Utility of the Repeat and Point Test for Subtyping Patients With Primary Progressive Aphasia

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Background: Primary progressive aphasia (PPA) may present with three distinct clinical sybtypes: semantic variant PPA (svPPA), nonfluent/agrammatic variant PPA (nfvPPA), and logopenic variant PPA (lvPPA).

Objective: The aim was to examine the utility of the German version of the Repeat and Point (R&P) Test for subtyping patients with PPA.

Method: During the R&P Test, the examiner reads out aloud a noun and the participants are asked to repeat the word and subsequently point to the corresponding picture. Data from 204 patients (68 svPPA, 85 nfvPPA, and 51 lvPPA) and 33 healthy controls were analyzed.

Results: Controls completed both tasks with >90% accuracy. Patients with svPPA had high scores in repetition (mean = 9.2 ± 1.32) but low scores in pointing (mean = 6 ± 2.52). In contrast, patients with nfvPPA and lvPPA performed comparably in both tasks with lower scores in repetition (mean = 7.4 ± 2.7 for nfvPPA and 8.2 ± 2.34 for lvPPA) but higher scores in pointing (mean = 8.9 ± 1.41 for nfvPPA and 8.6 ± 1.62 for lvPPA). The R&P Test had high accuracy discriminating svPPA from nfvPPA (83% accuracy) and lvPPA (79% accuracy). However, there was low accuracy discriminating nfvPPA from lvPPA (<60%).

Conclusion: The R&P Test helps to differentiate svPPA from 2 nonsemantic variants (nfvPPA and lvPPA). However, additional tests are required for the differentiation of nfvPPA and lvPPA.

Key Words: primary progressive aphasia, single-word comprehension, repetition, agrammatism, classification

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Patients with neurodegenerative diseases may present with a syndrome of progressive language impairment. The report in 1982 by Marsel Mesulam included 6 cases presenting with clinically isolated, slowly progressive language impairment.[1] The subsequent clinical and autopsy observations helped this as a syndrome termed primary progressive aphasia (PPA). However, the syndrome lacks homogeneity in atrophy patterns, as well as underlying pathologies and clinical profiles,[1–4] leading to subsequent subclassification. Exceptionally, challenges in the classification of PPA are not limited to pathologic and clinical heterogeneity. Since PPA is described as a "language-based dementia,"[5] cross-linguistic differences may lead to considerable difficulties in developing standardized tools for capturing distinct features of aphasia.

The first proposal for classification of PPA[6] suggested a binary clinical classification based on clinical assessment of semantic abilities and fluency: patients were to be grouped under syndromic designations of either as semantic dementia (SD) or as progressive nonfluent aphasia (PNFA), respectively. According to this proposal, patients with semantic impairment and fluent speech were classified as SD whereas patients with preserved semantics but impaired fluency were classified as PNFA. Both SD and PNFA were subsumed under a diagnosis of frontotemporal lobar degeneration (FTLD), where "the generic term FTLD refers to the circumscribed progressive degeneration of the frontotemporal lobes" with "2 main histologic types: prominent microvacuolar change without specific histologic features (frontal lobe degeneration type) or severe astrocytic gliosis with or without ballooned cells and inclusion bodies (Pick type)."[6] Considerable subsequent progress in neuropathology disclosed that Pick type is associated with deposits of the tau protein of the 3 repeat type (3R tau), yet tau pathology may also present in other distinct forms (4R tau, and mixed 3R and 4R tau).[7,8] Moreover, a significant number of cases are associated with inclusions that are negative for tau but stain with ubiquitin (FTLD-U). The most frequent histologic findings in FTLD-U are deposits of the transactive response DNA binding protein of 43 kDa (TDP-43), resulting in a neuropathologic diagnosis of FTLD-TDP.[9] In addition to these refinements of FTLD neuropathology, there were also findings of Alzheimer disease (AD) in cases of PPA[10,11] and several cases revealed pathologies outside the spectrum of both FTLD and of AD, such as Lewy body disease[12,13] and diffuse leukoencephalopathy with spheroids.[14] Thus, on the neuropathologic aspect, the 1998 criteria lacked the wider coverage of the heterogeneous FTLD spectrum and disregarded pathologies other than FTLD.

Clinically, SD included a language disorder characterized by loss of word meaning and a perceptual disorder including prosopagnosia and/or associative agnosia. PNFA was not homogenous either: in addition to the general essential feature of insidious onset and gradual progression, the core diagnostic feature was nonfluent spontaneous speech that included at least one of the following: agrammatism, phonemic paraphasias, and anomia.[6] Thus, nonfluent PPA with anomia and word-finding pauses but no agrammatism would equally qualify for the PNFA designation as would nonfluent PPA with agrammatism.[4]

"Logopenia" and "logopenic" (ie, lack of words, short of words) had originally been introduced as general descriptive terms in 1982 for long word-finding pauses.[1] These terms later became central denominators when a new PPA subtype was specifically proposed.[15] In contrast, the underlying cognitive mechanisms, neuroanatomical correlates, and histopathology of the logopenic pattern may be distinct from that of other nonfluent patients who present with agrammatism.[11,16]

Because of the difficulties caused by subgrouping PPA into 1 of the 2 clinical phenotypes (PNFA or SD) and limited clinicopathologic correlations because of the exclusion of non-FTLD cases, the classification criteria for were revised in 2011, and neurodegenerative aphasias were re-introduced as distinct clinical phenotypes within frontotemporal dementia spectrum.[17] The new classification included the logopenic pattern as a distinct "logopenic variant PPA" (lvPPA) phenotype. Impaired repetition was added as a core diagnostic feature for lvPPA which had not been a core feature in the original description of logopenia.[4] Patients with agrammatism and/or apraxia of speech were classified as "nonfluent/agrammatic variant PPA" (nfvPPA). Patients with selective impairment in word comprehension with relatively preserved face and object recognition were classified as "semantic variant PPA" (svPPA). In short, the new criteria provided a more comprehensive syndromic classification of PPA but also proposed the use of biomarkers, such as FDG-PET imaging, as evidence for specific neurodegenerative pathologies.[17] The new criteria acknowledged the problems of binary classification of progressive aphasia, yet were unable to encompass the variety of clinical phenotypes seen in neurobehavior clinics. Moreover, the definition of logopenic PPA remains controversial. Despite the apparent progress of leaving the mere binary approach and of increased attention to clinical detail, the 2011 classification is more challenging as it requires a more comprehensive language assessment.

However, pathologic classification of FTLD has also evolved and subgroups of TDP-proteinopathy and non-TDP ubiquinopathies were described.[18] The previously described subtypes of TDP proteinopaty[7,19] including Types A, B, C, and, D have expanded and a novel clinicopathologic subtype has been designated as Type E.[20] In contrast, Fused in sarcoma (FUS), Ewing's sarcoma (EWS), and TATA-binding protein-associated factor 15 (TAF15) also known as the FET protein family has been classified as non-TDP FTLD pathologic subtype.[18] Furthermore, although it is not pathognomonic of a specific neuropathology type clinicopathologic correlations have been reported between certain pathologies and PPA subtypes. FTLD-tau and FTLD-TDP (Type C) have been associated with nfvPPA and svPPA, respectively.[21] However, neuropathologic investigations of lvPPA cases showed that up to 76% of these patients had AD pathology.[22]

Interestingly, a significant number of PPA patients without repetition deficit, previously considered displaying a logopenic pattern, were re-classified as 'unclassified PPA' after the publication of the 2011 criteria.[4] Also, a data-driven cluster analysis conducted by Hoffman et al separated 43 PPA patients into three groups, which poorly correspond to the current guidelines. While cluster 1 largely consisted of svPPA patients, the distinction of clusters 2 and 3 was less clear and suggested difficulties in the differentiation of nonsemantic PPA variants.[23]

Strikingly, the debates summarized above were based on studies in English-speaking PPA cohorts. Although the final reports were created by an international board of experts, clinical features of non-English-speaking PPA patients were not adequately covered in the classification guidelines neither in 1998 nor in the 2011 classification.[6,17]

One of the challenges in PPA classification arises because of the involvement of repetition impairment as the core criterion in the 2011 classification. There is accumulating evidence showing that repetition impairment can be evident in all three subtypes of PPA with variable ranges of severity.[24–27] In contrast, subtyping of PPA in non-English-speaking cohorts can be even more problematic, especially in a routine clinical setting with limited evaluation time and support by specialized personnel such as speech pathologists or clinical linguists. Therefore, quick and reliable measures for discriminating PPA subtypes that could be used by general neurologists and general practitioners as well as behavioral neurologists and clinical neuropsychologists are warranted. To this end, repetition of a single word followed by pointing at the corresponding picture as an indicator of comprehension was proposed by John Hodges and collaborators as 2 axes to differentiate SD and PNFA. The approach was used to create the Repeat and Point (R&P) Test which successfully differentiated a SD group from a PNFA group.[28] A German version of the R&P Test was developed in 2010 by Heitkamp et al,[29] which was also successful in differentiating semantic PPA from nonsemantic PPA. Subsequently, the test was included in the evaluation battery of the German FTLD Consortium (http://www.ftld.de) in 2011 and is presented here in full for the first time. On the basis of our experience with the large cohort of the consortium, we analyzed the utility of the R&P test for subtyping PPA according to the criteria of 2011. We hypothesized that the test will successfully differentiate svPPA from nonsemantic PPA subtypes (nfvPPA and lvPPA) similar to the outcomes of the original study of Hodges and colleagues. Our second goal is to explore whether the test will differentiate the 2 nonsemantic variants, nfvPPA, and lvPPA respectively. On the basis of the criteria of 2011, one may expect that the repetition part of the test would be successful in differentiating nfvPPA from lvPPA as repetition is one of the core criteria for diagnosis of lvPPA. However, challenges in the classification of PPA and occurrence of repetition impairment in svPPA and nfvPPA with variable ranges of severity led to the questioning of the utility of repetition impairment as a core criterion. Our findings will add value to the debates on the classification of PPA using data from one of the largest PPA cohorts ever published. A failure in differentiating nfvPPA from lvPPA using a test containing comprehension and repetition as 2 main axes will highlight the significance of developing more sensitive tests based on the linguistic characteristics of German including the grammatical and phonological aspects.

METHODS

Participants

The study included 244 PPA patients and 33 healthy controls from 14 academic centers affiliated with the German Frontotemporal Lobar Degeneration Consortium (German FTLDc; http://www.ftld.de) recruited between 2011 and 2018. All patients met the root clinical diagnosis of PPA as progressive language impairment remained the most salient clinical feature for at least the first 2 years of the disease.[30] PPA patients were subtyped according to the classification criteria suggested by Gorno-Tempini et al[17] without reference to R&P performance. Sixty-eight patients had the diagnosis of svPPA, 85 patients had the diagnosis of nfvPPA, and 51 patients had the diagnosis of lvPPA. Radiologic atrophy patterns of the patients in our PPA cohort were in line with the current diagnostic criteria. Neuroimaging showed "predominant left posterior frontoinsular atrophy on magnetic resonance imaging and/or predominant left posterior frontoinsular hypoperfusion or hypometabolism on single-photon emission computerized tomography (SPECT) or positron emission tomography (PET) in nfvPPA cases, "predominant anterior temporal lobe atrophy and/or predominant anterior temporal hypoperfusion or hypometabolism on SPECT or PET" in svPPA and, "predominant left posterior perisylvian and parietal atrophy on magnetic resonance imaging and/or predominant left posterior perisylvian or parietal hypoperfusion or hypometabolism on SPECT or PET."[17]

Age differences existed between groups ($F_{3,233} = 5.08$, $P = 0.002$). Patients with svPPA were younger than other PPA groups (vs. nfvPPA $P = 0.004$; vs. lvPPA $P = 0.012$) (Table 1). An additional group of 40 PPA cases including (16% of the entire FTLDc PPA cohort) remained unclassified according to the current criteria and were excluded from the study. Mixed PPA patients[30] were also included in the unclassified group and were excluded from the study. The right temporal variant frontotemporal dementia patients do not meet the PPA criteria.[31] Therefore, those patients were excluded, as well. The study was approved by the local

TABLE 1. Demographics and Neuropsychological Characteristics of the Participants

	Controls, N = 33	svPPA, N = 68	nfvPPA, N = 85	lvPPA, N = 51
Age	66 ± 7.26	64 ± 8.63†‡	68.5 ± 8.34	68.6 ± 5.95
Disease duration	NA	3.53 ± 2	2.74 ± 1.5‡	4.2 ± 3.3
MMSE (30)	29.2 ± 0.8	21.4 ± 6.52*	23.7 ± 5.9*	22 ± 5.6*
Verbal fluency	27.5 ± 6.3	7.2 ± 4.68*†‡	11 ± 6.6*	9.8 ± 4.3*
Phonemic fluency	18.2 ± 4.25	6.5 ± 4*	4.8 ± 3.9*	6.1 ± 3.4*
BNT (15)	14.9 ± 0.29	6 ± 3.3*†‡	11.6 ± 3.6*	10.8 ± 3.3*
Written language (90)	89.6 ± 0.82	81.3 ± 10.8	74.8 ± 19.7*	77.4 ± 15.1*
TMT-A (s)	36 ± 9.67	63.4 ± 35.5*†	87.7 ± 43.9*	79.7 ± 41.6*
TMT-B (s)	76.7 ± 22.4	133.5 ± 67.4*†‡	213.4 ± 76.6*	212 ± 77.2*
Digit span forward	8.94 ± 1.5	5.97 ± 2.3*†‡	4.1 ± 1.7*	3.8 ± 2.2*
Digit span Backward	7.42 ± 2.06	4.7 ± 2.2*†‡	3.27 ± 1.78*	3.2 ± 1.7*

*$P < 0.05$ versus controls.
†$P < 0.05$ versus nfvPPA.
‡$P < 0.05$ versus lvPPA.
BNT indicates Boston Naming Test; lvPPA, logopenic variant primary progressive aphasia; MMSE, Mini-Mental State Examination; nfvPPA, nonfluent/agrammatic variant primary progressive aphasia; svPPA, semantic variant primary progressive aphasia; TMT, trail making test.

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Ethics Committees and written informed consent was obtained from each participant.

Neurocognitive Assessment

The neuropsychological assessment included both linguistic and nonlinguistic cognitive domains as well as the Mini-Mental State Examination (MMSE) as applied within the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) battery,[32] German version.[33] The demographic and neuropsychological characteristics of the participants are presented in Table 1. The language investigations included the assessment of phonemic and semantic word fluency ("S words" and "animals"), naming (Boston Naming Test, 15-item short CERAD version), spontaneous speech production (Cookie Theft picture)[34] and reading and writing abilities (written language-subtest of the German Aachener Aphasie Test).[35] In addition to the comprehensive language examination, all participants were administered digit span[36] and trail-making tests[37] for assessment of working memory and executive functions, respectively. Age at visit was added as a covariate in all between group comparisons of test performances (Table 1).

German Version of the R&P Test

Word length is one of the prominent factors that influence repetition both in healthy individuals and in patients with aphasia.[24] In contrast, in German-speaking patients, the syllable structure may also have a significant impact on repetition especially when the verbal stimuli consist of low-frequency syllables.[38] Therefore, concrete nouns with complex syllables that contain more than just simple vowel and consonant sequences were selected for the adaptation of the original R&P Test[28] to German. All selected words consisted of either more than 3 syllables or syllables occurring at low frequencies. The objects corresponding to the nouns as well as their respective 6 foils had to be easily represented with photos that were taken from the public domain. A variety of categories, including clothes, tools, animals, vehicles, household items, and famous buildings, were covered. An initial number of 21 nouns was piloted in normal control subjects and subsequently reduced based on observed difficulties in pronunciation or picture identification.[29]

The stimuli in the final set used in the current study included twelve nouns that ranged from "Matratze" [mattress] to "Reichstagsgebäude" [parliament building] in length and, with an average of 12.1 ± 2.9. The number of letters significantly exceeded those of the English version (9.6 ± 1.7; $t_{18} = 2.3$, $P = 0.03$). The number of syllables, however, in the German (3.2 ± 0.78) and English (3.5 ± 0.85) versions of the test did not differ significantly from each other ($t_{18} = 2.3$, $P = 0.42$). During test administration, 2 practice trials preceded the 10 test runs. The examiner read out aloud each noun for the participant first to repeat and then to indicate the corresponding picture by pointing on the 7-item array. Participants received scores of either 0 or 1 for correct/incorrect repetition and pointing, respectively. Scoring of responses was made according to the guidelines described in the original study.[28] Phonological errors and self-corrections during repetition were considered wrong answers (eg, "Kratze…ah. Matratze"). The responses were rated by a neuropsychologist or a clinical linguist and all neuropsychological battery administered during the FTLDc visits including the R&P Test was monitored by the supervisor and/or the primary investigator of that center.

For the scoring sheet with a list of 12 words, including 2 practice words, Supplementary Figure 1 (Supplemental Digital Content 1, http://links.lww.com/WAD/A372). The 12 corresponding stimulus sets, with the target and its foils arranged on landscape A4 cardboard paper for presentation, are shown in Supplementary Figure 2 (Supplemental Digital Content 2, http://links.lww.com/WAD/A373).

Statistical Analyses

A 4 by 2 repeated analysis of variance was used to evaluate the interaction between group (controls, svPPA, nfvPPA, and lvPPA) and task (repetition and pointing). As we expected heteroscedasticity between the 2 tasks and groups, this model was modified to have 8 residual variances, 1 for each test and group combination. Posthoc pairwise comparisons were conducted to determine which pairs of groups are different from each other. *P*-values were adjusted for multiplicity (adjusted *P*-values were based on the joint normal distribution). Adjustment for age and disease duration did not significantly improve the model fit and will not be shown here. The predictive ability of the R&P Test to discriminate between svPPA and nfvPPA, svPPA and lvPPA, as well as lvPPA and nfvPPA, was assessed with the use of logistic models with pointing and repetition scores as explanatory variables. Model predictions and observations were compared with the construction of the receiver operation characteristic curve and the computation of the area under a receiver operation characteristic curve (AUC). Percentages of correctly classified responses based on 10-fold cross-validation are also displayed. A cutoff of 0.5 was used. All tests were 2-sided and the significance level was set to 0.05. Analyses were performed in R (version 3.5.1) with the use of the packages nlme and multcomp.

RESULTS

Figure 1 shows the performance of controls and three PPA groups in the R&P Test. The interaction between group (controls, svPPA, nfvPPA, and lvPPA) and task (repetition, pointing) was statistically significant ($F_{3,226} = 32.63$, $P < 0.001$). Posthoc pairwise comparisons showed that the magnitude of the difference in repetition versus pointing subscores was significant between svPPA versus all other groups (vs. controls, constrate estimate $d = -3.15$, its SE = 0.35, and the corresponding *P*-value $P < 0.001$; vs. nfvPPA, $d = -4.58$, SE = 0.48, $P < 0.001$; vs. lvPPA, $d = -3.54$, SE = 0.53, $P < 0.001$). The

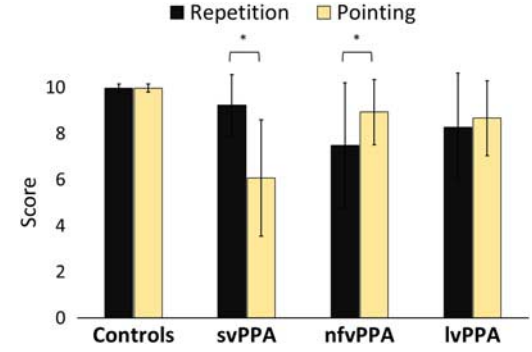

FIGURE 1. Repetition and pointing scores of controls and primary progressive aphasia patients. *Significant within-group comparisons of repetition and pointing scores. lvPPA indicates logopenic variant primary progressive aphasia; nfvPPA, nonfluent/agrammatic variant primary progressive aphasia; svPPA, semantic variant primary progressive aphasia. full color online

magnitude of difference between repetition and pointing scores did not differ between controls versus the lvPPA group ($d = -0.39$, SE = 0.40, $P = 0.96$). However, the comparison of controls and the nfvPPA group showed a significant difference ($d = -1.44$, SE = 0.34, $P < 0.001$). Moreover, the magnitude of difference between repetition and pointing scores did not differ between nfvPPA and lvPPA groups ($d = 1.05$, SE = 0.52, $P = 0.37$), as well.

Controls completed both parts of the test with high accuracy and without a difference between repetition and pointing scores ($d = 0$, SE = 0.04, $P > 0.999$). In the repetition part of the task, all three PPA groups (svPPA, nfvPPA and lvPPA) had significantly lower scores compared with controls (controls vs. svPPA, $d = -0.75$, SE = 0.16 $P < 0.001$; controls vs. nfvPPA, $d = -2.48$, SE = 0.30, $P < 0.001$ and; controls vs. lvPPA, $d = -1.69$, SE = 0.33, $P < 0.001$, respectively). The nfvPPA group also had lower repetition scores compared with svPPA ($d = -1.73$, SE = 0.34, $P < 0.001$), yet repetition scores did not significantly differ between the lvPPA and svPPA groups ($d = 0.95$, SE = 0.36, $P = 0.11$). Repetition scores in the nfvPPA and lvPPA groups were also comparable ($d = -0.79$, SE = 0.44, $P = 0.53$).

Also in the pointing part, the average score was significantly lower in all PPA groups (svPPA, nfvPPA, and lvPPA) compared with controls (svPPA vs. controls, $d = -3.90$, SE = 0.31, $P < 0.001$; nfvPPA vs. controls, $d = -1.30$, SE = 0.23, $P < 0.001$, and lvPPA vs. controls, $d = -1.04$, SE = 0.16, $P < 0.001$, respectively). The svPPA group had the lowest scores on average and performed significantly worse than the lvPPA ($d = -2.59$, SE = 0.38, $P < 0.001$) and nfvPPA groups ($d = -2.86$, SE = 0.34, $P < 0.001$). The nfvPPA group performed in a comparable manner as lvPPA in the pointing part ($d = 0.26$, SE = 0.27, $P = 0.97$).

The svPPA group had higher scores in repetition compared with pointing ($d = 3.15$, SE = 0.35, $P < 0.001$). The nfvPPA group had lower repetition scores compared with pointing scores ($d = -1.44$, SE = 0.33, $P < 0.001$). However, there was no significant difference between repetition and pointing scores in the lvPPA group ($d = -0.39$, SE = 0.40, $P = 0.96$). Variability depends highly on both the tasks and the patient groups.

Heteroscedasticity was clearly present (likelihood ratio test: $\chi^2_7 = 14.8$, $P < 0.0001$). As all patients in the control group had scores of 9 or 10, variability was 7 to 20 times smaller in this group relative to the other groups. Relative to the semantic group, variability in the repetition scores was 2.5 times higher in the nfvPPA group and 1.7 times higher in the lvPPA group. Variability in the pointing scores is reduced by a factor of 0.57 in the nfvPPA group and a factor of 0.63 in the lvPPA group compared with the semantic group. Logistic regression analysis showed that the R&P Test successfully discriminated svPPA patients from nfvPPA (83% accuracy, AUC = 0.9) and lvPPA patients (79% accuracy, AUC = 0.86). However, there was low accuracy discriminating nfvPPA from lvPPA (< 60%, AUC = 0.61) (Fig. 2).

DISCUSSION

In this study, we used a German adaptation of the R&P Test originally developed by Hodges et al[28] in a large cohort of German-speaking patients with PPA, diagnosed according to the criteria of Gorno-Tempini et al.[17] Our findings reveal that the combination of single-word repetition and word comprehension (indicated by pointing) can successfully differentiate svPPA patients from patients with nfvPPA and lvPPA. However, nfvPPA and lvPPA patients performed comparably on both tasks. The R&P Test thus appears insufficient to differentiate between nfvPPA and lvPPA patients.

To reveal the relationship between the linguistic task and the PPA subtype, the 2 parts of the test were evaluated separately. In the comprehension part of the test (assessed by pointing), all patient groups scored significantly lower than controls, and the svPPA patients showed significantly lower scores when compared with the other patient groups. Although the nfvPPA and lvPPA groups also had significantly lower pointing scores than controls, both on average performed above the 85th percentile. Thus, single-word comprehension as tested by the pointing part of the task is relatively preserved in these groups, a finding in agreement with previous studies.[39–42] Also in the repetition part, all three PPA groups performed significantly worse

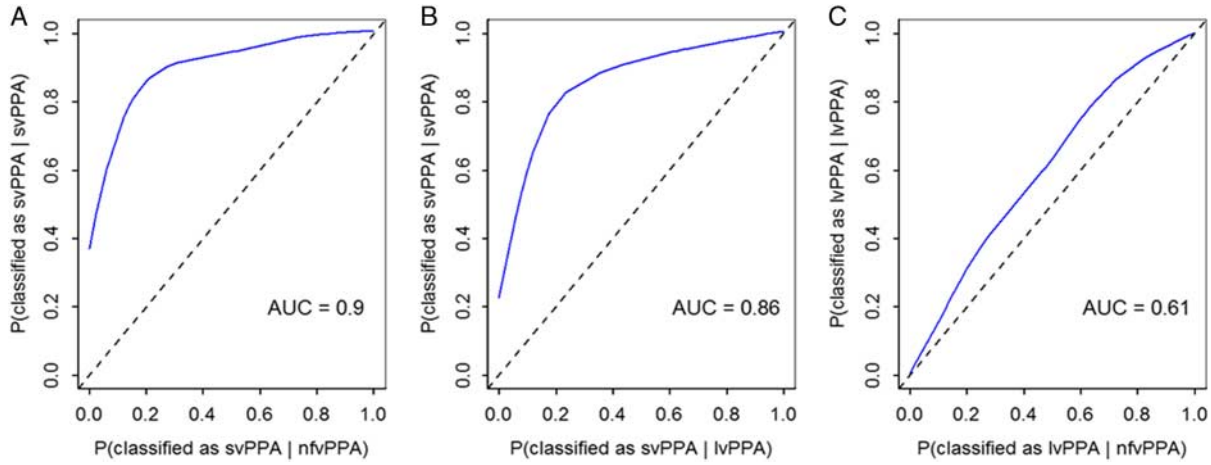

FIGURE 2. Receiver operation characteristic curves based on logistic regression for discrimination between different primary progressive aphasia (PPA) subtypes. A, Discrimination between semantic variant primary progressive aphasia (svPPA) and nonfluent/agrammatic variant primary progressive aphasia (nfvPPA). B, Discrimination between svPPA and logopenic variant primary progressive aphasia (lvPPA). C, Discrimination between lvPPA and nfvPPA. AUC indicates area under the curve. full color online

than controls. This, however, was more pronounced in nfvPPA and lvPPA patients than in the svPPA group. Despite minor differences in average scores between controls and svPPA patients in the repetition task, the large sample sizes and the low variability in controls might have magnified the effect. Nevertheless, svPPA patients scored above the 90th percentile on average, indicating their relatively preserved ability to repeat. In contrast, within-group variance in repetition scores was more pronounced in nfvPPA and lvPPA, suggesting some patients with relatively preserved repetition were included in these groups.

In contrast to single-word comprehension, the use of repetition as a language metric in PPA classification is controversial.[4,17] Impaired repetition is one of the most common aphasia symptoms regardless of subtype, likely with "variant-specific" underlying factors such as impaired working memory and apraxia of speech in lvPPA and nfvPPA, respectively.[27] Distinct mechanisms have been proposed.[43–47] The essential components of word repetition include phoneme recognition, retrieval of phonological codes and their storage in working memory, motor planning, and articulation. In the case of complex grammatical sentences, decoding grammatical relations between different components of a sentence is also essential.[48,49] Moreover, the ability to access word meaning facilitates repetition which suggests an interaction between the semantic and the phonological systems.[50] Therefore, patients with semantic impairment may also have difficulties in repetition tasks, in particular for words they fail to understand.[25,28]

Disruption at any stage explained above may lead to repetition impairment in aphasic individuals. Some linguistic models have been developed using lesion studies and computational approaches for characterization of the underlying cognitive mechanisms.[45,51] According to the *lexical route* model, repetition is impaired because of a deficit in the linkage between words and phonemes. This model requires recognition of the input word which is followed by the retrieval of phonology.[52] However, patients with *lexical route* interruption may have difficulty activating long-term semantic representations because of a deficit in input word recognition. Therefore, these patients use the *nonlexical route* where the input is directly mapped to output phonology and word recognition is not crucial for repetition.[51] Nevertheless, this cognitive strategy fails during reading and repeating irregular words since these words cannot be processed solely based on grapheme to morpheme conversion.[26,53,54] Impaired grapheme to morpheme conversion has been reported as a probable mechanism for repetition deficits in nfvPPA.[55] It is also suggested that the *lexical route* and the *nonlexical route* operate together to constitute a *dual-route* as combined activation of both is critical for auditory word repetition.[45,52]

Clinical observation of repetition difficulty in patients with limited access to the meaning of a word has been conceptualized within the framework of the *semantic access* hypothesis. According to this hypothesis, when access to the meaning of a word is interrupted, repetition of a given word can only be succeeded by mapping input phonemes to output phonemes that requires greater processing demands.[45,51] The relationship between word recognition and phonological processing has been shown not only in auditory verbal repetition tasks but also in word-list recall and paced reading tasks. Intact processing of the lexical route is critical for activating semantic representations. Therefore, interruption of the interaction between long-term semantic representations and temporary phonological activation has been proposed as the underlying cause of repetition deficit in patients with comprehension impairment.[26,50,53] Accordingly, svPPA patients may fail to repeat words incomprehensible for them in a similar manner as is observed in healthy individuals faced with nonword repetition tasks.[26,45] In our study, svPPA patients had lower scores than controls and similar findings have been reported previously.[25,28,53]

Retrieval of the phonology of a word to be repeated is followed by the motor planning of articulation. The planning stage is particularly critical for words that contain sequences of syllables as opposed to single-syllable words.[56] Patients with nfvPPA may present with effortful speech because of a deficit in articulation planning (apraxia of speech).[17] Although impaired repetition is not included in the diagnostic criteria for nfvPPA, apraxia of speech may underly repetition impairment in these patients particularly for words with syllable sequences.[17,56,57] For example, patients with apraxia of speech can repeat individual syllables of /pʌ/, /tʌ/, and /kʌ/ while the rapid repetitions of the sequence of /pʌtʌkʌ/ can be more effortful and erroneous with distorted sound substitutions.[58]

Furthermore, during sentence repetition, patients with agrammatic aphasia may omit some of the grammatical elements such as determiners and adjectives. They may also have difficulty repeating sentences with complex syntactical structure, for example, with noncanonical word-order and closed-class elements (ie, "No ifs, ands, or buts".).[49] The interaction between grammatical encoding and phonological processing may also become evident during the production of homonyms that belong to different grammatical classes. Stress, duration, even pronunciation of the same word may differ depending on its use as a noun, adjective, or a verb (ie, "record" as a noun vs. "record" as a verb; and "ragged" as a past participle adjective vs. "ragged" as the past tense of verb "rag").[48] Therefore, recognition of the grammatical class of a word is essential for intact processing of its phonology.

Finally, auditory verbal (phonological) working memory deficits may impair repetition and this type of impairment has been associated with lvPPA.[15,46] According to this model, the phonological loop operates as a component of verbal working memory as individuals need to hold verbal information for short periods before repetition is initiated.[40,44] The length of words or phrases to be repeated also plays a major role in the performance of lvPPA patients during auditory verbal repetition tasks.[15,44]

Because of the distinct underlying mechanisms, a double dissociation can be observed in single word and sentence repetition tasks.[59–61] In a recent study, the use of different conditions based on frequency, length, and meaning of phrases in a structured repetition task helped differentiate nfvPPA from lvPPA. Repetition subscores for long phrases were more sensitive in differentiating nfvPPA from lvPPA compared with other conditions. In contrast, lvPPA patients had greater difficulty repeating nonmeaningful short phrases compared with frequent long sentences suggesting that a limitation to activate meaningful representations diminished the advantage of lower working memory demands during the repetition of short phrases.[24] Sentence-to-word repetition ratio has also been used to control for the potential confounding effects of verbal working memory and sequencing impairment.[60] Thus, it is essential to use well-designed neurocognitive test tools for linguistic assessment of specific cognitive processing stages of repetition.

One limitation of the R&P test is that both English and German versions consist of single words rather than longer

phrases or sentences. Although the German version includes longer words compared with the English version, the lack of longer phrases or sentences might have limited the amount of workload on the phonological working memory that could have increased the magnitude of repetition deficit in lvPPA group. In contrast, complex grammatical sentences and/or sentences that consist of closed-class elements are also missing in the R&P test that would be more demanding to repeat for nfvPPA patients because of their difficulty of processing grammatical information. The amyloid status and genetic/pathologic confirmation were available in a subset of patients in our dataset. However, our study focused on the neurocognitive assessment, particularly the R&P Test, and clinical classification of PPA. Therefore, biomarker data was not included in the current study. Future studies with subgroups of PPA patients based on biomarker status would be more informative for understanding the correlations between different types of repetition impairments and underlying neuropathologies. In contrast, neither nfvPPA nor lvPPA represents uniform symptomatology and both phenotypes may be subclassified into more homogeneous syndromic clusters. One suggestion was to subdivide lvPPA according to the status of repetition.[4] Similarly, nfvPPA can also be subdivided according to the status of agrammatism and apraxia of speech. This approach may help decrease the ratio of unclassified cases, particularly in non-English-speaking PPA cohorts, and help overcome methodological difficulties in multicentered cross-linguistic studies.

CONCLUSION

As a simple, time-efficient tool, we recommend the use of the R&P Test for language testing in PPA. The test successfully discriminates svPPA patients from "non-semantic" patients (affected by nfvPPA or lvPPA). All PPA patients, however, are vulnerable to repetition deficits yet with variable ranges of severity. Additional tests are required to differentiate nfvPPA from lvPPA. Patients with nfvPPA may have selective impairments for processing verbs and syntactically complex sentences. Previous studies have shown that quantitative assessment of grammar can be very useful for discriminating nfvPPA and lvPPA.[30,39,41,62] Therefore, repetition tests in combination with tools that assess grammar and/or verb comprehension would add value to the subtyping in PPA. In contrast, classification based on repetition may only be successful if a structured test is used.[24,60] Such a test must control for factors such as length, meaning, frequency, syllable structure and grammatical complexity, and must include various conditions such as single word and sentence repetition to assess different levels of cognitive processes during repetition.

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REFERENCES

1. Mesulam MM. Slowly progressive aphasia without generalized dementia. *Ann Neurol*. 1982;11:592–598.
2. Kirshner HS, Tanridag O, Thurman L, et al. Progressive aphasia without dementia: two cases with focal spongiform degeneration. *Ann Neurol*. 1987;22:527–532.
3. Kertesz A, Hudson L, Mackenzie IR, et al. The pathology and nosology of primary progressive aphasia. *Neurology*. 1994;44:2065–2072.
4. Mesulam MM, Weintraub S. Is it time to revisit the classification guidelines for primary progressive aphasia? *Neurology*. 2014;82:1108–1109.
5. Mesulam MM. Primary progressive aphasia–a language-based dementia. *N Engl J Med*. 2003;349:1535–1542.
6. Neary D, Snowden JS, Gustafson L, et al. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology*. 1998;51:1546–1554.
7. Bigio EH. Making the diagnosis of frontotemporal lobar degeneration. *Arch Pathol Lab Med*. 2013;137:314–325.
8. Josephs KA, Hodges JR, Snowden JS, et al. Neuropathological background of phenotypical variability in frontotemporal dementia. *Acta Neuropathol*. 2011;122:137–153.
9. Neumann M, Mackenzie IRA. Review: neuropathology of non-tau frontotemporal lobar degeneration. *Neuropathol Appl Neurobiol*. 2019;45:19–40.
10. Greene JD, Patterson K, Xuereb J, et al. Alzheimer disease and nonfluent progressive aphasia. *Arch Neurol*. 1996;53:1072–1078.
11. Mesulam M, Wicklund A, Johnson N, et al. Alzheimer and frontotemporal pathology in subsets of primary progressive aphasia. *Ann Neurol*. 2008;63:709–719.
12. Teichmann M, Migliaccio R, Kas A, et al. Logopenic progressive aphasia beyond Alzheimer's–an evolution towards dementia with Lewy bodies. *J Neurol Neurosurg Psychiatry*. 2013;84:113–114.
13. Giannini LAA, Irwin DJ, McMillan CT, et al. Clinical marker for Alzheimer disease pathology in logopenic primary progressive aphasia. *Neurology*. 2017;88:2276–2284.
14. Oboudiyat C, Bigio EH, Bonakdarpour B, et al. Diffuse leukoencephalopathy with spheroids presenting as primary progressive aphasia. *Neurology*. 2015;85:652–653.
15. Gorno-Tempini ML, Brambati SM, Ginex V, et al. The logopenic/phonological variant of primary progressive aphasia. *Neurology*. 2008;71:1227–1234.
16. Grossman M. Primary progressive aphasia: clinicopathological correlations. *Nat Rev Neurol*. 2010;6:88–97.
17. Gorno-Tempini ML, Hillis AE, Weintraub S, et al. Classification of primary progressive aphasia and its variants. *Neurology*. 2011;76:1006–1014.
18. Mackenzie IR, Neumann M. Molecular neuropathology of frontotemporal dementia: insights into disease mechanisms from postmortem studies. *J Neurochem*. 2016;138(suppl 1):54–70.
19. Mackenzie IR, Neumann M, Baborie A, et al. A harmonized classification system for FTLD-TDP pathology. *Acta Neuropathol*. 2011;122:111–113.
20. Lee EB, Porta S, Michael Baer G, et al. Expansion of the classification of FTLD-TDP: distinct pathology associated with rapidly progressive frontotemporal degeneration. *Acta Neuropathol*. 2017;134:65–78.
21. Mesulam MM, Weintraub S, Rogalski EJ, et al. Asymmetry and heterogeneity of Alzheimer's and frontotemporal pathology in primary progressive aphasia. *Brain*. 2014;137(pt 4):1176–1192.
22. Bergeron D, Gorno-Tempini ML, Rabinovici GD, et al. Prevalence of amyloid-beta pathology in distinct variants of primary progressive aphasia. *Ann Neurol*. 2018;84:729–740.
23. Hoffman P, Sajjadi SA, Patterson K, et al. Data-driven classification of patients with primary progressive aphasia. *Brain Lang*. 2017;174:86–93.
24. Lukic S, Mandelli ML, Welch A, et al. Neurocognitive basis of repetition deficits in primary progressive aphasia. *Brain Lang*. 2019;194:35–45.
25. Patterson K, Graham N, Hodges JR. The impact of semantic memory loss on phonological representations. *J Cogn Neurosci*. 1994;6:57–69.
26. Hoffman P, Jefferies E, Ehsan S, et al. Semantic memory is key to binding phonology: converging evidence from immediate serial recall in semantic dementia and healthy participants. *Neuropsychologia*. 2009;47:747–760.

27. Tippett DC. Classification of primary progressive aphasia: challenges and complexities. *F1000Res*. 2020. doi:10.12688/f1000research.21184.1.
28. Hodges JR, Martinos M, Woollams AM, et al. Repeat and Point: differentiating semantic dementia from progressive non-fluent aphasia. *Cortex*. 2008;44:1265–1270.
29. Heitkamp N, Leiss E, Danek A. Repeat & Point: German Adaptation of a tool for differentiating semantic dementia and primary progressive aphasia. *Klin Neurophysiol*. 2010. Available at: https://www.thieme-connect.com/products/ejournals/abstract/10.1055/s-0030-1250931.
30. Mesulam M, Wieneke C, Rogalski E, et al. Quantitative template for subtyping primary progressive aphasia. *Arch Neurol*. 2009;66:1545–1551.
31. Ulugut Erkoyun H, Groot C, Heilbron R, et al. A clinical-radiological framework of the right temporal variant of frontotemporal dementia. *Brain*. 2020;143:2831–2843.
32. Morris J, Heyman A, Mohs R, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer's disease. *Neurology*. 1989;39:1159–1165.
33. Ehrensperger MM, Berres M, Taylor KI, et al. Early detection of Alzheimer's disease with a total score of the German CERAD. *J Int Neuropsychol Soc*. 2010;16:910–920.
34. Goodglass H, Kaplan E, Barresi B. *Boston diagnostic aphasia examination- 3rd ed (BDAE-3)*. Philadelphia, PA: Lippincott Williams & Wilkins; 2001.
35. Huber W, Poeck K, Weniger D, et al. Der Aachener Aphasie Test (AAT). Hogrefe; 1983.
36. Wechsler D. *Wechsler Gedächtnistest—Revidierte Fassung (WMS-R); Deutsche Adaptation der revidierten Fassung der Wechsler Memory Scale*. Bern: Verlag Hans Huber; 2000.
37. Reitan R, Wolfson D. *The Halstead-Reitan Neuropsychological Test Battery: Theory and Clinical Interpretation*.Tucson: Neuropsychology Press; 1993.
38. Staiger A, Ziegler W. Syllable frequency and syllable structure in the spontaneous speech production of patients with apraxia of speech. *Aphasiology*. 2008;22:1201–1215.
39. Mesulam MM, Wieneke C, Thompson C, et al. Quantitative classification of primary progressive aphasia at early and mild impairment stages. *Brain*. 2012;135(pt 5):1537–1553.
40. Henry ML, Gorno-Tempini ML. The logopenic variant of primary progressive aphasia. *Curr Opin Neurol*. 2010;23:633–637.
41. Bonner MF, Ash S, Grossman M. The new classification of primary progressive aphasia into semantic, logopenic, or nonfluent/agrammatic variants. *Curr Neurol Neurosci Rep*. 2010;10:484–490.
42. Grossman M. Linguistic aspects of primary progressive aphasia. *Ann Rev Linguist*. 2018;4:377–403.
43. Pilkington E, Keidel J, Kendrick LT, et al. Sources of phoneme errors in repetition: perseverative, neologistic, and lesion patterns in Jargon aphasia. *Front Hum Neurosci*. 2017;11:225.
44. Meyer AM, Snider SF, Campbell RE, et al. Phonological short-term memory in logopenic variant primary progressive aphasia and mild Alzheimer's disease. *Cortex*. 2015;71:183–189.
45. Nozari N, Kittredge AK, Dell GS, et al. Naming and repetition in aphasia: steps, routes, and frequency effects. *J Mem Lang*. 2010;63:541–559.
46. Baldo JV, Katseff S, Dronkers NF. Brain regions underlying repetition and auditory-verbal short-term memory deficits in aphasia: evidence from voxel-based lesion symptom mapping. *Aphasiology*. 2012;26:338–354.
47. Caramazza A, Basili AG, Koller JJ, et al. An investigation of repetition and language processing in a case of conduction aphasia. *Brain Lang*. 1981;14:235–271.
48. Kelly MH. Using sound to solve syntactic problems: the role of phonology in grammatical category assignments. *Psychol Rev*. 1992;99:349–364.
49. Kemmerer D. Classic aphasia syndromes. In: Kemmerer D, ed. *Cognitive Neuroscience of Language*. New York, NY: Psychology Press; 2015:71–92.
50. Jefferies E, Grogan J, Mapelli C, et al. Paced reading in semantic dementia: word knowledge contributes to phoneme binding in rapid speech production. *Neuropsychologia*. 2012;50:723–732.
51. Nozari N, Dell GS. How damaged brains repeat words: a computational approach. *Brain Lang*. 2013;126:327–337.
52. Dell GS, Martin N, Schwartz MF. A case-series test of the interactive two-step model of lexical access: predicting word repetition from picture naming. *J Mem Lang*. 2007;56:490–520.
53. Jefferies E, Hoffman P, Jones R, et al. The impact of semantic impairment on verbal short-term memory in stroke aphasia and semantic dementia: a comparative study. *J Mem Lang*. 2008;58:66–87.
54. Henry ML, Beeson PM, Alexander GE, et al. Written language impairments in primary progressive aphasia: a reflection of damage to central semantic and phonological processes. *J Cogn Neurosci*. 2012;24:261–275.
55. Wilson SM, Brandt TH, Henry ML, et al. Inflectional morphology in primary progressive aphasia: an elicited production study. *Brain Lang*. 2014;136:58–68.
56. Rong F, Isenberg AL, Sun E, et al. The neuroanatomy of speech sequencing at the syllable level. *PLoS One*. 2018;13:e0196381.
57. Croot K, Ballard K, Leyton CE, et al. Apraxia of speech and phonological errors in the diagnosis of nonfluent/agrammatic and logopenic variants of primary progressive aphasia. *J Speech Lang Hearing Res*. 2012;55:S1562–S1572.
58. Duffy JR, Strand EA, Clark H, et al. Primary progressive apraxia of speech: clinical features and acoustic and neurologic correlates. *Am J Speech Lang Pathol*. 2015;24:88–100.
59. Rogalski E, Cobia D, Harrison TM, et al. Anatomy of language impairments in primary progressive aphasia. *J Neurosci*. 2011;31:3344–3350.
60. Forkel SJ, Rogalski E, Drossinos Sancho N, et al. Anatomical evidence of an indirect pathway for word repetition. *Neurology*. 2020;94:e594–e606.
61. McCarthy RA, Warrington EK. The double dissociation of short-term memory for lists and sentences. Evidence from aphasia. *Brain*. 1987;110(pt 6):1545–1563.
62. Thompson CK, Meltzer-Asscher A, Cho S, et al. Syntactic and morphosyntactic processing in stroke-induced and primary progressive aphasia. *Behav Neurol*. 2013;26:35–54.