Nonpharmacological interventions for cognitive impairments following primary progressive aphasia

A systematic review of the literature

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ABSTRACT. This study provided a systematic review on nonpharmacological interventions applied to patients diagnosed with Primary Progressive Aphasia (PPA) and its variants: Semantic (SPPA), Nonfluent (NFPPA) and Logopenic (LPPA) to establish evidence-based recommendations for the clinical practice of cognitive rehabilitation for these patients. **Methods:** A PubMed and LILACS literature search with no time restriction was conducted with the keywords *PPA* (and its variants) AND *rehabilitation* OR *training* OR *intervention* OR *therapy* OR *treatment* OR *effectiveness*. To develop its evidence-based recommendations, a research committee identified questions to be addressed and determined the level of evidence for each study according to published criteria (Cicerone et al., 2000). Overall evidence for treatments was summarized and recommendations were derived. **Results:** Our search retrieved articles published from 1995 to 2013: 21 for SPPA, 8 for NFPPA, 3 for LPPA and 8 for PPA with no specification. Thirty-five studies were rated as Class III, consisting of studies with results obtained from one or more single-cases and that used appropriate single-subject methods with adequate quantification and analysis of results. The level of evidence of three functional interventions could not be established. One study was rated as Class II and consisted of a nonrandomized case-control investigation. **Conclusion:** Positive results were reported in all reviewed studies. However, in order to be recommended, some investigation regarding the intervention efficacy was required. Results of the present review allows for recommendation of some nonpharmacological interventions for cognitive deficits following PPA as Practice Options. Suggestions for further studies on PPA interventions and future research are discussed.
Key words: primary progressive aphasia, treatment, speech and language therapy, intervention, cognitive rehabilitation.

INTERVENÇÕES NÃO-FARMACOLÓGICAS PARA DISTÚRBIOS COGNITIVOS NA AFASIA PROGRESSIVA PRIMÁRIA: UMA REVISÃO SISTEMÁTICA DA LITERATURA

RESUMO. Este estudo ofereceu uma revisão sistemática de intervenções não-farmacológicas aplicadas a pacientes com Afasia Progressiva Primária (APP) e suas variantes: Semântica (APPS), Não-fluente (APPNF) e Logopênica (APPL) com o objetivo de estabelecer recomendações baseadas em evidências para a prática clínica de reabilitação cognitiva para estes pacientes. **Métodos:** Conduziu-se busca por literatura, sem restrição de período, no PubMed e LILACS com as palavras-chave *PPA* (e variantes) AND *rehabilitation* OR *training* OR *intervention* OR *therapy* OR *treatment* OR *effectiveness*. Para desenvolver recomendações baseadas em evidências um comitê de pesquisadores identificou as questões relevantes para investigação e determinou o nível de evidência para cada estudo de acordo com critérios publicados (Cicerone et al., 2000). A evidência total para os tratamentos foi sumarizada e recomendações redigidas. **Resultados:** Foram encontrados artigos publicados de 1995 a 2013: 21 para APPS, 8 para APPNF, 3 para APPL e 8 para APP sem especificações. Trinta

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e cinco estudos foram classificados como Classe III, consistindo de resultados obtidos com um ou mais indivíduos e utilizando metodologia apropriada para estudo de casos. O nível de evidência de três intervenções funcionais não pôde ser estabelecido. Um estudo foi classificado como Classe II e consistiu de pesquisa caso-controle não-randomizada. **Conclusão:** Resultados positivos foram reportados em todos os trabalhos analisados mas, para serem recomendados, os tratamentos requerem investigação em relação a sua eficácia. Resultados da presente revisão permitiram recomendação de algumas intervenções como Opções Práticas. Ademais, apresentamos sugestões para futuros estudos de intervenção em APP.
Palavras-chave: afasia progressiva primária, terapia fonoaudiológica, tratamento, intervenção, reabilitação cognitiva.

INTRODUCTION

The term Primary Progressive Aphasia (PPA) was first used by Mesulam[1,2] in order to designate a progressive and circumscribed language disorder (aphasia) with relative preservation of functioning in activities of daily living and in the absence of deficits on other cognitive domains in the first two years post-symptoms onset. Cases of PPA were generally categorized as Nonfluent Progressive Aphasia or Semantic Dementia according to the consensus of Neary et al.[3] or as fluent and nonfluent progressive aphasia[2] in many studies conducted since then. A third syndrome, logopenic aphasia was reported in 2004.[4] The past three decades have seen a clear advance in the characterization of these syndromes with detailed descriptions of prominent speech and language deficits, regions of brain atrophy/ hypometabolism and also specification of the underlying pathology in many cases. In 2011, an international group of PPA investigators agreed on diagnostic criteria for PPA and on clinical, imaging-supported and definite pathology criteria for the diagnosis of three distinct variants: non-fluent/ agrammatic (NFPPA), semantic (SPPA) and logopenic (LPPA).[5]

In a considerable number of patients with PPA the onset of the disease occurs at a young age and has a devastating effect on their functional status and quality of life. The extensive progress in PPA diagnosis has led to a growing number of patients in need of treatment alternatives. In the absence of clearly effective pharmacological options,[6] there has been increasing interest in other approaches, particularly behavioral interventions. Croot et al. (2009) performed a broad literature review on clinical management in PPA whose main objective was to assist clinicians to make choices about speech pathology service provision. The authors reviewed 25 studies and made important considerations about intervention features and their results as well as suggestions for future research in this area. However, to our knowledge, no systematic review on nonpharmacological interventions has been conducted thus far. In addition, several studies have emerged since 2009 including biomarkers and more rigorous experimental control to measure treatment effects. Therefore, our objective was to conduct a systematic review on nonpharmacological interventions applied to patients diagnosed with PPA syndromes aimed at establishing evidence-based recommendations for the clinical practice of cognitive rehabilitation for patients with PPA. Specifically, we considered the evidence-based practice guidelines provided by the ASHA[7] and the evidence classification criteria for cognitive rehabilitation established by Cicerone et al.[8].

According to the International Classification of Functioning, Disability and Health (ICF)[9] the term disability covers impairments, activity limitations and participation restrictions. Nonpharmacological interventions can focus on any of these levels. In the present paper, we classify treatments into impairment-directed and functional interventions. The former target remediation or focus on slowing the progression of specific speech and language impairments, such as naming deficits, dysgraphia, agrammatism and apraxia of speech, whereas the latter focus on functional communication including environmental modifications, compensatory strategies or increasing levels of participation in communication activities.

In 1995, McNeil et al.[10] published a study combining pharmacological and non-pharmacological treatment for a patient with PPA. They found equivalent results for the pharmacological plus behavioral treatment compared to the provision of behavioral treatment alone. Almost 20 years on, cognitive rehabilitation in PPA is still considered a "new" area in Neuropsychology and Speech and Language Therapy with many unanswered questions. There is no consensus on recommendation criteria of different types of interventions, intensity, duration and periodicity of treatments. In addition, therapy gains concerning both evolution of cognitive symptoms, functioning in activities of daily living and quality of life of patients, their carers and family still need further investigation.

It is crucial to analyze critically the accumulated knowledge in this area to provide guidelines for future research that may increase the level of evidence about these interventions and support treatment choices in a

clinical context. Moreover, we intend this paper to provide a summary and an update of recent findings for therapists practicing this area.

METHOD

In order to carry out a systematic review that would encompass international as well as Latin-American studies, two indexing databases were consulted: PubMed, from the National Library of Medicine of the United States of America, and LILACS, the Latin American and Caribbean Health Sciences Literature database. The terms entered in both databases were the following: [1] "Primary Progressive Aphasia AND (rehabilitation OR training OR intervention OR therapy OR treatment OR effectiveness)", [2] "Semantic Dementia AND (rehabilitation OR training OR intervention OR therapy OR treatment OR effectiveness)", [3] "Nonfluent Progressive Aphasia AND (rehabilitation OR training OR intervention OR therapy OR treatment OR effectiveness)", [4] "Logopenic aphasia AND (rehabilitation OR training OR intervention OR therapy OR treatment OR effectiveness)". The retrieved titles were submitted to the following exclusion criteria: Titles that were clearly not about PPA, papers that were not written in English, French, Portuguese or Spanish were all excluded. Subsequently, abstracts of the selected titles were read, and the following exclusion criteria were applied: review studies were excluded, except for those that mentioned treatments and interventions for Frontotemporal Lobar Degeneration syndromes. All papers that made no mention of any type of non-pharmacological treatment were also excluded. Case studies were kept for further analysis, since they may mention a nonpharmacological treatment undertaken by the patient in the body of the text. After abstract selection, their respective articles were read. References of selected papers were also scanned in order to identify other related papers that were not indexed in the searched databases but would also contribute to this review. The same exclusion criteria mentioned before were applied to the titles found in the references of the selected papers. Only complete manuscripts published in indexed journals were included, therefore interventions published as book chapters and conference abstracts were not analyzed.

This selection procedure was performed by three of the authors of this study, so as to ensure an acceptable degree of agreement. To develop its evidence-based recommendations, a research committee identified questions to be addressed and determined the level of evidence for each study according to published criteria for cognitive rehabilitation.[8] After reading the papers, the authors agreed on the following variables to be observed and used as classifying criteria in the studies: diagnosis, duration of the disease at intervention, age at intervention, sex, educational level, study design, intervention type, intervention features (goals, procedures, language spoken, individual/group sessions, intervention length, frequency and duration of sessions, home-practice, involvement of a caregiver, materials), outcome measures, results, maintenance of gains, generalization, follow-up and comparison of measures of brain activity pre and post-treatment. Overall evidence for treatments for each PPA subtype was summarized and recommendations were derived from consideration of the strengths of evidence. The main features of the studies are summarized in the tables presented in the results section of this paper.

RESULTS

Searches on PubMed and LILACS databases retrieved 814 and three titles, respectively. More specifically, combined with "(rehabilitation OR training OR intervention OR therapy OR treatment OR effectiveness)", the term "Semantic dementia" retrieved 537 titles, "Non-fluent progressive aphasia", 133, "Primary progressive aphasia" 124, and "Logopenic aphasia", 20 titles on PubMed. The three titles found on LILACS were all retrieved with the term "Primary progressive aphasia", whereas all other combinations retrieved no titles. Many of the search results overlapped, and after applying the exclusion criteria, only one article from LILACS remained, whereas 19 articles from PubMed were selected. Scanning the references from these selected papers, and also references from case studies and review articles previously found on PubMed and LILACS, retrieved another 19 papers, which were added to the final list in order to be analyzed. In summary, this paper analyzed a total of 39 articles related to interventions on PPA. The search took place on November of 2012 and was repeated in January 2013. The complete list of selected papers is found in Tables 1-4. Detailed information including study design, description of interventions, pre and post-assessment tools, and results is provided in Appendix 1, available when this manuscript is accessed online from the Dementia & Neuropsychologia site (at www.demneuropsy.com.br).

Interventions were grouped first by diagnosis and then intervention type (impairment-directed vs. functional, similarly to Croot et al.[9]). Thus, Table 1 summarizes findings for SPPA, with 21 papers revised (19 impairment-directed and two functional interventions). Table 2, NFPPA, lists eight papers, five impairment-directed

Table 1. Intervention studies in Semantic Variant PPA.

	Studies grouped by type of intervention	Characteristics of participant(s) Age (years), sex, education, disease duration	Intervention goals
Impairment-directed interventions	Graham et al. (1999; 2001)[11,12]	69; male; Doctorate; 4 years	Naming and lexical retrieval
	Snowden, Neary (2002)[13]	61; female; N/A; N/A 54; female; N/A; N/A	Naming
	Bozeat, Patterson, Hodges (2004)[14]	58; female; N/A; 3 years	Object use
	Frattali (2004)[15]	66; male; Higher education; N/A	Naming
	Jokel, Rochon, Leonard (2002; 2006)[16,17]	63; female; Bachelor's; 7 years	Naming
	Bier et al. (2009)[18]	70; female; High school; 5 years	Concept relearning (Naming and semantic attributes)
	Dewar et al. (2009)[19]	63; male; Bachelor's; 4 years	Naming and learning semantic attributes
	Heredia et al. (2009)[20]	53; female; Well-educated civil servant; 2 years	Naming
	Newhart et al. (2009)[21]	60; female; Master's; N/A	Naming and lexical retrieval
	Robinson et al. (2009)[22]	63; female; Some college; 3 years 63; female; N/A; 3 years	Naming, definition and object use
	Dressel et al. (2010)[23]	48; male; College; 2 years	Naming
	Jokel, Rochon, Anderson (2010)[24]	N/A; male; Bachelor's; 2 years	Naming
	Montagut et al. (2010)[25]	68; male; Elementary; 7 years	Naming and lexical retrieval
	Senaha, Brucki, Nitrini (2010)[26]	55; female; Some college; 2 years 77; male; Bachelor's; 1 year 56; male; Bachelor's; 2 years	Naming and lexical retrieval
	Mayberry et al. (2011)[27]	65; female; N/A; 4 years 53; male; N/A; 4.5 years	Naming
	Jokel, Anderson (2012)[28]	From 56 to 87; 3 males and 4 females; from high school to Master's degree; from 2 to 6 years	Naming
	Savage et al. (2012)[29]	From 54 to 69; 4 males; Some college; from 4 to 5 years	Naming and lexical retrieval
Functional interventions	Wong et al. (2009)[30]	63; male; 14 years; 2 years	Communication effectiveness: improvement/ maintenance of discursive skills
	Bier et al. (2011)[31]	68; female; Bachelor's; 4 years	Learning semantic attributes/ activity participation rehabilitation

and three functional interventions. Table 3, LPPA, contains three manuscripts reporting impairment-directed interventions. And finally, Table 4 is for PPA, including studies that have not been classified into PPA subtypes or studies that analyzed groups of PPA patients with no concern for specific variants or that included patients that do not conform to the prototypes defined in the international consensus. Eight papers were included in Table 4, five impairment-directed interventions and three functional interventions.

Papers regarding SPPA interventions (Table 1) were published between 1999 and 2012, most of them were case reports of a maximum of four patients. The mean age of patients described in treatments was 62.48 years old (SD=8.50, range 53-87) at intervention baseline, 52% were men, and patients reported an average disease duration of 3.6 years (SD=1.55). In general, therapies varied from one single session to 18 months for impairment-directed therapies, and from five to 48 months for the functional interventions. Six interventions were exclusively based on home practice, where therapies at home varied from three to 10 weeks. From 2009 onwards, strategies that included pictures began to include not only presentation on paper cards, but also on the computer screen. Except for two, all interventions included follow-up that ranged from two weeks to

Table 2. Intervention studies in Nonfluent / Agrammatic Variant PPA.

	Studies grouped by type of intervention	Characteristics of participant(s) Age (years), sex, education, disease duration	Intervention goals
Impairment-directed interventions	Schneider, Thompson, Luring (1996)[32]	62; female; Some college; 2.5 years	Agrammatism
	Louis et al. (2001)[33]	64; female; N/A; N/A 71; female; N/A; N/A 77; male; N/A; N/A	Phonological skills
	Jokel et al. (2009)[34]	58; female; Bachelor's; N/A 75; female; Bachelor's; N/A	Naming and lexical retrieval
	Marcotte, Ansaldo (2010)[35]	60; male; Professional; 2 years	Naming
	Henry et al. (2013)[36]	73; female; Professional; 5 years	Speech production (apraxia of speech)
Functional interventions	Murray (1998)[37]	64; female; High school; 4 years	Auditory and reading skills/ Communicative skills
	Rogers, Alarcon (1999)[38]	69; male; Master's; 4 years	Communicative skills
	Pattee, Von Berg, Ghezzi (2006)[39]	57; female; N/A; 5 years	Communicative skills

Table 3. Intervention studies in Logopenic Variant PPA.

	Studies grouped by type of intervention	Characteristics of participant(s) Age (years), sex, education, disease duration	Intervention goals
Impairment-directed interventions	Newhart et al. (2009)[21]	65; female; Master's; N/A	Naming and lexical retrieval
	Beeson et al. (2011)[40]	77; male; Professional; 2.5 years	Naming and lexical retrieval
	Tsapkini, Hillis (2013)[41]	62; female; Bachelor's; 6 years	Spelling

Table 4. Intervention studies in PPA.

	Studies grouped by type of intervention	Characteristics of participant(s) and further information on PPA	Intervention goals
Impairment-directed interventions	McNeil, Small, Masterson, Fossett (1995)[10]	61; male; N/A; 9 months (no further information about patient's impairment was given)	Lexical semantic retrieval
	Finocchiaro et al. (2006)[42]	60; male; N/A; N/A	Naming and lexical retrieval
	Henry, Beeson, Rapcsak (2008)[43]	N/A; N/A; N/A; 5 years (fluent with characteristics towards non- fluent aphasia, incl. mild agrammatism, phonemic paraphasias, and apraxia of speech) N/A; N/A; N/A; 6 years (fluent aphasia, surface dysgraphia)	Naming and lexical retrieval
	Rapp, Glucroft (2009)[44]	55; female; College; 9 years (dysgraphia)	Dysgraphia
	Snowden et al. (2012)[45]	60; male; Academic; 2 years	Facilitating access to letter names and sounds (to assist reading words aloud)
Functional interventions	Cress, King (1999)[46]	59; female; N/A; 5 years 60; male; Doctorate; 7 years For both cases, MRI revealed atrophy of the left temporal lobe, and defined a diagnosis of PPA without dementia	Communication, comprehension and expression
	Cartwright, Elliott (2009)[47]	From 59 to 66; Tertiary education; 4 PPA (3 nonfluent aphasic women, 1 man with dense semantic deficits); N/A	Enhancing participant's access to TV content
	Farrajota et al. (2012)[48]	68 (mean); 11.6 years (mean); 3 years (mean); N/A 10 patients (2NFPPA, 2SAPPA, 6LPPA)	Ability to communicate by verbal means in everyday life situations

two years. Only one study addressed post-intervention changes in brain activity[23] and similarly only one calculated effect sizes for therapy results.[29] Twenty studies were rated as Class III, consisting of results obtained from one or more single-cases and that used appropriate single-subject methods with adequate quantification and analysis of results. The level of evidence of the functional intervention carried out by Wong et al.[30] could not be established due to absence of reliable methodological control to determine treatment effects.

NFPPA papers (Table 2) were published between 1996 and 2013 and described patients whose mean age was 66.45 years old (SD=6.96, ranging from 58 to 77 years). 72% of the cases were women, varying from one to three patients. On average, impairment-directed interventions had around 22 sessions (SD=20.57), ranging from 8 to 60 training sessions. When home-practice sessions were not taken into account for calculation, the average number of sessions was 10.6 (SD=3.43). Only three studies reported follow-up testing, which ranged from one to 12 months. One study reported fMRI investigation supporting therapy results.[35] Functional interventions presented longer durations, from 9 weeks to 4 years of therapy. Seven studies were rated as Class III, consisting of results obtained from one or more single-cases and that used appropriate single-subject methods with adequate quantification and analysis of results. The level of evidence of the functional intervention carried out by Rogers & Alarcon[38] could not be established due to absence of reliable methodological control to determine treatment effects.

Regarding LPPA interventions (Table 3), papers were published between 2009 and 2013 and the reported cases presented a mean age of 68 years old (SD=7.93). Therapy duration ranged from two to 11 weeks and home practice and was emphasized in only one study[40] which was also the only study that included follow-up testing (six months after intervention). Two interventions aimed to treat naming and lexical retrieval deficits and one targeted spelling deficits. Only one study reported use of cerebral imaging data (fMRI) as a post-treatment measure.[40] The three studies were rated as Class III, consisting of results obtained from one or more single-cases and that used appropriate single-subject methods with adequate quantification and analysis of results.

The PPA table (Table 4) summarized eight papers published from 1995 to 2013, including a total of 21 cases whose mean age was 60.88 years old (SD=3.88, ranging from 55 to 68 years). Patients' clinical features varied in these studies, as did intervention goals. One of these studies employed high-frequency repetitive Transcranial Magnetic Stimulation.[42] Half of the studies entailed follow-up testing, which ranged from one month up to 3 years. One study reported the effect size of the intervention.[43] Six studies were rated as Class III, consisting of results obtained from one or more single-cases and that used appropriate single-subject methods with adequate quantification and analysis of results. The level of evidence of one functional intervention [46] could not be established due to absence of reliable methodological control to determine treatment effects. One study was rated as Class II and consisted of a nonrandomized case-control investigation.[48]

Overall, among the thirty-nine selected manuscripts, thirty-five studies were rated as Class III and one study was rated as Class II. The level of evidence of three functional interventions could not be established due to absence of reliable methodological control to determine treatment effects.

DISCUSSION

In the present study, we conducted a systematic review of the literature aimed at establishing evidence-based recommendations for the clinical practice of cognitive rehabilitation for patients with PPA. In order to achieve this, we summarized and examined the accumulated knowledge concerning non-pharmacological treatments for patients with PPA. We deliberately chose not to restrict our search to a specific period of time or to define strict inclusion and exclusion criteria for the studies in order to gather as many reports as possible. To accomplish this, we singled out papers from two widely used databases and followed up all relevant references cited in the selected manuscripts. Even using very inclusive criteria we were able to report only 39 studies which described treatments applied to 67 patients to date. This lack of studies was found to be even more critical when we analyzed treatment alternatives according to specific PPA subtypes. This analysis revealed the scarcity of reports for NFPPA and LPPA cases.

We organized this section under five topics. Firstly, we discuss separately the main research findings for SPPA, NFPPA and LPPA variants. Considerations were then made concerning treatments targeting patients whose impairments either do not conform to the above-mentioned prototypical syndromes, or were not classified according to the 2011 international consensus, or treatments directed to a group of PPA patients with no special concern about different subtypes. We then made our concluding comments and evidence-based recommendations for the clinical practice of cognitive rehabilitation for patients with PPA.

Non-pharmacological interventions for patients with semantic variant PPA. We found descriptions of treatments applied to 33 patients with SPPA.

Functional interventions targeted communication effectiveness through improvement or maintenance of discursive skills[30] or used an ecological-approach aimed at increasing participation in meal preparation.[31] The strength of these proposals is that they focused on the patients' needs and try to establish a direct link between therapy practices and performance in daily routine tasks. Their weakness is the difficulty achieving the necessary experimental control to measure treatment effects. In their pilot study, Bier et al.[31] provided a good example of how this can be achieved in future research. Despite several limitations imposed by the patient's personality, authors were able to employ ABA design (baseline condition followed by treatment and then returning to baseline) and include control tasks and quantitative measures to determine therapy gains.

Most impairment-directed interventions targeted picture naming skills and lexical retrieval. Only two studies addressed face-name associations[19,26] and another two addressed object use.[14,22] It has been shown consistently across studies that SPPA patients are able to relearn target vocabulary during the active phase of treatment and to maintain gains above baseline levels for variable periods after ceasing intervention. This last point, however, needs to be further investigated since differences in study design and patients' profile (demographic, neuropsychological and disease duration) preclude drawing conclusions on how long therapy gains are maintained.

Another point of concern is generalization of learning to untrained stimuli or even to the same stimuli presented in a different context. Overall, this has not been achieved (e.g. Snowden and Neary[13]) with a few exceptions.[19,24,25,27,28] This aspect should be a point of concern when selecting the set of stimuli to be trained and may also suggest the need for more context-based interventions. Recent studies have tried to fulfill this need by using personalized materials such as digital photos of individual household items[29] or by training relevant activities for the patient such as cooking, as in the study of Bier et al.[31] The impact of interventions on connected speech measures or quality of life has not been consistently investigated in studies and when reported have shown modest results.[19,20,28] Future studies should address functional communication measures such as analysis of discursive skills to reliably establish transference of therapy gains.

Regarding learning mechanisms, studies have shown that patients relearn significantly more items when they retain residual semantic knowledge about them[13,17,28] and are able to link them to personal experience and context.[13] This is said to be due to overreliance on the hippocampus and adjacent medial temporal lobe structures (episodic memory system) for learning verbal labels and no reliance on temporal anterior lobe structures (affected by the disease) crucial for semantic generalization. This view has been recently challenged.[27] By careful selection of foils the authors showed that patients used verbal labels incorrectly for foils visually and semantically associated with the target (overgeneralizations) but not for other types of foils and suggested that the impaired neocortex also plays a role in SPPA relearning skills. Overall, these findings have practical implications and suggest that therapy benefits are maximized if interventions start as early as possible in the presence of very mild semantic memory deficits and low levels of brain atrophy.

Recent studies experimentally addressed important questions concerning treatment duration and intervention strategies. It has been shown that longer therapies are more effective in the maintenance of gains than shorter ones,[29] errorless learning is more effective than errorful learning, but same gains are achieved for active and passive learning,[28] simple repetition of verbal label leads to similar gains to spaced-retrieval techniques,[18] and simple picture-word matching leads to similar gains to sentence generation and to providing definitions for specific items.[29] Nevertheless, all these issues need replication in future studies.

It is interesting to note that learning was achieved in SPPA patients after interventions of a single session;[14] individual home-practice,[11,12] and computer-based therapies.[24,18] Future studies should compare these treatments to long-term interventions delivered by a therapist and also to combined interventions, in order to characterize suitable patients for each therapy type. Individual home-practice, especially aided by a computer,[31] seems to be a very promising alternative both economically and also in terms of reducing caregivers' load.

Finally, the only study that addressed changes in brain activity after behavioral interventions in SPPA[23] suggested that patients engage unimpaired structures such as the right superior and inferior temporal gyrus to compensate for the brain damage. This finding needs to be explored in more depth by future studies to confirm these results.

Non-pharmacological interventions for patients with NFPPA variant. This paper presents the results of non-pharmacological treatment applied to 11 patients in eight ar-

ticles. With a few exceptions,[33,34] most studies consisted of analyses of treatments applied to a single case.

All three studies that reported functional interventions used Augmentative and Alternative Communication (AAC) devices.[37-39] Although positive results in communication were reported with these interventions, some patients may show reluctance to use these tools. For instance, the patient studied by Pattee et al.[39] preferred American Sign Language and mentioned she did not feel "normal" using the digitized speech device introduced in the intervention. Moreover, successful long-term therapies using AAC devices should be described in more detail to be replicated with other patients. A study described a 4-year intervention without a clear description of the procedures, therefore rendering it difficult to reproduce.[38]

Impairment-directed interventions aimed at different aspects in NFPPA: agrammatism,[32] phonological skills,[33] apraxia of speech[36] and naming and lexical retrieval deficits.[34,35] Unlike SPPA, most NFPPA patients presented generalization of therapy gains to some extent, verified in untreated items,[32,34] different tasks[33,34] or functional communication evaluated through self-ratings of treatment effects.[36] These results are encouraging but need to be replicated in a larger number of patients.

In this variant subtype, only one study evaluated treatment gains through imaging methods. Using fMRI, Marcotte and Ansaldo[35] proposed that adaptive brain plasticity operates differently in NFPPA and post-stroke lesions, both for spontaneous recovery and therapy-induced effects. Spontaneous recovery in NFPPA involved bilateral compensation whereas in the post-stroke patient the right hemisphere was recruited. After a therapy involving the semantic approach, the authors observed an expansion of networks involving semantic processing areas (i.e., left middle and superior temporal gyrus and inferior parietal lobe bilaterally) in the patient with NFPPA, whereas in the patient with stroke, a contraction of the network occurred involving phonological processing and speech programming areas. These findings imply different brain plasticity mechanisms for aphasia depending on etiology (reorganization post-stroke vs. reactivation in NFPPA) and must be readdressed in future research.

Non-pharmacological interventions for patients with LPPA. As LPPA has been only recently described,[4] it is unsurprising that the number of intervention studies with this subtype is still limited. Only three single-case studies were found, all describing impairment-directed interventions designed to improve naming/lexical retrieval and spelling. In addition, we found no studies focusing on discursive abilities. One possible explanation is that multi-modalities cognitive training directed for the mixed symptoms of this subtype, linking executive and working memory to discursive abilities, have yet to be developed.

The three studies found showed significant treatment effects for trained items while two also demonstrated generalization to untrained items[21,40] and also to conversation skills.[40] It is important to consider that the study which showed limited results[41] involved a patient with six years of disease duration at intervention, a possible explanation for the unremarkable results observed.

Regarding intervention procedures, Beeson et al.[40] attributed the success of their intervention to the approach employed which was active, errorful and intensive, involving problem-solving and generation of semantic information to facilitate lexical-retrieval. This hypothesis must be addressed empirically (as in the study of Jokel et al.[28] with SPPA patients) and, if confirmed, suggests that naming deficits should be treated with different approaches according to PPA subtypes.

Lastly, post-treatment fMRI activation changes in an LPPA patient suggest that the behavioral improvements are supported by increased reliance on the left prefrontal cortex during word retrieval, thus recruiting relatively unimpaired networks as compensatory mechanisms.[40] As previously mentioned for studies on the SPPA variant, this finding must be further explored in future studies.

Non-pharmacological interventions for patients with PPA. We identified eight studies that reported interventions for 21 patients with PPA. Again, most studies reported treatments offered to one (five studies) or fewer patients (two studies) with no special concern about a specific PPA subtype. One exception in this section, and in the entire review, is the study of Farrajota et al.[48] in which speech-therapy gains were studied by comparing two groups of patients with PPA, one receiving treatment and another not. This is the first study designed with a control-group of PPA participants, matched by age, education and language deterioration measures. The authors used the international consensus classification but did not take subtypes into consideration when analyzing their results. This poses some limitations to the interpretation of the findings (i.e. treatment resulted in better naming skills post-treatment but group not receiving treatment comprised more SPPA patients, tending to have more severe naming deficits.[49]

Two studies included patients with atypical profiles and described effective interventions for dysgraphia[44,45]. The need for detailed assessment to design personalized interventions directed to specific cognitive deficits is emphasized.[45] Another promising alternative for PPA is high-frequency repetitive Transcranial Magnetic Stimulation[42] and ecological approaches such as aphasia-friendly TV viewing.[47] Both interventions showed positive results but need replication in a larger number of patients.

Final considerations. We conclude this systematic review attempting to answer the following questions: [1] Can treatment be beneficial for patients with PPA and specifically for SPPA, NFPPA and LPPA?; [2] What are the interventions with sufficient evidence of benefits?

Positive results were reported in all studies included in this review. It is important to mention that given the nature of the diseases no decline over variable periods can also be considered a positive outcome. Yet in order to be recommended these treatments require investigation regarding their efficacy. The approach characterized by randomized clinical trials is mandatory in the scientific literature pertaining to evidence-based medicine, but resorting to this approach is not always feasible when research addresses neuropsychological rehabilitation[50] and, in particular, language and speech disorders.[51] In the case of PPA, most studies consisted of single-case descriptions, which are very informative but do not allow for extensive generalization to other groups of patients. However, a large number of studies, combined with good study design, can help increase the treatments' level of evidence.

Results of the review of available scientific literature allows for recommendation of some nonpharmacological interventions for cognitive deficits following PPA. Using published criteria[8] we recommend impairment-directed therapies aimed at naming and lexical retrieval in SPPA as Practice Options, based on 18 studies rated as Class III. For treatment aimed at object use, current evidence is based on two Class III studies. For functional interventions evidence is drawn from one Class III study. Therefore, more research is needed before we can reliably recommend these interventions.

Practice recommendations regarding interventions for NFPPA and LPPA are constrained by the small number of studies and patients that underwent nonpharmacological interventions reported to date.

Evidence for behavioral therapies aimed at improving typical deficits in NFPPA such as agrammatism, phonological skills and apraxia of speech is based on one study (for each deficit) rated as Class III[32,33,36] respectively. Evidence from two Class III studies supports therapy targeting naming deficits[34,35] and functional interventions using AAC[37,39] in this group of patients.

The evidence for treatments targeting naming and spelling deficits in LPPA is based on two Class III studies[21,40] and one Class III study,[41] respectively.

One Class II study with PPA[48] provides evidence that speech therapy can be beneficial for this group of patients compared to the condition of no treatment.

Generalization of gains has been observed in NFPPA and LPPA but there are very few reports to date. In SPPA, generalization to untreated items or functional communication situations has not been consistently reported. In general, better study design has been employed for impairment-directed interventions, however functional interventions have strong ecological validity and their gains should be investigated in further studies.

Post-treatment changes in brain activity have been addressed in only three studies and findings must be interpreted cautiously and replicated with comparable techniques and cognitive tasks. The current findings suggest that the brain plasticity mechanism engaged in therapy is reactivation and that patients recruit cortical areas that are typically preserved for the specific PPA variant to compensate for their dysfunctional language networks.

Concerning methodological issues, it is important that single-case studies include multiple baseline measures, treatment and control stimuli and/or treatment phases in which multiple measures are taken in the active phase of intervention and compared to measures when treatment is withdrawn. Long-term follow-up and measuring of treatment effects, as in the Henry et al.[43] and Savage et al.[29] studies, is also necessary. Controlled-group studies comparing interventions to placebo treatments are a challenge in this field but may be achieved with research collaborations (as in Farrajota et al.[48]).

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APPENDIX 1

Table 1. Description of the variables analyzed in the intervention studies on Primary Progressive Aphasia - Semantic variant

Studies ıped by type ıtervention	**Characteristics of the participant(s)** *Age (years), sex, education, disease duration*	**Intervention goals**	**Characteristics of the intervention** *Duration; frequency and length of intervention*	**Materials**	**Procedures**	**Outcome measures**	**Main Results**	**Generalization**
IMPAIRMENT-DIRECTED INTERVENTIONS								
Graham et al., 1999; 2001	69; male; Doctor; 4 years	Naming and lexical retrieval	10 weeks; daily 30 min of controlled home practice (practiced items established by research team); 2 years; free daily home practice (as desired by patient)	lists of words and pictorial encyclopedias (e.g. Oxford English Picture Dictionary)	Repeated rehearsal of the name of concepts paired with pictures and real items, usually grouped by semantic categories.	Number of items generated in semantic verbal fluency tests including trained vs. untrained categories. Baseline assessment, trained and control items, comparison to a cognitive unimpaired control group that did not undergo practice 10 week and 2 year follow-up	Better performance on semantic verbal fluency tasks involving categories that the patient underwent naming practice compared non-practiced categories. Slower language deterioration compared to typical PPAS descriptions: no decline or even better performance in some language tests and verbal fluency tasks at follow-up	1) no generalization to semantic association tasks (i.e. Pyramids and Palm Trees Test) 2) Only trained items are retrieved in verbal fluency tasks
Snowden & Neary, 2002	61; female; N/A; N/A	Naming	Experiment I: 2 weeks; 1	booklet with pictures	Experiment I. Attempt to name the picture but not	Accuracy on trained items compared to	Proved ability to relearn vocabulary.	Naming performance deteriorated when

	54; female; N/A; N/A		session/week Experiment II: 20 days; 20min of daily home practice		to guess followed by its presentation in written and spoken forms. Patient asked to read aloud written word matched to picture (errorless learning strategy) Experiment II. One day training with therapist in which naming was trained as in experiment I added to definition and meaningful context association cues. Self-study phase: patient got a booklet with test materials for 20 days. Naming and personalized contextual cues were practiced with the help of spouse.	baseline assessment. Reverse-order control. Follow-up: 2 week- and 4 month- (experiment I) 6 month- (experiment II)	Experiment I: mild improvement in naming, better for pictures that patient retained semantic knowledge After 4 months, naming declines but not to baseline level. Experiment II: relearning of items for which patient retained no semantic knowledge before training in the contextualized cued condition. Maintenance of gains after 2 months and decline, but not to baseline levels after 6 months.	test items were presented out of context (i.e. cards instead of booklet) and in randomized order, but not in the reverse order condition.
Bozeat, Patterson & Hodges, 2004	58; female; N/A; 3 years	Object use	1 single session	Objects and their respective recipients	Following each object display, the patient was given the object and its recipient and asked to copy the movement made by the examiner. The objects in the	Accuracy of ability to use target trained objects vs. control set. Baseline assessment, after-training retest,	Patient relearned how to manipulate objects through observation of their use, despite being at advanced stage of PPAS. Maintenance of gains	There was a small increase in performance over time on the untrained objects

					control set were simply given to the patient, along with their recipients, and patient was asked again to demonstrate the use of each.	same day retest Follow-up: one and five weeks	over five weeks.	
Frattali, 2004	66; male; higher education; N/A	Naming	3 months; 1 session of 2 hours/week	Picture cards	A set of cards within a semantic category was presented and patient and experimenter engaged in a conversational interchange, focused on associative and analytical skills (effortful and errorless learning strategy). Patient discouraged to name items. No explicit reinforcement was given when patient occasionally named it. After each set, cards were shown again and if the name of it came to the patient, he was allowed to say it.	Naming accuracy on treated vs. untreated items. ABA design. Multiple baseline assessment, randomized order of presentation of stimuli and semantic categories across trials. Follow-up: 3 month.	Significant improvement in naming during the active phases of treatment. No maintenance of gains at follow-up.	No generalization of naming ability to novel stimuli.
Jokel, Rochon & Leonard,	63; female; Bachelor; 7 years	Naming	3 weeks; daily home practice;	Picture cards with name and	Picture naming (looking at the picture and reading	Naming accuracy on treated vs.	Better performance on naming treated words and	Not achieved

2002; 2006			30 min/day	definition on the back	aloud name/definition)	untreated items. Multiple baseline assessment, trained and control items, Follow-up: one and six months	maintenance of vocabulary trained. Decline on untrained words.	
Bier et al., 2009	70; female; High school; 5 years	Concept relearning (Naming and semantic attributes)	3 months, 12 sessions	Pictures and names belonging to four different semantic categories	Formal-semantic therapy and spaced-retrieval method: picture was presented along with its spoken name, specific attribute and written name of the category twice; pictures presented again with increasing time-recall intervals and patient was asked to name them and generate semantic attributes. Semantic feedback and cueing technique was used when patient was unable to name items. Simple repetition method was added to procedures above in half of sessions.	Accuracy in naming and generation of general and specific semantic attributes Multiple-baseline assessment.	Significant improvement in naming and learning specific semantic attributes of trained items. No advantage observed for the spaced-retrieval condition compared to repetition Maintenance of gains at follow-up of 5 weeks	Not achieved for untrained categories

Dewar et al., 2009	63; male; Bachelor; 4 years	Naming and learning semantic attributes	5 sessions (total)	Black and white photographs of famous people in UK	Combination of three methods: mnemonic, vanishing cues and expanded rehearsal. Photograph was first presented, paired with its name and semantic fact, to form a mnemonic of it. Then, photograph was presented with written name and semantic fact, but words and letters were removed little by little, and patient had to repeat information with less cues than at the preceding point, till the moment when patient could state the name and fact without any cueing. Consolidation of this learning was undertaken with expanded rehearsal.	Baseline assessment (free recall and free plus cued recall measures) Naming and recalling of the semantic fact accuracy on treated vs. untreated photographs. Reverse-order control. Follow-up: 2-week.	Five training sessions improved naming without cues in virtually all stimuli names. Cued recall was not necessary to boost the performance of the patient. Maintenance of practiced and non-practiced items even after 2 weeks by free recall.	Generalization of naming to different photographs of the same famous people was observed. No influence of a change in order was observed.
Heredia et al. 2009	53; female; well-educated civil servant; 2 years	Naming	Trained daily at home for a month	Power-point presentation of 28 items. Items were selected from	Presentation of a picture on a computer screen for naming followed by the same picture with	Naming accuracy on trained vs. control items; report of carer about use of trained items in	Improved performance on trained items and maintenance after 6 months	Not achieved for untrained items. Anedoctal report of

				pictures patient failed to name in the language assessment.	correspondent written name to read aloud.	conversation, Follow-up: one and six month.		generalization to spontaneous speech.
Newhart et al., 2009	60; female; Master; N/A	Naming and lexical retrieval	8-9 weeks; approx. 2-3 sessions of 30-60min/week, total of 29 sessions	Picture cards of objects (of 3 semantic categories) and notebook with the written name of all items organized by category	Cueing hierarchy treatment: 1) spontaneous oral naming of the pictured object; 2) written naming and oral reading of it, 3) notebook search, reading aloud the written name; 4) repetition of reading aloud the written word; 5) repeat the name of the pictured object. 6) Then, all the steps backwards.	Multiple baseline assessment. Naming accuracy on Trained vs. untrained items, pre and post test assessment.	Temporary improvement of naming on treated items. Less deterioration in untreated items from treated categories (when compared to untreated items of untreated categories)	Not achieved for untrained items.
Robinson et al., 2009	63; female; some college; 3 years 63; female; N/A; 3 years	Naming, definition and object use	3 weeks; 2 sessions/week. Home practice was emphasized.	Kitchen utensils, stationary items, tools and their respective utensils. Video for self-modeling.	Errorless learning strategy: 1. Object was presented with its name and description. Patient was prompted to repeat it. 2. Object and its recipient were shown and its name was said. Patient was prompted to repeat the name again. 3. A personally relevant definition	Baseline assessment: Performance in naming, definition and object use before and after therapy were measured. Familiarity with objects was controlled. Matched control group. Randomized order of presentation of	Both patients produced significantly more definitions rated as "good" for trained and untrained objects (post-therapy), and improved some aspects of object use. Improvement for untrained objects was not evident at follow-up.	Not clear generalization of this therapy to everyday use .

					to the object was provided. Patient repeated the definition. 4. Demonstration of use was provided, and the patient was prompted to replicate the actions.	stimuli. Trained and untrained items. Follow-up: 1-month.	Only one of the patients had significant improvements in naming. The same patient maintained therapy gains over time, but the other declined for definitions and some aspects of object use (but still remained above the baseline)	
Dressel et al., 2010	48; male; college; 2 years	Naming	4 weeks; 5 sessions/week	Picture cards with line drawings presented on a computer screen	A picture was presented and patient should name it, assisted by a hierarchy of oral cues. Cues were either phonological or semantic, composing the lexical-phonological and lexical-semantic access training	Accuracy on naming treated and untreated items. Error pattern analysis (errors were coded as semantic, phonological, mixed, unrelated, etc.). Multiple baseline assessment with naming tests, one pre-test and both post-tests were made inside the MR scanner. Follow-up: 2-month.	Cueing hierarchies were successful to achieve immediate training effects. Most common error types were omission, semantic paraphasias and mixed errors. fMRI data informed that improved naming following therapy was also mirrored by changes in cortical activities (right superior and inferior temporal gyrus) – authors interpreted it as compensatory mechanisms of the RH. Maintenance of therapy gains was	No significant generalization to control items.

							limited.	
Jokel, Rochon & Anderson, 2010	N/A; male; bachelor; 2 years	Naming	4 months; 3 sessions of 60min/week	MossTalk words computer program	Picture was presented on computer screen, a software-generated spoken definition and written word was provided. Patient looked at the picture, listened to the description and then repeated the word.	Accuracy on treated vs. untreated items. Post-test checking generalization to different contexts (language battery of tests), connected speech and quality of life Multiple baseline across behaviors design. Follow-up at 1 and 3 months later	Better performance on treated words vs. untreated. Maintenance of vocabulary trained but decline on untrained. Better performance and maintenance for items that patients retained some semantic knowledge.	Patient could name trained items in different contexts (better performance in a naming test that included some items that were practiced in the computer-based therapy). Retrieved more items in animal verbal fluency test but did not reach statistical significance. No significant improvement in quality of life or connected speech measures, although scores were a bit higher after treatment.
Montagut et al., 2010	68; male; elementary; 7 years	Naming and lexical retrieval	5 weeks; 4 sessions of 15min/week	Picture cards of frequent use (of 5 semantic categories)	Picture naming without cues first and, if necessary, written name matched with picture.	Accuracy on trained items compared to baseline assessment. Follow-up: one and six month.	Improvement of naming on treated items. After 1 and 6 months, naming declines progressively, but not to baseline level.	Generalization of naming ability to another picture of the same concept.

Senaha, Brucki, Nitrini, 2010	55; female; some college; 2 years 77; male; bachelor; 1 year 56; male; bachelor; 2 years	Naming and lexical retrieval	6-18 months; 1-2 sessions/weeks	Picture cards, photographs and written descriptions	Naming pictures, photographs and descriptions. With progression in correct answers in naming, cues were gradually removed	Naming accuracy on treated vs. untreated items, pre and post test assessment. Baseline assessment.	Improvement in naming treated items, in spite of decline in performance on untreated items	No generalization was achieved.
Mayberry et al., 2011	65; female; N/A; 4 years 53; male; N/A; 4,5 years	Naming	3 weeks; daily training at home In the first session researcher introduced training procedures, other sessions were carried out over the phone	A booklet containing picture stimuli to be trained	Picture naming without cues first. Then, turning page and reading aloud written name matched with picture.	Naming accuracy of trained vs. untrained items; baseline, pre and post treatment assessments. Analyses of naming errors to study learning mechanisms (errorful learning) Follow-up: 1 month	All items learned by the two patients and total maintenance of gains after a month without training	There was limited, but appropriate generalization to untrained items in one case and this was maintained at follow-up. Overgeneralization (making use of trained labels incorrectly) was observed in the two patients, particularly for foils which were visually and semantically related to the treated items.
Jokel & Anderson, 2012	From 56 to 87; 3 males and 4 females; from high school to master degree; from 2 to 6 years	Naming	8-12 weeks; 2 to 3 sessions of 60 minutes per week	Sets of pictures that patients failed to name on baseline. 50% of the	Four types of treatment were compared: Errorless passive picture is shown on computer screen and semantic and	Naming accuracy of treated and untreated items pre and post treatment; Effect sizes calculated	Naming accuracy improved for trained items. Errorless learning techniques lead to	Patients could name trained items in different contexts (better performance in a naming test that included some items that were

				pictures participants were unable to name and comprehend.	phonemic cues are provided; Errorless active: picture is shown and questions about it are made; Errorful passive: picture is shown, wrong semantic and phonological cues are provided, patient is asked to guess; Errorful active: picture is shown, open questions about item are made.	Follow-up at 1 and 3 months	better results than errorful ones. No difference between active or passive learning. Better results on items for which patients retained semantic knowledge.	practiced). Retrieved significantly more items in animal verbal fluency test. No significant improvement in quality of life or connected speech measures, although scores were a bit higher after treatment. Three participants reported use of learned words in functional communication situations, but this was not formally tested.
Savage et al., 2012	From 54 to 69; 4 males; some college; from 4 to 5 years	Naming and lexical retrieval	3-6 weeks; 30-60min of daily home practice	Digital pictures of individual's household objects, lists of names and definitions of objects, recordings of definitions and names provided by	Study I: Word-picture matching training program: 1) Picture of item was shown on screen, patient was asked to recall (but not to guess) the name; 2) Picture and word paired were shown on screen, patient read it aloud; 3) Written form and audio	Multiple baseline approach with three word lists. Naming accuracy, with treated vs. untreated items (presented in a randomized order); effect sizes calculated Follow-up: 2-, 3-	Better performance on ability to name trained items, and no changes in untrained items. Large effect sizes measured to patients with severe deficits. Medium/small effect sizes for the milder patient. High levels of	No generalization reported.

				the patient. (Used items were at least partially still meaningful to patients)	recording of item description provided by the patient were shown, and patient listened to it; 4) Word and picture paired disappeared and patient concentrated on the word; 5) Word and picture reappeared, and voice recorded name of item was played, patient repeats it aloud. Study II: Included a semantic description task to the prior study.	and 6-week.	achievement produced within a 3-week period. Items trained for longer periods (six weeks) showed better maintenance than items trained for three weeks. No need to provide definitions or ask for sentence generation to achieve same levels of improvement.	
FUNCTIONAL INTERVENTION								
Wong et al., 2009	63; male; 14 years; 2 years	Communication effectiveness: improvement/ maintenance of discursive skills	4 years of intervention Combined intervention (group and individual sessions and carer trained to use intervention principles in communication activities with the patient)	pictures, flyers, newspaper articles, books, personal photographs	Individual and group sessions. Client-focused discourse intervention to develop turn-taking awareness, combined use of verbal and nonverbal modes of expression and communicative functions. Facilitation of communication	Scale of communication effectiveness, pre-test and two years later post-test.	Therapy results are of difficult interpretation due to patient's language decline over the years and absence of a control group or measure.	Not reported in the study

					effectiveness with education and training of the care-giver. Themes included: social exchange, discussion of current events, discussion of informational topic and discussion of life story events.			
Bier et al., 2011	68; female; bachelor; 4 years	Learning semantic attributes/ activity participation rehabilitation	5 months; 1 session biweekly	Kitchen with ingredients and utensils; a computer program called SemAssist, which provided the steps to prepare the target recipe; a target recipe (shrimp); other three control/ neutrals recipes.	Ecological rehabilitation. Practicing cooking a target recipe many times. SemAssist software was installed in a notebook in patient's kitchen, and was used whenever she wanted to provide her with the steps of the activity (cueing). Experimenter measured generation of semantic attributes of ingredients found in the target recipe while cooking, time taken during preparation, type of errors, frequency of use of SemAssist, etc.	Multiple baseline assessment (ABA); Target vs. control and neutral recipes comparison. Follow-up: 2- and 6-month.	The number of errors and cues needed during food preparation decreased with therapy. With the use of SemAssist, patient was able to prepare recipes on her own. Generation of semantic attributes of ingredients of cooked meals increased compared to control recipes. Therapy led patient to spontaneously cook again; but cooked less often at post-measures.	Not achieved. Abilities and knowledge were very specific to the practiced context. Naming abilities were tested and did not improve, even for pictures of ingredients found in the recipes.

Table 2. Description of the variables analyzed in the intervention studies on Primary Progressive Aphasia - Nonfluent/Agrammatic variant

Studies grouped by type of intervention	**Characteristics of the participant(s)** *Age (years), sex, education, disease duration*	**Intervention goals**	**Characteristics of the intervention** *Duration; frequency and length of intervention*	**Materials**	**Procedures**	**Outcome measures**	**Main Results**	**Generalization**
IMPAIRMENT-DIRECTED INTERVENTIONS								
Schneider, Thompson & Luring, 1996	62; female; some college; 2,5 years	Agrammatism	16 sessions (total)	Drawings and videotapes showing gestures to facilitate sentence production	Target picture placed in front of the patient, demonstration of a gesture in video and production of a sentence combined with gesture. Pre-training of gestures at home before treatment.	Accuracy in oral and gesture production of verb tenses in sentences. Narrative discourse production compared to controls. Multiple baseline across behaviors. Follow-up: 3 months after treatment	Improved production of sentences on trained items and untrained verbs within trained tenses. In the follow up: gestural responses were maintained at criterion while verbal responses declined for future and pasts tenses.	Generalization to untrained items
Louis et al, 2001	64; female; N/A; N/A 71; female; N/A; N/A	Phonologic skills	42 days of daily 15-20min home practice. One patient	Audio CD with auditory exercises tapping syllabic and	Auditory exercises based on the "odd-one-out model". For facilitation and improvement of	Baseline assessment; mean performance on trained tasks was calculated.	Significant improvement in fluency in 1 case; written comprehension in	Patients demonstrated improvement in tasks involving oral expression

	77; male; N/A; N/A		received additional 60-day treatment	phonemic segmentation;	auditory perception, signal of speech was slowed by 166% in the exercises.	Pre and post-test assessment with Boston Diagnostic Aphasia Examination	1 case; repetition in 2 cases; reading in 2 cases. No improvement in neither naming nor oral comprehension. Number of phonemic paraphrasias reduced in one case, and unchanged in two.	although the training focused auditory skills.
Jokel et al., 2008	58; female; bachelor; N/A 75; female; bachelor; N/A	Naming and lexical retrieval	2-4weeks; 2-3 sessions of 1hours/week	Digital pictures, MossTalk Words® (computer-based treatment for anomia)	Picture naming. Presentation of a cueing hierarchy consisting of written initial letter, written whole word cues, and repetition (when necessary) .	Multiple baseline assessment. Accuracy in naming. Follow-up: 6-month after	Improvement in naming skills. Score returned to the baseline after 6 months	Generalization to untreated items did not occur Some generalization of therapy effects was seen at the syntactic level immediately after treatment.
Marcotte & Ansaldo, 2010	60; male; Professional; 2 years	Naming (nouns and verbs)	3 weeks; 3 sessions of 60min/week	Picture cards and objects	SFA – Semantic Feature Analysis therapy. Picture naming. When unable to name it, semantic features were prompted	Accuracy in naming tasks. Event-related fMRI measures during oral picture naming. Comparison to a patient with stroke.	Improved naming performance. Activation of areas related with semantic processing, especially the left middle and superior temporal gyrus and	Not evaluated

							bilateral inferior parietal lobe for nouns and left inferior and middle temporal gyrus for verbs Recruitment of larger networks (more voxels activated) compared to the stroke patient.	
Henry et al. 2013	73; female; Professional; 5 years	Speech production (apraxia of speech)	12 weeks; 1 session of 1 hour/week Oral reading practice at home was advised	Paragraphs with multisyllabic words included	Structural oral reading of texts: Patient reads aloud a randomly-selected paragraph from the previously given homework to have pronunciation of words therein assessed. Therapists corrects major speech sound errors or incomplete productions in multisyllabic words	Baseline assessment. Accuracy in the production of multisyllabic words follow-up: 3- and 6-month and 1-year.	Multisyllabic word production in trained text became more accurate and stable over the course of treatment and was error-free over the last four treatment sessions.	Self-ratings of treatment effects indicated perceived improved performance in reading aloud and speaking (fluency) as well as improved confidence and reduced frustration in communication with familiar and unfamiliar people.
FUNCTIONAL INTERVENTIONS								

Murray, 1998	64; female; high school; 4 years	Auditory and reading skills/ Communicative skills	2,5 years, three treatment phases (T1, T2,T3) T1: twice a week, 45 minutes, total 46,5 h T2:individual treatment T3: 41 h of individual treatment + 10 h of group sessions	T1:Oral and Written paragraphs T2: drawing board T3: AAC device	T1: Traditional stimulation, facilitation approach Reading or listening to a paragraph then answering orally or in written form to yes/no questions or questions that required responses of two to four words T2: Back to the drawing board program – train the use of drawings to improve functional communication T3: Functional communication approach including AAC device Patient tries to speak after therapist and feedback is provided	T1:Accuracy on trained and untrained language tasks during active phase of training and comparison to no-treatment phases T2: pre and post treatment evaluation including accuracy in producing drawings T3:Qualitative analysis comparing pre- and post-treatment conversational interactions	T1: improvement on practiced tasks T2: drawings depicted main events more accurately and had greater detail and clarity T3: patient and her spouse increased their repertoire and use of repair strategies	T1: no generalization to functional communication T2: poor generalization to functional communication, although patient started to mix drawing and writing to answer questions T3: does not apply
Rogers & Alarcon, 1999	69; male; Master; 4 years	Communicative skills	4 years	AAC device, paper, pen, etc.	Activity-participation focus led to increasing use of AAC including gesture, writing, drawing, partner training, communication book, AAC device.	Not mentioned	Not mentioned	Not mentioned

Pattee C, Von Berg S, Ghezzi P. (2006)	57; female; N/A; 5 years	Communicative skills	9 weeks; 8 sessions	Colored cards of photographs depicting daily activities	Patient describes the activities depicted in the photographs using two modes: 1) American sign language (ASL) 2) Alternative Communication text-to-speech device (ACD)	Baseline assessment No follow up	Increases in content information across all measures, but more so for ASL.	No generalization task was tested.

Table 3. Description of the variables analyzed in the intervention studies on Primary Progressive Aphasia - Logopenic variant

Studies grouped by type of intervention	**Characteristics of the participant(s)** *Age (years), sex, education, disease duration*	**Intervention goals**	**Characteristics of the intervention** *Duration; frequency and length of intervention*	**Materials**	**Procedures**	**Outcome measures**	**Main Results**	**Generalization**
IMPAIRMENT-DIRECTED INTERVENTIONS								
Newhart et al., 2009	65; female; Master; N/A	Naming and lexical retrieval	8-9 weeks; approx. 2-3 sessions of 30-60min/week, total of 24 sessions	Picture cards of objects (of 3 semantic categories) and notebook with the written name of all items organized by category	Cueing hierarchy treatment: 1) spontaneous oral naming of the pictured object; 2) written naming and oral reading of it, 3) notebook search, reading aloud the written name; 4) repetition of reading aloud the written word;	Multiple baseline assessment Nming Accuracy in trained vs. untrained items, pre and post test assessment.	Improvement in naming of treated items and untreated items in both treated and untreated categories	Generalization to untreated items in treated categories as well as untreated items in untreated categories

					5) repeat the name of the pictured object. 6) Then, all the steps backwards.			
Beeson et al., 2011	77; male; professional; 2,5 years	Naming and lexical retrieval	2 weeks; 6 sessions of 2 hours/week + 1 hour of daily home practice	Colored photographs cards with removable written labels	Repeated retrieval of words from a semantic category under a time constraint	Generative naming performance Multiple baseline assessment trained and control items Follow-up: 3 weeks, 4 and 6 months after	Improvement of ability to retrieve exemplars for the trained and untrained categories. Performance on the trained categories was significantly better than pre-treatment performance at the 6- month follow-up Changes in post-treatment fMRI activation suggested the behavioral improvements were supported by increased reliance on left prefrontal cortex during word retrieval	There were improvement in discourse efficiency, generalization of the semantic elaboration and self-cueing strategies
Tsapkini & Hillis, 2013	62; female; bachelor; 6 years	Spelling	11 weeks; 1 session of 1-2hours/week	Paper, pen, lists of English most-	learning of phoneme-to-grapheme correspondences with help from key words	Baseline assessment, trained and untrained items.	Patient was able to learn associations between	Generalization to other untrained tasks post

				common word initial phonemes and words starting with that sound		No follow-up for the PPA patient	phonemes and graphemes as well as between phonemes and words. No difference between treated and untreated items. Generalization to other untrained tasks such as pointing to named letters	intervention

Table 4. Description of the variables analyzed in the intervention studies on Primary Progressive Aphasia (general)

Studies grouped by type of intervention	**Characteristics of the participant(s) and further information on PPA**	**Intervention goals**	**Characteristics of the intervention** *Duration; frequency and length of intervention*	**Materials**	**Procedures**	**Outcome measures**	**Main Results**	**Generalization**
IMPAIRMENT-DIRECTED INTERVENTIONS								
McNeil, Small, Masterson, Fossett, 1995	61; male; N/A; 9 months (no further information about the patient's	Lexical semantic retrieval (adjectives, prepositions and verbs)	5 months; approx. 2hours/week (1 hour of treatment and 1 of baseline probes collection)	Lists of words (nouns were excluded) grouped as antonyms and synonyms	Orally presenting to the patient a series of lexical items from a list of 10 predicative adjectives and	Multiple baseline. Accuracy on trained items compared to baseline assessment. Scores improved beyond baseline in	Extended practice of treatments were effective for both antonym and synonym adjectives.	Generalization to untrained adjectives, verbs and prepositions was observed.

	impairment was given)				asking him to vocally produce either antonyms or synonyms for the word or phrase. Cueing (hierarchically provided) was added after an error. Correct answers were verbally reinforced. Treatment combined phases of only behavioral with behavioral and pharmacological (dextroamphetamine), manipulations.	the antonym task	Only behavioral treatment phase was compared to combined behavioral and pharmacological phase and there were "essentially equivalent results". Maintenance was initially high (1 month) for all treated and probe lists, but performance approached baseline around 3,5 months after treatment.	No effects could be noticed regarding subject's discourse level.
Finocchiaro et al., 2006	60; male; N/A; N/A	Naming and lexical retrieval	75 days; 5 sessions/week with 15 days of intervals	hf-rTMS equipment	10 consecutive stimulations of 40 pulses each, followed by a 30-sec pause	Baseline assessments, use of a controlled condition for comparison	Improved performance in verb production and not in other tasks	Difficult to rule out. Some limitations, for instance performance in tasks with nouns was at ceiling in baseline
Henry, Beeson & Rapcsak, 2008	N/A; N/A; N/A; 5 years (fluent with characteristics towards non-fluent aphasia,	Naming and lexical retrieval	16 days; daily sessions of 90min + home practice	Cards with pictures and words, picture dictionary organized thematically	Guided lexical retrieval prompted by identification and elaboration of items within subcategories, and	Multiple baseline assessment, trained and untrained categories. Randomization of presentation order of	Improved lexical retrieval was observed on the generative naming task for trained categories	No generalization for untrained items.

	incl. mild agrammatism, phonemic paraphasias, and apraxia of speech) N/A; N/A; N/A; 6 years (fluent aphasia, surface dysgraphia)			by category	other semantic tasks (sorting pictures and words by subcategory, identifying semantic attributes of exemplars, and picture naming using a picture dictionary)	stimuli. Effect size calculation. Comparison between subjects (and with a stroke case). Follow-up: 3-week and 4-month, for one of the cases	Study has accounted for effect size, but noted a very small effect on the treated list. The one patient who took follow-up probes maintained improved performance.	
Rapp & Glucroft, 2009	55; female; college; 9 years (dysgraphia)	Spelling	15 weeks; biweekly 1,5 hour sessions; homework assignments.	Notecards with written words	Spell-study-spell intervention: 1) To spell each word to dictation, 2) to study the word presented on a written notecard while the experimenter repeated the word and orally named each of its letters, and if the word was spelled incorrectly, 3) to attempt to spell it again.	Baseline assessment, accuracy on trained vs. control words, 6- and 12-month follow-up	Significant improvement of trained words compared to baseline; Advantage in accuracy of trained words over control homework and repeated word sets; Accuracy on trained words persisted over control words in 6-month follow-up. At 12-month follow-up, all word sets had significantly	No generalization effects documented

							declined to baseline.	
Snowden et al. 2012	60; male; Academic; 2 years	Facilitating access to letter names and sounds (to assist reading words aloud)	12 months; daily home practice	Pictures and word cards, country name lists associated with each written letter of the alphabet	Written letters of the alphabet were associated with country names. Consonants trained before vowels (according to patient's performance in baseline assessment) When patient could not retrieve a written letter sound, he spoke the associated country name thus providing him with the letter sound. An associative strategy by which letter names were linked to concrete words and pictures was also adopted to teach him letter names.	Accuracy in the ability to name and sound letters as assessed by Palpa letter naming/sounding test. Ability to generate country names associates. Baseline assessment, two assessments during intervention (6 and 12 months) and follow-up 2 and 3 years later without further training	Improvement on treated but not untreated letters (consonants vs vowels according to the phase of treatment) Letter naming and sounding performance declined to 0% two years after therapy completion. Ability to generate country's names in response to a letter learnt in language therapy remained relatively robust 3 years after therapy.	The semantic strategy used in therapy was employed functionally to write object names in the period patient was participating in therapy.
FUNCTIONAL INTERVENTIONS								
Cress and King, 1999	59; female; N/A; 5 years 60; male; doctor; 7 years.	Communication, comprehension and expression	Case 1: 3 sessions Case 2: 1 month; 3-4 sessions of 1 hour/week. Home	Case 1: Communication book, cards with pictures and names	Several specific intervention techniques. Case 1 used writing skills to	Case 1: subjective analysis from the therapist point-of-view.	Case 1 e 2: therapy was described generally as a positive	There was improvement in the communication, but it was not

	For both cases, MRI revealed atrophy of the left temporal lobe, and got the diagnosis of PPA without dementia.		practice with his relatives involved in therapy	Case 2: AAC boards	communicate and graphical images, such as maps to communicate with therapist, for instance. Case 2: Training with the AAC pictures.	Case 2: qualitative analysis of conversation samples recorded at home by "communication partners"	experience. No specific control and measures were mentioned.	described about generalization for untrained items
Cartwright & Elliott, 2009	From 59 to 66; tertiary education; 4 PPA (3 nonfluent aphasic women, 1 man with dense semantic deficits); N/A	Enhancing participant's access to TV content	10 weeks including pre and post-test sessions; 90 minute-group weekly sessions plus two additional practices in the same week with care-giver at home	Glossary of vocabulary items commonly used within the genre of television viewing, 10 episodes of Australian story series, whiteboard where plot information was written/drawn available to participants throughout the session, feature analysis guide sheet providing each participant with accessible summary of	Participants viewed a total of 10 novel episodes of the Australian story series over a total of 10 weeks. Strategies to facilitate comprehension and recall of episode content were applied. Care-giver trained to assist patient at home.	Number of episode story information units in spoken discourse; Transactional success (discourse analysis undertook by an independent listener); Discourse comprehension questions Pre and post intervention assessments and comparison to a control group of cognitive unimpaired individuals in the first measure. Control group was not exposed to treatment only pre and post-test assessments.	Higher number of episode story information units in spoken discourse post treatment, close to control level; more story information units conveyed to a naive non-expert listener (transactional success), improved ability to answer discourse comprehension questions in one subject (patient with semantic deficits).	Not reported

				episode content.				
Farrajota et al., 2012	68 (aprox.); N/A; 11,6 years (aprox.); N/A 2 PNFA, 2 SD, 6 LPA (10 patients analysed as group)	Improvement of the patient`s ability to communicate by verbal means in everyday life situations	11 months; 1 session of 1hour/week, approximately 38 sessions	Pictures and materials for multimodal stimulation	Schuell's multimodality stimulation approach – includes picture naming, descriptions of picture actions, complex auditory-verbal comprehension, reading and writing, facilitation of expression of feelings and opinions, and enhancement of conversational skills	Accuracy in Snodgrass and Vanderwart naming test (primary) plus other language measures testing auditory comprehension, repetition and object identification (secondary) Patients were assessed before and after intervention and their performance compared to a PPA no-speech therapy control group matched for age, education and language deterioration but not by PPA subtype.	Significant main effect of therapy was found in the naming test when compared to control group. No difference in other language measures.	Not reported in the study.