 67 | 70 | 74 | 63 (8) | 70 | 57 | 66 | 70 | 61 | na |
| PET SUVR | 1.1 (0.1)c | 1.23 | 2.4 | 2.01 | 2.28 | 1.2 (0.1)c | 1.36 | 1.72 | 2.33 | 2.2 (0.3) | 1.3 | 2.22 | 2.33 | 2.25 | 1.05 | na |
| ApoE e4 copies (0; ≥1) | 15; 9 | E3/E4 | E3/E3 | E3/E4 | E3/E4 | 25;3c | E3/E4 | E3/E3 | E3/E3 | 13;11b | E3/E3 | E3/E3 | E3/E3 | E3/E3 | E3/E3 | na |
| TAU Haplotype (H1/H1; other) | 16; 7 | H1/H1 | H1/H1 | H1/H2 | H1/H1 | 21;6 | H1/H1 | H1/H1 | H1/H1 | 14;9 | H1/H2 | H1/H1 | H1/H1 | H1/H1 | H1/H2 | na |
| Pathologic Diagnosis | table-2 | ? | TDP-C + AD | TDP-C + AD | ? | table-2 | CBD +AD +TDP-A | PiD + AD | ? | table-2 | ? | ? | ? | ? | PiD | na |
| GENERAL COGNITION | amyloid – svPPA | A | B | C | D | amyloid – nfvPPA | E | F | G | amyloid + lvPPA | H | W | X | Y | Z | |
| CDR total | 0.7 (0.4)b | 0.5 | 0.5 | 1 | 1 | 0.5 (0.3)a | 0.5 | 0 | 0.5 | 0.6 (0.2) | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0 |
| CDR sum of boxes | 3.9 (2.3)b | 3.5 | 1 | 6 | 5 | 1.9 (1.5)ac | 2 | 0 | 2 | 3.3 (1.8)b | 3 | 1.5 | 4 | 3 | 3 | 0 |
| MMSE | 23 (7.3) | 22 | 29 | 26 | 14* | 26 (3.7)c | 27 | 25 | 25 | 22 (6.2)b | 22 | 28 (-3.9) | 19 (-24) | 27 (-6.1) | 13 (-37.5) | 29.7 (0.7) |
| NPI total | 32.3 (18.7)bc | 7 | 16 | 24 | 36 | 17.3 (14.5)a | 25 | 0 | 0 | 10 (8.4)a | 8 | 16 | 3 | 4 | 5 | na |
| UPDRS | 2 (2.4)b | 6* | 0 | 0 | 0 | 13 (12)ac | 0 | 13 | 2 | 5.7 (9.1)b | 2 | 1 | 10 | 1 | 21 | na |
| Benson figure copy ( /17) | 15.1 (1.3) | 16 | 17 | 16 | 16 | 14.9 (1.9) | 16 | 15 | 16 | 13.8 (3.6) | 14 | 15 (-0.9) | 0 (-13.9) | 12 (-3.5) | 12 (-3.5) | 15.7 (1.4) |
| VOSP Number Location ( /10) | 8.9 (1.3)c | 7* | 10 | 10 | 10 | 8.5 (1.5) | 2*** | 8 | 9 | 7.3 (2.5)a | 10 | 9 (-1.1) | 1 (-16.7) | 6 (-7) | 6 (-7) | 9.4 (1.1) |
| Facial matching ( /12) | 11.8 (0.7) | 11* | 12 | 9*** | 12 | 11.3 (1.4) | m | 12 | 12 | 11 (3.1) | 12 | 12 (0.4) | 12 (0.4) | 12 (0.4) | 10 (-5.5) | 11.9 (0.3) |
| Calculations ( /5) | 3.9 (2.3)c | 5 | 5 | 4 | 3 | 4.4 (0.8)c | 5 | 5 | 5 | 3.2 (1.1)ab | 4 | 3 (-2.8) | 2 (-4.5) | 5 (0.5) | 0 (-7.8) | 4.8 (0.4) |

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CVLT-MS Total recall | 17 (8.3) | 15 | 18 | 17 | 11 | 22.4 (6.2)c | 31 | 28 | 25 | 17.4 (7.5)b | 5* | 23 (-3.8) | 9 (-10.4) | 32 (0.4) | 17 (-6.6) | 30.9 (3.1) |
| CVLT-MS 10m free | 2.5 (2.5)b | 0 | 3 | 0 | 0 | 5.5 (2.6)ac | 7 | 9 | 8 | 3.3 (2.9)b | 2 | 6 (-1.5) | 2 (-4.6) | 9 (0.8) | 0 (6.2) | 8.1 (1.3) |
| Benson figure recall ( /17) | 7.9 (4.6) | 8 | 7 | 10 | 0* | 10.1 (3.6)c | 4* | 10 | 7 | 6.3 (3.6)b | 6 | 6 (-2.3) | 0 (-4.4) | 5 (-2.7) | 7 (-2) | 12.7 (3.3) |
| Digits Forward | 6.3 (1.8)bc | 7 | 7 | 6 | 7 | 4.6 (1.1)a | 3* | 5 | 5 | 4.2 (1.2)b | 4 | 4 (-4.4) | 4 (-4.4) | 6 (-1.9) | 5 (3.1) | 7 (1.2) |
| Digits Backward | 4.4 (1.3)bc | 5 | 6 | 5 | 5 | 3.4 (1.2)a | 2* | 5 | 3 | 2.8 (1.1)b | 3 | 3 (-1.8) | 2 (-2.6) | 4 (-1) | 0 (-4.2) | 4.8 (1.1) |
| Modified trails (lines | 21.3 (12.5)bc | 1.5* | 15.8 | 16.2 | 5.5* | 13.4 (8.6)a | 1.5* | 17.5 | 3.5* | 8.8 (8.8)b | 1 | 24 (-1.1) | 1.5 (-3.7) | 5.5 (-3.3) | u | 29.7 (8.1) |
| Design fluency | 8.4 (2.4) | 15 | 11 | 9 | 4* | 6.3 (3.4) | 7 | 6 | 5 | 6.7 (3.7) | 7 | 9 (-1) | 1 (-3.8) | 9 (-1) | u | 11.8 (2.9) |
| Stroop interference | 38.7 (18.7)bc | 27 | 42 | 38 | u | 22.8 (11)a | 32 | 21 | 20 | 16.1 (11.1)b | 16 | 20 (-2.5) | 5 (-3.7) | 22 (-2.3) | u | 52 (12.8) |
| **LANGUAGE** | amyloid – svPPA | A | B | C | D | amyloid – nfvPPA | E | F | G | amyloid + lvPPA | H | W | X | Y | Z | |
| Boston Naming Test ( BNT, 15) | 4.6 (3.2)bc | 1* | 3 | 3 | 0* | 12.1 (2.8)a | 12 | 9* | 13 | 9.9 (4.1)a | 4* | 14 (-0.9) | 13 (-2.1) | 8 (-8.4) | 5 (12.2) | 14.8 (0.4) |
| Speech fluency (WAB, 10) | 9 (0.5)b | 10 | 9 | 8 | 8* | 7.1 (2)ac | 4* | 2** | 9 | 8.5 (1.4)b | 8 | 9 | 9 | 9 | 9 | na |
| Information content (WAB, 10) | 9.1 (1) | 9 | 9 | 10 | 8* | 9 (0.9) | 9 | 8* | 8* | 8.9 (1.7) | 6* | 8 | 9 | 9 | 9 | na |
| Semantic fluency (animals) | 7.3 (4.4) | 2* | 5 | 5 | 1* | 10.3 (5.3) | 9 | 9 | 13 | 9.9 (4.1) | 5* | 12 (-2.8) | 9 (-3.5) | 12 (-2.8) | 0 (-5.4) | 24 (6.4) |
| Phonemic fluency (D | 7 (4.3) | 8 | 8 | 5 | 3 | 5.6 (2.6) | 3* | 5 | 6 | 7.5 (4) | 2* | 16 (-0.3) | 4 (-2.7) | 17 (-0.1) | 0 (-3.6) | 18.3 (3.4) |
| AOS (MSE, 7) | 0b | 0 | 0 | 0 | 0 | 2.4 (2)ac | 2 | 6* | 4 | 0b | 0 | 4 | 2 | 0 | 0 | 0 |
| Dysarthria rating (MSE, 7) | 0b | 0 | 0 | 0 | 0 | 1.8 (2.1)ac | 0 | 2 | 1 | 0b | 0 | 3 | 0 | 0 | 0 | 0 |
| PPVT total ( /16) | 8.1 (3.8)bc | 9 | 11 | 5 | 2* | 14.5 (2)a | 12* | 15 | 13 | 13.9 (2)a | 9** | 15 (-1.4) | 16 | 11 (-8) | 8 (-13) | 15.3 (0.7) |
| PPTp total ( /52) | 40 (7.2)bc | 42 | 49 | 32* | 30* | 48.1 (5.1)a | 49 | 49 | m | 48.5 (2.8)a | 46 | 50 (-1.8) | m | 41 (-12.4) | 45 (-7.6) | 51.5 (0.8) |
| Sequential commands (WAB, | 74.5 (11.6) | 59* | 80 | 70 | 54* | 70.3 (12.7) | 57* | 80 | 72 | 66.8 (14.3) | 58 | 70 (-5.5) | 70 (-5.5) | 72 (-4.3) | 65 (-8.4) | 79.2 (1.7) |
| Grammar comprehension^ (%) | 93.1 (10.6) | 87 | 100 | 87 | 90 | 87.9 (11.3) | 60** | 94 | 83 | 84.5 (12.7) | m | 85 (-5.1) | 90 (-3.2) | 88 (-3.9) | 74 (-9.3) | 98.4 (2.6) |
| Repetition (WAB, 100) | 87.6 (15.6)c | 89 | 100 | 84 | 81 | 83.9 (15) | 72 | 67* | 90 | 73.9 (16)a | 54* | 84 (-10.9) | 79 (-14.4) | 84 (-10.9) | 81 (-13) | 99.2 (1.4) |

**For svPPA, nfvPPA, and lvPPA:** Scores expressed as mean (standard deviation); [a]significantly different than svPPA; [b]significantly different than nfvPPA; [c]significantly different than lvPPA; *>1 standard deviation worse than group with typical amyloid status; **>2 standard deviations worse than group with typical

amyloid status; ***>3 standard deviations worse than group with typical amyloid status. **For PPAm:** Patient scores followed by (z-score) with respect to control group mean.

m= missing; u= unable to perform; na= not applicable; AD: alzheimer's disease; AOS: apraxia of speech; CBD: Corticobasal degeneration; CDR: Clinical dementia rating scale; CVLT: California verbal learning test; MMSE: mini mental state examination; MSE: motor speech exam; NPI: neuropsychiatric inventory; PiD: Pick's disease; PPVT: Peabody's picture vocabulary test; PPTp: pyramids and palm trees picture version; SUVR: standardized uptake value ratio; UPDRS: unified parkinsons disease rating scale; TDP: transactive response DNA binding protein; VOSP: visual object & space perception battery; WAB: western aphasia battery.

^Grammar comprehension tests used were either the Curtiss Yamada Comprehensive Language Evaluation receptive language test (CYCLE-R) and the UCSF grammar comprehension test and their scores are expressed as percentage correct.

**Table 2: Pathological diagnoses and amyloid imaging for all PPA.**

| | | Primary pathologic diagnosis | Contributing pathologic diagnosis | Incidental pathologic diagnosis | Alzheimer's disease neuropathological change (ADNC) | Amyloid imaging | PIB SUVR |
|---|---|---|---|---|---|---|---|
| svPPA | 1 | FTLD-TDP-C | PSP | | *Braak 1, CERAD 0 | - | 1.12 |
| | 2 | FTLD-TDP-C | FTLD-tau unclassifiable | mild Ascl | Low ADNC (A1, B1, C0) | - | 1.21 |
| | 3 | FTLD-PiD | | | *Braak 1, CERAD moderate | - | 0.98 |
| | 4[B] | FTLD-TDP-C | AD | mild Ascl; VID, mild CAA | Intermediate ADNC (A3, B1, C2) | + | 2.40 |
| | 5[C] | FTLD-TDP-C | AD | AGD, mild Ascl; severe CAA | High ADNC (A3, B3, C3) | + | 2.01 |
| nfvPPA | 1[F] | FTLD-PiD | AD | moderate CAA & Ascl | *Braak 5, CERAD frequent | + | 1.72 |
| | 2 | FTLD-PSP | | AGD; LBD | No ADNC (A0, B1, C0) | - | n/a |
| | 3 | FTLD-PiD | | mild Ascl | No ADNC (A0, B0, C0) | - | 1.08 |
| | 4 | FTLD-PSP | | | No ADNC (A0, B1, C0) | - | 1.20 |
| | 5 | FTLD-CBD | FTLD-TDP unclassifiable; AGD; LBD | mild Ascl, AD | Low ADNC (A1, B2, C0) | - | 1.08 |
| | 6 | FTLD-CBD | VID; moderate Ascl | LBD; AD | Low ADNC (A1, B1, C1) | - | 1.16 |
| | 7[E] | FTLD-CBD | AD; FTLD-TDP-A | mild Ascl | Intermediate ADNC (A2, B2, C3) | + | 1.36 |
| | 8 | FTLD-CBD | | mild Ascl; AD | Low ADNC (A1, B3, C0) | | 1.07 |
| | 9 | FTLD-PiD | | mild Ascl; AD | Low ADNC (A1, B1, C0) | - | 1.08 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | **10** | FTLD-CBD | VID | mild Ascl; AD | Low ADNC (A1, B0, C0) | - | 1.16 |
| | **11** | FTLD-CBD | | mild Ascl | No ADNC (A0, B1, C0) | - | 1.19 |
| | **12** | FTLD-CBD | LBD | | No ADNC (A0, B1, C0) | - | 1.31 |
| **lvPPA** | **1** | AD | | VID; mild Ascl; moderate CAA | High ADNC (A3, B3, C3) | + | 2.01 |
| | **2** | AD | | mild Ascl; mild CAA | High ADNC (A3, B3, C3) | + | 2.33 |
| | **3** | AD | | Mild CAA; limbic AGD | High ADNC (A3, B3, C3) | + | 2.25 |
| **PPAm** | **1**[Z] | FTLD-PiD | | LBD; AD | Low ADNC (A1, B0, C0) | - | 1.04 |

[B, C, E, F, Z] Patient identifiers corresponding with table-1. *Complete ADNC score not available; SvPPA, nfvPPA, lvPPPA, PPAm: semantic, nonfluent/agrammatic, logopenic, and mixed PPA variants; AD: Alzheimer's disease; AGD: Argyrophilic grain disease; Ascl: arteriolosclerosis; CAA: Cerebral amyloid angiopathy; CBD: Corticobasal degeneration; FTLD: frtontotemporal lobar degeneration; LBD: Lewy body disease;; PiD: Pick's disease; PSP: progressive supranuclear palsy; SUVR= standardized uptake value ratio; TDP: transactive response DNA binding protein; VID: vascular ischemic disease;

**Figure captions:**

Figure-1: Scatter plot depicting PET PIB standardized uptake value ratios (SUVr) across PPA variants (**A**). PET PIB axial slices of a representative patient with svPPA (**B**), nfvPPA (**C**), and lvPPA (**D**). SUVR= standardized uptake value ratio.

Figure-2: Voxel-based morphometry of grey matter atrophy patterns for amyloid negative svPPA, amyloid negative nfvPPA, and amyloid positive lvPPA groups. Single subject VBM of amyloid discordant patients. **A, B, C, D**: amyloid positive svPPA. **E, F, G**: amyloid positive nfvPPA. **H**: amyloid negative lvPPA. $\mathcal{L}$= left, $\mathcal{R}$= right.

Figure-3: **W, X, Y**: amyloid positive PPA mixed (PPAm). **Z**: amyloid negative PPAm. $\mathcal{L}$= left, $\mathcal{R}$= right.

Figure 1

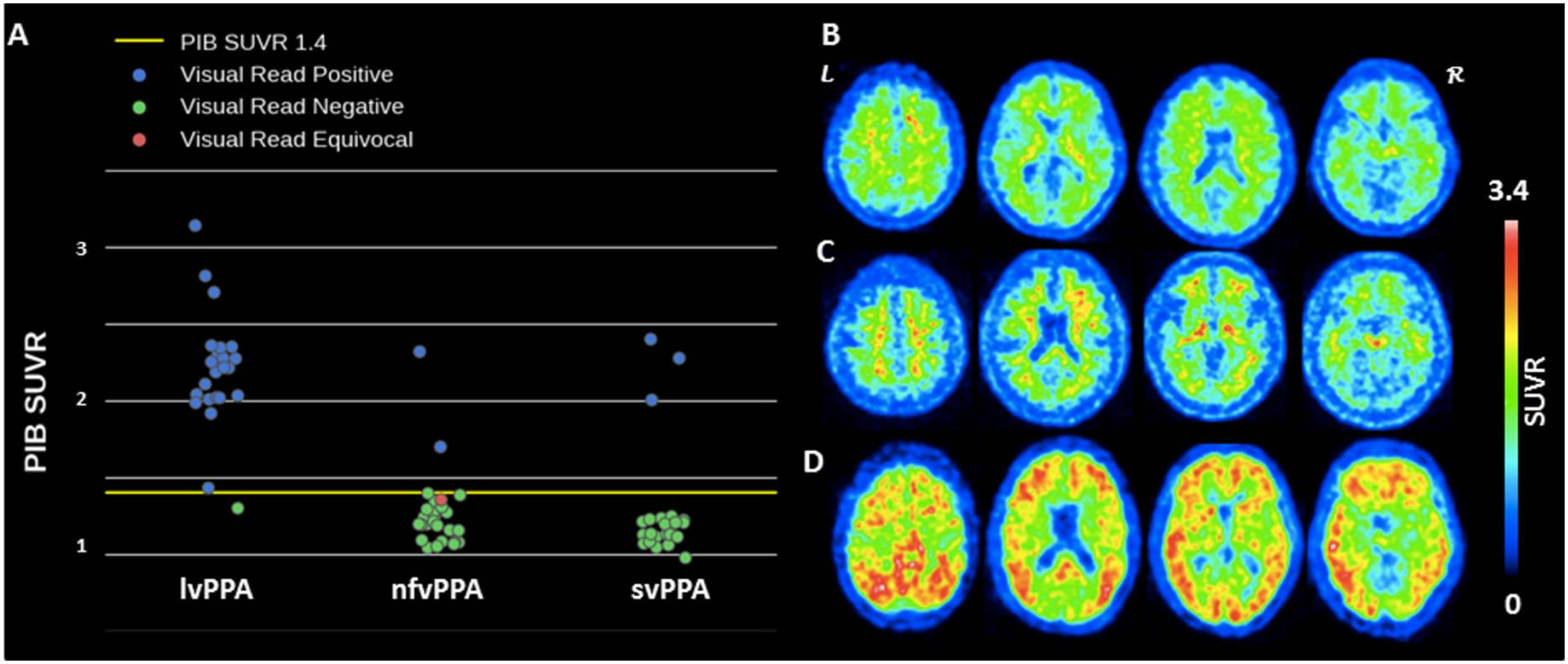

A
PIB SUVR 1.4
Visual Read Positive
Visual Read Negative
Visual Read Equivocal
PIB SUVR
3
2
1
lvPPA
nfvPPA
svPPA
B
L
R
C
D
3.4
SUVR
0

Figure 2

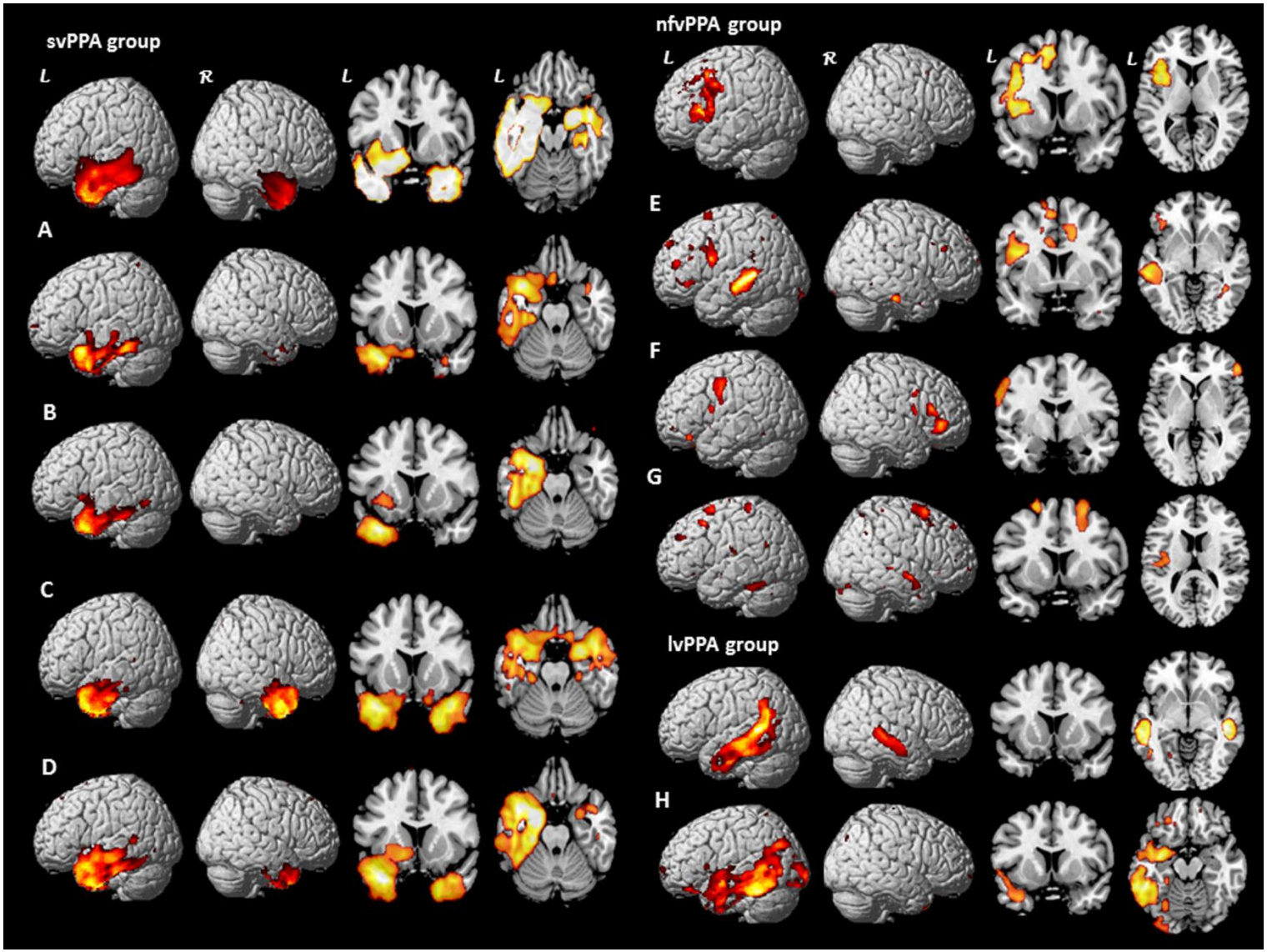
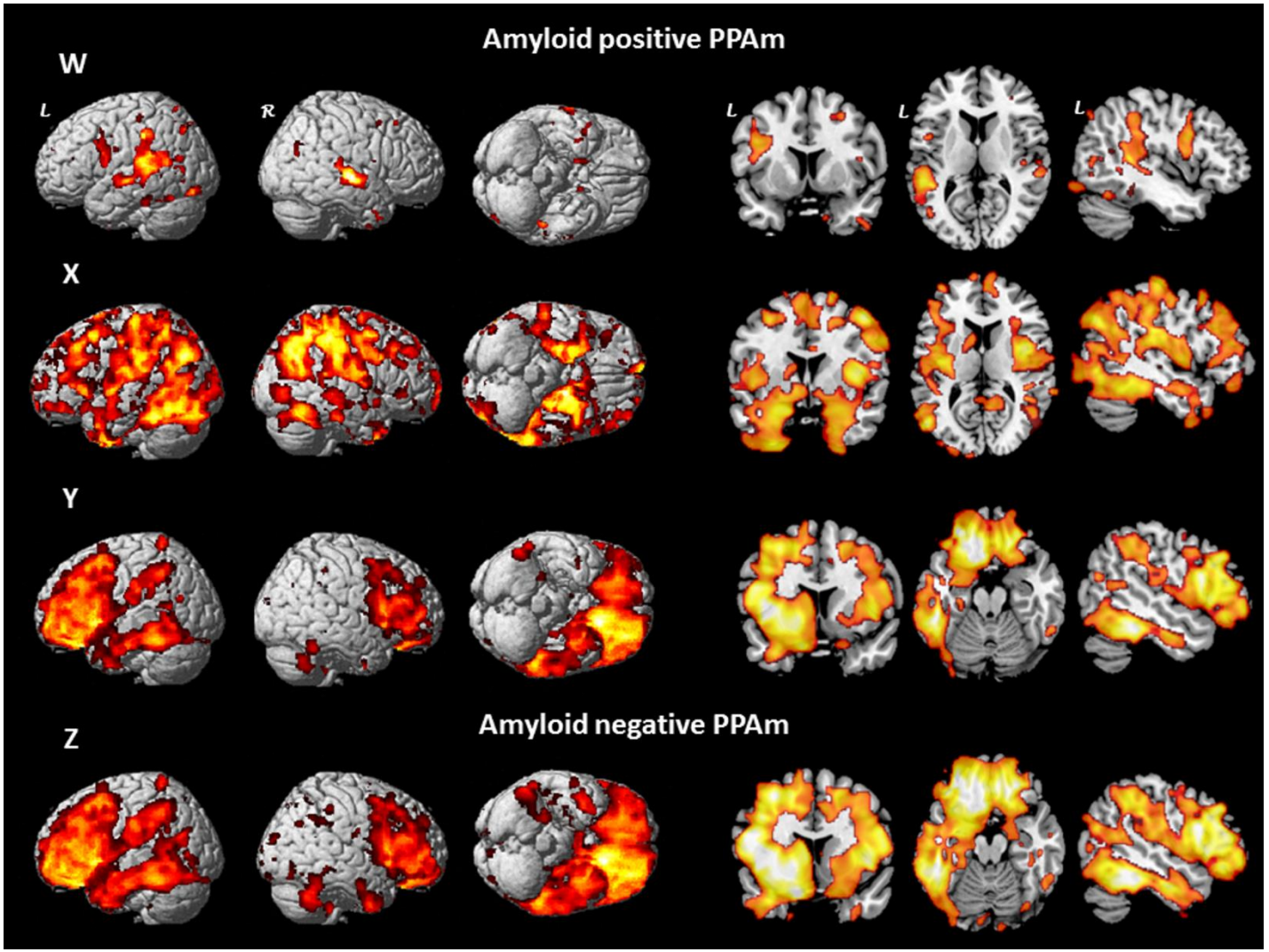


Figure 3



# XI. ANNEX #2

# Cross-sectional and longitudinal features of non-fluent/agrammatic primary progressive aphasia with underlying corticobasal degeneration or progressive supranuclear palsy pathology.

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Key Words: primary progressive aphasia, nonfluent/agrammatic variant, voxel based morphometry, corticobasal degeneration, progressive supranuclear palsy.

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**AUTHOR DISCLOSURES**

Dr. Santos, Dr. Mandelli, Dr. Binney, Dr. Ogar, Dr. Hubbard, Dr. Henry, Mr. Attygalle, Mr. Pakvasa, Ms. Rosenberg, Dr. Trojanowski, and Dr. Grinberg report no disclosures. Dr. Boxer is funded by grants R01 AG038791 and U54NS092089. He helped with the design and conceptualization of the study, analysis and interpretation of the data, drafting and revising the manuscript. Dr. Rosen is funded by grants K24 AG045333 and R01 AG032306. Dr. Seeley is funded by NIH grants P50 AG1657303, the John Douglas French Alzheimer's Disease Foundation, Consortium for Frontotemporal Dementia Research, James S. McDonnell Foundation, Larry Hillblom Foundation, has received support for travel by the Alzheimer's Association, and received payment for lectures by the Alzheimer's Association, American Academy of Neurology, and Novartis Korea. Dr. Miller serves as board member on the John Douglas French Alzheimer's Foundation and Larry L. Hillblom Foundation, serves as a consultant for TauRx, Ltd., Allon Therapeutics, Siemens, BMS, the Tau Consortium and the Consortium for Frontotemporal research, has received institutional support from Novartis, and is funded by NIH grants P50AG023501, P01AG019724, P50 AG1657303, and the state of CA. Dr. Gorno-Tempini is funded by NIH grant NINDS R01 NS050915.

## AUTHOR CONTRIBUTIONS

Collection, management, analysis, or interpretation of the data: Dr. Santos, Dr. Mandelli, Dr. Binney, Dr. Ogar, Dr. Hubbard, Ms. Meese, Dr. Henry, Mr. Attygalle, Mr. Pakvasa, Ms. Rosenberg, Dr. Trojanowski, Dr. Grinberg, Dr. Boxer, Dr. Rosen, Dr. Seeley, Dr. Miller, Dr. Gorno-Tempini.

Preparation, review, or approval of the manuscript: Dr. Santos, Dr. Mandelli, Dr. Binney, Dr. Hubbard, Dr. Boxer, Dr. Rosen, Dr. Seeley, Dr. Miller, Dr. Gorno-Tempini.

**ABSTRACT**

**Importance:** The ability to predict the pathology underlying different neurodegenerative syndromes is of critical importance due to the advent of molecule-specific therapies. We report on the largest known prospectively studied cohort of non-fluent/agrammatic primary progressive aphasia (nfvPPA) patients with autopsy proven progressive supranuclear palsy (PSP) or corticobasal degeneration (CBD) and provide novel evidence of specific clinical and neuroimaging features that may help for the in vivo prediction of underlying pathology.

**Objective**: To characterize the neurological, cognitive and neuroimaging characteristics, at initial presentation and at one-year follow-up, and identify features that may aid in predicting underlying pathology in patients with nfvPPA in whom either PSP or CBD was eventually confirmed at autopsy.

**Design**: Prospective longitudinal clinical-pathological study

**Setting**: Tertiary research clinic specialized in cognitive disorders

**Participants**: Subjects were evaluated as part of a prospective, longitudinal research study between the years 2002-2014. Inclusion criteria: clinical diagnosis of nfvPPA, availability of speech, language, and cognitive testing for at least one evaluation, magnetic resonance imaging within 6 months of initial evaluation, and a postmortem pathological diagnosis of PSP or CBD.

**Main Outcomes and Measures**: Clinical, cognitive, and neuroimaging longitudinal data were analyzed to characterize the whole nfvPPA-4R tau group and identify differences between nfvPPA-PSP and nfvPPA-CBD at presentation and longitudinally.

**Results**: Motor speech impairment and left frontal white matter atrophy were the most prominent common features. At presentation, dysarthria, depression and relatively selective white matter atrophy were typical of nfvPPA-PSP, while greater grey matter atrophy and a trend for greater sentence comprehension deficits were found in nfvPPA-CBD. At follow-up after 1-year, we observed no significant differences in any speech or language measures. Furthermore, atrophy in PSP progressed within the subcortical/brainstem motor system generating greater oculomotor deficits and swallowing difficulty, while in CBD, it spread anteriorly in prefrontal regions consistent with their greater working memory and development of behavioral symptoms.

**Conclusion**: In patients presenting with nfvPPA, presence of early severe dysarthria, relatively selective white matter atrophy at presentation and greater rate of change in the

brainstem measured by longitudinal imaging may be useful for differentiating underlying PSP from CBD pathology during life.

## INTRODUCTION

The non-fluent/agrammatic variant of primary progressive aphasia (nfvPPA) is a clinical syndrome strongly linked to underlying frontotemporal lobar degeneration (FTLD) pathology [1,2]. The majority of cases are caused by abnormal aggregation of the microtubule-associated protein tau (FTLD-tau) while most of the remaining cases are associated with the transactive response DNA binding protein of 43 kD (TDP) inclusions, usually type A (FTLD-TDP-A)[2]. The FTLD-tau cases are caused by either 4 repeat (4R) tauopathies - progressive supranuclear palsy (PSP) or corticobasal degeneration (CBD), or Pick's disease, a 3 repeat tauopathy.

Motor speech (apraxia of speech [AOS] and dysarthria) and grammar impairment along with predominant left posterior frontal lobe and insular atrophy are well established features of clinically defined nfvPPA [3-5]. However, prospectively collected speech, language, and neuroimaging data in pathologically confirmed cohorts are scarce and, to our knowledge, no longitudinal neuroimaging study of pathologically confirmed nfvPPA has been conducted. Consequently, it is not known whether different types of FTLD-tau presenting as nfvPPA can be distinguished by early clinical and neuroimaging features or by their longitudinal trajectories. The small number of clinicopathological studies in nfvPPA [1,6-11] show that 4R tauopathies, CBD and PSP, are the most common cause of nfvPPA making the identification of early clinical and neuroimaging biomarkers associated to these pathologies a matter of great interest. Despite significant clinical and pathological overlap, PSP and CBD are considered two distinct diseases presenting specific pathological lesions, biochemical features, and cellular and network vulnerabilities [12,13]. Also, recent evidence suggests that CBD and PSP may relate to

distinct tau strains, which may require different therapies [14]. While it is possible that both diseases might respond to the same 4R-tau targeted therapy, the ability to differentiate these two syndromes at early stages when molecule-specific disease-modifying drugs are most likely to be effective may prove to be critical for successful treatment. Furthermore, the ability to prognosticate future clinical symptoms holds great value for patients and care-givers.

The purpose of this study was to characterize the early features and longitudinal trajectories of neurological, cognitive and neuroimaging impairment in patients with sporadic nfvPPA and autopsy confirmed PSP or CBD pathology.

## METHODS

### Subjects

Subjects were evaluated at the University of California San Francisco (UCSF) Memory and Aging Center (MAC) as part of a prospective, longitudinal research study between the years 2002-2014. Inclusion criteria: clinical diagnosis of nfvPPA according to current criteria[5], availability of speech, language, and cognitive testing for at least one evaluation, magnetic resonance imaging (MRI) within 6 months of initial evaluation, and a postmortem pathological diagnosis of FTLD-4R-tau. This resulted in a cohort of 15 patients: 5 with pathologically confirmed PSP, 9 with CBD, and one with an unclassifiable 4R tauopathy. Tau immunohistochemistry demonstrated evidence of globose tangles and tufted astrocytes [15] in all PSP and astrocytic plaques [16] and thread-like inclusions in all CBD. Genetic screening for mutations in MAPT and Progranulin genes were negative in all subjects. Since our primary objective was to characterize and

contrast features of nfvPPA-PSP and nfvPPA-CBD, the unclassifiable case of 4R tauopathy was excluded. Subjects were followed for 2.9 (± 1.6) years.

We recruited healthy controls from the San Francisco community. Controls were matched for age, gender, and scanner type and had a Clinical Dementia Rating Scale sum of boxes score of 0, a normal neurologic examination, and no cognitive complaints. All subjects underwent informed consent and the UCSF human research committee approved the study.

**Clinical and cognitive data:**

All subjects received a standardized clinical evaluation [17], the UCSF neuropsychological[18], and speech and language[19-21] batteries at initial visit and follow-up as described in previous reports. Speech production, motor speech and grammatical processing are of particular interest in nfvPPA and were considered in detail by reviewing videotaped evaluations[22]. A detailed description of the speech and language evaluation is included in the supplementary material (emethods-1).

Presence of clinical symptoms and neurological signs were compared between groups at presentation (PSP n=5; CBD n=9), at 1 year follow-up (PSP n=5; CBD n=6), and follow-up closest to time of death (PSP n=4; CBD n=5) using the Chi-squared test. The criteria used for the syndromic diagnosis of probable PSP and CBD are published previously [23] and included in the supplemental material (emethods-2). We compared cognitive test scores between nfvPPA-PSP (n=5), nfvPPA-CBD (n=9), and controls (n=10) at initial evaluation and 1 year follow-up (PSP=4; CBD=6). Mann-Whitney U and Kruskal –Wallis tests were used for two and three group comparisons respectively. For

analysis of longitudinal cognitive data, we performed a paired Wilcoxon test to compare performance at initial evaluation and follow-up within each group.

**Neuroimaging**

Acquisition: All patients and controls underwent whole-brain structural MRI using either a 1.5 T[3], 3T[24], or 4T[25] scanner.

Subjects: *Cross-sectional analysis:* We compared nfvPPA-PSP (n=5) and nfvPPA-CBD (n=9) groups to each other and to healthy controls (n=80). *Longitudinal analysis:* Only subjects with two MRI scans performed on consecutive years and on the same scanner were included (5 nfvPPA-PSP, 5 nfvPPA-CBD, and 42 controls).

Voxel based morphometry (VBM) analysis: Image processing was performed using the unified segmentation procedure, DARTEL toolbox, and Pairwise Longitudinal Registration toolbox [26] implemented in SPM12 according to standard procedures described elsewhere [27,28]. Whole brain analyses of differences in grey matter (GM) and white matter (WM) and differences in annual rate of volume change were investigated using an analysis of variance (ANOVA) test across groups, including age, gender, total intracranial volume (TIV), and scanner type as nuisance variables. For the figures, we depicted t-maps at a $p<0.001$ uncorrected threshold for better visualization of differences and similarities between groups. SPM Anatomy toolbox version 2.0[29] was used for reporting of GM coordinates (etables-1&2). Also see the supplementary material for a region-of-interest analysis (emethods-3; etable-3).

**Neuropathology:**

Autopsies were performed at UCSF (n= 14), University of Pennsylvania (n=3), and Vancouver General Hospital (n=1). Pathological diagnosis was based on consensus guidelines for FTLD[30] following standard procedures described previously[17,31].

## RESULTS

**Demographic data** (Table-1)**:**

PSP and CBD did not differ significantly in age of symptom onset or age at initial evaluation. However, four out of five PSP and only 2 out of 9 CBD cases presented after the age of 65. PSP showed a trend ($p = 0.058$) towards longer survival following onset of first symptom.

**General Cognitive and Language data:**

**At initial evaluation** (Table-1)**:** In nfvPPA-4R-tau, tests of general cognition (MMSE), memory, and executive function were significantly worse than controls. Speech and language measures showed impairment in measures of motor speech, verbal fluency, naming, and sentence comprehension.

nfvPPA-PSP was significantly more depressed than nfvPPA-CBD, and only nfvPPA-CBD was significantly worse than controls in a test of working memory (digits backward). All 14 patients showed AOS. Mixed hypokinetic and spastic dysarthria was present and rated as more severe than AOS in all of the nfvPPA-PSP cases. In CBD, dysarthria was present in only 4 out 9 cases. Dysarthria was significantly more severe in nfvPPA-PSP. Only nfvPPA-CBD was significantly worse than controls in both measures of sentence comprehension and showed a trend for lower scores compared to nfvPPA-PSP in these measures. No significant differences were found when directly comparing patient groups in the measures derived from the recorded speech sample. However, both groups

scored significantly worse than controls in words per minute, distortions per hundred words, proportion of syntactical errors, and proportion of words in sentences. Only nfvPPA-CBD produced significantly fewer narrative words than controls.

**At 1-year follow-up** (Table-2)**:** In nfvPPA-4R-tau, MMSE scores showed significant decline, while visuospatial and visual memory tests were still not significantly impaired compared to controls. Digits backward remained impaired but did not decline significantly. All speech and language measures declined significantly except phonemic fluency, sequential commands, and dysarthria (which only showed a trend towards significant decline).

At follow-up, cross-sectional comparisons did not show significant differences between patient groups in any cognitive measure. Accordingly, nfvPPA-CBD showed higher dysarthria scores and nfvPPA-PSP performed worse on grammar comprehension than before. However, longitudinal change in these measures was not significant. In nfvPPA-CBD longitudinal analysis showed significant decline in MMSE, AOS, speech fluency, and auditory word recognition (although patients continued to be relatively preserved in this single word comprehension task, as they missed only one out 60 items). nfvPPA-PSP showed significant decline in semantic fluency only. Both groups showed a trend towards significant decline in grammar comprehension.

**Neurological symptoms and signs at initial and follow up evaluations** (table-3)**:**

At presentation, all cases reported difficulty with speech production as their initial and main complaint as well as the primary cause of impaired daily function. A significantly greater proportion of nfvPPA-PSP cases reported sensation of reduced balance and presence of at least 2 falls in the previous year. Also at presentation, a significantly

greater proportion of nfvPPA-PSP cases showed buccofacial apraxia and mild axial rigidity in the neurological exam. At 1-year follow-up, more patients with nfvPPA-PSP complained of some swallowing difficulties and showed slower or lower amplitude of vertical than horizontal eye movements on neurologic exam. nfvPPA-CBD patients showed a trend for greater impulsive and obsessive-compulsive behaviors that were nevertheless present in both groups at follow-up.

**Cross-sectional neuroimaging analysis at initial evaluation** (figure-1)**:**

**Grey Matter:** nfvPPA-4R-tau showed atrophy primarily in a left posterior frontal insular- basal ganglia and superior medial frontal network. The most significant atrophy peaks were located in left precentral, middle and inferior frontal gyri, left medial supplemental motor area (SMA), left putamen, and left insula.

nfvPPA-CBD showed significant GM atrophy compared to controls in all regions mentioned above, while nfvPPA-PSP only showed small areas of significant GM atrophy in left SMA, precentral and middle frontal gyri, and right cerebellum. Direct group comparison showed greater GM atrophy in nfvPPA-CBD primarily in the left insula and putamen.

**White Matter:** nfvPPA-4R-tau showed extensive left frontal involvement predominantly affecting the WM between the striatum, premotor and prefrontal regions. Other smaller areas of significant atrophy were found in mid corpus callosum, underlying right premotor cortex, and in the midbrain-diencephalic junction.

Both pathological groups showed predominant WM atrophy beneath the left precentral gyrus and SMA and less significant atrophy in mid corpus callosum, right frontal, and left midbrain-diencephalic regions. As shown in figure 2, in nfvPPA-CBD atrophy extended considerably more

anteriorly affecting WM underlying left frontal middle and inferior gyri. The relative proportion of GM to WM damage was strikingly different between patient groups, with PSP showing more WM than GM atrophy. Direct comparison of patient groups showed small regions of greater left prefrontal WM atrophy in nfvPPA-CBD.

**Longitudinal Neuroimaging analysis** (figure-2)**:**

**Grey Matter:** The area that showed greatest annual rate of change in nfvPPA-4R-tau included left precentral, middle frontal, and inferior frontal cortex. A homotopic area in the right hemisphere showed the second greatest rate of change followed by contiguous regions of bilateral SMA and middle cingulate cortex.

Both patient groups displayed significant longitudinal atrophy compared to controls in left precentral gyrus and SMA. nfvPPA- PSP showed more areas of significant GM longitudinal change including bilateral precentral, dorsal midbrain and right cerebellar regions. nfvPPA-CBD showed significant change in more anterior parts of left prefrontal cortex. Direct comparison did not reveal any significant differences.

**White Matter:**

The area showing greatest rate of change in nfvPPA-4R-tau compared to controls was located underlying the left premotor region and extending anteriorly beneath prefrontal cortex and downwards through the corona radiata, posterior limb of the internal capsule, midbrain-diencephalic junction, left cerebral peduncle, and pons. Another less significant area of contraction was located in right frontal WM.

nfvPPA-CBD only showed significant longitudinal atrophy in one WM cluster underlying left precentral and middle frontal gyrus which extended farther anterior than in nfvPPA-PSP. In nfvPPA-PSP, the greatest rate of annual change included WM in the left half of the midbrain

and pons and extended bilaterally into the cerebellar peduncles. Large areas of significant WM change were also visible underlying left and right precentral gyri. Direct comparison did not reveal any significant differences.

## DISCUSSION

This study analyzed cross-sectional and longitudinal clinical, cognitive and neuroimaging data in a cohort of prospectively evaluated nfvPPA patients found to have CBD or PSP at autopsy. CBD was the most common pathological subtype in our cohort. Although the two groups showed major similarities, with AOS and left posterior frontal gray and white matter involvement being the most salient, common features, our results highlight specific characteristics that might help predict the nfvPPA presentation of PSP. In particular, the presence of severe dysarthria and greater WM than GM atrophy at presentation, and the appearance of midbrain anatomical and clinical signs at follow-up were typical of PSP. These findings are discussed in terms of previous literature on nfvPPA and on the anatomical structures involved.

It has been known for a decade that AOS and agrammatism are the most typical features of the nfvPPA clinical presentation[3,4]. In recent years, the term primary progressive apraxia of speech has been introduced when AOS is the main feature and no apparent agrammatism is detected [32]. In our experience, it is often difficult to judge whether grammar production is spared in patients with severe output difficulties. In our cohort, all patients were diagnosed by a speech pathologist as having AOS, while grammatical difficulties were variable and sometimes only detected in written language or at follow-up. Thirteen out of 14 of our patients could have been classified as having greater motor speech than grammatical deficits but nfvPPA-PSP had significantly more dysarthria and buccofacial apraxia at presentation. In contrast, nfvPPA-CBD

was significantly worse than controls in sentence comprehension while nfvPPA-PSP was not. In the direct comparison between patient groups the difference in sentence comprehension was only a trend ($p \leq 0.10$). A recent clinicopathological study in nfvPPA suggested PSP is more likely when AOS dominates the syndrome whereas CBD is more likely when AOS and aphasia are equal[6]. In our cohort the presence of dysarthria, together with AOS, was responsible for greater motor speech deficits compared to grammar in patients with PSP. Dysarthria has previously been reported in pathologically confirmed PSP cases presenting as both PPA[6] and Richardson's syndrome[33]. The early predominance of motor speech deficits in both PSP and CBD supports a potential role as an outcome measure if one were to test a tau directed therapeutic in this population. However, more quantitative and reliable measures of AOS and dysarthria are needed for adequate assessment of change in these areas.

Consistent with their clinical presentation, CBD and PSP showed atrophy that overlapped in left SMA and precentral regions, important components in the motor speech production network [21,34,35]. These results are consistent with previous reports of cross-sectional neuroimaging in clinically [3,36,37] and pathologically [6,10,17,38] confirmed cases of nfvPPA. Our finding of early predominance of WM over GM atrophy in PSP is also in accordance with previous neuroimaging[17,38] and quantitative pathology [33] studies and may explain why dysarthria was more severe than AOS in PSP. In CBD, the atrophy extended further into left frontal GM and WM providing a substrate for their significantly impaired working memory and grammar comprehension compared to controls [20,39]. Early, severe WM damage has been proposed as typical of FTLD-tau pathology presenting as nfvPPA [9]. Our current results refine this association, suggesting that early predominant white versus gray matter atrophy should be considered as a possible neuroimaging biomarker of PSP pathology, but always in the context of a multi-domain approach considering clinical, molecular, genetic, and neuroimaging features.

Analyzing prospectively collected longitudinal data in pathologically confirmed nfvPPA was a unique opportunity of this study. Only PSP showed highly significant GM and WM longitudinal changes in the midbrain, particularly at the level of the cerebral and cerebellar peduncles presumably affecting the corticospinal tract, pontine crossing fibers, and other afferent and efferent cerebellar fibers. Accordingly, nfvPPA-PSP developed mild ocular and axial motor abnormalities. In contrast, nfvPPA-CBD showed greater longitudinal changes in prefrontal anterior, medial, and lateral GM and WM corresponding with their greater longitudinal decline in speech fluency and development of behavioral symptoms. Rohrer et al also found more prominent midbrain atrophy but less marked perisylvian atrophy in cases of nfvPPA that developed a typical PSP clinical syndrome compared to cases that did not, though this study did not include longitudinal imaging or pathological data[36]. Greater presence of behavioral symptoms in cases of CBD pathology was also reported in a recent study that compared cases of CBD versus PSP presenting as Richardson's syndrome[33]. Similar to other longitudinal clinical-pathological reports[40,41], CBD-syndrome was more common than Richardson's syndrome at later visits. Our results might be relevant for prognosis in nfvPPA because significant initial dysarthria at presentation may indicate considerable subcortical disease and imminent swallowing and balance problems. This study also suggests that differential longitudinal neuroimaging changes in GM and WM may be a sensitive biomarker of disease-specific patterns of progression[42].

Despite being the largest cohort of prospectively studied and pathologically confirmed nfvPPA that has been reported, this study is necessarily based on a relatively small sample which limits generalization of results and entails low-powered statistical analyses. To address this issue and help with interpretation of results, we included individual subject cognitive data in the

supplementary material (etables-4&5). We also performed a region-of-interest (ROI) analysis to address the concern that nfvPPA-CBD's larger sample size was driving the finding of more extensive atrophy in nfvPPA-CBD presentation. The ROI analysis supports the VBM findings and is included in the supplementary material. Combining MRIs from three different scanners is also not ideal, however we controlled for this by matching controls and including it as a nuisance variable in the VBM analysis. Finally, DTI combined with tractography would have been the optimal technique to investigate WM damage in specific tracts. However, VBM was able to show important differences between groups that are consistent with a recent DTI tractography study in the same clinical population that included four (two PSP and two CBD) of the same subjects[35].

In-vivo prediction of the pathology underlying the nfvPPA syndrome is an increasingly important endeavor as future molecule-specific treatments are developed. Our results indicate a promising role of combining early cross-sectional and longitudinal clinical and neuroimaging features in the in-vivo differentiation between nfvPPA-PSP and nfvPPA-CBD.

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Miguel A. Santos had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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## FIGURE CAPTIONS

**Figure 1. Cross-sectional VBM at presentation of nfvPPA: 4R tau (n=14), PSP (n=5), and CBD (n=9).** p<0.001 uncorrected for multiple comparisons; 3 group anova (PSP=5, CBD=9, controls= 80). 4 covariates (age, scanner, tiv, gender). Color bar indicates t-values (min: 0, max: 6). Images are in neurological view (left=left).

**Figure 2. Longitudinal VBM of nfvPPA: 4R tau (n=10), PSP (n=5), and CBD (n=5).** p<0.001 uncorrected for multiple comparisons; 3 group anova (PSP=5, CBD=5, controls= 42). 4 covariates (age, scanner, tiv, gender). Color bar indicates t-values (min: 0, max: 6). Images are in neurological view (left=left).

**Table 1. Demographic and cognitive data in nfvPPA-PSP, nfvPPA-CBD, and controls at initial visit.**

| Demographic Data | All 4R tau | PSP (n=5) | CBD (n=9) | control (n=10) |
|---|---|---|---|---|
| Gender (M/F) | 4/10 | 1/4 | 3/6 | 3/7 |
| Handedness (R/L) | 13/1 | 4/1 | 9/0 | 10/0 |
| Education, y | 17 (12-21) | 16.4 ± 3.9 | 18 (12-20) | 17 (14-20) |
| Age at symptom onset, y | 62.5 (51-79) | 15 (12-21) | 61 (51-79) | n/a |
| Age at initial evaluation, y | 66.5 (54-81) | 70 (62-72) | 65.3 ± 9.1 | 71.5 (57-78) |
| Survival, y | 7.23 (4.4-11.6) | ***9.6 (6.4-11.6)*** [c] | ***6.4 (4.4-10.3)*** [c] | n/a |
| **General Cognitive Data** | | | | |
| MMSE | 27 (20-30) [a] | 28 (24-30) [a] | 27 (20-29) [a] | 30 (28-30) |
| CDR sum of boxes | 2 (0-4.5) | 1.5 (0-2.5) | 2 (1-4.5) | n/a |
| GDS total | 5 (0-28) [a] | **19 (3-28)** [ab] | 4 (0-16) | 3.5 (0-13) |
| NPI total | 10.5 (1-50) | 16.5 (8-50) | 10.5 (1-38) | n/a |
| Digits Backward | 3 (2-6) [a] | 3 (2-6) | 3 (2-4) [a] | 5 (3-7) |
| Modified trails (lines per min) | 9.3 (0.5-32.3) [a] | 2 (0.5-32.3) [a] | 10.1 (4-26.3) [a] | 30 (14-40) |
| Calculation | 5 (2-5) | 5 (2-5) | 5 (3-5) | 5 (4-5) |
| Benson figure copy | 15 (13-17) | 15 (13-16) | 15 (13-17) | 16 (13-17) |
| Benson figure recall | 11.5 (3-17) | 10 (3-13) | 12 (9-17) | 14 (7-17) |
| CVLT-MS Total recall | 25 (16-34) [a] | 26 (16-28) [a] | 23.5 (17-34) [a] | 32 (26-35) |
| CVLT-MS 10min free recall | 6 (4-8) [a] | 7 (4-8) [a] | 6 (5-8) [a] | 8.5 (5-9) |
| **Language Cognitive test** | | | | |
| AOS rating (MSE, 7) | 2 (1-4) | 1 (1-4) | 2 (1-4) | n/a |
| Dysarthria rating (MSE, 7) | 2 (0-7) | **4 (2-7)** [b] | **0 (0-4)** [b] | n/a |
| Speech fluency (WAB, 10) | 9 (4-10) | 9 (6-9) | 9 (4-10) | n/a |
| Information content (WAB, 10) | 10 (5-10) | 10 (5-10) | 10 (9-10) | n/a |
| Sequential commands (WAB, 80) | 73.5 (49-80) [a] | ***80 (69-80)*** [c] | ***68 (49-80)*** [ac] | 80 (76-80) |
| Grammar comprehension (%) | 81 (65-100) [a] | ***98 (80-100)*** [c] | ***81 (65-98)*** [ac] | 100 (92-100) |
| Repetition (WAB, 100) | 91.5 (52-100) [a] | 95 (52-100) [a] | 88 (64-100) [a] | 100 (96-100) |
| Word recognition (WAB, 60) | 60 (55-60) | 60 (59-60) | 60 (55-60) | 60 (60-60) |
| Boston Naming Test (BNT, 15) | 13.5 (11-15) [a] | 12 (11-15) [a] | 14 (11-15) [a] | 15 (14-15) |
| Phonemic fluency (D words) | 4.5 (0-13) [a] | 5 (2-13) [a] | 4 (0-6) [a] | 17 (14-24) |
| Semantic fluency (animals) | 9 (4-22) [a] | 9 (6-22) [a] | 9 (4-13) [a] | 26 (14-33) |
| **Spontaneous Speech sample analysis (Picnic scene)** | | | | |
| Total narrative words | 66.5 (9-452) [a] | 69 (9-452) | 64 (14-131) [a] | 140 (89-238) |
| Words per minute | 55.5 (11-90.5) | 65.9 (18.8-90.5) | 54.8 (10.7-70.4) | 154.7 (112-198) |
| Proportion of syntactic errors | 4 (0-35) [a] | 3.3 (0-11.11) [a] | 4.8 (0-35) [a] | 0 (0-1.02) |
| Proportion of words in sentences | 0.91 (0-1) [a] | 0.9 (0.6-1) [a] | 0.83 (0-1) [a] | 1 (0.88-1) |
| Proportion of distortions (per 100wrds) | 6.3 (0-33.3) [a] | 10.7 (1.5-33.3) | 4 (0-31.25) [a] | 0 (0-1.33) |

[a] p< 0.05 vs controls; [b] **p< 0.05 PSP vs CBD**; [c] ***Italicized= trend p≤0.10 PSP vs CBD.*** Kruskal-Wallis and post-hoc Mann-Whitney U tests performed. MMSE: minimental state examination. CDR: clinical dementia rating scale. GDS: geriatric depression scale. NPI: neuropsychiatric inventory. CVLT: California verbal learning test. AOS: apraxia of speech.

**Table 2. Cognitive data at baseline and 1 year follow-up evaluation**.

| | All 4R tau (n=12) | | PSP (n=5) | | CBD (n=7) | |
|---|---|---|---|---|---|---|
| | Baseline | Follow-up | Baseline | Follow-up | Baseline | Follow-up |
| MMSE | 27 (23-30) | ***23 (15-29)***[1 x] | 28 (24-30) | *23 (18-29)*[y] | 27 (23-29) | ***23.5 (15-26)***[1x] |
| Digits Backward | 3 (2-6) | *3 (0-6)*[1] | 3 (2-6) | 3 (0-6) | 3 (3-4) | *3 (0-3)*[1] |
| Benson figure copy | 15 (13-17) | 16 (9-17)[3] | 15 (13-16) | 16 (9-17) | 15 (13-17) | 15.5 (14-17)[3] |
| Benson figure recall | 11.5 (3-17) | 9 (5-16)[3] | 10 (3-13) | 8 (5-13) | 12 (9-17) | 9.5 (7-16)[3] |
| AOS (MSE, 7) | 2 (1-4) | **4 (1-7)**[3x] | 1 (1-4) | 4.5 (1-7)[1] | 2 (1-4) | **4 (3-7)**[2x] |
| Dysarthria (MSE, 7) | 2 (0-7) | 5 (0-7)[3y] | 4 (2-7) | 5.5 (2-7)[1] | 1 (0-4) | 2 (0-7)[2] |
| Speech fluency (WAB, 10) | 9 (5-10) | **5 (1-9)**[2x] | 9 (6-9) | 5.5 (1-9)[1] | 9 (5-10) | **4.5 (2-9)**[1x] |
| Information content (WAB, 10) | 10 (5-10) | **8 (4-10)**[2x] | 10 (5-10) | 5.5 (4-10)[1] | 10 (9-10) | **9 (5-9)**[1x] |
| Sequential commands (WAB, 80) | 75.5 (61-80) | *78 (54-80)*[2] | 80 (69-80) | *78 (66-80)*[1] | 72 (61-80) | *77.5 (54-80)*[1] |
| Grammar comprehension (%) | 86.5 (74-100) | ***73 (58-98)***[2x] | 98 (80-100) | *80 (73-94)*[1y] | 81 (74-98) | *71 (58-98)*[1y] |
| Repetition (WAB, 100) | 88 (52-100) | ***70.5 (12-98)***[2x] | 95 (52-100) | *58 (23-98)*[1y] | 88 (64-100) | *71 (12-98)*[1] |
| Word recognition (WAB, 60) | 60 (59-60) | ***59 (58-60)***[2x] | 60 (59-60) | *59 (58-60)*[1] | 60 (60-60) | ***59 (58-60)***[1x] |
| BNT (15) | 13.5 (11-15) | ***12 (7-15)***[1x] | 12 (11-15) | *12 (10-15)* | 14 (11-15) | *11.5 (7-14)*[1] |
| Phonemic fluency | 5 (2-13) | *3.5 (1-13)*[2] | 5 (2-13) | *5 (1-13)* | 5 (3-6) | *3 (2-9)*[2] |
| Semantic fluency | 10 (6-22) | ***6.5 (1-20)***[2x] | 9 (6-22) | ***8 (1-20)***[x] | 11 (6-13) | ***5 (2-10)***[2x] |

[1] missing one case, [2] missing two cases, [3] missing three cases.

Longitudinal within group comparison: [x] **Baseline vs Follow-up significant at p<0.05;** [y] Baseline vs Follow-up trend at p<0.10**;**

Cross-sectional comparison between groups at time-point 2: *Indented* = p<0.05 vs Controls at follow-up**.** PSP and CBD did not differ significantly in any measure at time-point 2 when compared directly. Kruskal-Wallis and post-hoc Mann-Whitney U tests performed.

**Table 3. Neurological symptoms and signs at presentation, 1 year, >1 year follow-up evaluations and overall**. Number of cases that reported or presented each symptom or sign. Percentages in parenthesis.

| | Presentation | | 1yr follow-up | | >1yr follow-up | |
|---|---|---|---|---|---|---|
| **SYMPTOMS** | **psp (n=5)** | **cbd (n=9)** | **psp (n=5)** | **cbd (n=6)** | **psp (n=4)** | **cbd (n=5)** |
| Swallowing complaints | 3 (60) | 1 (11) | **5 (100) [a]** | 1 (17) | 4 (100) | 4 (80) |
| Reduced manual dexterity | 2 (40) | 2 (22) | 4 (80) | 2 (33) | 4 (100) | 3 (60) |
| Gait / Balance | **3 (60) [a]** | 0 (0) | 3 (60) | 1 (17) | 4 (100) | 3 (60) |
| Falls | **2 (40)[a]** | 0 (0) | 3 (60) | 0 (0) | 4 (100) | 2 (40) |
| Incontinence | 0 (0) | 0 (0) | 2 (40) | 0 (0) | 3 (80) | 1 (20) |
| Impulsive | 1 (20) | 4 (44) | 2 (40) | 5 (83) | 2 (40) | 5 (100) |
| Obsessive/ Compulsive | 1 (20) | 2 (22) | 1 (20) | 2 (33) | 1 (20) | 3 (60) |
| **SIGNS** | | | | | | |
| Ocular movements* | 2 (40) | 1 (11) | **5 (100) [a]** | 1 (17) | 4 (100) | 4 (80) |
| -Vertical movements worse^ | 1 (20) | 0 (0) | **4 (80) [a]** | 1 (17) | 4 (100) | 2 (40) |
| Buccofacial apraxia | **4 (80) [a]** | 0 (0) | 5 (100) | 3 (50) | 4 (100) | 3 (60) |
| Asymmetric limb rigidity | 2 (40) | 2 (22) | 4 (80) | 2 (33) | 4 (100) | 3 (60) |
| Axial rigidity | **3 (60) [a]** | 0 (0) | 3 (60) | 2 (33) | 4 (100) | 3 (60) |
| Limb Dystonia | 0 (0) | 2 (22) | 3 (60) | 1 (16) | 3 (75) | 3 (60) |
| Limb Apraxia | 3 (60) | 3 (33) | 3 (60) | 2 (33) | 4 (100) | 3 (60) |
| Postural instability | 1 (20) | 0 (0) | 2 (40) | 1 (17) | 4 (100) | 2 (40) |
| Cortical sensory/neglect | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 2 (40) |
| Met probable PSP-S criteria | 0 (0) | 0 (0) | 1 (20) | 0 (0) | 2 (50) | 0 (0) |
| Met probable CBD-S criteria | 0 (0) | 0 (0) | 3 (60) | 1 (16) | 4 (100) | 3 (60) |

Chi squared test performed [a] **p< 0.05 PSP vs CBD.** *Includes mild abnormalities such as decreased initiation, velocity, or amplitude of saccades. ^Indicates vertical movements were more impaired than horizontal movements (only one PSP case presented clear vertical supranuclear gaze palsy at 1yr follow-up and thus met PSP-S criteria). PSP-S, CBD-S: PSP, CBD, syndrome (It was possible for one subject to meet both sets of diagnostic criteria).

**Figure 1. Cross-sectional VBM at presentation of nfvPPA: 4R tau (n=14), PSP (n=5), and CBD (n=9).** p<0.001 uncorrected for multiple comparisons; 3 group anova (PSP=5, CBD=9, controls= 80). 4 covariates (age, scanner, tiv, gender). Color bar indicates t-values (min: 0, max: 6). Images are in neurological view (left=left).

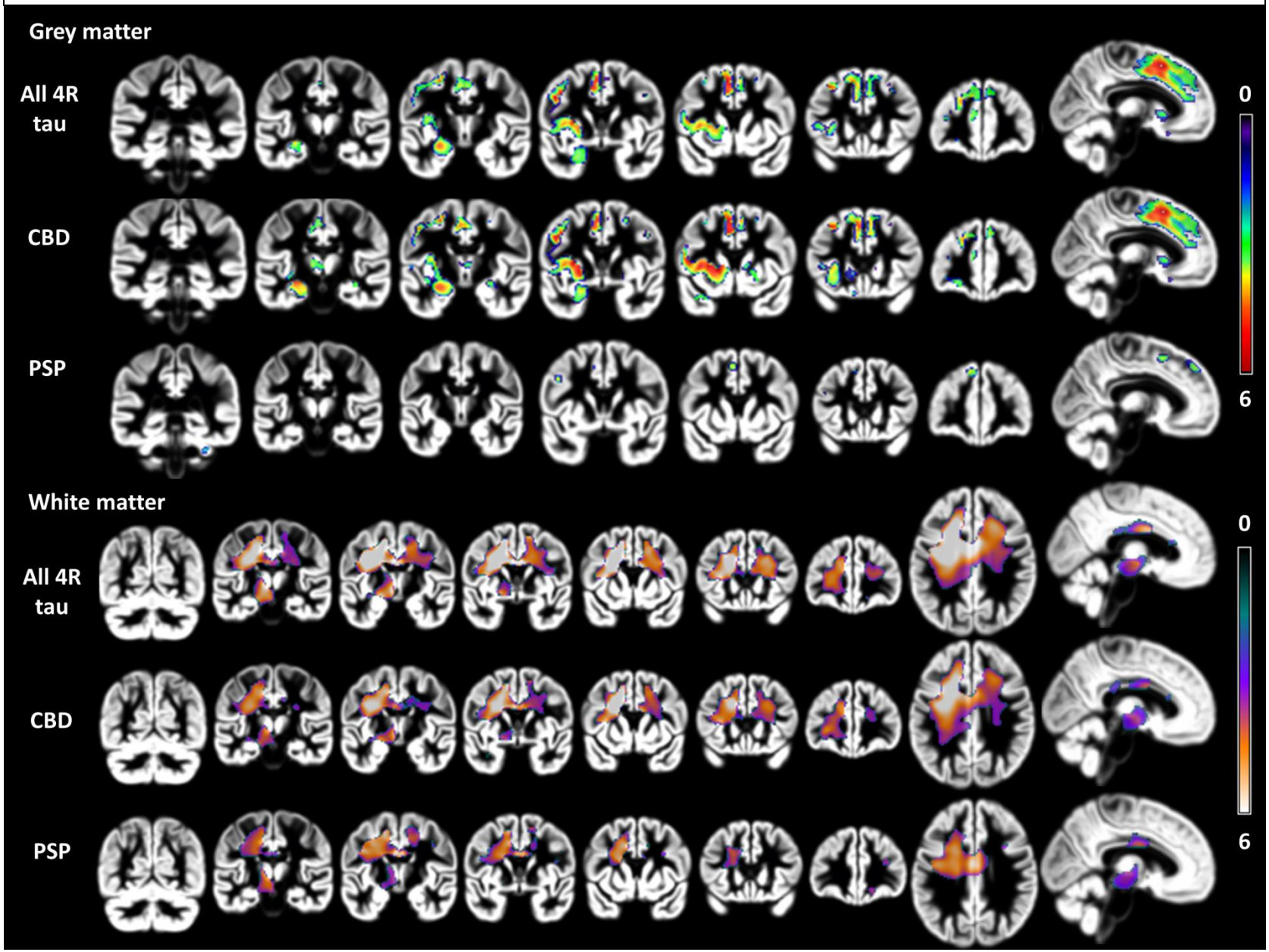

**Figure 2. Longitudinal VBM of nfvPPA: 4R tau (n=10), PSP (n=5), and CBD (n=5).** p<0.001 uncorrected for multiple comparisons; 3 group anova (PSP=5, CBD=5, controls= 42). 4 covariates (age, scanner, tiv, gender). Color bar indicates t-values (min: 0, max: 6). Images are in neurological view (left=left).