Supplementary Online Content

Santos-Santos MA, Rabinovici GD, Iaccarino L, et al. Rates of amyloid imaging positivity in a prospective cohort of primary progressive aphasia. *JAMA Neurol*. Published online January 8, 2018. doi:10.1001/jamaneurol.2017.4309

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix 1. Evolution of Primary Progressive Aphasia Clinical Variant Diagnostic Criteria Used at the UCSF Memory and Aging Center

One of the main objectives of this study is to determine if prospective diagnosis using a tripartite classification system will result in patient groups with homogeneous biomarker profiles and therefore any changes in the diagnostic criteria could potentially affect the results if these changes distorted the nature of the identified patient groups. We addressed this concern by retrospectively reviewing each case that presented before the current criteria were published in 2011 and confirming that none of the diagnoses warranted change. In the following section we will review the evolution of the criteria as described in the UCSF Memory and Aging Center publications cited below and show that the criteria identify the same patient groups. The UCSF MAC primary progressive aphasia longitudinal study has classified patients with PPA into semantic, non-fluent/agrammatic, and logopenic variants since its start in 2002 using the same core clinical evaluation presented in this manuscript. The features used for classification have remained largely analogous since they were first described in 2004 (Gorno-Tempini *et al.*, 2004), however they have been refined and operationalized by senior investigators in the field as described in 2008 and 2011 (Rabinovici *et al.*, 2008; Gorno-Tempini *et al.*, 2011).

The 2004 publication stated a diagnosis of progressive non-fluent aphasia (PNFA) required at least two of the following: (1) motor speech deficits; (2) agrammatism in language production; (3) spared single-word comprehension and impaired comprehension of complex syntactic structures. The criteria described in 2008 resulted from a PPA workshop attended by senior investigators in the field. A diagnosis of PNFA required: (1) motor speech deficits; (2) agrammatism in language production; (3) deficit in comprehension of complex sentences; and (4) spared single-word comprehension and object knowledge. According to current consensus diagnostic criteria published in 2011, a diagnosis of nfvPPA requires at least one of the following core features: (1) Agrammatism in language production; (2) Effortful, halting speech with inconsistent speech sound errors and distortions (apraxia of speech) and at least 2 of 3 of the following features: (1) Impaired comprehension of syntactically complex sentences; (2) Spared single-word comprehension; (3) Spared object knowledge.

The criteria for semantic dementia or the semantic variant in 2004 required at least three of the following: (1) no grammatical errors and normal language output (circumlocutions and usage of nonspecific words were accepted); (2) scores below two standard deviations from the control mean in the 60-item Boston naming test (BNT); (3) scores below two standard deviations from the control mean in the Pyramid and Palm Trees (PPT) test; and (4) normal syntactic comprehension; In 2008 the following were required (1) fluent and grammatically correct language output, (2) semantic memory deficit, (3) confrontation naming deficit, and (4) surface dyslexia. The 2011 criteria require, both core features: (1) Impaired confrontation naming; (2) Impaired single-word comprehension; and at least 3 of the following features: (1) Impaired object knowledge, particularly for low frequency or low-familiarity items; (2) Surface dyslexia or dysgraphia; (3) Spared repetition (4) Spared speech production (grammar and motor speech).

The 2004 publication which first described the logopenic variant did not present operationalized criteria, instead these patients were characterized as not showing “a pattern of speech and language deficit compatible with NFPA or SD… their language output was slow in rate, grammatically simple but correct, and halted by frequent word-finding pauses… Agrammatism in production and articulation deficits were not typical of LPA patients. Single word comprehension, recognition of nonnamed items, and performance on the semantic association test were relatively spared, whereas syntactic comprehension was markedly impaired. The deficit was not limited to the most complex structures, as in the NFPA, but also included other constructions, such as simple passives. This finding, together with a significant deficit in sentence repetition, suggests that a short-term phonological memory deficit could be the core mechanism underlying the clinical presentation of LPA.” In 2008 the following features were required: (1) word retrieval deficits in spontaneous speech and confrontation naming, (2) impaired repetition of sentences, (3) errors in spontaneous speech and naming (eg, phonological errors), and (4) sparing of word and object knowledge and motor speech. The 2011 criteria require, both core features: (1) Impaired single-word retrieval in spontaneous speech and naming; (2) Impaired repetition of sentences and phrases; and at least 3 of the following features: (1) Speech (phonologic) errors in spontaneous speech and naming; (2) Spared single-word comprehension and object knowledge; and (3) Spared motor speech (4) Absence of frank agrammatism.

As shown above, all the features described in 2004 are also present in posterior versions of the criteria and the core deficits are the same for each variant. The main differences are additions of supporting features such as spared object knowledge in the non-fluent variant and surface dyslexia for the semantic variant. Another difference is the way in which

some deficits are operationalized. For example, the deficit in word and object knowledge characteristic of the semantic variant was operationalized as impaired scores on the BNT and the PPT tests in 2004, whereas later publications did not specify particular tests, instead requiring impaired confrontation naming and semantic memory in 2008 and confrontation naming, single word comprehension, and object knowledge in 2011. The changes in the criteria have not changed the framework of the tripartite classification system, which is delineation of one variant with a predominant deficit in motor speech and grammar production, another variant with a predominant deficit in semantics, and another variant with a predominant deficit in word retrieval and phonologic processing. Therefore use of clinical judgment in the application of any of the versions of the criteria described above will result in identification of the same patients. In addition, classification was based on the same core clinical evaluation since 2002 further minimizing any potential effects produced by the changes in criteria.

eTable. Patients Who 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)

eAppendix 2. Voxel-based Morphometry Analyses

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 $p<0.05$.

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 $p<0.01$. Image processing and statistics were performed with Statistical Parametric Mapping (SPM12) software using the DARTEL toolbox according to standard procedures (Ashburner and Friston, 2005; Ashburner, 2007).

eAppendix 3. Neuropathology Methods

All brain autopsies were performed by the UCSF Neurodegenerative Disease Brain Bank. 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 (Mackenzie *et al.*, 2010; Hyman *et al.*, 2012). Blocks were embedded in paraffin wax, cut into 8 micron-thick sections, and stained with hematoxylin/eosin. Immunohistochemistry for Aβ (4G8, 1:2000, Covance, NJ), hyperphosphorylated tau (CP-13, 1:500, gift from Peter Davies, NY), α-synuclein (1:500, LB509, Invitrogen, CA), and transactive response DNA binding protein 43 (TDP-43, 1:500, Proteintech, , Chicago, IL) was performed. Immunoperoxidase staining was performed using an avidin-biotin complex detection system (Vectastain ABC kit; Vector Laboratories, Burlingame, CA) with 3,3 diaminobenzidine as the chromogen (Montine *et al.*, 2012).

eReferences.

Ashburner, J. (2007) 'A fast diffeomorphic image registration algorithm', *Neuroimage*, 38(1), pp. 95–113. doi: 10.1016/j.neuroimage.2007.07.007.

Ashburner, J. and Friston, K. J. (2005) 'Unified segmentation', *Neuroimage*, 26(3), pp. 839–851. doi: 10.1016/j.neuroimage.2005.02.018.

Gorno-Tempini, M. L., Dronkers, N. F., Rankin, K. P., Ogar, J. M., Phengrasamy, L., Rosen, H. J., Johnson, J. K., Weiner, M. W. and Miller, B. L. (2004) 'Cognition and anatomy in three variants of primary progressive aphasia', *Ann Neurol*, 55(3), pp. 335–346. doi: 10.1002/ana.10825.

Gorno-Tempini, M. L., Hillis, A. E., Weintraub, S., Kertesz, A., Mendez, M., Cappa, S. F., Ogar, J. M., Rohrer, J. D., Black, S., Boeve, B. F., Manes, F., Dronkers, N. F., Vandenberghe, R., Rascovsky, K., Patterson, K., Miller, B. L., Knopman, D. S., Hodges, J. R., Mesulam, M. M. and Grossman, M. (2011) 'Classification of primary progressive aphasia and its variants', *Neurology*. 2011/02/18. Memory and Aging Center, Department of Neurology, UCSF, 350 Parnassus Avenue, Suite 905, San Francisco, CA 94143-1207, USA. marilu@memory.ucsf.edu, 76(11), pp. 1006–1014. doi: 10.1212/WNL.0b013e31821103e6.

Hyman, B. T., Phelps, C. H., Beach, T. G., Bigio, E. H., Cairns, N. J., Carrillo, M. C., Dickson, D. W., Duyckaerts, C., Frosch, M. P., Masliah, E., Mirra, S. S., Nelson, P. T., Schneider, J. A., Thal, D. R., Thies, B., Trojanowski, J. Q., Vinters, H. V. and Montine, T. J. (2012) 'National Institute on Aging–Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease', *Alzheimer's & Dementia*, 8(1), pp. 1–13. doi: 10.1016/j.jalz.2011.10.007.

Mackenzie, I. R., Neumann, M., Bigio, E. H., Cairns, N. J., Alafuzoff, I., Kril, J., Kovacs, G. G., Ghetti, B., Halliday, G., Holm, I. E., Ince, P. G., Kamphorst, W., Revesz, T., Rozemuller, A. J., Kumar-Singh, S., Akiyama, H., Baborie, A., Spina, S., Dickson, D. W., Trojanowski, J. Q. and Mann, D. M. (2010) 'Nomenclature and nosology for neuropathologic subtypes of frontotemporal lobar degeneration: an update', *Acta Neuropathol*. 2009/11/20. Department of Pathology and Laboratory Medicine, Vancouver General Hospital and University of British Columbia, Vancouver, BC, Canada. ian.mackenzie@vch.ca, 119(1), pp. 1–4. doi: 10.1007/s00401-009-0612-2.

Montine, T. J., Phelps, C. H., Beach, T. G., Bigio, E. H., Cairns, N. J., Dickson, D. W., Duyckaerts, C., Frosch, M. P., Masliah, E., Mirra, S. S., Nelson, P. T., Schneider, J. A., Thal, D. R., Trojanowski, J. Q., Vinters, H. V., Hyman, B. T., National Institute on Aging and Alzheimer's Association (2012) 'National Institute on Aging–Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: a practical approach', *Acta Neuropathologica*, 123(1), pp. 1–11. doi: 10.1007/s00401-011-0910-3.

Rabinovici, G. D., Jagust, W. J., Furst, A. J., Ogar, J. M., Racine, C. A., Mormino, E. C., O'Neil, J. P., Lal, R. A., Dronkers, N. F., Miller, B. L. and Gorno-Tempini, M. L. (2008) 'Abeta amyloid and glucose metabolism in three variants of primary progressive aphasia', *Ann Neurol*. 2008/11/11. Memory and Aging Center, University of California San Francisco, San Francisco, CA 94143, USA. grabinovici@memory.ucsf.edu, 64(4), pp. 388–401. doi: 10.1002/ana.21451.

Villeneuve, S., Rabinovici, G. D., Cohn-Sheehy, B. I., Madison, C., Ayakta, N., Ghosh, P. M., La Joie, R., Arthur-Bentil, S. K., Vogel, J. W., Marks, S. M., Lehmann, M., Rosen, H. J., Reed, B., Olichney, J., Boxer, A. L., Miller, B. L., Borys, E., Jin, L.-W., Huang, E. J., Grinberg, L. T., DeCarli, C., Seeley, W. W. and Jagust, W. (2015) 'Existing Pittsburgh Compound-B positron emission tomography thresholds are too high: statistical and pathological evaluation', *Brain*, 138(7), pp. 2020–2033. doi: 10.1093/brain/awv112.