

# Is it time to revisit the classification guidelines for primary progressive aphasia?

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Hair-splitting details of syndromic classification can hardly be expected to generate much excitement. As in all areas of science, however, sound nosology and uniform nomenclature are important for progress in neurology. This is particularly true for the neurodegenerative syndromes, including primary progressive aphasia (PPA), where heterogeneity of phenotype and cellular pathology has defied attempts to find coherent clinicopathologic correlations.

PPA is a distinctive neurodegenerative dementia syndrome characterized by a relatively selective loss of language function. Frontotemporal lobar degeneration (FTLD) causes slightly more than half of cases, while atypical forms of Alzheimer disease (AD) pathology cause the rest. As the features of this syndrome were being delineated between 1982 and 1992, it became clear that the associated language impairments were heterogeneous and that they did not quite fit the familiar patterns of classic aphasiology. At that time, the descriptive terms “logopenia” and “logopenic” were introduced to define a language abnormality that appeared peculiar to PPA.<sup>1,2</sup> The abnormality was characterized by word-finding failures that led to intermittent loss of fluency but without dysarthria, agrammatism, or comprehension deficits. The initial clinical descriptions of logopenia in PPA were not accompanied by specific diagnostic criteria. In 1998, Neary et al.<sup>3</sup> introduced the first widely accepted classification of progressive aphasias in a consensus report aiming to capture the clinical spectrum of FTLD. The report assigned the progressive nonfluent aphasia (PNFA) designation to all cases with impaired fluency and defined semantic dementia (SD) as a syndrome with both word comprehension impairments (i.e., aphasia) and object recognition impairments (i.e., associative agnosia) but preserved fluency.

Although the 1998 criteria by Neary et al.<sup>3</sup> were not designed to characterize PPA as a whole, their use as such created unanticipated consequences. First, the logopenic pattern of aphasia was not recognized as a distinct entity. Second, the SD designation potentially included some patients whose most prominent problem was an associative agnosia and who would therefore not fit the PPA diagnosis.

Third, patients with PPA with non-FTLD pathologies appeared implicitly excluded. All 3 of these problems were addressed by the 2011 guidelines of Gorno-Tempini et al.<sup>4</sup>: a logopenic variant was identified, inclusion into the semantic subgroup required prior fulfillment of the root PPA criteria, and no assumption was made as to the nature of the underlying pathology. The 2011 guidelines have become the gold standard in the field and received nearly 100 citations in 2012 alone. Nonetheless, challenges have emerged in the form of unclassifiable patients and patients who simultaneously fulfill criteria for more than one subtype.<sup>5–7</sup> The 2011 criteria also added impaired repetition as a core feature of the logopenic variant, a feature that was not part of the original description of logopenia, leading to the possible use of this term in more than one way.

Correct classification in PPA is important, both for its own sake and also because each subtype has a differential probability of being associated with AD vs FTLD pathology. The report by Wicklund et al.<sup>8</sup> in this issue of *Neurology*® gives the 2011 guidelines a comprehensive stress test. The verdict is mixed. The good news is that 69% of the 84 participants were assigned to 1 of the 3 canonical variants: nonfluent/agrammatic, logopenic, and semantic. The troublesome finding is that 31% of the sample did not find a suitable home within any of the categories. Some had both agrammatism and word comprehension deficits, a combination that does not fit any of the 2011 variants, while others had word retrieval and naming impairments that came close to fitting the logopenic variant but lacked the core criterion of abnormal repetition. Furthermore, some patients who fit the semantic or agrammatic classification also fulfilled criteria for the logopenic variant.

These are serious limitations. One could quibble with the choice of tests, control group, or statistical threshold of normality, but other laboratories have reported similar problems. This is not surprising given the challenge of capturing the multiple impairments that emerge as neurodegeneration spreads through components of the language network. In fact, if the founders of aphasiology had been given the task of

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squeezing all stroke-induced language impairments into 3 categories, they would surely have failed. Many remedies will undoubtedly be suggested for revising the 2011 guidelines. A few that might have the potential to address the major issues identified by Wicklund et al. are as follows:

1. The double-assignment problem can be resolved by making the “absence of definite grammar and comprehension impairment” a core criterion for the logopenic variant.
2. Some patients, who fit the clinical description of “logopenic” because of prominent word retrieval and naming deficits, remain unclassifiable by the 2011 guidelines if they do not have abnormalities of repetition. Making the repetition impairment an ancillary rather than a core criterion for the logopenic variant would allow these patients to fit into the existing classification system. If necessary, the logopenic variant could then be subdivided further according to the status of repetition.
3. Patients with a combination of agrammatism and semantic impairments even at early stages of disease have been reported and classified into a variant of “mixed” PPA.<sup>6,9</sup> Wider recognition of this fourth variant would further decrease the number of unclassifiable cases.

A fine-tuning of the 2011 guidelines will further enhance uniformity of nosology and nomenclature in PPA. The process should aim to make the classification system as inclusive as possible, prevent instances where one patient can fit multiple subtypes, and eliminate ancillary tests and criteria that are of marginal value. Such revisions will have the most staying power if they are based on empirical data and have the support of international consensus.

## AUTHOR CONTRIBUTIONS

M.-Marsel Mesulam: drafting/revising the manuscript, study concept or design, analysis or interpretation of data. Sandra Weintraub: drafting/revising the manuscript.

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## DISCLOSURE

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