Title Page

Assessment tools accuracy for classification and diagnosis of Primary Progressive Aphasia: A systematic review and meta-analysis protocol.

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Abstract:

Introduction.

Primary Progressive Aphasia (PPA) is a syndrome characterized by progressive decline in language function. There are three main PPA syndromes, each one features different language profiles and neuropathologic substrates. Although there are current clinical diagnostic criteria for PPA categorization, the utility of these requires evaluation(s) by specialized staff and the administration of extensive cognitive batteries. A diagnostic tool for PPA is not currently standardized, though some batteries have been developed and/or validated exclusively for PPA categorization. We aim to describe which cognitive/aphasia diagnostic tool has the best accuracy for PPA diagnosis and categorization.

Methods and Analysis.

MEDLINE (PubMed), EMBASE and Web of Science databases will be searched using adequate search strategies. Studies including original data of possible, probable, and definite PPA cases according to current clinical diagnostic criteria for PPA will be included. Inclusion criteria will be 1) Studies describing data of a cognitive/aphasia clinical battery including at least one test measure (e.g., specificity, positive predictive values, etc.) and 2) PPA diagnosis according to current clinical criteria as the reference standard. Two reviewers will perform the screening and data extraction. Quality assessment will be performed according to the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) guidelines. This systematic review protocol is reported as stated by with the Preferred Reporting

Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA-P) 2015 statement.

Ethics and dissemination.

Ethics approval is not required. Findings of this systematic review protocol will be disseminated through a publication in a peer-reviewed journal. Results will be helpful to improve the diagnosis and classification of PPA syndromes.

Key-words: 'Primary Progressive Aphasia', 'Diagnostic test', Diagnostic battery'

Introduction.

Primary Progressive Aphasia (PPA) is a syndrome of neurodegenerative nature characterized by progressive decline of language function. There are three main PPA syndromes: 1) semantic variant PPA (svPPA), non-fluent variant PPA (nfvPPA) and logopenic variant PPA (lvPPA) (1). Each one is affected by different language profiles, brain volume loss patterns and neuropathology. (2) The identification and classification of PPA in clinical settings is still challenging. Furthermore, around 30 to 40% of PPA syndromes are not classifiable in any of the three main different phenotypes, these are known as mixed PPA syndromes (3). Accurate classification of these variants is important for prognosis, clinical care improvement, clinical research, and enrollment in clinical trials.

Diagnosis and clinical classification of PPA is typically implemented through the addition of features of clinical history, characteristics of language deficits (e.g., anomia,

agrammatism, speech apraxia etc.), neurological and cognitive examination, and structural and functional brain imaging or other biomarkers. (4,5). This approach is ideal, however is time consuming and requires a multidisciplinary method. Some aphasia batteries such as the Boston Diagnostic Aphasia Examination (BDAE) (6) and the Western Aphasia Battery (WAB) (7) have been applied for PPA classification/diagnosis. However, these instruments were not originally developed for PPA, require special training for application and are time consuming. In search for a standardized and brief assessment tool for PPA identification and classification, some clinical batteries have been developed and/or validated in the last few years. (8) Examples include an automatic calculator that was created using individual item analysis of the Addenbrooke's Cognitive Examination III, demonstrating good sensitivity for classification of PPA syndromes (9). A new brief language battery developed for PPA classification called 'Mini Linguistic State Examination'(10) demonstrated excellent accuracy for classification of each of the main three PPA variants. Another recently created brief screening tool named Progressive Aphasia RatIng Scale 'PARIS' is useful to distinguish between AD and PPA, and even between lvPPA and svPPA. (11). And the effectiveness for PPA categorization has been demonstrated through the validation of the Sydney Language Battery 'SYDBAT' (12).

Rationale.

The current classification of patients with PPA in a clinical scenario requires the evaluation by professionals with diverse type of training (e.g., cognitive neurology, neuropsychiatry, neuropsychology, etc.). Although a multidisciplinary approach is

ideal, it is expensive, time consuming and it is not available in most health centers worldwide. A clinical battery for an accurate classification of PPA variants is necessary for a better characterization even in places with trained physicians where there is not enough time to perform an extensive evaluation or in sites without trained staff for a good screening. Despite several batteries have demonstrated their effectiveness identifying PPA variants, to date, there are no evidence synthesis reports comparing the classification/diagnosis accuracy between these batteries. We performed a search in the International prospective register of systematic reviews (PROSPERO) and the Open Science Framework (OSF) on June 28, 2023. We found one scoping review protocol similar than our proposal (https://osf.io/hw82g). However, the present protocol will be focused exclusively on the comparison of the accuracy of diagnostic tools with a systematic review/meta-analysis methodology.

Research question.

The primary research question is what the accuracy of standardized cognitive batteries to correctly identify and classify patients with PPA syndromes is. The target population are patients with diagnosis of any of the three PPA variants. The index test will be any cognitive or language battery that has demonstrated usefulness in the classification/diagnosis of a PPA syndrome considering PPA current clinical diagnostic criteria (1). A diagnosis of PPA according to current clinical criteria including a language battery, brain imaging and follow up establishing the diagnosis will be taken as the reference standard.

Table 1. Research question according to PIRD framework

PIRD (**P**opulation, **I**ndex Test, **R**eference Test, **D**iagnosis of Interest)	In patients with PPA (P) what is the clinical/cognitive/aphasia battery with the best classification accuracy (I) considering current clinical diagnostic criteria the reference (R) for PPA diagnosis (D)

Objectives

Primary objective: a) To compare the accuracy of cognitive/aphasia batteries for diagnosis of PPA (any variant) according to current clinical diagnostic criteria.

b) To compare the accuracy of cognitive/aphasia batteries for diagnosis and classification of PPA specific variants.

c) To describe the accuracy of cognitive/aphasia batteries comparing specific PPA variants (e.g. svPPA versus nfvPPA, svPPA versus lvPPA, etc.)

Secondary objective: To describe the mean time of application of the different cognitive/aphasia batteries that are useful for classification/diagnosis of PPA.

Methods

Literature search

Search strategy will be performed including MEDLINE (PubMed), EMBASE and Web of Science. We developed a search strategy using 2dsearch. The search algorithm is publicly available https://app.2dsearch.com/query/649b3268c26f12b434eb0aac.

Additionally, we will perform a search in Google Scholar including the first 100 results using Publish or Perish software. Titles and abstracts will be screened for eligibility by two independent reviewers, duplicates will be removed using Covidence and discrepancies will be resolved by discussion. This protocol is reported according to the 2020 Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement (13) and complemented with PRISMA Protocols statement (PRISMA-P). Results will be exhibited in a PRISMA flow diagram.

Inclusion criteria

Full texts of any type of test accuracy study including grey literature published since 2011 (as specific PPA diagnostic criteria were published in this year) in English or Spanish. Articles written in other languages will be included only if an appropriate translation is available using DeepL or Google translate.

The following inclusion criteria will be applied: Studies with original data (e.g. case-control, cross sectional, cohort designs, etc.) 1) describing patients with a PPA diagnosis established with the current clinical diagnostic criteria, including possible, probable or definite cases (1). 2) Details of cognitive batteries describing measures for classification/diagnosis of PPA variants (e.g., sensitivity, specificity, positive predictive values, Receiver-operating characteristic [ROC] curves, etc.). 3) Data of imaging, neuropsychological examination, genetic testing, and other type of evidence supporting the diagnosis of PPA according to current clinical diagnostic criteria.

Initial stage will include title and abstract screening for potential eligibility. Subsequently full text articles will be

evaluated to determine inclusion and exclusion criteria. Data extraction will be performed using data collection forms by two independent reviewers. This form will be pilot tested using the first 25 samples. Screening and data extraction will be performed using Covidence.

Exclusion criteria

1. Studies describing PPA cases in advanced stages of the disease (severe dementia) according to a standardized cognitive battery such as Dementia Rating Scale (14), Clinical Dementia Rating (15), Mini Mental State Examination (16) or other.
2. PPA cases with mixed phenotypes that are difficult to categorize in one of the three main PPA variants according to current clinical diagnostic criteria (1)
3. Studies in other languages than English or Spanish that could not be appropriately translated.

Data extraction

Extracted data will include the following:

1. Details of the study: title, year of publication, country of origin, name of the first author, diagnostic cut point of each tool and source(s) of funding.
2. Demographic data of participants
3. Average time of battery administration.
4. Details of study methodology registering procedures, materials, ethics procedures
5. Number of participants and details of how PPA diagnosis was performed, including biomarkers if available for each included study.

6. Type of test/battery applied to diagnose and classify PPA syndromes.
7. Data of raters (e. g. if they were full trained to perform a specific battery).
8. Test accuracy features to classify or diagnose a PPA syndrome (e.g., specificity, sensitivity, positive predicate values [PPVs], negative predictive values [NPVs], ROC curves, etc.)

Quality assessment

The study design and methods of selected studies will be evaluated according to the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) guidelines (17). The assessment of evidence quality in QUADAS-2 guidelines include four domains. 1) Participant selection: we will consider studies evaluating patients with PPA with a standardized battery, and current clinical diagnostic criteria. 2) The index test will be any standardized cognitive or language battery tested for PPA categorization. 3) The reference standard will be the current clinical PPA diagnostic criteria. 4) For the flow and timing of assessments we will consider 90 minutes as it is an approximate average time for the application of standardized aphasia batteries. Two reviewers will assess the quality independently and discrepancies will be resolved by discussion. A third reviewer will be consulted if discrepancies remained.

Data analysis

The test accuracy of each index test will be displayed in 'paired' forest plots and Summary receiver-operating characteristic (SROC) curves of sensitivity and specificity including confidence intervals and means for each selected

primary study. We will compute forest plots and SROC using RevMan software (Cochrane collaboration 2020). Heterogeneity will be estimated by visual inspection of SROC curve and objectively with Fisher exact test.

Where clinical and methodological characteristics of included studies are homogeneous a bivariate random effect model for sensitivity and specificity will be performed using SPSS V.27.0. A narrative summary will be considered if a meta-analysis is not suitable.

Ethics and dissemination

This systematic review will use publicly available data of studies that obtained ethical approval without directly involving human participants. Therefore, ethics approval is not required. This protocol is registered and publicly available at the International prospective register of systematic reviews (PROSPERO) registration number CRD42023440682. Findings of this systematic review protocol will be disseminated through a publication in a peer-reviewed journal. Results will be helpful in terms of diagnosis and classification of PPA syndromes.

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