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Early and differential diagnosis of Primary Progressive Aphasias: contribution of motor and language analyses

Alexandra Plonka

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Alexandra Plonka. Early and differential diagnosis of Primary Progressive Aphasias: contribution of motor and language analyses. Human health and pathology. Université Côte d'Azur, 2023. English. NNT : 2023COAZ6015 . tel-04234536

HAL Id: tel-04234536

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THÈSE DE DOCTORAT

Diagnostic précoce et différentiel des Aphasies Primaires Progressives : apport d'analyses motrices et langagières

Early and differential diagnosis of Primary Progressive
Aphasias: contribution of motor and language analyses

Alexandra PLONKA

Laboratoire Cognition Behaviour Technology (CoBTek), EA7276

**Présentée en vue de l'obtention
du grade de docteur** en Sciences de la
Vie et de la Santé d'Université Côte
d'Azur

Dirigée par : Pr Philippe Robert
Co-encadrée par : Dre Auriane Gros,
Dre Valeria Manera

Soutenue le : 27 juin 2023

Devant le jury, composé de :

Pr Gilles Allali, PO, Université de Lausanne
Dre Stéphanie Borel, MCF, Sorbonne
Université
Pr Jean Dellamonica, Doyen, PU-PH,
Université Côte d'Azur
Pre Peggy Gagnol, PU, Sorbonne Université
Dre Auriane Gros, MCF-HDR, Université Côte
d'Azur
Pr Laurent Lefebvre, PO, Université de Mons
Pr Philippe Robert, PU-PH, Université Côte
d'Azur
Pre Thi Mai Tran, PU, Université de Lille

Diagnostic précoce et différentiel des
Aphasies Primaires Progressives : apport de marqueurs
moteurs et langagiers

Early and differential diagnosis of Primary Progressive Aphasias: contribution
of motor and language analyses

Jury :

Président du jury :

Prof. Thi Mai Tran, Professeure des Universités, Université de Lille

Rapporteurs :

Prof. Peggy Gatignol, Professeure des Universités, Sorbonne Université

Prof. Laurent Lefebvre, Professeur Ordinaire, Université de Mons

Examineurs :

Prof. Gilles Allali, Professeur Ordinaire, Université de Lausanne

Dre Stéphanie Borel, Maîtresse de Conférences, Sorbonne Université

Prof. Jean Dellamonica, Doyen de l'Unité de Formation et de Recherche de Médecine de Nice,

Professeur des Universités - Praticien Hospitalier, Université Côte d'Azur

Dre Auriane Gros, Maîtresse de Conférences - HDR, Université Côte d'Azur

Membres Invités :

Prof. Olivier Beauchet, Professeur Titulaire, Université de Montréal

Dre Valeria Manera, Ingénieure de Recherches, HDR, Université Côte d'Azur

Directeur :

Prof. Philippe Robert, Professeur émérite - Praticien Hospitalier, Université Côte d'Azur

Abstract

Early and differential diagnosis of Primary Progressive Aphasias: contribution of motor and language analyses

Primary Progressive Aphasia (PPA) is a neurodegenerative syndrome initially characterized by an isolated language disorder and which diagnosis is mainly clinical. Three main PPA subtypes have been described in the literature: logopenic PPA (lvPPA), semantic PPA (svPPA) and non-fluent/agrammatic PPA (nfavPPA). The latest data in the literature have highlighted a late diagnosis, sometimes erroneous, associated with the need for an early medical-care management. The creation of new tools for the diagnosis and classification of PPAs seems to be crucial for an early and adapted patients' care.

The objective of this thesis is to verify the interest of the analysis of markers using new technologies such as motor activity parameters (graphic and gestural) and language activity parameters (linguistic and acoustic) within the speech therapy evaluation, to improve the early and differential diagnosis of PPAs.

Initially, this thesis work made it possible to analyze the specificities of the PPA diagnosis among the 167,191 diagnoses recorded in the French National Alzheimer Bank between 2010 and 2016. We highlighted diagnostic wavering and misdiagnosis of patients with PPA. These results underline the importance of developing tools that can be integrated into speech therapy practice and that can allow a greater accuracy in diagnosis.

Following these observations, we have demonstrated the interest of using new technologies that can be easily integrated into a diagnostic approach. By using touch tablets, we have demonstrated the interest of the analysis of graphic parameters, such as writing pressure and strokes, for the differential diagnosis of PPA patients in comparison with patients with Alzheimer's Disease (AD) or patient with Posterior Cortical Atrophy. These parameters have also proven to be useful in the classification of the three main subtypes of PPA.

To complete the evaluation of strokes for which the gestural behaviors during the pencil lifting times cannot be directly recovered on an electronic tablet, we were interested in the evaluation of the writing gesture in the context of a nfavPPA type of impairment. The video analysis showed a complementary interest for the more specific diagnosis of this non-fluent variant.

In a third step, and in a perspective of multimodal analysis, we verified the interest of the contribution of language and acoustic analyses of patients with PPA.

The ‘sentence span’ test was used to compare the memory span of PPA and AD patients. Our results showed a significantly different verbal span.

The vocal analysis allowed us, beyond the differential diagnosis PPA/AD and via temporal and prosodic acoustic markers, to differentiate the physiopathological profiles of lvPPA patients.

Finally, in a post-Covid-19 pandemic context and more specifically because of the neurological disorders observed in post-acute Covid-19 syndrome, we questioned, through a systematic review and an experts’ consensus, the relevance of using these motor and language markers for the early diagnosis of AD. Indeed, cognitive impairments in post-acute Covid-19 syndrome may, in the future, complicate the early diagnosis of neurodegenerative diseases due to common disorders.

Key words: Primary Progressive Aphasia, Motor Markers, Linguistic Markers, Alzheimer’s Disease, Differential Diagnosis, Early Diagnosis

Diagnostic précoce et différentiel des Aphasies Primaires Progressives : apport d'analyses motrices et langagières

L'Aphasie Primaire Progressive (APP) est un syndrome neurodégénératif caractérisé initialement par un trouble isolé du langage et dont le diagnostic est principalement clinique. Trois formes principales d'APPs sont décrites dans la littérature : l'APP logopénique (APP_l), l'APP sémantique (APP_{vs}) et l'APP non fluente/agrammatique (APP_{nf}). Les dernières données de la littérature ont mis en évidence un diagnostic tardif, parfois erroné, associé à la nécessité d'une prise en charge précoce. La création de nouveaux outils pour le diagnostic et la classification des APPs semblent à ce jour indispensables pour une prise en charge précoce et adaptée des patients.

L'objectif de cette thèse est de vérifier l'intérêt de l'analyse de marqueurs utilisant les nouvelles technologies tels que les paramètres d'activités motrice (graphique et gestuelle) et les paramètres d'activité langagière (linguistique et acoustique) au sein de l'évaluation orthophonique afin d'améliorer le diagnostic précoce et différentiel des APPs.

Dans un premier temps, ce travail de thèse a permis d'analyser les spécificités du diagnostic des APPs parmi les 167 191 diagnostics enregistrés au sein de la Banque Nationale Alzheimer en France entre 2010 et 2016. Nous avons mis en évidence une errance et des erreurs de diagnostic des patients présentant une APP. Ces résultats soulignent l'importance du développement d'outils intégrables à la pratique orthophonique et permettant une meilleure précision dans le diagnostic.

Suite à ces constats, dans un second temps et à travers différentes études, nous avons démontré l'intérêt de l'utilisation des nouvelles technologies facilement intégrables à une démarche diagnostique. Par l'utilisation de tablettes tactiles, nous avons démontré l'intérêt de l'analyse des paramètres graphiques, comme la pression d'écriture et les stroke, pour le diagnostic différentiel des patients atteints d'APP en comparaison avec des Malades d'Alzheimer (MA) ou de patient atteint d'Atrophie Corticale Postérieure. Ces paramètres se sont avérés également d'utilité dans une démarche de classification des trois sous-types principaux d'APPs.

Pour compléter l'évaluation des stroke pour lesquels les comportements gestuels lors des temps de levers de crayons ne peuvent être récupérés directement sur tablette électronique, nous nous sommes intéressés à l'évaluation du geste d'écriture dans le cadre d'une atteinte de type APP_{nf}. L'analyse vidéo a montré un intérêt complémentaire pour le diagnostic plus spécifique de ce variant non fluent.

Dans un troisième temps, et dans une perspective d'analyse multimodale, nous avons vérifié l'intérêt de l'apport d'analyses langagière et acoustique des patients présentant une APP.

Le « sentence span », épreuve de répétitions de phrases, a été utilisé pour comparer l'empan mnésique de patients atteints d'APP et de patients atteints de MA. Nos résultats ont mis en évidence un empan verbal significativement différent.

L'analyse vocale a permis de, au-delà du diagnostic différentiel APP/MA et via des marqueurs acoustiques temporels et prosodiques, de différencier les profils physiopathologiques des patients APPI.

Enfin, dans un contexte de post pandémie Covid-19 et plus spécifiquement du fait des troubles neurologiques constatés dans le cadre de Covid-long, nous avons, par le biais d'une revue systématique de la littérature et d'un consensus d'experts, interrogé la pertinence de l'utilisation de ces marqueurs moteurs et langagiers pour le diagnostic précoce de la MA. En effet, les atteintes cognitives dans les Covid-long risquent, dans le futur, de compliquer le diagnostic précoce des pathologies neurodégénératives du fait de troubles communs.

Mots-clefs : Aphasie Primaire Progressive, Marqueurs moteurs, Marqueurs Langagiers, Maladie d'Alzheimer, Diagnostic différentiel, Diagnostic Précoce

Acknowledgments

I would like to express my gratitude to my thesis supervisor, Prof. Philippe Robert, who gave me the opportunity to carry out my research work without compartmentalization and always with a great open-mindedness.

A special thanks to Dr. Auriane Gros who directed this project both in its clinical and scientific aspects. From the idea to the realization, all the steps were marked by Dr. Auriane Gros who also contributed to my development in the field of neurosciences by the possibility of communicating and enriching my work by my participation in various national and international projects, scientific conferences, or educational courses.

I wish to acknowledge the true help provided by Dr. Valeria Manera without whom this work would not have been possible. Dr. Valeria Manera co-directed and guided me throughout this project and instilled in me the value of scientific integrity and of working in a caring manner.

I would like to thank the reviewers Prof. Peggy Gatignol and Prof. Laurent Lefebvre and the members of the jury, Prof. Gilles Allali, Dr. Stéphanie Borel, Prof. Jean Dellamonica, Prof. Thi Mai Tran, and Pr. Olivier Beauchet, who each represent the exemplary in the scientific field, whether it be their vision of scientific research, their long-term perspective on the work that is being carried out, or the importance of teamwork, even beyond borders.

I would also like to thank the members of my thesis monitoring committee, Prof. Lucile Sassatelli and Dr. Fanny Meunier, who were able to find the right words in the follow-up of my work, to reassure me and to open-up perspectives.

I would like to thank the NeuroMod Institute for having granted me a thesis scholarship for this work, the Fonds France-Canada pour la Recherche for their travel grant and the Fondation Université Côte d'Azur for having valued my work by granting me the Academic Excellence Award.

I wish to extend my special thanks to Prof. Joël Macoir for his welcome at Laval University in Quebec, Dr. Aurélie Mouton for her always accurate vision, Justine Lemaire for her unfailing follow-up, Alexandre Derremeaux who gave life, with great patience, to the application we use, Dr. Rénald Delanoue for being a thoughtful mentor, Dr. Clair Vandersteen and Lyne Daumas for their solidarity, the whole CMRR of Nice, CoBTeK laboratory, all the investigators of the MarCo-Sens study in which my thesis work is integrated and all those who directly or indirectly contributed to this work, the co-authors, colleagues, patients, students, friends and family: Thank you, Merci, Dziękuję.

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Acronyms

<i>PPA</i>	Primary Progressive Aphasia
<i>lvPPA</i>	Logopenic variant of Primary Progressive Aphasia
<i>svPPA</i>	Semantic variant of Primary Progressive Aphasia
<i>nfavPPA</i>	Nonfluent and agrammatical variant of Primary Progressive Aphasia
<i>AD</i>	Alzheimer's Disease
<i>BNA</i>	Banque Nationale Alzheimer - French National Alzheimer's Data Bank
<i>SLT</i>	Speech and Language Therapy
<i>FTLD</i>	Frontotemporal Lobar Degeneration
<i>PCA</i>	Posterior Cortical Atrophy
<i>SD</i>	Semantic Dementia
<i>LBD</i>	Lewy's Body Dementia
<i>PACS</i>	Post-Acute Covid-19 syndrome
<i>RAPA</i>	Remote digital Assessments for Preclinical Alzheimer's Disease
<i>MRI</i>	Magnetic Resonance Imaging
<i>SPECT</i>	Single Photon Emission Computed Tomography
<i>PET</i>	Positron Emission Tomography
<i>CSF</i>	Cerebrospinal Fluid

Introduction

Neurodegenerative pathologies represent a major challenge in scientific and clinical research in a worldwide scale and a crucial public health issue. With an aging population, the number of people affected by a neurodegenerative disease is increasing. An estimation of 35,6 million people living with dementia was made in 2010, with a total cost of US\$ 604 billion [1,2]. In France, the prevalence of people having a neurodegenerative disease varies from 9,2% people above 70 years old to 17,8% people above 75 years old [3–5]. Alzheimer's Disease (AD) remains the most highly prevalent disorders affecting memory, behavior, autonomy and thus quality of life. In 2023, just in the US, the only AD disease represents for itself a cost of US\$304 billion, with approximatively 6 million patients diagnosed. These numbers prediction will grow in 2050, achieving nearly 13 million Americans that could be living with Alzheimer's, with costs reaching nearly \$1 trillion [6]. Nevertheless, its diagnosis remains challenging because of the constant evolution of the descriptive epidemiology based on clinical criteria still considered as insufficient for an early diagnosis and for the characterization of its phenotypes [7]. Furthermore, early diagnosis is even more strenuous due to the clinical disorders observed, which often vary greatly from one subject to another, depending on factors such as the age at onset, the evolution of the disease, but also the heterogeneity of cognitive and behavioral disorders. AD's diagnostic criteria have been refined in particular by the description of the criteria for typical AD, atypical AD, mixed AD and AD's preclinical stage [8] but their manifestation can be dependent of the previous cognitive and educational level, personality, psychic defense and family circle of the patient [9–11]. The evolution of AD is mostly slow and progressive with an insidious onset, and the variability of its clinical forms makes it diagnosis even more challenging. In addition, atypical clinical pictures that may occur earlier such as Primary Progressive Aphasia may be related to Alzheimer's Disease or another underlying pathology as Frontotemporal Lobar Degeneration (FTLD).

Primary Progressive Aphasia (PPA) is a group of neurodegenerative syndromes in which language impairment is the most prominent symptom at the onset of the disease [12,13], associated with a frontal, temporal and/or a parietal atrophy of the left hemisphere [14]. PPA affects patients around 60 years old with an estimated prevalence between 3.6 and 8.1/100,000 inhabitants and an incidence estimated of 1/100,000. The disease's duration varies between 4 and 14 years, with a mean time of 8 years [15–17]. PPA's disease evolution can have a severe impact on daily life within 7 years after the first symptoms [18], with the emergence of behavioral disorders affecting the patient's autonomy and more global cognitive disorders leading to severe comprehension disorders and mutism [19].

Diagnostic criteria of PPA have evolved during the past years and are based on multiple research that led to their actual definition. The first case of progressive language disorder associated with frontotemporal atrophy of the left hemisphere was described in the 1890's [20–22] while it's only about a hundred years later that another observation of a progressive language disorder was described on three patients presenting a progressive semantic trouble leading to an incapacity of recognizing or identifying common objects [23]. In 1982, the first description of the syndrome known as the actual Primary Progressive Aphasia was reported on the analysis of six patients having a left perisylvian focal atrophy which resulted on a slowly progressive aphasia without any other cognitive or behavioral disorder. This new description has changed the modern approach of neurodegenerative diseases, showing that a single function can remain impaired during a long period of time and that the focal symptoms described in this study can stand out from other neurodegenerative diseases such as AD in particular [24]. Other studies considered PPA as secondary to non-AD pathologies and suggested to include them in the group of FTLD. Two PPA variants were then described: the nonfluent PPA and the semantic dementia (SD) [25].

PPA's first diagnostic criteria were suggested in 2001, defining PPA as a language disorder of insidious onset and progressive evolution. This definition can only be valid if these disorders are inaugural and isolated for a couple of years. During the disease's progression, other cognitive impairments may appear but always with language difficulties in the foreground. The first diagnostic criteria are described in Table 1. Two types of PPA were then described: the fluent and nonfluent PPA [19].

Table 1: Primary Progressive Aphasia Diagnostic criteria – adapted from Mesulam (2001) [19]

All criteria must be included	1. Insidious onset and gradual progression of word finding, object-naming, or word-comprehension impairments as manifested during spontaneous conversation or as assessed through formal neuropsychological tests of language
	2. All limitation of daily living activities attributable to the language impairment, for at least 2 years after onset
	3. Intact premorbid language function (except for developmental dyslexia)
	4. Absence of significant apathy, disinhibition, forgetfulness for recent events, visuospatial impairment, visual recognition deficits or sensory-motor dysfunction within the initial 2 years of the illness. (This criterion can be fulfilled by history, survey of daily living activities, or formal neuropsychological testing.)
	5. Acalculia and ideomotor apraxia may be present even in the first 2 years (Mild constructional deficits and perseveration (as assessed in the go no-go task) are also acceptable as long as neither visuospatial deficits nor disinhibition influences daily living activities.)
	6. Other domains possibly affected after the first 2 years but with language remaining the most impaired function throughout the course of the illness and deteriorating faster than other affected domains
	7. Absence of "specific" causes such as stroke or tumor as ascertained by neuroimaging

A third type of PPA was added in 2004 after the observation of 31 patients having a language disorder mainly secondary to an AD focal form: the logopenic variant of PPA [26]. It's only in 2011 that the actual classification of the three main subtypes of PPA has been defined leading to an international consensus criteria, with the logopenic, nonfluent/agrammatic and semantic subtypes, based on the identification of the correlation between clinical features, atrophy localization and use of biomarkers [14].

Primary Progressive Aphasia: the three main variants

PPA clinical diagnostic criteria have evolved within the years. Mesulam et al. (2001) criteria are restrictive and therefore very specific since aphasia must remain as an isolated impairment for at least two years. Gorno-Tempini et al. (2011) criteria, summarized in Table 2, do not mention a minimum disease duration, but only a language complaint without describing a specific disorder. Moreover, language disorders are not considered as the unique cause of daily living activities reduction but as a main cause. Finally, premorbid language functions do not constitute an exclusion criteria anymore [14,19,27].

Table 2 : Clinical diagnostic criteria of Primary Progressive Aphasias, adapted from Gorno-Tempini (2011) [14]

Clinical diagnostic criteria	
Inclusion Criteria	Exclusion Criteria
Language disorder: conspicuous symptom.	Deficits better explained by other nondegenerative nervous system or medical disorders.
Aphasia: most prominent deficit at symptom onset and initial stages of the disease.	Psychiatric diagnosis as the cause of cognitive disorder.
Two previous disorders: principal cause of impaired daily living activities.	Initial deficit: episodic memory, visual memory, visuo-perceptual deficit.
	Initial deficit: behavioral disturbance.

Moreover, when the clinical diagnostic criteria were redefined, an objective of PPA standardization was made. A classification of PPA diagnoses was made in agreement with an expert consensus group for a better uniformity and reliability of research results. Three main

PPA variants were then described: the logopenic variant of PPA, semantic variant of PPA and the nonfluent/agrammatic variant of PPA [14].

Logopenic variant of Primary Progressive Aphasia

LvPPA is the most recently described variant in the literature, with a patients' proportion varying from 32% to 52% [15]. The mean age for disease onset is 63.0 years (SD 7.9) with a mean survival of 11.0 years (SD 4.1) [16]. In this variant, we observe an impaired sentences' repetition and/or an impaired single-word retrieval in spontaneous speech and naming. It must imperatively present the following at least three signs out of four to be diagnosed as such: 1. speech (phonologic) errors in spontaneous speech and naming, 2. spared single-word comprehension and object knowledge, 3. spared motor speech, 4. absence of frank agrammatism [14,27]. Thus, a short-term memory deficit in this variant leads to a phonological-loop dysfunction including phonological stock and subvocal repetition system that could be the cause of the language impairments [28–32]. Moreover, this deficit being length-dependent, can affect comprehension abilities in particular on long items, more than in other PPA subtypes [15]. But some authors also describe a deficit on short items such as words' repetition and digit-span memory [28,31,33–35].

Mostly, lvPPA patients do not have behavioral impairments at the onset [36], but anxiety and agitation can be present with neuropsychiatric disorders such as stereotypical behaviors, loss of empathy, apathy or agitation. These impairments are similar to that found in AD [37], which correlates with the fact that it has been demonstrated a high probability of lvPPA evolution to an AD [38].

In terms of imaging supporting diagnosis, abnormalities have been found in magnetic resonance imaging (MRI), with a predominant left posterior perisylvian or parietal atrophy and in single photon emission computed tomography (SPECT) or positron emission tomography (PET) with a predominant left posterior perisylvian or parietal hypoperfusion or hypometabolism [27,32,39–42]. LvPPA clinical and imaging diagnostic criteria are summarized in Table 3.

Semantic variant of Primary Progressive Aphasia

Semantic variant of PPA (svPPA), firstly called fluent PPA is the variant which description has achieved the most a consensus [43]. About 25% of FTLTD patients meet the clinical criteria of a fluent PPA with a prevalence of 0.8/100 000 [15,44]. The mean age for disease onset is 59.6

years (SD 7.2) with a mean survival of 11.6 years (SD 4.3) [16]. Secondly, it's the term of Semantic Dementia (SD) that was used to describe anomia with circumlocution and semantic paraphasia, single-word comprehension deficit, and reduced category fluency [45–47]. But last classifications propose to regroup pathologies that concern semantic memory with multimodal impairments (SD) and a verbal deficit with a unimodal impairment (PPA) which makes the semantic variant of PPA (svPPA). In this variant, we observe a deficit of word comprehension in particular in less common words with a low-frequency [48]. It must imperatively present these two clinical signs: impaired confrontation naming and impaired single-word comprehension. Usually, it's the semantic-memory deficit that is the most prominent at the onset, later associated with a lack of persons and objects recognition, even if they are presented in many modalities such as written words, images, real objects, tactile, olfactory, or gustatory modalities [49]. Moreover, at least three signs out of four signs must be associated with the two clinical signs: 1. impaired object knowledge, particularly for low frequency or low familiarity items, 2. surface dyslexia or dysgraphia, 3. spared repetition, 4. spared speech production (grammar and motor speech) [27,39,45,50].

SvPPA patients present neuropsychiatric disorders that are more common in this variant and appear earlier in the syndrome [51]. The troubles described are similar to the ones that we can find in behavioral FTLN with stereotyped behaviors (50%), dietary changes (22%), disinhibition (17%), apathy (11%) and lack of empathy (9%) [37]. Moreover, studies have demonstrated that svPPA patients present depressive symptoms that can constitute a diagnostic pattern. Indeed, in comparison to other neurodegenerative disease, svPPA patients present an abnormally high worry with higher dysphoria scores distinguishing svPPA from other patients at 70% accuracy [52]. Depressive symptom seems thus of interest for svPPA diagnostic sensitivity.

In terms of imaging supporting diagnosis, abnormalities have been found in MRI, with a predominant anterior temporal lobe atrophy and in SPECT or PET a predominant anterior temporal hypoperfusion or hypometabolism [27,53]. SvPPA clinical and imaging diagnostic criteria are summarized in Table 3.

Nonfluent/agrammatic variant of Primary Progressive Aphasia

NfavPPA diagnosis is estimated in about 45% of FTLN and its prevalence is of 0,5-3/100 000 and incidence of 0,4-0,7/100 000 a year [54]. The mean age for disease onset is 64.4 years (SD 7.5) with a mean survival of 8.0 years (SD 2.5) [16]. In this variant, we observe both

agrammatism in language production and effortful, halting speech with inconsistent speech sound errors and distortions (apraxia of speech). These core features reduce significantly speech fluency. It must imperatively present the following at least two signs out of three to be diagnosed as such: impaired comprehension of syntactically complex sentences, spared single-word comprehension and spared object knowledge [38,55,56]. We can also observe executive functions impairment with work memory alteration [51,57].

In this variant, neuropsychiatric disorders are less frequent at onset [58]. However, some studies have demonstrated the presence of behavioral troubles such as apathy (42%), loss of empathy (40%) with affecting emotion recognition in others [37]. Finally, we can also find agitation and depression in patients with nfvPPA [58].

In terms of imaging supporting diagnosis, abnormalities have been found in MRI, with a predominant left posterior frontoinsular atrophy and in SPECT or PET a predominant left posterior frontoinsular hypoperfusion or hypometabolism.

NfvPPA clinical and imaging diagnostic criteria are summarized in Table 3.

Table 3: Clinical and imaging supporting diagnosis of Primary Progressive Aphasia three main subtypes - adapted from Gorno-Tempini (2019) [27]

Clinical diagnosis			
	lvPPA	svPPA	nfvPPA
Core features	At least one:	Both:	Both:
	Impaired single-word retrieval in spontaneous speech and naming	Impaired confrontation naming	Agrammatism in language production
	Impaired repetition of sentences	Impaired single-word comprehension	Effortful, halting speech with inconsistent speech sound errors and distortions (apraxia of speech)
Supporting features	At least three:	At least three:	At least two:
	Speech (phonologic) errors in spontaneous speech and naming	Impaired object knowledge, particularly for low frequency or low familiarity items	Impaired comprehension of syntactically complex sentences
	Spared single-word comprehension and object knowledge	Surface dyslexia or dysgraphia	Spared single-word comprehension
	Spared motor speech	Spared repetition	Spared object knowledge
	Absence of frank agrammatism	Spared speech production (grammar and motor speech)	

Imaging supported diagnosis			
	lvPPA	svPPA	nfavPPA
MRI	Predominant left posterior perisylvian or parietal atrophy	Predominant anterior temporal lobe atrophy	Predominant left posterior frontoinsular atrophy
SPECT or PET	Predominant left posterior perisylvian or parietal hypoperfusion or hypometabolism	Predominant anterior temporal hypoperfusion or hypometabolism	Predominant left posterior frontoinsular hypoperfusion or hypometabolism

lvPPA: logopenic variant of Primary Progressive Aphasia, svPPA: semantic variant of Primary Progressive Aphasia, nfavPPA: nonfluent/agrammatic variant of Primary Progressive Aphasia, MRI: Magnetic Resonance Imaging, SPECT: Single photon emission computed tomography, PET: positron emission tomography.

Even though Gorno-Tempini's (2011) classification is still relevant and used nowadays, many studies have highlighted some PPA subtypes that do not correspond to the three main variants already described in the literature, and even if a noticeable proportion of patients with PPA have neither the semantic nor the nonfluent variants, they do not necessarily conform to a logopenic variant [59,60]. Some lvPPA subtypes present an unexplained lack of sentence repetition impairment, which questions on the existence of a fourth PPA variant [61]. Moreover, another study has demonstrated that 15% to 31% of PPA diagnosis remain unclassified, because of a lack of disease-conformity to the diagnostic criteria. Vandenberghe et al.(2016) [62] made two assumptions, first being that there is a fourth PPA variant having a combination of symptoms that is not actually described in the literature: the mixed PPA. This variant is defined by a word comprehension impairment associated to a speech apraxia or agrammatism. The second being the anomic-only PPA variant, having for only diagnostic criteria the anomia and absence of other features usually present in the other subtypes. To illustrate the new criterion, Vandenberghe et al. (2016) created a new root diagnosis of PPA with these new descriptions, showed in Figure 1.

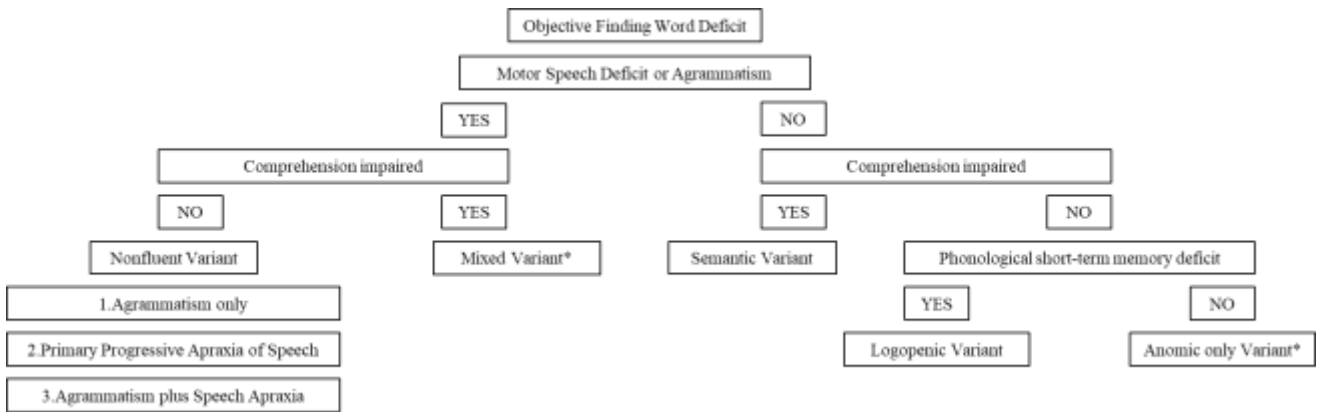


Figure 1: The new root diagnosis of PPA adapted from Vandenberghe (2016) [62]
 * Representing the new variants

These clinical criteria help to differentiate PPA subtypes, but it is important to specify that the final diagnosis rests however on several criteria defined previously by Gorno-Tempini (2011) that were redefined recently. The final diagnosis includes all clinical criteria and the presence of a histopathologic neurodegenerative disorder, or a known pathogenic mutation as described in Figure 2 [27].

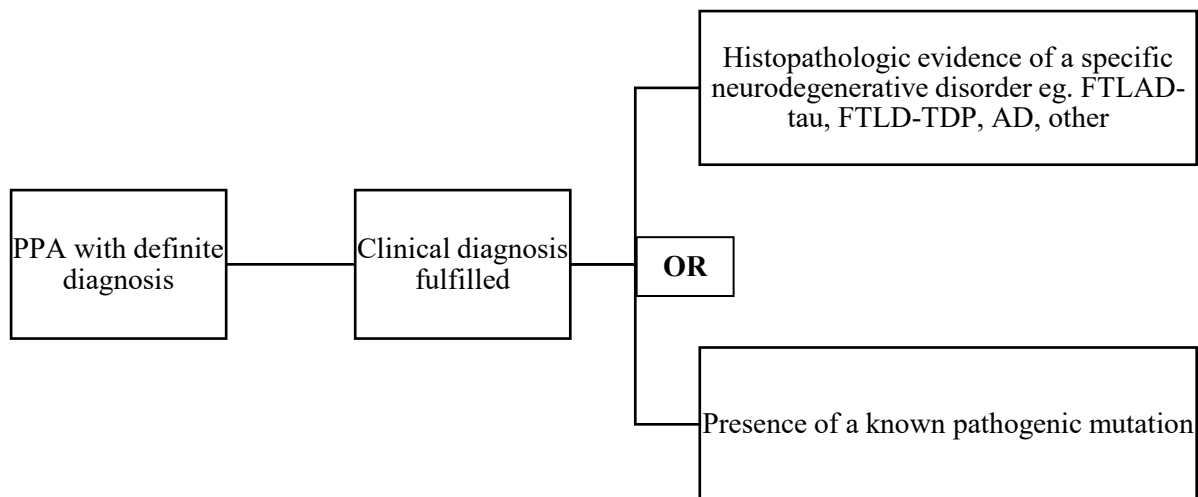


Figure 2: Primary Progressive Aphasia final diagnosis – adapted from Gorno-Tempini (2019) [25]
 PPA: Primary Progressive Aphasia; AD: Alzheimer’s disease; FTLAD-tau: frontotemporal lobar degeneration-tau; FTLD-TDP: Frontotemporal lobar degeneration with TDP-43-immunoreactive pathology.

PPA variants described by Gorno-Tempini (2011) do not always cover the entire pathology. Moreover, many studies question this classification highlighting new specificities in the

variants already described. For the logopenic variant for example, it has been shown that there can be a dysexecutive impairment at the onset of the disease, just as in the two other subtypes [63] questioning the differential diagnosis. Another study put forward the underlying neurodegenerative disorder in svPPA, usually being FTLN, but there are some patients having a svPPA-AD-related syndrome with another imaging than usual involving a parietal hypometabolism that constitutes a new biomarker in this variant, questioning the classification of svPPA [53]. Finally, in nfavPPA variant, it's the core feature of agrammatism that has been questioned, with a discrete syntactic disorder not always present and difficult to detect [64] and a lack of frank agrammatism that does not always appear at the onset but develop during the evolution of the disease [65].

PPA diagnosis is thus challenging, with a descriptive epidemiology that is constantly evolving leading to debate the types of biomarkers used for a more specific diagnosis, especially since patient's adapted care will rely on it [7].

Contribution of new markers in the diagnosis of Primary Progressive Aphasia

PPA diagnosis has progressively evolved, with better accuracy since the use of biomarkers such as neuroimaging, and diagnostic criteria have been defined following the emergence and definition of PPA's different subtypes [18,36,38]. But early diagnosis remains difficult because of the heterogeneity of patients' syndrome features and the evolution of the underlying neurodegenerative disease with a non-highly clinicopathological correlation (as FTLN, AD, progressive supranuclear palsy or coticobasal degeneration) [21]. The challenge of an early diagnosis is thus essential, especially since there is no pharmacological treatment for neurodegenerative syndromes such as PPA. It could lead to an earlier care with appropriate clinical interventions, according to the fact that non-pharmacological treatments like speech and language therapy (SLT), are for the moment the most effective in slowing down the evolution of the disease's effects and keeping communication skills as long as possible [66–68].

Even if many studies have highlighted the interest of the use of biomarkers in the diagnosis of neurodegenerative pathologies, few have put interest on the parameters that can be extracted from daily living activities such as writing or speaking, while it seems essential for a better analysis and better understanding of the changes observed at a preclinical stage. It has thus been

demonstrated that some patients may not present clinical symptoms at the onset, and that already existing biomarkers wouldn't be specific enough to detect an early impairment [69,70]. To go further, it has also been demonstrated that the use of new technologies as digital tablets, cameras or voice recorders can lead to high quality, temporal and spatial behavioral parameters which analyses can bring more reliability in the diagnosis, and not only for an early but also for a differential diagnosis with other pathologies [71–75]. Finally, implementing that kind of analyses could lead to the development of new noninvasive and less expensive tools supporting the already existing invasive techniques as lumbar puncture or PET-scan.

The interest of graphical and gesture analyses

Handwriting requires cognitive, executive, planning and coordination skills. In neurodegenerative diseases, these capacities are altered since the impairment of the peripheral nervous system impedes muscles functional control [76]. Handwriting performances experience therefore significant changes that it can be interesting to consider in the context of a classification of parameters characteristic of neurodegenerative diseases such as AD, PPA or Posterior Cortical Atrophy.

The relationship between gesture processing and language has already been demonstrated in the literature [77]. This feature was examined in PPA patients, in the framework of a study examining gesture discrimination and language processing. PPA patients presented a deficit in gesture discrimination, imitation in parallel with a deficit in imitative language tasks as repetition or writing-to-dictation. These deficits are due to the critical role of the left perisylvian parietotemporal area in the circle of parity between perception and production of both words and gestures [78]. Moreover, recent studies have described the presence of different gesture profiles in the three main PPA variants, especially svPPA presenting a deficit in hand posture for meaningful gestures [79].

These studies highlight the interest of carrying out analyzes of the gesture, allowing to deduce a praxis model of PPA that would improve PPA diagnosis. Moreover, a combination of graphic and gesture parameters would be even more specific in this purpose, regarding the recent studies highlighting the interest of machine learning application for neurodegenerative diagnosis and classification improvement [80–82].

The interest of language and vocal analyses

In Alzheimer's Disease, various studies have highlighted changes both in language but also in speech. The presence of a lack of words even in the first stages of the disease in language, but also a significant variation in speech pauses, as well as a degradation of voice amplitude in vocal analyses were described [83]. Among different vocal parameters, jitter and shimmer have been shown to discriminate AD [84]. These changes seem to appear early and could be detected by automatic speech analysis which allows both linguistic and paralinguistic features extraction [85].

Some studies have focused on the differential aspects of repetition abilities in AD compared to lvPPA., with lvPPA patients showing a greater deficit in long and non-meaningful sentences, with sentence repetition influenced by semantic reversibility and syntactic complexity. [86–89].

Acoustic measures were however explored in speech apraxia in comparison with the three main PPA subtypes. A study showed that speech apraxia patients' group had longer durations and reduced rate of syllable production for most words and sentences [90].

These studies of language and acoustic markers show that it would be interesting to investigate these features to determine a related speech and acoustic diagnostic profile. Moreover, a combination of language and acoustic parameters would be even more specific in this purpose, regarding the recent studies highlighting the interest of machine learning application for neurodegenerative diagnosis and classification improvement [80–82].

Aim of the Thesis and Outlines

The general aim of this thesis was to investigate the potential contribution of motor and language analyses in early and differential diagnosis of PPA. For this purpose, the analyses of different parameters such as handwriting pressure, velocity, jerk or stroke, video analyses, language or vocal analyses were investigated in clinical practice. To operationalize these analyses, this thesis work was integrated in a multimodal longitudinal study using ecological and sensory markers for the early and differential diagnosis of cortical and subcortical pathologies with cognitive disorders called MarCo-Sens (IDRCB: 2019-A00342-55).

The first step of this thesis work presented in **Chapter 1**, was to make an analysis of PPA diagnoses made in France. We relied on a French cohort, using data taken from the French

National Alzheimer's Data Bank (BNA), by describing the demographics and the evolution of subjects with PPA in comparison with Alzheimer's disease (AD) on a period of 7 years. With this work, we demonstrated the need of improving PPA diagnosis, which is often delayed, not only for clinical purpose but also for public health service.

We thus wanted to define how to improve this diagnosis by using tools that are easy to set up in clinical practice. For this purpose, we decided to implement the use of touchpads in SLT consultation. Clinical tests have been computerized, allowing new possibilities of assessments. Indeed, instead of using pen and paper tests, we decided to use a touchpad, on which patients could write directly with a connected pencil. In this way, we were able to extract new parameters such as writing pressure, velocity, jerk, and stroke. By adding new graphical tasks that we have defined and divided in three categories (whether they are linguistic, cognitive, or not), we could define which parameter was of interest in the early diagnosis of PPA, but also the differential diagnosis of AD and PPA, of PPA and PCA and finally the differentiation of the three main PPA subtypes. Moreover, we also used video analyses to verify if the pen-up time that cannot be collected on the touchpad could bring more specificity to the graphic markers. These studies are described in **Chapter 2**.

Given that language impairment is the most prominent in PPA, we also wanted to verify if language and acoustic markers can be of interest in the diagnosis. As presented in **Chapter 3**, we investigated sentence repetition deficit in patients with lvPPA, svPPA and AD by using a new sentence repetition task. We analyzed what kind of errors were made, whether there were phonological errors, difficulties with sentence length or number of mistaken content words. In parallel, we analyzed acoustic markers aiming to discriminate lvPPA and AD, as well as the influence of AD biomarkers on acoustic profiles at the beginning of the disease. This research was made to verify if the use of acoustic markers could help to discriminate PPA underlying pathologies, bringing a great alternative to invasive examination such as lumbar puncture, and predicting the disease evolution.

Finally, this thesis work was lead through Covid-19 pandemic which raised new observations and questions about the relevance of the new diagnostic markers. Indeed, studies increasingly discuss the risk of developing AD in adult patients having a Post-Acute COVID-19 Syndrome (PACS). A call for expert working groups has been initiated by the EU Joint Program – Neurodegenerative Disease Research Initiative to investigate the impact of COVID-19 on

research related to neurodegenerative diseases. On the funding of the French National Agency, we integrated a working group focusing on COVID-19 pandemic and its impact on Alzheimer's care. **Chapter 4** provides the systematic review made in the framework of this working group, examining the potential of using remote digital assessments for preclinical AD to identify impairments in PACS patients, examining the supporting evidence, and describing the recommendations of experts regarding their use.

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Chapter 1

DIAGNOSIS OF PRIMARY PROGRESSIVE APHASIAS

Primary Progressive Aphasia (PPA) is a neurodegenerative syndrome going from an isolated language disorder to a global cognitive impairment with associated multiple neuropsychiatric symptoms [1–3]. Because of the disease’s evolution and its underlying phenotypes depending on PPA subtypes, PPA diagnosis presents changes during its evolution, complicating the diagnostic process. Furthermore, the logopenic variant of PPA (lvPPA) is considered as an atypical phenotype of Alzheimer’s disease (AD), which further complicates its diagnosis [4,5].

In France, AD represents a public health policy, with the implementation of many Alzheimer’s Plans that lead to improve AD diagnosis, research, medical care and diagnostic data registration [6,7]. The latter element was created at the Nice’s University Hospital. The perspective of this data registration tool was to collect the diagnoses made in medical consultation within the framework of a national database called Banque Nationale Alzheimer, a French National Alzheimer’s Data Bank (BNA). The BNA records all medical acts made mainly in Memory Centers in France. It thus helps to register AD epidemiology, the type of medical acts led by clinicians in different structures, but also demographic, clinic and diagnostic data. PPA diagnosis, which nature is still debated [8–11], remains more rarely diagnosed than AD. It may be related to the fact that this syndrome is underdiagnosed or misdiagnosed because of its underlying neuropathologies [5,12].

The objective of this first study, was to make an objective description of the clinical characteristics and the evolution in diagnosis of PPA in comparison with AD.

This description covers a period of seven years, going from 2010 to 2016, in a large cohort of memory-clinic patients.

The secondary objectives were to determine if the diagnosis of PPA is more difficult to establish, with diagnostic changes occurring before the PPA diagnostic of interest, and more delayed, compared to AD diagnosis. It was also to compare the two syndromes according to the recommended therapeutic approaches, assuming, that language impairment present on both pathologies may lead to non-pharmacological therapies such as Speech and Language Therapy (SLT).

This study represents the main structure and basis of this thesis work. It represents a work of almost three years of requesting for agreements to have access to the BNA data, analyses, article writing and reviewing in collaboration with the co-authors.

I was implicated in every step of this study.

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Publication 1

The course of primary progressive aphasia diagnosis: a cross-sectional study

Mouton *et al.* *Alzheimer's Research & Therapy* (2022) 14:64
<https://doi.org/10.1186/s13195-022-01007-6>

Alzheimer's
Research & Therapy

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The course of primary progressive aphasia diagnosis: a cross-sectional study



A. Mouton¹, A. Plonka^{1,2}, R. Fabre¹, T. M. Tran³, P. Robert^{1,4}, J. Macoir^{5,6}, V. Manera^{4,7} and A. Gros^{1,4*}

Abstract

Background: The primary progressive aphasia (PPA) diagnosis trajectory is debated, as several changes in diagnosis occur during PPA course, due to phenotype evolution from isolated language alterations to global cognitive impairment. The goal of the present study, based on a French cohort, was to describe the demographics and the evolution of subjects with PPA in comparison with Alzheimer's disease (AD) on a period of 7 years.

Methods: We conducted a repeated cross-sectional study. The study population comprised individuals with PPA and AD diagnosis (N 167,191) from 2010 to 2016 in the French National data Bank (BNA). Demographic variables, MMSE scores, diagnosis status at each visit and prescribed treatments were considered.

Results: From 2010 to 2016, 5186 patients were initially diagnosed with PPA, 162,005 with AD. Compared to AD subjects, significant differences were found concerning age (younger at first diagnosis for PPA), gender (more balanced in PPA), education level (higher in PPA) and MMSE score (higher of 1 point in PPA). Percentage of pending diagnosis, delay between first consultation and first diagnosis and the number of different diagnoses before the diagnosis of interest were significantly higher in PPA group compared to AD group. Pharmacological and non-pharmacological treatments were significantly more recommended following PPA than AD diagnosis.

Conclusion: This study improves the knowledge of PPA epidemiology and has the potential to help adopting appropriate public health service policies. It supports the hypothesis that PPA is diagnosed later than AD. The PPA diagnosis increases the prescription of non-pharmacological treatments, especially speech and language therapy (SLT) that is the main treatment available and most effective when at the initial stage.

Keywords: Primary progressive aphasia, Alzheimer's disease, Diagnosis

Introduction

Current diagnosis classification identifies three PPA subtypes: The agrammatic subtype (nfvPPA), the semantic subtype (svPPA) and the logopenic subtype (lvPPA).

The age of onset of PPA is usually between 50 and 65 years [1,2]. PPA ultimately leads to dementia, and the survival duration is estimated between 10 and 15 years [3]. No disease-modifying pharmacological intervention treatment is available so far. However, non-pharmacological interventions, such as speech and language therapy (SLT), have proven to be useful to compensate and maintain functional communication.

Proper PPA diagnosis increases the opportunities of providing early appropriate clinical interventions, implementing coordinated care plans, managing symptoms, improving patient safety, cost savings, and postponing institutionalization [4]. The neurodegenerative diagnosis trajectory is still debated, as several changes in diagnosis occur during the course of PPA, due to phenotype evolution from isolated language alterations to global cognitive impairment with associated multiple neuropsychiatric symptoms [5,6]. Furthermore, lvPPA is considered as an atypical phenotype of Alzheimer's disease (AD), which further complicates diagnosis [7,8]. Even if the PPA duration is estimated at about 6 years before dementia onset, language symptoms could represent the only set of signs for as many as 10-14 years.

After a few years of disease progression, deficits in other cognitive domains than language appear, such as episodic memory or executive functions. However, the language dysfunction remains the most salient feature throughout the degeneration process [9,10]. The diagnosis of PPA is a major challenge in clinical practice as this phenotype is complex and constantly evolving.

Despite PPA has been object of investigation in several studies, given its low prevalence, most of the existing literature deals with small sample sizes, which limits the statistical power and the generalizability of the results. The main objective of this study was to describe the clinical characteristics and the evolution in diagnosis of PPA in comparison with AD, over a period of seven years, in a large cohort of memory-clinic patients. The secondary objectives were to determine if the diagnosis of PPA is more difficult to establish (more changes in diagnosis before the PPA diagnosis) and more delayed, compared to AD diagnosis, and to compare the two syndromes according to the recommended therapeutic approaches.

Participants

Participants of the present study were recruited from the French National data Bank (BNA) which is part of the French strategy to fight against dementia [11] and records information since the end of 2009. This database was created to provide information about the medical activity of the French memory centres in order to adapt healthcare provision and generate epidemiologic knowledge on the diseases and the medical practices. The BNA includes a limited set of demographical, diagnostic, and clinical information, selected by a national consensus group. The number of collected variables was limited to facilitate and enhance care providers to participate to this national database. Data are collected from 536 memory units in France: 434 memory centres (secondary level), 28 resource and research memory centres (tertiary level) and 74 independent neurologists who expressed the willingness to participate.

Each time a person consults one of these centres, a clinical record is generated and transferred to the database. Therefore, one patient can figure more than once in the BNA, depending on the number of medical acts he/she underwent.

The following variables were considered in the present study: gender, age, living conditions, education (five levels according to the French education system, corresponding to the following categories: no formal education, primary school level [equivalent to 1–5 years of education], secondary school level with 6–9 years of education, secondary school level with 10–12 years of education, and university level [over 12 years of education]), type of medical centre, referring modalities, score on the Mini Mental Score Examination (MMSE) [12] date of consultation, medical diagnosis and recommended treatments.

The BNA differentiates 38 diagnostic groups, based on International Classification of Diseases, Tenth Revision, ICD-10. For the AD diagnosis, ICD-10 criteria include insidious and irreversible onset dementia and clinical examination or special investigation that don't suggest any other etiology of the disorders (metabolic disorder, cerebral haematoma...). Therefore, AD diagnosis was established on clinical, biological, and cerebral imaging results. As the BNA is a large databank, reflecting usual clinical practice, on the period studied (2010 to 2016), no metabolic imaging or amyloid proof was required. For treatments, the BNA records the presence of a prescription at the time of the consultation for 6 groups of psychotropic drugs classified as follow, using ATC codes: antidepressant (N06A), anxiolytic (N05B), hypnotic (N05C), antipsychotic (N05A), cholinesterase Inhibitors (ChEIs) (N06DA) and N-Methyl-D-aspartate receptor antagonist (NMDA antagonist) (N06DX01). No data is available on drug

generics or brand names, nor on dosage. Psychosocial intervention and rehabilitation are recorded too. More details on this database are described in Le Duff et al., 2012 [13].

Study design and participant selection

Patients were selected in the BNA from January 1, 2010, to December 31, 2016. Patients with at least once a diagnosis of PPA according to the diagnostic criteria including progressive language disorders were included in the PPA group (including all PPA subtypes) [14,15]. Patients with at least once a diagnosis of AD, but never of PPA were included in the AD group. Individuals who already had the diagnosis of interest when first registered in the database were included only if their first consultation for memory problems was in the same year or the year before the first visit. This was intended to exclude patients who had a diagnosis established for a long time, and to collect data at the time of the first diagnosis. To describe the whole population included in the study, we selected data at the first diagnosis of interest. Given the importance of cognitive status, only patients with at least one existing MMSE evaluation at less than 1 year before or after the first diagnosis of interest were considered in the analyses (See Fig 1).

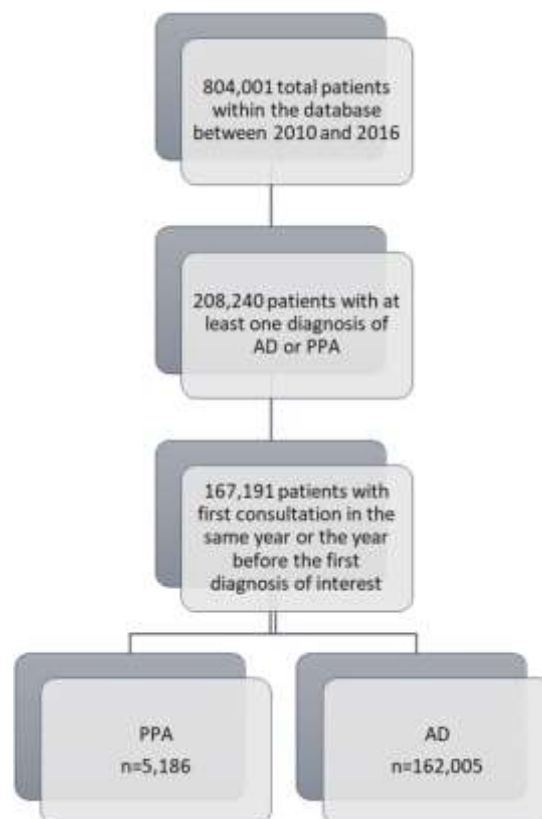


Figure 1: Flowchart - selection of the participants included in the study.

Statistical analysis

Incident cases were defined as those first diagnosed during the study period. Incidence was calculated by dividing the total number of incident cases by the total number of person-years for the catchment area population over 7 years (data from the French national institute for statistical and economic studies INSEE).

Descriptive analyses were conducted using percent and frequency for qualitative variables and mean with SD for quantitative variables. Variables associated with diagnosis (i.e., PPA, AD) were analysed using Student t-test for quantitative variables and chi-squared tests for qualitative variables. The change in treatment and the change in psychosocial interventions were determined using the McNemar test. In all analyses, a p value less than 0.05 was considered significant.

In addition, because of the large size of our cohort, we decided to run a second type of analysis: Bayesian analysis. This analysis was also performed as a simple way to deal with significantly labelled differences between large-sized groups. Here we used a burn-in of 1000 iterations (to allow Markov chains to reach stationary distribution) and 4000 useful iterations for estimates. Furthermore, the Bayesian techniques allow acceptance of a null hypothesis (not only rejection), which is not only a comparison with 0 (for example, for a difference). Statistical analyses were done with SAS Enterprise Guide software, version 5.1 (SAS Institute, Cary, NC, USA). Bayesian analyses were done with WinBugs 1.4 software.

Results

Clinical characteristics of the 2 groups

The PPA and the AD groups respectively included 5,186 and 162,005 patients. The incidence rate of PPA was 1.14 per 100,000 person-years, while the incidence rate of AD was 35.7 per 100,000 persons-years. Demographic characteristics of the two groups are presented in Table 1, and the results of Bayesian analysis are reported in Additional Table 1. Patients with PPA were significantly younger (mean = 73.7; SD = 9.1 years) than those with AD (mean = 81.4; SD = 8.0 years ($p < 0.001$), and this was observed in all age groups, except for the patients aged 80 years and older for which the opposite pattern was observed. As shown on Table 1, the sex ratio was more balanced in the PPA than in the AD group, and the educational level was higher in the PPA than in the AD group, with a larger proportion of patients with more than 6 years of education (secondary second school level).

Compared to the AD group, the patients of the PPA group were more often referred by neurologists and less by general practitioners. In PPA more often than in AD, the diagnosis was established in a tertiary centre, and patients lived farther from the centre.

In the PPA group, the MMSE score at first diagnosis was significantly different than in AD. Using Bayesian analytical methods, we found that there was a significant difference of 1 point between the two groups, while the difference of 2 points for MMSE was not significant. Patients were more to live in community compared to the patients with AD.

Table 1 : Demographic characteristics

	PPA (n=5,186)		AD (n=162,005)		p-value
	Mean	[SD]	Mean	[SD]	
Age when first diagnosed, years	73.7	[9.1]	81.4	[8.0]	<.001
MMSE at ±1 year after diagnosis	19.5	[7.3]	17.9	[5.9]	<.001
	n	(%)	n	(%)	p-value
Gender					<.001
Female	2,887	(55.7)	112,751	(69.6)	
Male	2,299	(44.3)	49,254	(30.4)	
Type of center					<.001
Memory clinic	2,739	(52.8)	120,750	(74.5)	
Regional specialized memory clinic	2,309	(44.5)	37,361	(23.1)	
Private neurologist	138	(2.7)	3,894	(2.4)	
Age at first consultation following diagnosis, years					<.001
< 50	38	(0.7)	462	(0.3)	
[50 ; 55[89	(1.7)	567	(0.4)	
[55 ; 60[205	(4.0)	1,493	(0.9)	
[60 ; 65[533	(10.3)	3,038	(1.9)	
[65 ; 70[807	(15.6)	6,694	(4.1)	
[70 ; 75[966	(18.6)	14,801	(9.1)	
[75 ; 80[1,191	(23.0)	31,774	(19.6)	
[80 ; 85[923	(17.8)	47,930	(29.6)	
≥ 85	834	(8.4)	55,246	(34.1)	
Education					<.001
No education	205	(4.0)	12,523	(7.7)	
Primary	1,536	(29.6)	75,615	(46.7)	
Secondary first cycle	1,067	(20.6)	26,893	(16.6)	
Secondary second cycle	805	(15.5)	14,715	(9.1)	
Superior	1,022	(19.7)	13,222	(8.2)	
Unknown	551	(10.6)	19,037	(11.8)	
Initially referred by					<.001
General practitioner	2,839	(54.7)	106,157	(65.5)	

Neurologist	1,152	(22.2)	9,751	(6.0)
Other specialists	592	(11.4)	17,665	(10.9)
Direct	233	(4.5)	6,974	(4.3)
Others	370	(7.1)	21,458	(13.3)
Community-dwelling				<.001
No	333	(6.4)	27,240	(16.8)
Yes	4,853	(93.6)	134,765	(83.2)
Patient location				<.001
Within 50 km from the memory clinic	4,245	(81.9)	148,844	(91.9)
Over 50 km from the memory clinic	941	(18.2)	13,161	(8.1)

Evolution in diagnosis.

As shown in Additional Table 2, the delay between the first consultation for cognitive disorders (that could be prior the first record in the BNA) and the first diagnosis visit was significantly longer in the PPA than in the AD group.

The number of different diagnoses before the diagnosis of interest was significantly different in the PPA group than in the AD group. Indeed, the mean number of diagnoses before the diagnosis of interest was 0.54 (SD=0.69) in the PPA group, and 0.45 in the AD group (SD=0.62). The mean time between the first consultation and the first diagnosis was 0.7 years in the PPA group and 0.6 years in the AD group ($p<0.001$) (see Additional Table 2).

We analyzed the diagnoses made before the diagnosis of interest in each group (Table 2). Except “pending diagnosis”, the most frequent diagnosis given before PPA diagnosis were AD (12.6%) then subjective cognitive complaint, followed by non-amnesic mild cognitive impairment. Though before AD diagnosis, except “pending diagnosis”, it was most often amnesic mild cognitive impairment (14%) then cognitive complaint then non-amnesic mild cognitive impairment.

The proportion of patients having received no other diagnosis after PPA was identified was lower than after an AD diagnosis was made (see Additional Table 2).

However, the proportion of patients having received more than one diagnosis after the first diagnosis visit was higher in the PPA than in the AD group. Diagnoses registered after a PPA diagnosis, were most often PPA (72.7%), then AD then behavioral variant of frontotemporal neurocognitive disorder then mixed neurocognitive disorder. And after AD diagnosis, it was most frequent AD diagnosis (90.7%) then mixed neurocognitive disorder (Table 2).

Table 2: Diagnoses before and after first diagnosis of interest.

	Diagnosis BEFORE first diagnosis of interest			
	PPA		AD	
	N	(%)	n	(%)
Pending Diagnosis	3,277	(49.6)	83,967	(53.4)
Alzheimer Disease (AD)	835	(12.6)	0	(0.0)
Memory complaints	492	(7.4)	11,781	(7.5)
MCI	467	(7.1)	10,256	(6.5)
Amnesic MCI	294	(4.4)	21,974	(14.0)
Huntington disease	205	(3.1)	754	(0.5)
Mixed Dementia	177	(2.7)	11,348	(7.2)
Anxiety disorder, depressive disorder	177	(2.7)	5,540	(3.5)
Frontotemporal Lobar Degeneration (FTLD)	90	(1.4)	280	(0.2)
Others	596	(9.0)	11,419	(7.3)
	Diagnosis AFTER first diagnosis of interest			
	PPA		AD	
	N	(%)	n	(%)
PPA	10,760	(72.7)	0	(0.0)
Alzheimer Disease (AD)	2,049	(13.8)	318,769	(90.7)
Frontotemporal Lobar Degeneration (FTLD)	328	(2.2)	672	(0.2)
Pending Diagnosis	323	(2.2)	3,761	(1.1)
Huntington disease	229	(1.5)	634	(0.2)
Mixed Dementia	223	(1.5)	14,267	(4.1)
MCI	146	(1.0)	1,924	(0.5)
Amnesic MCI	89	(0.6)	2,546	(0.7)
Others	1,107	(7.5)	27,576	(7.8)

Evolution in treatment

Patients with at least one BNA record before and after the diagnosis of interest and for whom the data about pharmacological (N=1,622) and non-pharmacological treatment (N=1,605) were registered were selected. The number of patients under pharmacological treatment was significantly higher after, than before the diagnosis of PPA, and this is true for the different psychotropic drugs and for anti-dementia treatments. After diagnosis, the treatment that was mainly added in the PPA group was antidepressants (for 20,6% of the patients). More patients received non-pharmacological treatments after a PPA compared to before the diagnosis, with the most common intervention being speech-language therapy (See Table 3). The delay between diagnosis and starting speech-language therapy was 6.9 (+/- 6.3) months.

Table 3: Treatments before and after first consultation with diagnosis of interest.

	Before first consultation with diagnosis of interest		After first consultation with diagnosis of interest		p-value
	n	(%)	n	(%)	
PPA patients					
Pharmacological treatments					
Antidepressant	330	(20.4)	629	(38.8)	<.001
Anxiolytic	130	(8.0)	237	(14.6)	<.001
Hypnotic	64	(4.0)	94	(5.8)	<.001
Neuroleptic	29	(1.8)	116	(7.2)	<.001
NMDA antagonist	77	(4.8)	306	(18.9)	<.001
ChEI	144	(8.9)	426	(26.3)	<.001
Non-pharmacological treatments					
Day hospital	24	(1.5)	158	(9.8)	<.001
Speech and Language Therapist (SLT)	365	(22.7)	1,060	(66.0)	<.001
Psychologist	66	(4.1)	130	(8.1)	<.001
Kinesiologist	35	(2.2)	169	(10.5)	<.001
Occupational therapist	17	(1.1)	50	(3.1)	<.001
Stakeholder group	24	(1.5)	84	(5.2)	<.001
AD patients					
Pharmacological treatments					
Antidepressant	10,261	(24.1)	16,528	(38.8)	<.001
Anxiolytic	5,226	(12.3)	8,626	(20.3)	<.001
Hypnotic	2,375	(5.6)	3,380	(7.9)	<.001
Neuroleptic	1,359	(3.2)	3,943	(9.3)	<.001
NMDA antagonist	1,801	(4.2)	11,670	(27.4)	<.001
ChEI	5,967	(14.0)	24,927	(58.6)	<.001
Non-pharmacological treatments					
Day hospital	628	(1.5)	5,272	(12.7)	<.001
Speech and Language Therapist (SLT)	2,785	(6.7)	8,807	(21.2)	<.001
Psychologist	1,214	(2.9)	2,377	(5.7)	<.001
Kinesiologist	1,562	(3.8)	4,311	(10.4)	<.001
Occupational therapist	658	(1.6)	1,546	(3.7)	<.001
Stakeholder group	941	(2.3)	3,038	(7.3)	<.001

*Mc Nemar test

In the AD group too, the number of patients under pharmacological treatment (N=42,571) was significantly higher after, than before the diagnosis (Table 3), and this is also true for the different psychotropic drugs and for anti-dementia treatments. After diagnosis, the treatment that was mainly added was cholinesterase inhibitors (for 46,4% of the AD patients). As for the PPA group, more patients received non-pharmacological treatments after receiving an AD

diagnosis compared to before the diagnosis. The delay between diagnosis and starting speech-language therapy was 9.0 (+/- 9.6) months.

Discussion and Conclusion

The present study, based on data gathered in the BNA, showed an incidence of PPA of 1.14/100,000 person-year, which is consistent with that was previously reported in FTLD and can be estimated in PPA [5,12,13].

Median age at first diagnosis was significantly lower in the PPA than in the AD group, which is in agreement with other studies that have shown that symptoms onset happened at a younger age in PPA than in AD [16]. However, the onset of PPA is known to occur before the age of 65 [17] and the disease is described as a progressive language deficit occurring between 45 and 70 years old [14]. So, our results are not aligned to those of previous studied cohort and indicates possible bias of recruiting older people in Memory Centres, because they are mostly known as a diagnostic facility for memory and not language disorders.

The other possible explanation would be the proportion of different PPAs in the database and the lack of literature on the age of onset of an lvPPA.

Sex ratio was more balanced in the PPA than in the AD group, with 55.7% of females. Unless a majority of women was described as usual, sex ratio varies from one cohort to another in AD, in PPA group our results are in agreement with the literature [3].

The educational level was higher in the PPA than in the AD group, which is more than described in other studies [3] but in agreement with the fact of early onset dementia patients are more educated than patients with late onset dementia [18]. So, compared to other studies, we can suppose that PPA will be able to cope better with greater brain damage than AD[19].

The mean MMSE score (in two points difference) at first diagnosis was not statistically different in the PPA than in the AD group, which is in agreement with the elements found in the literature [20]. MMSE's item scores could be useful to discriminate PPA patients and AD [22,23] but it was not possible to test this in this study [21,22].

About evolution of PPA diagnosis, the most frequently, the diagnosis stays PPA (72.7%), including temporal variant of FTLD, then AD then behavioral variant of FTLD. These results are in agreement with literature values [3].

Regarding the initially diagnosed PPA patients, the natural evolution to a FTD in temporal or frontal variant diagnosis is concordant as the language impairment will be accompanied by a more global cognitive deficit. In cognitively impaired patients, the appearance of a global

cognitive deficit or behavioural symptoms announces a future onset of dementia in the six following years of evolution, mostly with a frontal phenotype (75%) [23].

The second evolution observed in our study is AD with 13,8%. These results are in agreement with the fact of due to similar neuropathology and the clinical phenotype presented after the aphasic state, the logopenic subtype of PPA is considered as an atypical form of AD [24].

Other evolutive profile are also reported in our study like Lewy body dementia (0.5%), corticobasal degeneration (CBD) (0.5%) and Progressive supranuclear palsy (0.5%) in agreement with literature [25,26].

Indeed, some authors consider PPA-plus syndromes when aphasia is still not the only major deficit. They report that disinhibition by familiarity, blunted judgment, and difficulty in problem solving result in a personality change. Personality change and asymmetric extrapyramidal deficit occur frequently considering the PPA anatomical dysfunction evolution, which is supposed to be close to behavioural variant of FTD or CBD [27].

Also, initial language deficits are reported in one third of corticobasal dementia.

However, in our study some results are surprising, as the percentage of evolution in subjective complaint which is not a mode of evolution of PPAs and can bring into question on a possible diagnostic error at the beginning.

Our secondary objectives were to determine if diagnosis of PPA is more difficult to establish and more delayed than AD and what are the related prescribed treatment over seven years of follow-up.

For patients diagnosed of PPA at the end of the follow-up, the first diagnosis was 12,7 % Alzheimer's dementia, 7.1% subjective memory complaint, 4.4% non-amnesic mild cognitive impairment. Subjective memory complaint in the cohort is corresponding to the first consultation of the patient that could, at this time, stay at a subjective cognitive impairment report. We know that PPA patients can complain of memory loss and may perform poorly in standard tests of memory [28]. However, percentage of patients initially diagnosed with AD or with a pending diagnosis (49,6%) seem support the hypothesis that diagnosis of PPA is more difficult and more delayed than AD.

Other results seem to support this hypothesis, like:

- the delay between the first consultation for cognitive troubles and the first diagnosis that is significantly longer than in AD group.

- the number of different diagnoses before the diagnosis of interest that is significantly higher in PPA group than in AD group.

-the percentage of patients with more than one diagnosis that was higher in PPA group than in AD group.

To summarize, despite the evolution of the diagnostic criteria of Primary Progressive Aphasia over time [14,15], their diagnostic still does not seem optimal.

Our study shows also that PPA diagnosis is particularly important because modifies pharmacological and nonpharmacological interventions.

Indeed, the number of patients under pharmacological treatment increases of more than 50% after the diagnosis of PPA. Also, non-pharmacological treatments increase after the diagnosis and especially speech therapy (22.7% before and 66.0% after).

In the field of pharmacological interventions, to date, no medications have been shown to improve or stabilize cognitive deficits in patients with PPA[29]. Indeed, clinical trials on patients with FTD and controlled trials on PPA patients with bromocriptine [30] and memantine [31] have not demonstrated any efficiency. Studies on limited patient samples with, galantamine, rivastigmine, and selegiline have shown no results [32]. Also, although some patients with PPA, particularly with a logopenic subtype, may suffer from atypical AD, cholinesterase inhibitors have shown no results. No effect is expected as cholinergic deficit has been specifically identified in AD's physiopathology. Worsening of behavioural variant of FTD is also suspected under anticholinergic treatment. So on, actual recommendation is not favourable for anticholinesterase inhibitors use in FTD [33].

However, benefits have been found on behaviour but not on cognition with the cholinesterase inhibitor rivastigmine and the MAO-B inhibitor selegiline [34].

The use of antidepressants, such as trazadone, is known to be effective on the behavioural symptoms but has no impact on cognition is reported in FTD [35]. Antipsychotics with careful and limited use could improve behavioural symptoms but their side effect on wake and cognition limits their use. It's suspected that high-frequency repetitive transcranial magnetic stimulation (hf-rTMS) applied to the left prefrontal cortex produces improvement on language test that seems to last, other magnetic stimulations are suspected to maintain some language capacities [36].

In summary, although no drugs have shown an effectiveness on PPA. But, on behavioural disorders, some drugs have been deleterious, and others had positive effects. It thus appears essential to establish a diagnosis of PPA to set up an adapted medical treatment.

A key intervention on the PPA population is speech and language therapy (SLT): a specific form of cognitive intervention that evaluates communication skills and designs a personalized

intervention plan to improve communication abilities. This type of intervention has been shown to be effective and advised to be implemented in a more systematic way [37].

Also, in addition to the take care of language disorders, speech therapy is particularly important for swallowing disorders, which represent vital risks. Indeed, all variants showed swallowing difficulties and they were more frequent in PPA-S [38].

Finally, the put of diagnosis is essential whether it is for more adapted pharmacological or non-pharmacological interventions.

Logopenic variant of PPA (lv-PPA) is a neurodegenerative syndrome frequently associated with biomarkers of AD. Lv-PPA patients display characteristic linguistic deficits, a pattern of brain atrophy, and possibly genetic susceptibility, which warrant considering this variant as a discrete AD endophenotype [39]. Also, recent diagnostic criteria include lvPPA as an atypical early onset variant of AD because sporadic lvPPA clinical syndrome is both associated with AD biomarkers and AD pathological changes in about 85–90% of cases [8,40–42]. For these reasons, patients with PPAs are often included in studies on AD.

However, it has been shown that the classification of lvPPA does not successfully differentiate PPA due to AD from PPA due to other pathologies [43]. Furthermore, several underlying neurodegenerative etiologies have been reported in a few lvPPA cases, that can be linked to Lewy body disorder [44] and coexisting disorders or to biomarkers discordant with the clinical syndrome, especially in older individuals [42,45].

Understanding in-vivo pathological prediction is crucial in neurodegenerative diseases because therapeutic pharmacological strategies are, or soon will be, directed towards decreasing or clearing toxic molecules, such as amyloid, tau or TDP. This study highlights importance to improve early diagnosis of PPA to better understanding links with AD.

Finally, studies have demonstrated that toxic proteins including amyloid, tau, and TDP43 spread transneuronally through connected networks in a prion-like manner [46,47]. In PPA neuroimaging support these findings by showing network-specific damage. The studies comparing PPAs and ADs seem even more of interest because they permit to investigate the intricate relationship between protein deposition patterns and network susceptibility in neurodegenerative diseases. In summary, the comparison of clinical characteristics between PPA and AD patients could provide a better understanding of the reasons for network susceptibility generating clinical disorders increased on the language or memory.

Limitations of the present study

Despite BNA represents a valuable epidemiologic tool because it grants access to many patients with dementia and permits follow-up studies, several limitations should be noted.

First, data are entered into the BNA by different physicians and even though they all follow standard criteria for diagnosis, there is no external validation that those criteria were met. Also, criteria for diagnosis of PPA have been modified since 2010. Second, even though the BNA includes the great majority of individuals with PPA and associated disorders who are referred to specialized centres (French memory units), individuals included in the BNA are not fully representative of the total French population with PPA. Indeed, one part of the population with PPA is under general practitioner (GP) supervision only (GPs do not currently have access to the BNA), and another part of the population is referred to specialists (geriatricians, neurologists, psychiatrists) who are not using the BNA database. Finally, the data reported in the BNA do not include the information on the PPA variants, and thus do not allow to perform separate analyses for different patients' groups.

Conclusion

This study provided data on the clinical characteristics and the evolution of PPAs over a very large cohort.

It has also highlighted:

1. the current difficulty of making a diagnosis of PPA because of the varied symptomatology of the three variants and the underlying pathology (FTD or AD).
2. the use of poorly adapted diagnostic and severity assessment tools due to verbal instructions and proposed language tasks.
3. the importance of early diagnosis between PPA and AD due to differences in therapeutic approaches.

The perspectives of this study are to develop tools of diagnosis and severity assessment more adapted by including early markers of the pathology (graphic markers and vocal markers).

Authors' contributions: AM, AP, VM and AG contributed to the study concept and design, were involved in data synthesis and data interpretation and drafted the work. RF performed the statistical analysis. JM and MT contributed to draft the work. PHR and AM was involved in the supervision and quality control of the BNA database. All authors revised the final manuscript and approved it.

Funding: The French National Alzheimer Database (Banque Nationale Alzheimer) is funded by the French Ministry of Health.

Availability of data and materials: The data reported are part of an ongoing registration program. Deidentified participant data are not available for legal and ethical reasons. Anonymized data will be made available for research purposes, upon request and specific approval of the database advisory board and ethical committee.

Declarations, Ethics approval and consent to participate: The study was declared to the National Commission for Information Technology and Civil Liberties (CNIL) the number R04-051. All clinical work was conducted in compliance with current Good Clinical Practices as referenced in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines, local regulatory requirements and the principles of the Declaration of Helsinki. All patients enrolled in the study provided information before their participation. All clinical sites were required to sign a study-specific site blinding plan. This study is registered on ClinicalTrials.gov (NCT03687112).

Consent for publication: Not applicable.

Competing interests: The authors declare that they have no competing interests.

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Supporting Information

Additional files: Table S1. Comparison of descriptive characteristics of the AD vs PPA groups (Bayesian analyses). Table S2. Number of different diagnoses before and after first consultation.

Additional Table 1: Comparison of descriptive characteristics of the AD vs PPA groups (Bayesian analyses).

	AD vs PPA
Probability to get a difference of 5%	
Sexe	1
Community-living	1
Location of the patient	1
Center: Memory clinic vs Regional specialized memory clinic/Private practice neurologist	1
Center: Regional specialized memory clinic vs Memory clinic/Private practice neurologist	1
Center: Private practice neurologist vs Regional specialized memory clinic/Memory clinic	<0,001
Initially referred by: General practitioner vs all others	1
Initially referred by: Neurologist vs all others	1
Initially referred by: Other specialists vs all others	<0,001
Initially referred by: Direct vs all others	<0,001
Education: No education vs all others	<0,001
Education: Primary vs all others	1
Education: Secondary first cycle vs all others	0,039
Education: Secondary second cycle vs all others	0,999
Education: Superior vs all others	1
Probability to get a difference of	
2 years for the age	1
2 points for MMSE	<0,001
1 points for MMSE	1

Abbreviations: AD=Alzheimer's Disease, PPA=Primary Progressive Aphasia, MMSE=Mini Mental State Examination.

The probability corresponds to the numbers of iterations where the difference of 5% for qualitative variables and 2 points for quantitative variables were observed among all completed iterations. A probability = 1 means all iterations show the difference whereas a probability = 0 means no iteration shows the difference

Additional Table 2: Number of different diagnoses before and after first consultation.

	PPA (n=5,186)		AD (n=162,005)		p-value
	Mean	[SD]	Mean	[SD]	
	Period between first consultation and first diagnosis (years)	0.7	[1.4]	0.6	
	n	(%)	n	(%)	p-value
Number of different diagnoses BEFORE first consultation with diagnosis of interest					<.001
0	2,892	(55.8)	98,775	(61.0)	
1	1,890	(36.4)	54,709	(33.8)	
2	338	(6.5)	7,536	(4.7)	
3	54	(1.0)	880	(0.5)	
4	10	(0.2)	95	(0.1)	
5	2	(0.0)	10	(0.0)	
Number of different diagnoses AFTER first consultation with the diagnosis of interest					<.001
0	3,971	(76.6)	147,235	(90.9)	
1	992	(19.1)	13,234	(8.2)	
2	186	(3.6)	1,344	(0.8)	
3	33	(0.6)	164	(0.1)	
4	2	(0.0)	27	(0.0)	
5	2	(0.0)	1	(0.0)	

Chapter 2

THE USE OF MOTOR MARKERS: GRAPHICAL AND GESTURAL MARKERS

The use of graphical parameters in neurodegenerative pathologies diagnosis has been described as of interest in many studies. Graphical parameters may improve the interpretation and comprehension not only of a disease's consequences such as Alzheimer's Disease (AD), Parkinson's Disease (PD), Posterior Cortical Atrophy (ACP) or Primary Progressive Aphasia and its variants, but also to better understand its effects. Indeed, in neurodegenerative disease, a deterioration of the peripheral nervous system was detected, inducing direct damage in handwriting [1,2].

Handwriting or drawing involve brain areas bringing together cognitive, kinesthetic and perceptual-motor abilities [3], which impairment can cause fine motor changes. The use of new technologies allows us to use more specific parameters such as writing pressure, velocity, jerk (accelerations in writing), and stroke (pen-up time). It has been demonstrated that writing velocity for example is mostly affected in AD [4], but also jerk and stroke because of irregular movements due to a motricity lack [5,6]. Moreover, it has been demonstrated that, in the context of PD, the graphical parameters extracted within the use of touchpad, can be a great marker for quantifying a drug treatment effect [7,8]. Studies on the use of motor markers in PPA remain rare, even though an early language impairment can have consequences on motor activity [9].

In the purpose of the study presented in Chapter 2, patients were included in the context of a protocol created by the CoBTeK Laboratory of Nice, approved by CPP Ile de France X (N IDRCB: 2019-A00342-55 accepted on 11 September 2019). Before starting the studies presented in this Chapter, we added new graphical tasks in an already existing SLT assessment tool [10]. We conducted preliminary studies on small patients sample to verify if graphic parameters could be of interest in PPA diagnosis, regarding the increasing interest of the use of new technologies in neurodegenerative pathologies assessments [11]. After collecting graphical parameters on an touchpad, we showed that there are differences in writing pressure between a task involving language and another that doesn't in PPA patients, and that the affected tasks weren't the same whether it was for PPA patients or elderly patients [12,13]. These preliminary studies reinforced our hypothesis of affected motor markers in PPA. We thus wanted to go further in our researches, by analyzing other graphical parameters collected (pressure, velocity, stroke and jerk) not only in PPA but in other rare pathologies that are seen in Memory Centers as PCA and verified if adding a video analyses of the writing gesture could bring more specificity to PPA differential diagnosis.

These studies have been led throughout the thesis project.

They are the result of a constant reflection on the possibility of improving the analyses of motor markers, going from one writing pressure parameter to three other parameters which turned out to be of interest in PPA early but also differential diagnosis. The question of adding gestural marker was also highlighted after the increase of the need to improve telemedicine, an essential tool especially after Covid-19 pandemic. Most patients and control inclusions were conducted throughout this thesis work.

In the framework of these studies:

A Fonds France-Canada pour la Recherche (FFCR) grant was won during the thesis project. A one-semester mobility in the Laval University Faculty of Medicine of Quebec, Canada was made. It allowed us to open-up research perspectives and add our research on graphical markers into a French-Canadian research project.

I co-directed two graduation SLT thesis.

I also presented preliminary studies led in this chapter during two editions of the American Alzheimer's International Conference, leading to two published conference papers:

- Plonka, A., Macoir, J., Robert, P., Manera, V., & Gros, A. (2021). Use of graphical markers for the differential diagnosis of primary progressive aphasia subtypes. *Alzheimer's & Dementia*, 17(S4). <https://doi.org/10.1002/alz.053609>
- Gros, A., Plonka, A., Manera, V. (2019). Graphic markers: towards an early diagnosis of primary progressive aphasia. *Alzheimer's & Dementia*, 15(7), P351 P352. <https://doi.org/10.1016/j.jalz.2019.06.840>

Different studies of this chapter were exposed during two international conferences led in Quebec, Canada:

- Gros A., Plonka A., Conférences-midi du programme d'orthophonie, Apport des marqueurs moteurs et sensoriels dans le diagnostic précoce de la maladie d'Alzheimer et des aphasies primaires progressives, 29 novembre 2021, Université Laval, Québec.

- Plonka A., Rencontre scientifique des étudiant.e.s de l'Université Laval en recherche en langage et parole, « Diagnostic des Aphasies Primaires Progressives : utilisation des marqueurs graphiques », 10 novembre 2021, Université Laval, Québec.

And in national conferences listed below:

- Plonka, A., « Diagnostic des Aphasies Primaires Progressives : de nouveaux marqueurs d'intérêt », Conférence en Ligne d'Orthophonie et Recherche, 14 décembre 2022.
- Manera, V., Gros, A., Plonka, A., 14e Congrès Français de Psychiatrie : Session thématique « Rôle de l'analyse et de la perception du mouvement dans l'évaluation clinique ». 2 décembre 2022, Lille.
- Plonka, A. Journées de la Société Universitaire de Recherche en Orthophonie, « Les nouveaux marqueurs d'intérêt dans le diagnostic des Aphasies Primaires Progressives », 20 octobre 2022, Paris.
- Plonka, A., Soirée Recherche et Innovation en Santé, L'amélioration du diagnostic des Aphasies Primaires Progressives par le biais des marqueurs graphiques, en collaboration avec l'Université Laval de Québec », 18 octobre 2022, Nice.
- Gros, A., Pazart C., Plonka A., 12e Congrès Français de Psychiatrie, Journée Sciences Infirmières et Recherche Paramédicale : « Un mot sur le bout de la langue, quand cela devient une pathologie ». 23 novembre 2020.

Finally, I won the first prize of the 2021 "Three Minute Thesis competition" (Ma Thèse en 180s) conducted on the specific topic of the use of motor markers in PPA diagnosis.

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Publication 2

Primary Progressive Aphasia: Use of Graphical Markers for an Early and Differential Diagnosis



brain sciences

Article

Primary Progressive Aphasia: Use of Graphical Markers for an Early and Differential Diagnosis

Alexandra Plonka, Aurélie Mouton, Joël Macoir, Thi-Mai Tran, Alexandre Derremaux, Philippe Robert, Valeria Manera and Auriane Gros

Special Issue

Advances in Primary Progressive Aphasia

Edited by

Dr. Jordi A. Matias-Guiu, Dr. Robert Jr Laforce and Dr. Rene L. Utianski

Abstract

Primary progressive aphasia (PPA) brings together neurodegenerative pathologies whose main characteristic is to start with a progressive language disorder. PPA diagnosis is often delayed in non-specialised clinical settings. With the technologies' development, new writing parameters can be extracted, such as the writing pressure on a touch pad. Despite some studies having highlighted differences between patients with typical Alzheimer's disease (AD) and healthy controls, writing parameters in PPAs are understudied. The objective was to verify if the writing pressure in different linguistic and non-linguistic tasks can differentiate patients with PPA from patients with AD and healthy subjects. Patients with PPA (n = 32), patients with AD (n = 22) and healthy controls (n = 26) were included in this study. They performed a set of handwriting tasks on an iPad® digital tablet, including linguistic, cognitive non-linguistic, and non-cognitive non-linguistic tasks. Average and maximum writing pressures were extracted for each task. We found significant differences in writing pressure, between healthy controls and patients with PPA, and between patients with PPA and AD. However, the classification of performances was dependent on the nature of the tasks. These results suggest that measuring writing pressure in graphical tasks may improve the early diagnosis of PPA, and the differential diagnosis between PPA and AD.

Keywords: primary progressive aphasia; Alzheimer's disease; graphical markers; graphical parameters; writing pressure; differential diagnosis

Introduction

Primary progressive aphasia (PPA) assembles a heterogeneous syndromic group of neurodegenerative pathologies characterised by a foreground and initially isolated language impairment that can later extend to cognitive functions such as computation, praxis, memory or executive functions [1–3]. It is a focal form of atrophy with great neuropathological heterogeneity, ranging from tauopathy to amyloidopathy or TDP-43 inclusions [4]. The prevalence of this disease is estimated at 3 per 100,000 [4], with a starting age assessed between 50 and 65 years [5] and a life expectancy of 10 to 15 years [6].

Diagnosis and Classification

PPA is diagnosed when three criteria overlap: (1) language is mainly damaged; (2) daily living activities are impaired during the initial stages of illness; and (3) word production and comprehension are impaired due to a progressive aphasic disorder and there is an underlying neurodegenerative disease [7]. This last criterion is still debated, based on the fact that PPA evolution from isolated language alteration to global cognitive impairment with multiple neuropsychiatric symptoms can lead to a change in diagnosis [8]. Additionally, language impairment that commonly lasts for about 6 years can represent the only symptom for 10 to 14 years, and is quickly impaired all along the degenerative process before being added to psychiatric and neurologic symptoms [9,10].

In 2011, a broad-ranging International Consensus Group published recommendations for the diagnosis and classification of PPA, establishing three different subtypes of this disease depending of the affected brain regions and the type of aphasic disorder [7]: the logopenic subtype (lvPPA), the non-fluent/agrammatic subtype (nfavPPA) and the semantic subtype (svPPA). A fourth subtype came to complete this classification: a mixed form or non-classified form [11].

lvPPA is defined by impaired word retrieval and phonologic errors that alter language fluidity. Sentence and word repetition are difficult due to a phonological loop disorder that also affects the understanding of long sentences with illness evolution [7,12,13]. lvPPA is characterised by a left posterior parietal or Perisylvian hypometabolism and an atrophy in the left posterior parietal lobe [12,14,15]. Studies have shown that AD is the most common underlying pathology of lvPPA [16].

nfavPPA is characterised by the presence of agrammatism in speech production, with impairments in understanding syntactically complex sentences [3,17,18]. Language production is laborious due to apraxia of speech with phonetic errors, although word comprehension is preserved. nfavPPA is related to dysfunctions in the frontal lobe, in Broca's region, and the anterior parts of the insula [11,12,15,19]. Some studies have also exhibited parietal and temporal involvement [20]. Disorder of nfavPPA is most often frontotemporal lobar degeneration (FTLD) [16].

svPPA is characterised by the presence of a semantic language disorder with paraphasias in the expressive side and impairments in word comprehension in written or oral modalities, associated with a non-verbal semantic disorder [21,22]. svPPA's anatomical lesions are located in the anterior temporal cortex and the inferior and middle temporal cortex [12,23–25]. An infiltration of several connecting beams passing through the temporal lobe have also been

reported by fibre-tracking method (DTI) on a small sample (n = 5) [26]. As for nfvPPA, FTLD-type disorder changes are the most common in svPPA [16].

Mixed PPA is characterised by a combination of symptoms of the three main PPA variants with frequent impairment of word comprehension, apraxia of speech or agrammatism [27].

Early Diagnosis

Early diagnosis of PPA is important in clinical practice because its phenotype is complex, constantly evolving, and is crucial because it increases the possibilities of appropriate clinical interventions. In addition, diagnosis is complex: it has been shown that there is a delay of approximately 4 years between the onset of troubles and PPA diagnosis [6,28,29]. Moreover, the three PPA variants differ in terms of progression over time. lvPPA seems to follow the pattern of Alzheimer's disease (AD) [30], which evolves to a generalised cognitive impairment, whereas other PPA types can be related to different diseases such as behavioural variants of FTLD, corticobasal degeneration or progressive supranuclear palsy [31].

Thus far, there has been no pharmacological treatment modifying or delaying PPA, but non-pharmacological interventions, such as speech therapy, have proven to be useful in compensating for and maintaining functional communications [32]. Early diagnosis is thus crucial to implement early and adapted interventions. Most of the scales available so far for PPA diagnosis are based on language production and comprehension in oral and written modalities. The main parameters assessed are performance (correct responses and mistakes) and response times. Writing disorders are also considered, such as dysorthography and, more specifically, spelling impairment [33,34], but no study has used graphical parameters such as writing pressure so far.

The use of new technologies allows more ecological and reproducible tests in comparison to certain scales or paper–pencil tests [35,36]. Computerised assessment batteries can build upon standardised and validated pencil-and-paper tests [37].

Contribution of Graphical Markers

With language symptoms being the earliest and most prominent signs in the early stages of the disease, graphical writing markers may constitute ecological markers of great interest for the early diagnosis of PPA [38].

Several studies have shown that graphic parameters are affected early in people with moderate to severe Alzheimer's disease [38]. Studies have also shown that motor activity reveals

language-related characteristics, due to the involvement of motor areas of the brain in writing, and that even mild disorders can be detected using motor parameters (reduction in written pressure) during language production tasks [39].

Handwriting requires the implementation of cognitive processes related to language as well as planning, coordination and motor execution. It has thus been shown that people with cognitive decline overall have a lower writing speed and pressure with a longer writing time, especially when analysing cursive loops [40]. Handwriting performance therefore exhibits significant changes, which it would be interesting to take into account within the framework of a classification of parameters characteristic of the neurodegenerative diseases such as AD, Parkinson's disease (PD) or PPAs [41].

The use of a digital tablet with a stylus makes it possible to objectify the kinematic parameters of writing (pressure, stroke, velocity, jerk, and writing task time); therefore, this would allow a low-cost dissemination of this technology, especially if included in existing screening batteries [42].

The aim of this study was to confirm the initial findings of Gros et al. on a larger sample of PPA [41], concerning the role of writing pressure in differentiating PPA and controls, and to verify if writing pressure is also relevant to distinguish patients with PPA and Alzheimer's disease.

Materials and Methods

Ethics

This study was approved by CPP Ile de France X (N° IDRCB: 2019-A00342-55 accepted on 11 September 2019). At the time of diagnosis, patients and relatives were informed of their inclusion in this study and could decline their participation or withdraw consent. Data were anonymised before the analyses.

Population

This was a prospective, multicentric study that included 5 French Neurology Departments (Nice, Angers, Nîmes, Saint-Brieuc, and La Rochelle). The patients were recruited from memory consultations in the various centres from June 2019 to February 2020. Eighty adults participated in this study, including patients with PPA (n = 32), patients with typical AD (n = 22) and healthy controls (HC) (n = 26) recruited in the memory centres. All the healthy controls were in good physical and mental health, reported no significant complaints related to

cognition, and performed within the normal range on standardised neuropsychological tests. Only two patients (1 PPA, 1 HC) were left-handed. The demographic and clinical features of the three groups of participants are summarised in Table 1.

Table 1: Demographic features of the groups of participants.

	lvPPA	nfavPPA	svPPA	AD	HC	<i>p</i> -value
N	20	6	6	22	26	
<i>Female, n (%)</i> *	8 (40%)	3 (50%)	3 (50%)	9 (40.9%)	18 (69%)	0.081
<i>Age range (y)</i>	55-85	58-85	70-75	57-87	48-80	
<i>Mean age</i> **	73.1	69.5	71.3	73.6	65.7	
<i>SD age</i> **	8.2	8.9	3.1	8.9	8.6	0.004
<i>Mean Education (y)</i> **	10.1	11.5	9.8	10.1	11.1	
<i>Education SD</i> **	3.8	3.7	5	4.8	5.4	0.738
<i>Mean MMSE score</i> **	23.6	20.5	20.7	21.5	28.5	
<i>MMSE SD</i> **	5.4	4.2	5	4.9	1.7	<0.001
<i>Mean DTLA score</i> ***	74.5	44.6	58.3	74.8	95.9	
<i>DTLA SD</i> ***	16.6	10.9	19.9	17.1	5.6	<0.001

* χ^2 ; ** ANOVA; *** *Kruskal–Wallis*, *p*-values refer to the overall comparisons between the three diagnostic groups (PPA, AD and HC).

To be included in the study, the patients had to: be aged 40 years or more, have been diagnosed with PPA or AD according to the DSM-5TM criteria [42], have consulted in one of the investigation centres for cognitive, behavioural and/or motor difficulties, be able to read, write and speak French, benefit from social security coverage, and have no objection for inclusion on the study after reading the information note. The exclusion criteria for the patients and the healthy controls were the presence of a protective measure (guardianship or curatorship), a history of cerebrovascular disease, a history of psychiatric disorder according to the DSM-IVTR criteria [43], any neurological condition (except PPA and AD), traumatic brain injury, untreated medical or metabolic condition (e.g., diabetes, hypothyroidism) uncorrected hearing and vision problems, or prescribed medication with central nervous system sides effects likely to interfere with the carrying out of the tests.

Clinical data were reported retrospectively by the investigators and included: the etiological diagnosis of PPA, PPA variant according to Gorno-Tempini et al. criteria [7], the etiological diagnosis of AD according to the DSM-5TM criteria [42], the results of the various paraclinical examinations (cerebral MRI, PET-Scan, DAT scan, lumbar puncture), the current treatments, including the use of anticholinesterases or Memantine, the global level of cognitive functioning

with the Mini Mental State Examination (MMSE), and the status of memory and language capabilities as well as their severity level.

Procedure

During the first visit, patients received explanations about the study and were given an information sheet. The investigator checked the inclusion criteria and signed a no-objection form. Various elements of the anamnesis were collected: age, gender, level of education, laterality, duration of the disease and familiarity or not with the touchpad devices.

When a patient was included in the study, the practitioner administered the Detection Test of Language impairments in Adult (DTLA) and the tasks of graphic markers on an iPad[®] tablet [43]. The DTLA test was chosen because of its accuracy for language disorders associated with neurodegenerative diseases. It is a standardised, rapid test, scored on 100 points, validated, and standardised in four French-speaking countries, as well as standardised according to 2 age groups and 2 levels of study. The DTLA test is composed of 9 subtests exploring the language functions most affected in neurodegenerative diseases, and its validation study showed that it has a good convergent validity, a good discriminant validity with healthy controls and a good test–retest fidelity.

Material and Variables

Graphical markers were collected on the written tasks of the DTLA with an Apple iPad[®] 2018 touchpad (model MR7F2NF/A) and an Apple Pencil[®] stylus model A1603. The stylus sample rate was 60 Hz, the screen accuracy was 1 pixel, and its resolution was 2048 × 1536. The application retrieved the position and tap pressure provided by the Apple stylus through the Safari browser. Pressure was measured as a percentage of the maximum pressure allowed by the stylus. These values were measured during plots and updated every 17 ms.

The following ten written tasks were analysed: four linguistic tasks, consisting of writing words to dictation, writing nonsense words to dictation, writing a spontaneous sentence, all part of the DTLA, and writing letter ‘l’ loops. Four cognitive non-linguistic tasks, consisting of writing vertical and horizontal lines, diagonals, and a spiral, and two non-cognitive non-linguistic tasks, consisting of writing dots and filling loops were performed. For the cognitive non-linguistic tasks of writing diagonals, the participants had 30 s to go back and forth as fast as possible between two squares presented on the screen. For the non-cognitive non-linguistic tasks, they had to fill the screen with dots and loops (Figure 1). For each task, we extracted the average

(avgP) and the maximum (maxP) writing pressure, representing the pressure of the stylus on the screen (ranging from 0 to 1).

Linguistic Tasks	Cognitive-Non-Linguistic Tasks	Non-Cognitive-Non-Linguistic Tasks

Figure 1: Graphical marker tasks. Linguistic tasks: words, nonsense words, sentence, letter 'l' loops. Cognitive non-linguistic tasks: vertical and horizontal lines, spiral, diagonals. Non-cognitive non-linguistic tasks: dots, filling loops. Writing pressure was collected on an iPad® tablet. Red colour indicates the maximum pressure.

Statistical Analyses

Descriptive statistics were used to present demographic and clinical characteristics. Qualitative variables (sex) were presented using the frequency and percentage, and quantitative variables (age, years of education, MMSE score, and DTLA score) were presented using the mean and standard deviation (SD). The effects of the diagnostic group (PPA, AD and healthy controls) on quantitative demographic variables were tested using one-way ANOVAs for normally distributed variables (followed by LSD-corrected post hoc tests) and Kruskal–Wallis for non-normally distributed variables (followed by Bonferroni-corrected post hoc tests). The diagnostic groups differed in terms of mean age; therefore, we performed ANCOVAs on the average and maximum writing pressure using the diagnostic group (PPA, AD and healthy

controls) as between-subject factor, and the age as a covariate (followed by LSD-corrected post hoc tests).

Qualitative variables (such as sex) were compared using the χ^2 test. All statistical analyses were performed using IBM SPSS Statistics V20.0 software.

Results

Demographic and Clinical Information

Characteristics and clinical information of each group are reported in Table 1. No significant differences in gender ($\chi^2(2) = 5.03, p = 0.081$) and the number of years of education ($F(2,77) = 0.31, p = 0.738$) were found across the three groups. Age varied significantly across the groups ($F(2,77) = 6.34, p = 0.003$). Specifically, post hoc LSD tests showed that participants in the control group were significantly younger than participants with PPA ($p = 0.005$) and AD ($p = 0.002$), whereas no difference between PPA and AD groups was found ($p = 0.521$). As expected, MMSE scores varied significantly across groups ($F(2,51) = 8.66, p = 0.001$), with participants in the control group showing significantly higher MMSE scores than participants in the PPA ($p = 0.001$) and the AD ($p < 0.001$) groups. No difference between PPA and AD groups was found ($p = 0.493$). A significant difference in the results of the DTLA scale was found ($H(2) = 46.20, p < 0.001$). Bonferroni-corrected post hoc tests revealed that participants in the control group had significantly higher DTLA scores than participants in the PPA ($p < 0.001$) and the AD ($p < 0.001$) groups. The difference between PPA and AD groups did not reach statistical significance ($p = 0.838$).

Graphical Markers

Average Pressure (avgP)

Descriptive analyses (mean and standard deviation) for the average pressure in each task and for differences between linguistic and non-linguistic tasks are reported in Table 2. The ANCOVA with Group as the between-subject factor and Age as a covariate revealed a significant effect of Group on avgP in the horizontal lines (cognitive non-linguistic) task ($F(2,41) = 3.26, p = 0.049$). Specifically, paired post hoc comparisons (LSD-corrected) revealed that avgP was significantly higher in AD compared to controls ($p = 0.035$), and almost significantly higher in AD compared to PPA ($p = 0.057$). No significant effect of Group was found for the other tasks.

Concerning the differences between linguistic and non-linguistic tasks, a significant effect of Group was found on the difference between words and horizontal lines ($F(2,40) = 3.94, p = 0.027$); specifically, subjects with AD showed a higher avgP in the horizontal lines compared to the words task, whereas the opposite was true for controls ($p = 0.016$) and PPA subjects ($p = 0.049$). The same pattern was also found for the difference between non-words and horizontal lines ($F(2,40) = 4.24, p = 0.021$)—subjects with AD showed a higher avgP in the horizontal lines compared to the non-words task, whereas the opposite was true for controls ($p = 0.016$) and PPA subjects ($p = 0.031$)—and for the difference between horizontal lines and sentence tasks ($F(2,40) = 3.99, p = 0.026$), with subjects with AD showing a higher avgP in the horizontal lines compared to the sentence task, whereas the opposite was true for controls ($p = 0.032$) and PPA subjects ($p = 0.021$). Finally, a significant effect of Group was found on the difference between letter ‘l’ loops (linguistic) task and (cognitive non-linguistic) diagonals task ($F(2,74) = 3.38, p = 0.039$), with subjects with PPA showing a higher avgP in the diagonals compared to the cursive loops task, whereas the opposite was true for controls ($p = 0.026$) and AD subjects ($p = 0.046$). No other significant difference was found.

Table 2: Average writing pressure in participants with PPA, AD and Healthy Controls.

	Task	Diagnosis	Mean	Standard Deviation
Linguistic Tasks	Words	PPA	0.20	0.09
		AD	0.22	0.13
		Controls	0.20	0.08
	Nonsense words	PPA	0.22	0.10
		AD	0.23	0.14
		Controls	0.21	0.09
	Sentence	PPA	0.23	0.11
		AD	0.26	0.13
		Controls	0.22	0.09
Letter ‘l’ loops	PPA	0.25	0.12	
	AD	0.28	0.15	
	Controls	0.26	0.10	
Cognitive Non-Linguistic Tasks	Diagonal	PPA	0.28	0.14
		AD	0.26	0.13
		Controls	0.24	0.10
	Vertical	PPA	0.28	0.08
		AD	0.30	0.15
		Controls	0.22	0.12
	Horizontal	PPA	0.21	0.55
		AD	0.31	0.21
		Controls	0.18	0.08
	Spiral	PPA	0.25	0.12
		AD	0.26	0.11
		Controls	0.25	0.09

Non-Cognitive Non-Linguistic Tasks	Dots	PPA	0.17	0.07
		AD	0.19	0.09
		Controls	0.13	0.04
	Filling Loops	PPA	0.28	0.11
		AD	0.31	0.15
		Controls	0.27	0.09

Maximum Pressure (maxP)

Descriptive analyses (mean and standard deviation) for the average pressure in each task and for differences between linguistic and non-linguistic tasks are reported in Table 3.

The ANCOVA with Group as a between-subject factor and Age as a covariate revealed a significant effect of Group on maxP for the sentences (linguistic) task ($F(2,74) = 3.65, p = 0.031$), with AD subjects showing a significantly higher maxP compared to the controls ($p = 0.009$). A significant effect of Group was also found for the horizontal lines (cognitive non-linguistic) task ($F(2,41) = 3.24, p = 0,049$)—AD subjects showed a significantly higher maxP compared to the controls ($p = 0.021$)—and for the dots (non-cognitive non-linguistic) task ($F(2,74) = 4.12, p = 0,020$), with subjects with PPA ($p = 0.007$) and AD ($p = 0.032$) showing a higher maxP compared to the controls. No significant effect of Group was found for the other tasks.

Concerning the differences between linguistic and non-linguistic tasks, a significant effect of group was found on the difference between letter ‘l’ loops and dots ($F(2,75) = 5.27, p = 0.007$). Specifically, all subjects showed a higher maxP in the dots compared to the cursive loops task, but the difference was higher for PPA ($p = 0.002$) and AD subjects ($p = 0.027$) compared to the controls. Furthermore, an almost-significant effect of Group was found on the difference between letter ‘l’ loops and horizontal lines ($F(2,42) = 3.03, p = 0.059$) with controls showing a higher maxP in the letter ‘l’ loops vs. the horizontal lines task, whereas the opposite was true for subjects with AD ($p = 0.028$). No other significant difference was found.

Table 3: Maximum writing pressure in participants with PPA, AD and Healthy Controls.

	Task	Diagnosis	Mean	Standard Deviation
Linguistic Tasks	Words	PPA	0.61	0.30
		AD	0.66	0.26
		Controls	0.55	0.23
	Nonsense Words	PPA	0.58	0.30
		AD	0.61	0.30
		Controls	0.54	0.22
	Sentence	PPA	0.65	0.33
		AD	0.78	0.27
		Controls	0.53	0.25
	Letter 'l' loops	PPA	0.45	0.23
		AD	0.48	0.22
		Controls	0.44	0.23
Cognitive Non-Linguistic Tasks	Diagonal	PPA	0.54	0.27
		AD	0.49	0.25
		Controls	0.42	0.21
	Vertical	PPA	0.55	0.19
		AD	0.57	0.23
		Controls	0.43	0.21
	Horizontal	PPA	0.45	0.21
		AD	0.58	0.30
		Controls	0.32	0.16
	Spiral	PPA	0.44	0.26
		AD	0.47	0.21
		Controls	0.40	0.19
Non-Cognitive Non-Linguistic Tasks	Dots	PPA	0.73	0.27
		AD	0.71	0.25
		Controls	0.53	0.24
	Filling Loops	PPA	0.52	0.20
		AD	0.54	0.22
		Controls	0.51	0.20

Summary of the Main Differences between PPA and Healthy Controls

Considering post hoc corrected comparisons, the most relevant tasks to distinguish PPA patients from healthy controls seemed to be the dots (non-cognitive non-linguistic) task and the letter 'l' loops (linguistic) task. Specifically, the maxP ($p = 0,007$) in the dots task was higher in PPA compared to healthy controls. Furthermore, the difference in maxP in the dots compared to the letter 'l' loops task was higher for PPA than for controls ($p = 0.002$). Finally, subjects with PPA had a higher avgP in the diagonals compared to the letter 'l' loops task, whereas the opposite was true for controls ($p = 0.026$) (Figure 2).

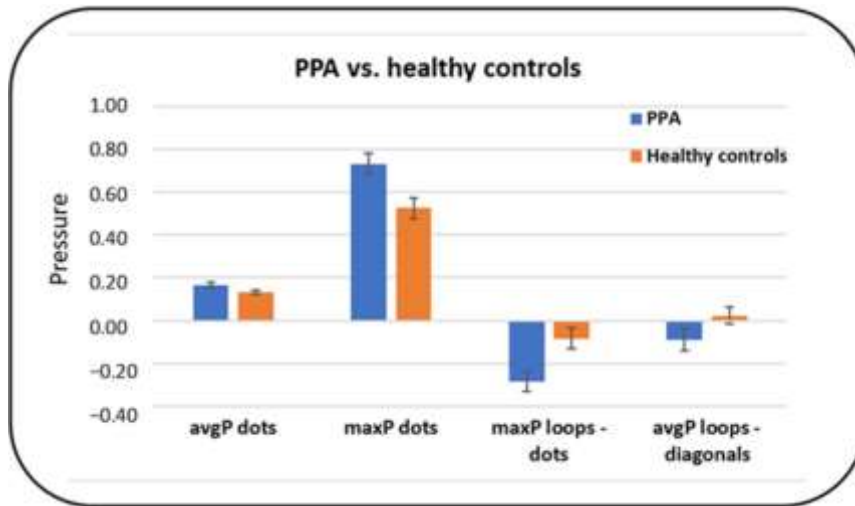


Figure 2: Differences in average and maximum writing pressure between patients with PPA and healthy controls.

Summary of the Main Differences between PPA and AD

Considering post hoc corrected comparisons, the most relevant feature distinguishing between PPA and AD patients was the avgP, whereas no significant differences were found for the maxP. In terms of tasks, the most relevant seemed to be the horizontal lines and diagonal lines (cognitive non-linguistic) tasks and the linguistic tasks. Indeed, differences in avgP were found for the horizontal lines task (AD>PPA, $p = 0.057$) and for the difference between horizontal lines and three linguistic tasks (words, non-words and sentence, $p = 0.049$, 0.031 and 0.021 , respectively). Specifically, avgP in AD was higher in the cognitive non-linguistic tasks compared to the linguistic tasks, whereas avgP in PPA was higher in the linguistic tasks compared to the cognitive non-linguistic task. Finally, subjects with PPA showed a higher avgP in the diagonals task compared to the letter 'l' loops (linguistic) task, whereas the opposite was true for AD subjects ($p = 0,046$) (Figure 3).

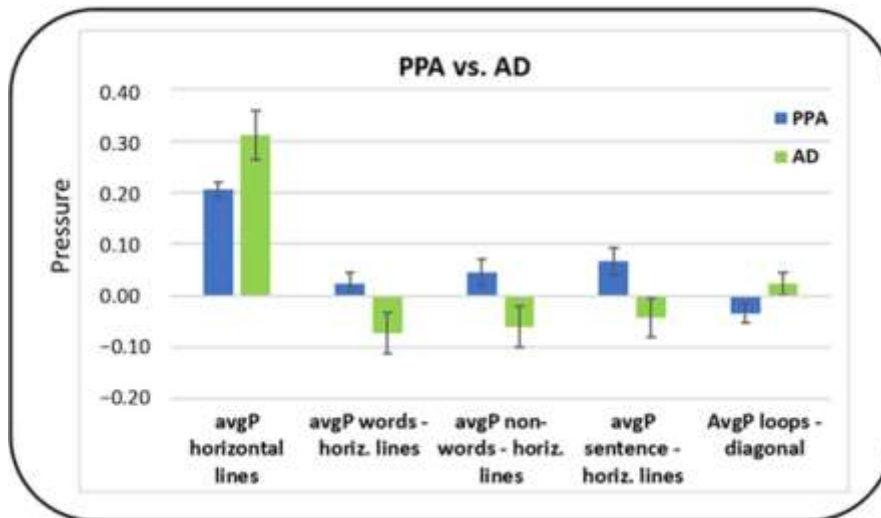


Figure 3: Differences in average and maximum writing pressure between patients with PPA and patients with AD.

Discussion and Conclusion

In the present study, we investigated the usefulness of graphical parameters collected in a handwriting protocol to differentiate patients with PPA from healthy controls, and patients with PPA from patients with AD. Significant differences in the average pressure and maximum pressure between PPA participants and healthy controls were found in the non-linguistic non-cognitive ‘dots’ task, and in the pressure difference between linguistic and non-linguistic ‘letter l loops’ and ‘dots’ tasks. These results show that PPA patients have a higher difference in the maximum pressure between a linguistic (‘letter l loops’) and a non-linguistic non-cognitive task (‘dots’) than healthy controls. A previous study already showed that motor activity reveals language-related characteristics, due to the involvement of motor areas of the brain in writing [39]. This suggests that motor performance involved in linguistic and non-linguistic tasks may change in the presence of language disorders.

Other studies have shown an overall lower writing pressure in people with cognitive decline associated with AD compared to healthy people [40], with a lower pressure in most cognitively deteriorated groups [44]. Our results suggest the opposite with PPA patients in whom writing maximum pressure was significantly higher compared to healthy controls in the non-cognitive ‘dots’ task. Two major processes enter in handwriting: language processes and motor processes. Thus, writing could experience variations in different tasks depending on which process is reached [45].

Differences in pressure between a non-linguistic task and a linguistic task may suggest a decrease in the activity of the motor cortex during the graphic act, associated with a linguistic task for PPA patients (with a smaller difference between both). These results may be explained by the need for recruiting more cognitive resources during a linguistic task than during a non-linguistic task for PPA participants. Indeed, non-linguistic areas of the brain are usually more preserved in PPA than linguistic areas. This interpretation must be confirmed by an EEG exploration during writing in linguistic and non-linguistic tasks. These results are in line with other studies that show a relationship between language and gesture processing and the partial overlap of their neural representations. Indeed, a study demonstrated that PPA patients showed significant deficits on gesture discrimination tasks clustered with linguistic tasks as word and nonsense-word repetition, and writing-to-dictation [46].

The last aim of this study was to verify if graphical parameters could differentiate participants with PPA from participants with AD. Several studies have analyzed graphical markers in patients with AD, but none in PPAs. Indeed, studies on PPAs focused only on the content of language in writing, and not on the graphic parameters. Thus, studies have shown letter insertion errors in patients with PPA, whereas they were absent in AD and mild cognitive impairment (MCI) patients, and that patients with PPA use more verbs than patients with AD [47].

Although the symptoms of AD are more cognitive than motor, it has been shown that motor dysfunction quantified by kinematic handwriting analysis is significantly correlated with MMSE scores in AD [48], and that pressure is lower in more cognitively deteriorated groups [44]. Graphic parameters and variability in the performance of patients with AD have been explained by a degradation of the motor programming, resembling that of Huntington's rather than Parkinson's disease patients, and may reflect frontal rather than basal ganglia dysfunction [49]. Finally, these studies suggest that MCI is also characterized by motor dysfunction and that writing with accuracy constraints may help identify those at risk of AD [50]. According to these studies, these deficits in graphical parameters seem to be more related to a motor dysfunction than a language impairment. Indeed, it has already been shown that in the mild phase of AD, lexico-semantic problems in the speaking process are possible but not predominant [51]. Thus, graphical markers in patients with AD seem more related to a deterioration in fine motor control and coordination [52,53].

Indeed, graphical markers seem to reflect the type of specific disorders in different pathologies and permit better comprehension of the nature of these deficits. In the same way, we have recently demonstrated a reduction in pressure, particularly in graphical activities, which have a

spatial component in posterior cortical atrophy [54]. This result of a writing pressure change depending on the graphical task performed is in line with the results of a previous study on AD, and can be explained by the different type of impairment between these pathologies [55].

Inconsistently with the literature on writing in patients with AD, our results show a difference between patients with PPA and patients with AD, with a predominant impairment in linguistic tasks in AD. Indeed, significant differences between the two groups were found for the cognitive non-linguistic horizontal lines task and for the difference between horizontal lines and three linguistic tasks. The average pressure in AD was higher in the cognitive non-linguistic tasks compared to the linguistic tasks, whereas the average pressure in patients with PPA was higher in the linguistic tasks compared to the cognitive non-linguistic tasks.

Contrary to the literature, these results suggest that graphical markers are not only a sign of motor and coordination disorders, but also a sign of cognitive and, more specifically, language disorders. Indeed, our results may suggest that patients with AD, despite an overall cognitive impairment, have a higher cognitive load than patients with PPA in linguistic tasks. In the same way, patients with PPA seem to have a high cognitive load for linguistic tasks but also in cognitive tasks (dysexecutive impairment). These results are in line with other studies that show early dysexecutive symptoms in patients with PPA [56] and a severe language impairment in patients with AD [57].

In conclusion, graphical markers may allow the performance of an early and differential diagnosis of patients with PPA and patients with AD. Writing pressure comparisons between linguistic and cognitive non-linguistic tasks reveal a difference in pressure between patients with PPA and healthy controls and patients with PPA and patients with AD. Indeed, in patients with AD, although the cognitive impairment is global, language impairment appears as an important diagnosis marker, such as in patients with PPA.

Other graphical kinematic parameters such as writing velocity could also be of interest for the classification of different subtypes of PPAs, because of the different anatomical pathways of degeneration. Thus, it has been shown that people with cognitive decline have a lower writing speed and pressure overall, with longer writing times [40]. However, to confirm these first results, a larger and more balanced PPA sample seems necessary.

Finally, this study highlights two main elements.

First, and on the scientific side, studying patients suffering from primary progressive aphasia, a clinical syndrome characterised by comparatively isolated language deficits, may provide

direct evidence for anatomical and functional association between language deficits and gesture graphic particularity.

Second, on the clinical side, this study has shown the benefits of associating graphical markers to a rapid screening battery such as DTLA for the earlier and differential diagnosis of PPAs.

Author Contributions: Conceptualization, A.G., V.M. and A.P.; methodology, A.G.; validation, A.G., J.M. and P.R.; formal analysis, V.M. and A.D.; investigation, A.P. and A.G.; resources, A.G. and A.P.; data curation, A.G.; writing—original draft preparation, A.P.; writing—review and editing, A.G., V.M., J.M., and T.-M.T.; supervision, P.R. and A.G.; project administration, A.G., P.R. and A.M.; funding acquisition, A.G. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of CPP Ile de France X (N IDRCB:2019-A00342-55 accepted on 11 September 2019). At the time of diagnosis, patients and relatives were informed of their inclusion in this study and could decline their participation or withdraw consent. Data were anonymized before the analyses.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data reported are part of an ongoing registration program. Deidentified participant data are not available for legal and ethical reasons. Anonymized data will be made available for research purposes, upon request and specific approval of the database advisory board and ethical committee.

Acknowledgments: This work was supported by University Côte d'Azur and NeuroMod Institute and by a grant from the Association Innovation Alzheimer. Thanks to all patients that participated in this study and to all participants.

Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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Supporting Information

Table SI: Average Writing Pressure in participants with PPA, AD and Healthy Controls.

	Task	Diagnosis	Mean	Standard Deviation
Linguistic Tasks	Words	PPA	0.20	0.09
		AD	0.22	0.13
		Controls	0.20	0.08
	Nonsense words	PPA	0.22	0.10
		AD	0.23	0.14
		Controls	0.21	0.09
	Sentence	PPA	0.23	0.11
		AD	0.26	0.13
		Controls	0.22	0.09
	Letter 'l' loops	PPA	0.25	0.12
		AD	0.28	0.15
		Controls	0.26	0.10
Cognitive Non-Linguistic Tasks	Diagonal	PPA	0.28	0.14
		AD	0.26	0.13
		Controls	0.24	0.10
	Vertical	PPA	0.28	0.08
		AD	0.30	0.15
		Controls	0.22	0.12
	Horizontal	PPA	0.21	0.55
		AD	0.31	0.21
		Controls	0.18	0.08
	Spiral	PPA	0.25	0.12
		AD	0.26	0.11
		Controls	0.25	0.09
Non-Cognitive-Non-Linguistic Tasks	Dots	PPA	0.17	0.07
		AD	0.19	0.09
		Controls	0.13	0.04
	Filling Loops	PPA	0.28	0.11
		AD	0.31	0.15
	Controls	0.27	0.09	

a: independent-sample T-test; b: Mann-Whitney test

Table S2: Maximum Writing Pressure in participants with PPA, AD and Healthy Controls.

	Task	Diagnosis	Mean	Standard Deviation
Linguistic Tasks	Words	PPA	0.61	0.30
		AD	0.66	0.26
		Controls	0.55	0.23
	Nonsense words	PPA	0.58	0.30
		AD	0.61	0.30
		Controls	0.54	0.22
	Sentence	PPA	0.65	0.33
		AD	0.78	0.27
		Controls	0.53	0.25
	Letter 'l' loops	PPA	0.45	0.23
		AD	0.48	0.22
		Controls	0.44	0.23
Cognitive-Non-Linguistic Tasks	Diagonal	PPA	0.54	0.27
		AD	0.49	0.25
		Controls	0.42	0.21
	Vertical	PPA	0.55	0.19
		AD	0.57	0.23
		Controls	0.43	0.21
	Horizontal	PPA	0.45	0.21
		AD	0.58	0.30
		Controls	0.32	0.16
	Spiral	PPA	0.44	0.26
		AD	0.47	0.21
		Controls	0.40	0.19
Non-Cognitive-Non-Linguistic Tasks	Dots	PPA	0.73	0.27
		AD	0.71	0.25
		Controls	0.53	0.24
	Filling Loops	PPA	0.52	0.20
		AD	0.54	0.22
		Controls	0.51	0.20

a: independent-sample T-test; b: Mann-Whitney test



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Case Report

Handwriting graphical parameters analysis in Posterior Cortical Atrophy: A case report



Alexandra Videt-Dussert^{a,*}, Alexandra Plonka^{a,b,c}, Alexandre Derreumaux^b, Valeria Manera^{a,b},
Elsa Leone^d, Auriane Gros^{a,b,d}

^a Université Côte d'Azur, Département d'Orthophonie de Nice, Nice, France

^b Université Côte d'Azur, Laboratoire CoBTeK, Nice, France

^c Université Côte d'Azur, Institut NeuroMod, Sophia Antipolis, France

^d Université Côte d'Azur, Centre Hospitalier Universitaire de Nice, Service Clinique Gériatrique du Cerveau et du Mouvement, Nice, France

Abstract

Posterior Cortical Atrophy (PCA) is a rare neurodegenerative syndrome characterized by an occipital atrophy resulting in a progressive impairment of upper visual functions. The inconsistency of terminology of this pathology makes its diagnosis difficult and delayed. We present a 76-year-old patient with PCA having difficulties in reading, writing, and daily manipulations. The objective was to evaluate the kinematic writing parameters. Linguistic, cognitive-non-linguistic and non-cognitive-non-linguistic graphical tasks were performed. The kinematic parameters extracted were jerk, velocity and pressure. We found a kinematic profile for all these parameters different from what observed in healthy controls and patients with Alzheimer's Disease. This study, through an analysis of writing features never studied before in PCA, shows the interest of handwriting kinematic analysis in the clinical diagnosis of PCA.

Keywords: Posterior Cortical Atrophy, Neurodegenerative disease, Handwriting, Graphic parameters, Kinematic features

Introduction

Posterior Cortical Atrophy (PCA) is a rare clinico-radiological syndrome characterized by progressive disorders of superior visual function. These disorders are caused by an atrophy of the posterior cortical regions, followed by a progressive dementia. PCA is described as an atypical Alzheimer's disease (AD) visual variant [1].

To overcome the inconsistency of terminology of PCA that makes its diagnosis difficult and delayed, an international consensus settled around the pathology [2]. PCA includes: impaired recognition, object manipulation, and spatial localization [2]. Due to the neurovisual impairments, PCA patients have reading and writing deficits [1]. Studies showed the interest of using graphical parameters (pressure, velocity and jerk) in early differential diagnosis of neurodegenerative diseases like AD [3,4] and Primary Progressive Aphasia [5]. However, these parameters have never been studied in PCA.

We present a specific analysis of graphical parameters (velocity, pressure, jerk) in a patient with PCA.

Case Report

A 76-year-old woman diagnosed with PCA and hypertension. She had several depressive episodes between 1990 and 2011 treated by ZOLOFT. She is currently treated with TEMERIT DUO, OROCAL and NEBIVOLOV.

The patient mentions an onset of disorders in 2016–2017 with difficulties in writing and reading and difficulties in daily life manipulations (folding laundry). She has a high educational and is ambidextrous. She reports during the anamnestic interview not to be familiar with writing on a tablet. The patient indicates that she stopped activities such as painting or sewing because of her in-hand manipulation difficulties. Her first Memory Center examination is done in January 2019 for cognitive disorders.

January 2019 MRI shows leukopathy and 2 frontal meningiomas. August 2020 FDG PET scan reveals bilateral occipital cortical hypo- metabolism predominantly on the right side.

The November 2020 lumbar puncture shows beta-amyloid at 528 pg/ml (lab standards 700–1800 pg/ml); total tau at 428 pg/ml (standards 130–600 pg/ml) and Phospho Tau at 65 pg/ml (standards 20–60 pg/ml). These examinations reveal a biochemical profile suggestive of a pathogenic amyloidogenic process.

The November 2020 clinical examination reveals the following neuropsychological test scores: MMSE 27/30 (mild cognitive impairment); BREF: 14/18 (pathological score); TMT A: 0.416 SD; TMT B: percentile 5 (pathological score); Gestural Praxis: 8/23 (pathological score); DO80 language test: 78/80; Span right: 6; Span back: 4 (pathological score); Semantic fluency (animals): 11 (pathological score); DTLA: 98/100; VOSP: dot counting, discrimination, number location (pathological scores). This examination shows a mild cognitive impairment with praxis, executive, memory, and visual deficit.

The graphical evaluation lasted about 10 min, the graphical markers were collected on an Apple IPAD® 2018 touch tablet (model MR7F2NF/ A) and an Apple Pencil® stylus model A1603. The sampling rate of the Pen was 60-Hz, the accuracy of the screen was 1-pixel, and its resolution was 2048 1536.

The PCA patient performed eight written tasks (Fig. 1): four linguistic tasks (L), part of the DTLA-test: words to dictation, nonsense words to dictation, a spontaneous sentence and writing letter L loops. Two cognitive-non-linguistic tasks (CNL): drawing a spiral and diagonals; and two non-cognitive-non-linguistic tasks (NCNL): writing filling loops and dots.

Three kinematic data are studied: writing velocity, measured in pixels/ms. Jerk, corresponding to the fluency of writing (variation of the acceleration/derivative of the acceleration at each point of the trace), measured in pixels/ms³, and Pressure of the stylus on the screen, represented by a number between 0 and 1, ratio in percentage of the maximum pressure detected.









<p>Word (W)</p> 	<p>Nonsense Word (NW)</p> 
<p>Sentence (Sen)</p> 	<p>L-Loops (L-L)</p> 
<p>Dots (Do)</p> 	<p>Loop Filling (LF)</p> 
<p>Diagonals (D)</p> 	<p>Spiral (S)</p> 
<p>Graphic tasks :</p> <ul style="list-style-type: none"> ■ Linguistic tasks (L) ■ Cognitive Non-Linguistic (C/NL) ■ Non-Cognitive Non-Linguistic (NC/NL) 	

Figure 1: Patient's writing productions.

Writing velocity (pixels/ms) Fig. 2.a

Compared to the average velocity of her own performances on all graphical tasks, the patient had a lower writing velocity on the L tasks of words (5.42), nonsense-words (5.52), sentence (5.27) and in the NCNL dots task (3.1). The writing velocity increased in the visual NCNL tasks of filling loops (24.05) and the CNL tasks diagonals (31.13) and spiral (23.65).

On average, velocity was lower in the L tasks (6.02) compared to the other tasks. The average velocity of the CNL tasks (27.39) was higher than the velocity of the NCNL (13.58) and L tasks (6.02).

Jerk (pixels/ms³) Fig. 2.b

We observed, compared to the average jerk of the patient's own performances on all graphical tasks, an increasing jerk in the tasks of filling loops (0.25), dots (0.21), L-loops (0.21) and especially in the sentence writing task (2.41). Jerk was low on half of the L tasks: words (0.04) and nonsense-words (0.11) as well as in all visual CNL tasks of diagonal (0.05) and spiral (0.08).

On average, the PCA patient's jerk was higher in the L tasks (0.69) than in the NCNL (0.23) and CNL (0.06) tasks.

Handwriting pressure (N) Fig. 2.c

Compared to the patient own performances on all graphical tasks, handwriting pressure in all NCNL visual-spatial tasks: dots (0.10) and filling loops (0.09) was lower than handwriting pressure in L tasks. The patient had a low writing pressure in the visuo-spatial CNL task of spiral (0.10) compared to the CNL diagonal task (0.23). In all L tasks, writing pressure was equivalent.

On average, pressure was low in the NCNL tasks (0.10) and higher in the L (0.16) and CNL (0.17) tasks.

Compared to reference data [5] on the difference in pressure between words L task and NCNL dots task, our subject (0.07; Standard Deviation (SD): 2.22) was above control subjects (0.04; SD: 0.05) and shows results close to subjects with AD (0.08; SD: 0.09).

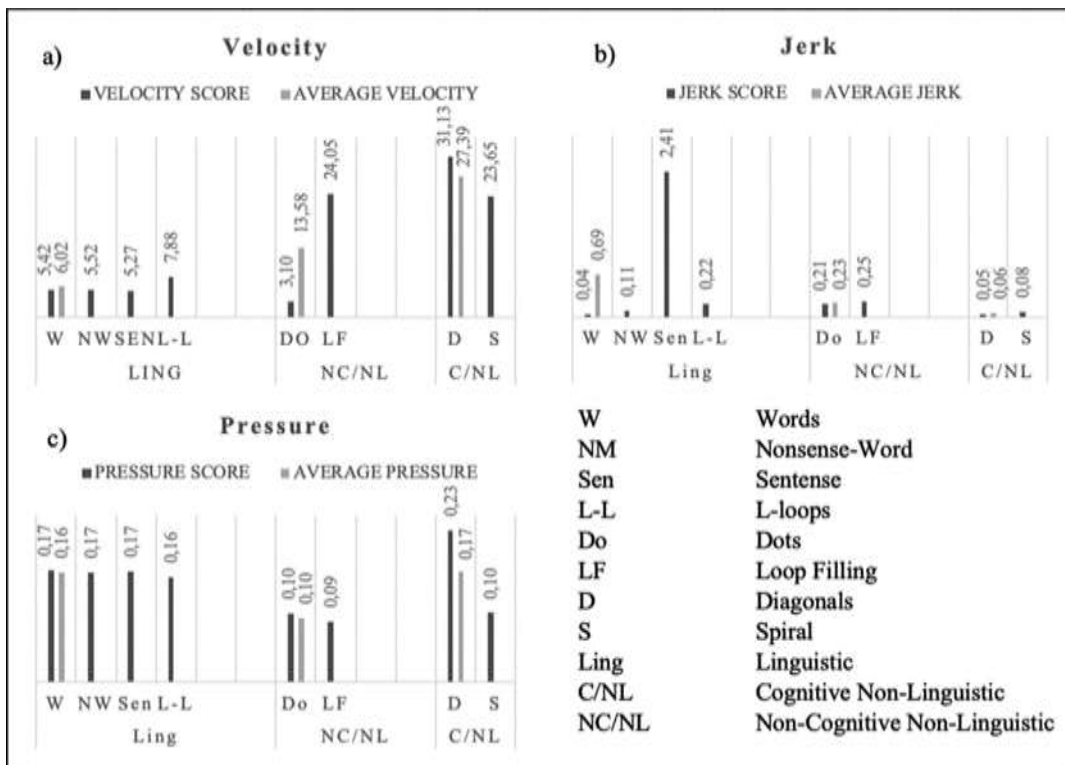


Figure 2: Graphical parameters of a 76-year-old woman with PCA. Writing velocity, measured in pixels/ms; Jerk, measured in pixels/ms³; and Pressure, represented by a number between 0 and 1, ratio in percentage of the maximum pressure detected.

Discussion and Conclusion

PCA is characterized by neuro-visual dysfunctions that impaired daily living tasks like reading and writing [1,2]. We present a case of a patient with PCA with a specific analysis of graphical features not previously studied in this pathology.

Concerning the writing velocity in the linguistic tasks, the patient showed a greater velocity decrease in the words, nonsense-words and sentences, than in the linguistic L-loop task. These results differ from those of healthy controls, whose velocity is regular, and from those of patients with AD, showing a velocity lowering especially in the linguistic L-loops task [3]. This case report thus shows an increased difficulty in writing words, more than isolated letters. These difficulties may be due to the spatial organization of words altered by the neuro-visual impairment of PCA.

Concerning the writing jerk, the patient showed a higher number of jerks in the sentence task. This jerk increase is also found in patients with AD, but in the diagonals tasks [4]. This difference can also be explained by the increased spatial difficulties during linguistic tasks in PCAs [1]. The results show a reduction in pressure, particularly in the cognitive-non-linguistic visuo-spatial task of drawing a spiral and the non-cognitive-non-linguistic tasks of dots and filling loops. The pressure lowering appears in graphical activities having a spatial component, while in AD patients pressure lowering appears in the linguistic L-loops task [3]. This can be explained by the difference type of impairment between PCA and AD, with PCA patients having an impairment on visual features. This result of a writing pressure change depending on the graphical task performed is in line with the results of a previous study on AD [4].

Conclusion

Even though PCA is an atypical form of AD, graphical markers are yet different. This report case highlights the interest of combining graphical markers with classical assessment in the clinical and differential diagnosis of PCA.

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Use of graphical and gestural markers for Primary Progressive Aphasia subtypes differentiation

The use of graphical markers for the differentiation of Primary Progressive Aphasia subtypes

In this thesis work, we verified the interest of the use of graphical markers for the early and differential diagnosis of PPA, specifically in PPA compared to Alzheimer's Disease. In our first study, we focused on one specific graphical parameter that was the handwriting pressure (mean and maximum) [1]. This parameter was chosen because of the motor activity decrease due to cognitive overload when there is a language disorder [2]. In patients with PPA, language disorder being the first clinical sign of the disease, the use of writing pressure parameter seemed relevant for its diagnosis. The language impairment and its specificity allows the differentiation of PPA from other neurodegenerative diseases to which it is clinically similar but also towards which it can evolve, such as AD, Frontotemporal Lobar Degeneration (FTLD) and Lewy's Body Dementia [3]. Moreover, several subtypes of PPA have been described in the literature, and specifically three main PPA subtypes were established, depending on the affected brain regions and the type of language disorder: the logopenic subtype (lvPPA), the non-fluent and agrammatic subtype (nfavPPA) and the semantic subtype (svPPA) [4]. After we verified the interest of using writing pressure for PPA diagnosis in general, we wanted to go further in our analyzes and verify if graphical parameters could be useful for the differentiation of the three main PPA subtypes. We know by previous studies that the analyze of writing velocity for example can be useful for an early AD diagnosis [5]. According to the fact that the main PPA subtypes depend on the affected brain region and can evolve to different neurodegenerative diseases, we wanted to verify whether, depending on the nature of the disease, the relevant graphic parameters could be different from one PPA subtype to another.

This work led to a preliminary study presented during the Poster Session of the 2021 Alzheimer's Association International Conference that was held in Denver (USA) and published as a conference-paper in 2022 [6].

Method

In this study, we included 29 subjects with Primary Progressive Aphasia (lvPPA N=18; nfavPPA N=6; svPPA N=5). They all performed the ten graphical markers tasks that we added

the DTLA-test (2 non-cognitive and non-linguistic tasks, 4 cognitive and non-linguistic tasks and 4 linguistic tasks) on an I-Pad® tablet. For this study, we extracted different writing parameters: writing pressure, velocity, jerk and stroke.

Results

Preliminary results presented in figure 1 revealed a main effect of diagnosis in linguistic tasks on average velocity ($p= 0,041$) and on average stroke ($p= 0,029$).

The two-by-two comparison of different variants of PPA also showed significant differences:

1) lvPPA vs nfavPPA: significant differences in the average velocity, jerk and stroke were found, with lvPPA participants showing a higher velocity ($p= 0,037$), jerk ($p= 0,046$) and stroke ($p= 0,014$) than nfavPPA participants in linguistic tasks.

2) lvPPA vs svPPA: significant difference in velocity was found in linguistic task ($p=0,037$).

3) nfavPPA vs svPPA: significant difference in maximum pressure was found in linguistic task ($p= 0,044$), with nfavPPA participants showing a lower maximum pressure than svPPA participants.

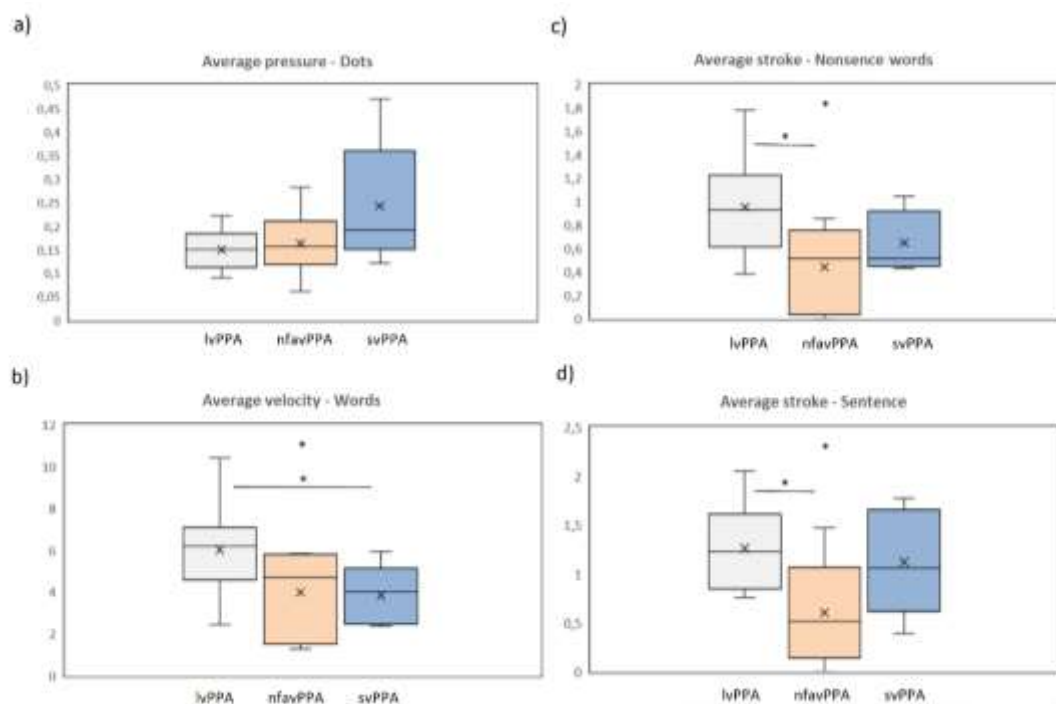


Figure 1: Graphical parameters in the PPA subtypes. a) Average pressure in the Dots task. b) Average velocity in the word task. c) Average stroke in the Nonsense word task. d) Average stroke in the Sentence task.

lvPPA: logopenic variant of Primary Progressive Aphasia; nfvPPA: agrammatic variant of Primary Progressive Aphasia; svPPA: semantic variant Primary Progressive Aphasia

Conclusion

These preliminary results suggest that the use of graphical markers can be helpful in the differential diagnosis of PPA subtypes. MarCo-Sens study is ongoing to collect a bigger and more balanced PPA sample. We therefore saw by this study that beyond the graphical pressure that is of interest, the stroke parameter is significant in nfvPPA.

In our next study, we wanted to go deeper in the analysis of this parameter, not by the analysis of the parameters collected directly on the tablet, but with the analysis if the writing gesture, recorded on video.

The use of gestural markers for the early detection of the non-fluent and agrammatic subtype of Primary Progressive Aphasia

The non-fluent and agrammatic Primary Progressive Aphasia subtype (nfvPPA) is related to dysfunctions in the inferior frontal cortex and the anterior parts of the insula. Some studies have also highlighted parietal and temporal involvement [7–10]. The underlying pathology of nfvPPA is most often Frontotemporal Lobar Degeneration (FTLD) [11]. NfvPPA is clinically characterized by the presence of agrammatism or language economy, hesitant speech with arthritic production effort, as well as phonetic errors and distortions [12,13]. Oral-linguofacial apraxia may be present with swallowing disorders such as apraxia of swallowing. Early diagnosis of this variant is even more essential since swallowing disorders, which represent a vital risk, must be identified, and treated as quickly as possible. These clinical signs are associated with disorders in the understanding of syntactically complex sentences and a preservation of the understanding of isolated words and concepts [14].

Our recent study of the French National Bank nationwide cohort of patients with PPA highlighted the difficulty in making their diagnosis due to the varied symptomatology of the three variants and the underlying pathology, as well as the insufficiency of diagnostic tools currently used [15].

Unlike the voice, which has often been studied in neurodegenerative pathologies [16], graphical markers have been explored less often [17]. Nevertheless, their interest in AD [5,18], PPA [19] as well as in Posterior Cortical Atrophy (PCA) [20] has been highlighted in the framework of this thesis researches. Graphical markers, such as the writing pressure exerted on a tablet during a handwriting task, can thus be altered. The contribution of these markers, particularly in relation to voice analysis, is that they are less dependent on external factors that can modify them (such as a viral pathology, smoking, etc.). They would also be of particular interest in the differential diagnosis since these markers would be affected differently depending on the task to be performed. For example, while the language task would undergo the most modifications in the PPA, it is the visuo-spatial tasks that would be the most altered in the case of PCA [1,20]. The graphic markers can then allow to make an early and differential diagnosis of patients with PPA and patients with AD by comparing the writing pressure between linguistic and cognitive-non-linguistic tasks [1]. Finally, other graphic kinematic parameters such as the number of pencil lifts (stroke), writing speed and accelerations (jerk) would be interesting for the classification of the different PPA subtypes due to the different anatomical pathways of

degeneration. It has thus been raised that patients with a non-fluent variant of PPA had lower strokes (pencil lifts) than patients with the logopenic variant [6].

Nevertheless, the implementation of telemedicine, which has increased in recent years due to the Covid-19 pandemic [21], does not allow the recovery of these graphic markers collected to date on iPad type tablets.

The objective of our study was therefore to verify whether the manual data collected by a video recording were related to the graphic markers recovered on iPad by studying more particularly the stroke which has been shown to be of interest in nfvPPA. We also wanted to verify whether the manual data could provide useful additional data for clinicians, and which could be interesting to use in the context of supervised learning for automated gesture processing in future studies.

This preliminary study was published in the journal *La Revue de Gériatrie (Rev Geriatr 2022 ; 47 (7) : 311-8)*.

Method

We collected gestural and graphical data from a 62-year-old man with a diagnosis of nfvPPA. The patient has a higher level of study, is right-handed and not accustomed to using touch tablets. The patient is a translator, he is married and has children. He has no traumatic or vascular history. He reports no mood disorders in the past but a contextual drop in mood due to his current difficulties. In terms of language, there are arthritic difficulties with slow speech. Spontaneous speech also highlights an economy of effort or even an agrammatism. His score on the Detection Test for Language impairments in Adults and elderly (DTLA) is 41/100 with a loss of points in the repetition of nonsense-words and sentences, in verbal fluency, in verbal span, in reading and in writing and syntactic comprehension tasks.

The graphic markers were retrieved at the same time as the DTLA was run on its automated format that was made in CoBTeK laboratory and used in research called DTLA+. Gesture markers were collected through video recording. Graphic markers were collected on an Apple iPad® 2018 touchscreen tablet (model MR7F2NF/A) and an Apple Pencil® model A1603 stylus. The pen's sampling rate was 60 Hz, the screen precision was 1 pixel, and its resolution was 2048 x 1536.

The patient was asked to perform eight written tasks: three linguistic tasks (Ling), part of the DTLA: writing words to dictation, nonsense-words to dictation and a spontaneous sentence.

Four cognitive-non-linguistic (CNL) tasks: spiral drawing, diagonals, vertical and horizontal lines; and a non-cognitive-non-linguistic (NCNL) task: filling the screen with loops.

We decided to study the stroke as the only kinematic data given its specificity in the case of nfvPPA. The stroke corresponds to pencil lifts and therefore when the stylus is in the air and does not touch the tablet. It is calculated in terms of duration and frequency (number of strokes/second).

Gestural stroke markers were annotated using an ontological language to conceptualize and model the events of interest.

We have thus defined a set of behaviors with subsumption relations (figure 1).

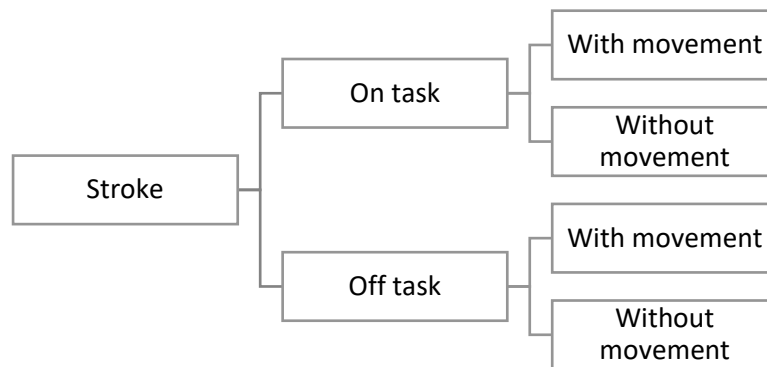


Figure 1: Subsumption ontology for stroke annotations.

We defined a stroke state, including “On task” and “Off task” including “with movement” and “without movement” behaviors. “On task” means that the patient stops while doing the spiral or writing the word; “Off task” means that the patient raises the pencil when he has finished writing the requested word or drawing. The notion “with” and “without movement” describes the presence or absence of disorganized and disruptive movements during pencil lifts.

Clinical characterization of strokes

One of the advantages of video recording and manual annotation by the clinician is that it allows a finer characterization of the features detected by the tablet, which may allow the identification of additional specific features.

In the context of strokes, some pencil lifts may be considered as inherent to the task (such as "Off task" strokes) and others more clinically significant (such as strokes "On task" with movement).

Correspondence with gestural markers and manual annotations

Specifically, we studied the total number of strokes collected by the graphical markers (Nstroke) and the total number of strokes counted and visually annotated by the clinician (TotL). The number of strokes that lasted more than one second was also automatically collected by the tablet (Ndstroke) and compared to the strokes during the task with movements annotated by the clinician (LPM).

Results

Graphical markers

The results obtained by the nfavPPA patient (Figure 2) show that the duration of the strokes (2B) is not related to the frequency of the strokes (2A). There even seems to be a negative association, since the duration of the strokes is more important in linguistic tasks than in cognitive-non-linguistic ones, and that the frequency is greater in some non-cognitive-non-linguistic tasks only than in linguistic tasks. Horizontal lines production tasks have the same duration and the same stroke frequency than those of producing vertical lines. These results demonstrate a duration and a frequency inherent of the type of task since they are similar in identical tasks.

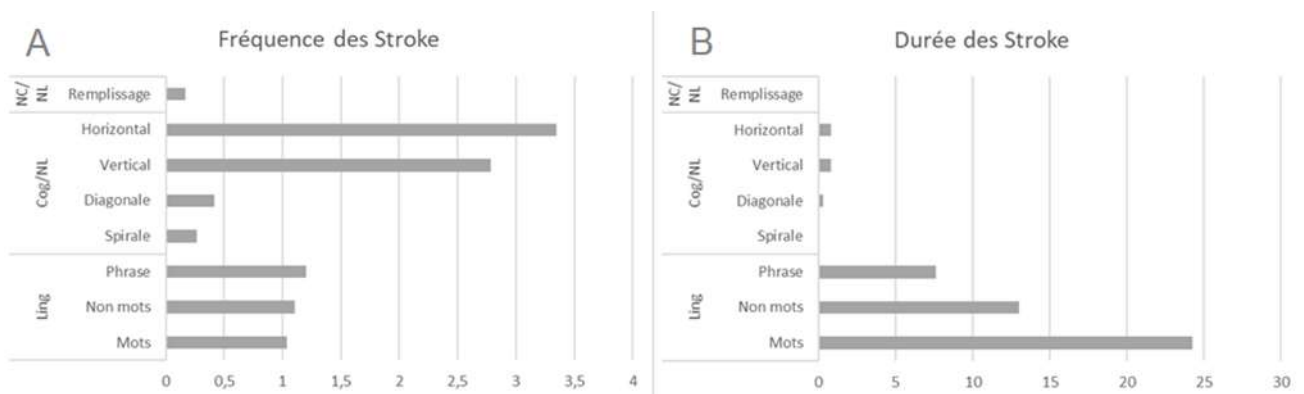


Figure 2: Frequency (A) and duration of strokes (B) in the different types of tasks

Ling: Linguistic tasks; Cog/NL: Cognitive-non-linguistic tasks; NC/NL: Non-cognitive-non-linguistic tasks.

Gestural markers

Clinical characterization of strokes:

Gestural markers analyze showed stroke types specific to linguistic tasks in the nfvPPA patient that we do not find in cognitive-non-linguistic tasks and non-cognitive-non-linguistic tasks. Thus, the strokes “On task” (with or without movement) and the strokes “Off task” with disruptive movement are only found in linguistic tasks (Figure 3).

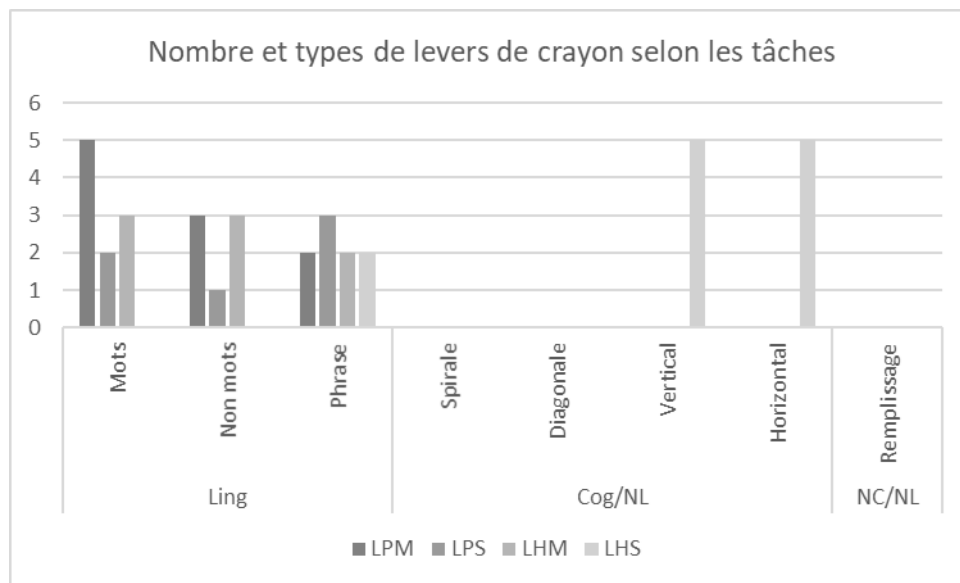


Figure 3: Characterization of the number of pencil lifts according to their type

LPM: Stroke during the task with movements; LPS: Stroke during the non-moving task; LHM: Stroke off task with movement.

Correspondence with gesture markers and manual annotations:

The results of the nfvPPA patient (Figure 4) showed that the number of strokes collected automatically with the graphical parameters (Nstroke) is higher than the total number of strokes manually annotated by the clinician (TotL). Also, the number of manually annotated strokes (TotL) for sentences was higher than for nonsense-words while the automated graphical evaluation (Nstroke) showed the opposite. However, strokes lasting longer than one second (Ndstroke) showed a great correspondence with pencil lifts during the task with movements annotated by the clinician (LPM). They were found only in linguistic tasks and were absent in cognitive-non-linguistic and non-cognitive-non-linguistic tasks in both types of analyzes (Ndstroke and LPM). These results showed that qualitative LPM data can also be collected

indirectly by automated analysis of graphical markers parameters through the number of strokes lasting longer than one second (Ndstroke).

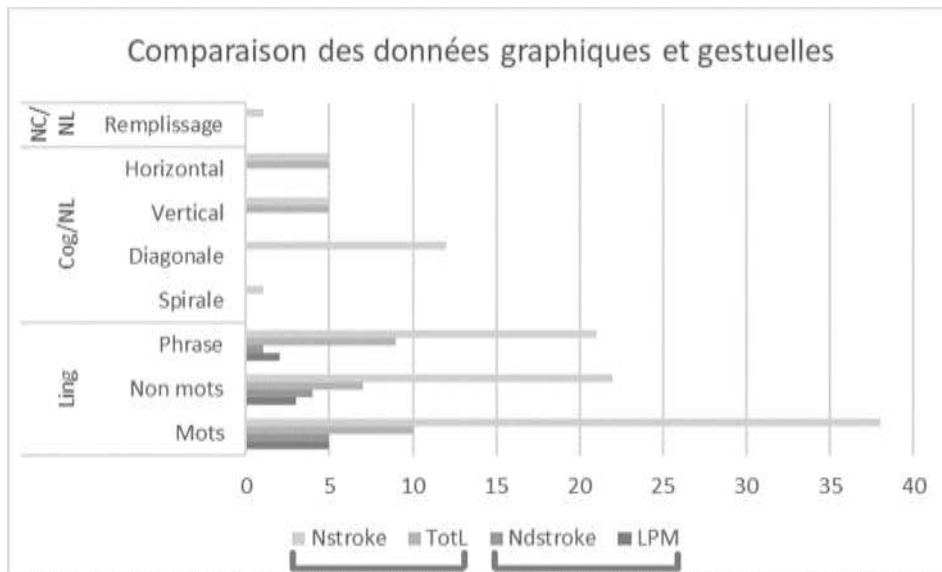


Figure 4: Comparison of the number and type of strokes, according to automated graphic measurement and gestural annotation

Nstroke: number of strokes automatically annotated by graphical evaluation. TotL: total number of strokes annotated by the clinician. Ndstroke: strokes lasting more than one second. LPM: strokes lasting more than one second annotated by the clinician.

Discussion and conclusion

The objective of this study was to compare automated graphical analysis with clinician-annotated manual analysis in a patient with a diagnosis of nfavPPA.

Among the graphical data analyzed automatically, the frequency allows counting the number of strokes per second. This data can be inherent to the task because it will be modified according to the type of production required (for example, the spiral will require fewer pencil lifts than vertical lines which will have to be repeated on the screen and will therefore generate a pencil lift to achieve the next line). The duration of the strokes may reflect the time needed to program the task and therefore be of interest [18]. Nevertheless, the fact that its duration is dependent on the examiner's dictation time in words and nonsense-words tasks makes this type of production also inherent to the task. The correspondence of the frequency and duration of strokes analyzed automatically agrees with this statement. This is one reason why, when we examine strokes, whether in terms of frequency or duration, we have to compare differences in stroke frequency and duration across task types (linguistic and non-linguistic) between controls and patients

[1,6]. This allows to keep only the durations due to programming efforts and not those due to the task type. The use of graphical markers in the diagnosis of nfvPPA has been shown to be of interest with stroke parameters weakened in the linguistic writing task compared with other PPA subtypes due to language impairment that is specific to this subtype [6].

Gestural data, allowing to observe when the pen is in the air and what is the patient's behavior during this time, could thus provide major complementary data, essential to identify manual behaviors characteristic of language disorders. Our results showed that the nfvPPA patient performs strokes during the task with and without movement only in linguistic tasks. These pencil lifts during the linguistic writing task could thus represent the need for patients with language impairments, to have more time for letter programming (without movement) and letter representation through motion (with movement) when the pen is in up. However, this type of characteristic strokes cannot be collected by the automated graphical analysis since the graphical data collected by the iPad-tablet can only track the trajectory of the pen when it is resting on the tablet (and thus not when it is up).

The analysis of the automated graphical data and the gestural data annotated by the clinician in this patient thus highlight that the gestural data could allow for a better characterization at the clinical level by getting away from the effects due to the task itself. By comparing the two types of data in the nfvPPA patient, our results showed that manual annotations by the clinician were less accurate than automated graphical data. This lack of accuracy could be improved by implementing an automatic gestural analysis.

Finally, our results showed a great correspondence between the number of strokes that lasted longer than one second and the number of events annotated as pencil lifts during the tasks with movement in the nfvPPA patient. These results highlight the fact that automated graphical analysis could collect qualitative data indirectly by considering the strokes duration.

From a scientific and fundamental point of view, our results suggest a relationship between language and gestural processing and a partial overlap of their neural representations. They are in agreement with previous studies which have shown, in particular, a deficit in the discrimination of non-verbal gestures in patients with PPA and some links between their scores in gestural discrimination and words repetition or writing under dictation tasks [22]. The gestural apraxia found in PPA [23] could thus be a consequence of the language disorder and have a severity depending on the latter.

From a clinical point of view, the results obtained lead us to recommend the use of video recording and movement analysis in telemedicine evaluations to improve the diagnosis of PPA. Special attention should be paid to strokes during the writing task with movements in the void,

as it has been demonstrated in other neurodegenerative pathologies [24]. These video data could be integrated among other already known markers using an automatic signal processing such as vocal markers [25] in order to increase their specificity and sensitivity. It would thus be interesting to validate these results on a bigger patients' cohort.

In summary, if graphical markers have recently already showed their interest in PPAs diagnosis, it appears to be important in nfvPPA to take into account the associated behaviors or gestural markers (movements in the void when lifting the pencil) which could be useful for diagnostic assistance for the clinician, whether during a consultation or teleconsultation.

This observation underlines thus the importance of the direct clinical and video analysis that telemedicine does not allow by itself, so as not to lose sensitivity for the diagnosis of complex neurocognitive syndromes such as PPA.

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Chapter 3

THE USE OF LANGUAGE MARKERS: LINGUISTIC AND ACOUSTIC MARKERS

Language is the most salient impairment at the onset of Primary Progressive Aphasia (PPA) [1]. Studies have demonstrated that more specifically, we can find a phonological-loop deficit in the logopenic variant of PPA (lvPPA). The phonological-loop functioning is dependent on the short-term memory, and represents even one of its components [2,3]. Sentences repetition ability relying on the phonological-loop functioning, its dysfunction causes an impairment of the sentence repetition ability [4].

PPA can be caused by different underlying pathologies such as tauopathy associated with frontotemporal lobar degeneration (FTLD), alpha-synucleopathy associated with subcortical neurocognitive disorders like Parkinson (PD), or amyloidopathy associated with Alzheimer's disease (AD). It is often difficult to differentiate some PPA symptoms from those found in AD, regarding the short-term memory alteration in both pathologies [4,5]. Moreover, in the early stages of the disease, it is oftentimes hard to provide a clear lvPPA diagnosis since symptoms may start with isolated word finding difficulties, or phonological errors and omissions, but then evolve into an AD type global neurocognitive disorder [3].

Given the language disorders observed in lvPPA and the difficulties of diagnosing it at the onset, we administered a new sentence repetition task whether to verify if that kind of tool could be useful in the differentiation of lvPPA from other neurocognitive disorders as AD but also from other PPA subtypes as the semantic variant of PPA (svPPA). Also, to bring more specificity to the test, we conducted the analysis of acoustic markers. It has been demonstrated that vocal analyses of fundamental frequency, shimmer or jitter can give essential information about a disease, even at its onset [6–8]. We thus analyzed not only the language performances, but also the acoustic parameters.

In the purpose of the studies presented in Chapter 4, patients were included in the context of a protocol created by the CoBTeK Laboratory of Nice, approved by CPP Ile de France X (N IDRCB: 2019-A00342-55 accepted on 11 September 2019). A preliminary study was held with a small cohort of patients, in which we demonstrated that sentence repetition deficits in PPA have different characteristics than those in AD [9], which is consistent with our previous studies which associated PPA assessment with graphic markers [10].

But what was more interesting in this work, is that these results were not confirmed in the second bigger study, the only phonological features being different in the lvPPA and AD population. It thus conducted us to analyze acoustic markers. We demonstrated that the use of

a repetition task alone is not specific enough to differentiate PPA patients from AD. But if we correlate the sentence span with acoustic parameters, it brings very specific features that can lead to differentiate not only lvPPA from AD, but also prevent lvPPA evolution. Indeed, patients presenting AD biomarkers had correlated acoustic features to AD patients, but lvPPA patient that didn't have AD biomarkers had different acoustic markers.

This Chapter emphasizes the importance of favoring a multimodal approach of new markers, given that one feature is not specific enough to determine a pathology, but that the association of many markers can give significant diagnostic differences.

It would thus be interesting to correlate motor and acoustic markers to determine detailed syndrome specificities.

These studies have been led throughout the thesis project.

They are the result of a constant reflection on the possibility of improving PPA diagnosis, bringing other diagnostic supportive parameters such as language and acoustic parameters. These parameters showed their interest in a better understanding of PPA disease and its subtypes specificities that could support the diagnosis improvement. But also, vocal parameters may help to improve PPA evolution prediction, regarding the acoustic parameters' differences found even in one PPA subtype having however different underlying neuropathology.

I was implicated in every step of the presented studies.

In the framework of these studies:

I was in relation with the Bases Corpus Langage Laboratory (BCL) team that created the sentence span test, to assess, discuss, analyze, and readapt the final tool.

I co-supervised one graduation SLT thesis and co-directed a second one.

The preliminary results of the use of the Sentence Span test were published as a conference paper in the 2020 Alzheimer's Association International Conference:

- Arslan, S., **Plonka, A.**, Payne Cogordan, M., Manera, V., Gros, A., Meunier, F. (2020). Répéter s'il vous plait: Working memory intensive sentence repetition deficits as a sensitive neuropsychological marker of primary progressive aphasia. *Alzheimer's & Dementia*. <https://doi.org/10.1002/alz.042842>

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Publication 4

*Sentence repetition span in primary progressive aphasia and Alzheimer's disease:
Insights from preliminary results*



Frontiers in Communication
November 2022

TYPE Original Research
PUBLISHED 15

DOI
10.3389/fcomm.2022.
934487

Sentence repetition span in primary progressive aphasia and Alzheimer's disease: Insights from preliminary results

Seçkin Arslan^{1*}, Alexandra Plonka^{2,3,4,5}, Aurélie Mouton^{2,4}, Justine Lemaire², Magali Payne Cogordan^{3,4}, Guillaume Sacco^{2,4,6}, Valeria Manera^{3,4}, Auriane Gros^{2,3,4} and Fanny Meunier¹

Abstract

Primary Progressive Aphasia (PPA) is a form of neurocognitive disorder ascribed to cortical atrophy impacting language abilities. It is widely classified into three main variants: logopenic PPA (lvPPA), the semantic variant of PPA (svPPA), and the non-fluent PPA (nfvPPA) showing different impairment patterns across variants. However, in the early phases of PPA, it is not always easy to dissociate different PPA variants and distinguish PPA from other neurodegenerative disorders. One characteristic language symptom that seems to distinguish PPA, especially the logopenic variant, is impaired sentence repetition. Nonetheless, studies examining sentence repetition in PPA, and Alzheimer's disease (AD) more broadly, have resulted in mixed findings. To be able to better understand the working memory intensive nature of sentence repetition deficits, we designed a sentence repetition span task. We seek to understand (i) whether three diagnostic groups (lvPPA, svPPA and AD) encounter greater sentence repetition difficulties than the controls, and (ii) whether using a span task design, in which the number of content words increases as the span length increase, would help dissociate PPA variants from AD type dementia. In this study we administered a sentence repetition span task to four groups of French-speaking individuals with lvPPA (n = 14), svPPA (n = 5), and with AD (n = 13) and their age-matched healthy controls (n = 63). The results showed that all the three diagnostic groups (lvPPA, svPPA, and AD) performed equally poorly as compared to the controls on the repetition span task virtually in all measures (i.e., sentence span, number of content words, number of omission and substitution errors). One intriguing finding was that the lvPPA group produced an exalted number of phonological errors during repeating sentences, while this type of error was somewhat moderate in the svPPA group and only minimal in the AD group. We conclude that sentence repetition difficulty in PPA and AD should be modulated by working memory capacity, as our participants undoubtedly demonstrated greater difficulty as the span length increased. However, we note that working memory-intensive sentence repetition deficits based on the number of content words might not reveal critical diagnostic differences between the neurodegenerative groups.

Keywords: Primary progressive aphasia, short-term memory, sentence repetition span task, Alzheimer's Disease (AD), sentence repetition

Introduction

Primary Progressive Aphasia (PPA) is referred to as ‘focal’ dementia caused by progressive atrophy or neurodegeneration impacting language network areas of the brain [1,2]. PPA is a progressive form of aphasia meaning that it is mainly characterized by ‘salient’ language problems and these problems become more severe as the disease progresses in time [3]. PPA can be caused by different underlying pathologies such as *amiloïdopathy* associated with Alzheimer’s disease (AD), *tauopathy* associated with some frontotemporal lobar degeneration or *alpha-synucleopathy* associated with some subcortical neurocognitive disorders like Parkinson or Lewy bodies disease. Unlike in AD, rather isolated language problems surface in PPA. However, depending on the locus of brain neuropathology, individuals with PPA might show different language impairment profiles [4]. According to the widely accepted Gorno-Tempini et al. (2011) classification three main variants of PPA have been described: the non-fluent variant of PPA (nfvPPA) with prominent non-fluent speech and wide range of grammatical errors; the logopenic variant of PPA (lvPPA) exhibiting moderate to severe word finding difficulties and impaired sentence repetition; and the semantic variant (svPPA) with often severely impaired naming and word comprehension difficulties. However, it is important to note that several PPA cases have then been reported to show mixed impairments, not fitting in well with a single variant classification [5].

Certain language-related difficulties including naming and word finding problems are often common symptoms, especially in frontotemporal lobar degeneration; however, rather isolated and progressive language-related symptoms dissociate PPA from other degenerative syndromes [6]. Individuals with nfvPPA are best characterized by the presence of simplified grammatical structure in speech output, and reduced complexity in grammatical processing. Single word comprehension and object naming often stay relatively spared [7,8]. Cortical atrophy is often found to be extensive in the left inferior frontal gyrus and in the insular lobe [9]. Symptoms in svPPA are often characterized by a settled pattern of anomia with associated atrophy in anterior sectors of middle and superior temporal gyri extending to other anterior parts of the perisylvian areas [10]. Although salient deficits in all PPA phenotypes are often observed in the language, other cognitive difficulties involving executive functioning or working memory may arise as the severity of symptoms increases over time [11]. Reduced visual and semantic memory performances are more often found in svPPA as compared to different PPA variants, while verbal memory performance is rather more commonly impaired across all phenotypes [12]. This

is clinically quite relevant because verbal memory in the early stages of PPA is often found impaired compared to AD, dissociating the two syndromes, while either the reverse happens or no strong dissociations are found for visual memory [12,13].

While having said that cognitive tasks can be informative clinical markers for PPA, it is often difficult to differentiate certain PPA symptoms from those found in AD or other neurocognitive disorders without salient language impairments. Although, AD type neuropathology can be the underlying cause of most PPA variants, this type of pathology seems to be slightly more often associated with the logopenic variant [14]. Therefore, in the early stages of the disease, it is oftentimes hard to provide a clear lvPPA diagnosis since symptoms may commence with somewhat isolated word finding difficulties but then evolve into an AD type global neurocognitive disorder. As briefly mentioned, a characteristic symptom in lvPPA is an inability to repeat sentence stimulus. Henry & Gorno-Tempini (2010) report that people with lvPPA experience sentence repetition deficits especially when the compositional probability is low, and that semantically loaded content words are likely to be omitted or substituted [15]. For instance, a person with lvPPA has been reported to repeat the sentence “*The valuable watch was missing*” as “*The watch was gone*”.

An associated reason for impaired repetition ability in PPA is thought to be disrupted verbal short term memory [7]. This is not surprising at all since a large portion of lvPPA diagnosed cases demonstrate poor short term memory performances accompanied by atrophy in the left temporo-parietal regions [7,12,16,17]. These findings seem compatible with Baddeley’s working memory model, which holds that verbal and visual information are separately stored for a temporary duration in the “phonological loop” and “visual sketchpad”, and that a central-executive component subserves the memory system with a shared pool of executive functions during processing information [18,19]. These memory components have been conventionally examined using “span tasks” which is based on the idea that increasing complexity in stimulus manipulation reaches a maximum span at which individuals cannot retain stimulus accurately in memory anymore. There have been several different adaptations of span tasks but for our purpose the most relevant ones would be “sentence span” or digit span tasks in which individuals read or repeat increasing length of sentences or digits, respectively [20,21]. Although not always fully warranted, scholars often distinguish tasks that require forward repetition as “short term memory” while backward modality would tap into “working memory”. Phonological short term memory tasks have in fact been associated with several regions at the

junction of the posterior part of the temporal lobe and the parietal lobe including the supramarginal gyrus, the planum temporale and the posterior part of the superior temporal sulcus [22–24]. It is therefore logical to assume that in lvPPA, these regions might be affected due to ongoing atrophy, leading to underlying difficulties in processes following the perception of speech input that enable the retainment of verbal information in memory and processing it. This is compatible with Foxe et al. (2020) findings, who using a set of forward spatial and digit span tasks, examined three variants of PPA in comparison to AD and healthy controls [25]. The authors found that lvPPA and AD groups showed impaired recall in spatial span while all groups except for svPPA showed impaired performance in digit span tasks. The authors found strong correlations between impaired recall and grey matter intensity decrease in temporo-parietal regions extending into occipital regions.

It is quite remarkable that PPA is a very heterogeneous syndrome, and some cases have been reported to exhibit blended language symptoms fitting in with more than one PPA variant criteria. There have been volumes of research attempting to identify relevant clinical markers of PPA dissociating different phenotypes from each other, and/or distinguishing PPA from other neurocognitive disorders [26]. One highlighted clinical marker proposed for the classification of lvPPA from other phenotypes seems to be the presence of repetition impairments [3,27]. However, there seem to be some inconsistencies in results from studies that looked at sentence repetition in PPA and AD. Leyton et al. (2014) report that both groups of PPA and AD patients they tested with diagnostic sentence repetition tasks failed to perform at control participant norms, while the authors found no significant between group differences, suggesting that repetition errors in PPA and AD do not necessarily dissociate these syndromes from each other [28]. However, results from Meyer et al. (2015) showed a pattern in which, unlike in AD, their lvPPA patients performed less accurately in repeating both meaningful sentences/words and pseudowords as compared to healthy controls. Lukic et al. (2019) examined the repetition of meaningful and non-meaningful phrases in a variety of length in groups of English-speaking individuals suffering from lvPPA, nfvPPA and svPPA as compared to a control group [29]. The authors' findings have demonstrated that their people lvPPA were impaired in the repetition of all types of phrases disregarding length and meaningfulness, while people with nfvPPA and svPPA were shown to have difficulty in repeating long and meaningless phrases.

Hohlbaum et al. (2018) conducted a longitudinal investigation on the dissolution of sentence repetition ability in a German-speaking group of people with lvPPA [30]. A large portion of the individuals tested showed worsening phonological errors and the omission of words in time over re-test intervals. The authors used sentences with different syntactic structures including word order variation, yes/no questions, and different forms of tense marking. The authors conclude that the omission of words leads to syntactic problems. Beales et al., 2019 studied groups of lvPPA, svPPA and AD patients speaking English with a sentence repetition task adapted from Hohlbaum et al. (2018) and a number of complementary digit span tasks [30,31]. The authors report that people with svPPA performed better than lvPPA and AD in their response accuracy on sentence repetition; however, the authors found no significant differences between people with lvPPA and AD. Beales et al. (2019) found significant correlations between their participants' group performances on sentence repetition and digit span tasks, contemplating that a relationship between sentence repetition and working memory in deed exists [31]. Seckin et al. (2022), using word reading and repetition tasks (the Repeat and Point Test), studied groups of German-speaking people with three variants of PPA [32]. Their findings have shown that repetition task outcomes might be useful in dissociating people with svPPA from lvPPA and nfvPPA, as people with svPPA performed more accurately in repeating words over people with lvPPA and nfvPPA. The latter two groups performed poorly and showed no group differences.

Research on sentence repetition deficits in PPA has shown mixed results, which is much likely due to different stimulus materials, varying number of individuals with PPA, varying severity of symptoms and different task designs used across different studies. One certain commonality is that people with lvPPA are likely to experience relatively severe sentence repetition difficulty. However, whether or not this profound deficit in repetition dissociates lvPPA from other neurocognitive disorders requires further understanding. While a number of authors found worse performance in lvPPA as compared to AD [33], or compared to semantic dementia [31,32], suggesting that sentence repetition deficits constitute a reliable clinical marker, others found equally affected repetition ability in both AD and PPA populations [28]. Interestingly a number of authors have underlined the impact of stimulus length linking this impairment with diminished phonological short-term capacity in PPA [29–31]. Since a majority of sentence repetition tasks manipulated syntactic variables [30], further understating on the limits of sentence repetition capacity in PPA is warranted. The most viable way to test this would be

blending sentence repetition responses within a span task in which sentence length and number of semantically loaded content words systematically vary.

The current study

In the current study we explore how French-speaking individuals with PPA both the semantic and logopenic variants experience sentence repetition difficulties as compared to broader neurocognitive disorders in AD when sentences are presented within a span task design. The available research on French speaking PPA and AD individuals' sentence repetition ability is scant. Epelbaum et al. (2021), developed a rapid language test to dissociate PPA from other Alzheimer's type neurocognitive disorder, which includes word and sentence repetition subtasks containing five items each [34]. These authors reported that sentence repetition performance distinguishes lvPPA from semantic variant, as the lvPPA perform more poorly on this task. Macoir et al. (2021), using the French sentence repetition subtask initially developed for post-stroke aphasia by Bourgeois-Marcotte (2015), tested four cases of French speaking PPA as compared to a group of healthy controls [35,36]. The authors found that all four lvPPA cases performed poorly in comparison to their controls, and that involvement of semantic reversibility of verb used and syntactic constructions used (i.e., active passive) only influenced performance in one or two participants. Building upon the aforementioned literature, we aim to understand:

- (i) whether three diagnostic groups (lvPPA, svPPA and AD) experience sentence repetition difficulties to a larger extent than healthy ageing adults
- (ii) and whether testing sentence repetition within a span task would dissociate the logopenic variant of PPA from other types of neurocognitive disorders (svPPA and AD type).

In the current study we administered a sentence repetition span task to groups of French-speaking individuals with PPA (lvPPA = 14; svPPA = 5), and with Alzheimer's disease (n = 13) and their age-matched healthy controls (n = 61). Given the results from previous research implying that sentence repetition difficulties in PPA might be associated with working memory intensive nature of the processing, which seems affected especially in the logopenic variant, we aimed to test sentence repetition deficits employing a sentence span task. The rationale behind this was that as the span of content words increases, PPA patients would encounter greater difficulty potentially dissociating them from individuals with other neurocognitive disorders.

Materials and Methods

Participants

For this study, we recruited three groups of participants. Our PPA group included a total of 19 individuals suffering from progressive aphasia symptoms, 14 of which were classified as logopenic variant with atrophy patterns in anterior temporal regions at the junction of parietal areas (8 females and 6 males; *Age mean* = 75.07, *SD* = 9.48), and the other 5 individuals had semantic PPA variant who typically were diagnosed with frontotemporal lobar degeneration (2 females and 3 males; *Age mean* = 69, *SD* = 11.66). The second group included 13 individuals suffering from Alzheimer's disease most of whom had a diagnosis with either rather global atrophies overall or bilateral atrophy in hippocampal regions (7 females, 6 males; *Age mean* = 79.15, *SD* = 8.17). See Table 1 for further demographic and aetiological details of these participants. As it might seem that the number of participants with neurodegeneration is relatively few,

These two diagnostic groups of participants were recruited at the Nice University Hospital's Resources and Research Memory Centre and Cognition and Behaviour and Technology (CoBTeK) facilities located at the Institute Claude Pompidou in Nice, France. All these diagnostic group participants have been selected from the Nice University Hospital's neurology follow-up patient database. The patient groups had been initially diagnosed with the presence of neurodegeneration by a neurologist according to the diagnostic criteria from the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychological Association). Trained speech and language pathologists had documented their aphasiological assessment using the GREMOTs battery [37].

In order for us to detail out cognitive profiles, the diagnostic patient groups were screened with the Detection Test for Language Impairments in Adults and the Aged [38] which is a quick language screening for ageing individuals to determine potential neurodegenerative language problems developed for French-speaking regions, and *La Batterie Rapide d'Efficienc Frontale* [39] which is a French adaptation of the Frontal Assessment Battery at Bedside [40]. The BREF is a short screening task for cognitive abilities including mental flexibility, motor programming, interference, and inhibitory control. Finally, the diagnostic participants were screened with the French version of the Mini Mental State Examination to verify their cognitive abilities [41].

Our third group included a total of 63 healthy ageing individuals without any neurological and/or psychiatric impairments, who acted as control participants. The control group contained 47 females and 16 males, and their ages ranged between 40 and 91 with a mean of 60.03 (sd = 11.5). The control participants were screened with the MMSE before being admitted to the study, and individuals who scored below 27 out of 30 on this task were removed from our participant pool.

All the participants in this study were reported to be native French speakers without a significant effect of bilingualism. None reported to be bilingual from birth or having learned French as a second language. None of the participants had extended stays in a foreign country. They all were residents in the Côte d’Azur region including the metropolitan Nice and its surroundings.

Materials and procedures

We designed a sentence repetition span task in French to measure potential sentence repetition difficulty in PPA. The task contained 14 sentence stimuli in total with two items per span. We arranged “span” according to the number of content words, following a similar logic to the Sentence Repetition subtest of the Comprehensive Aphasia Test [42], which showed that sentence repetition span is a useful measure in aphasia assessment. The spans used in the current task ranged from simple sentences containing three content words (i.e., *Un étudiant fait ses devoirs*. “A student does his homework.”) to complex sentences with nine content words (*Les chercheurs en archéologie ont découvert une grande tombe romaine dont des squelettes et des outils tranchants*. “Researchers in archaeology have discovered a large Roman tomb including skeletons and sharp tools.”). The total number of words in those sentences ranged between 5 and 18. We particularly took the number of semantically loaded content words as sentential complexity, rather than manipulation of syntactic variables. This is because syntactic complexity is already known to pose processing challenges in PPA [43]. Therefore, we tried to reduce the impact of syntactic complexity while profiling sentence repetition deficits and we deliberately avoided using syntactically demanding structures as much as possible, such as embedded clauses, inversion, or passive structures. All the sentences used in this task were grammatically correct and semantically coherent. See Appendix 1 for a full list of materials used in the sentence repetition span task. Psychometric properties of the content words used in materials including word frequencies and syllable length were extracted from the LEXIQUE-2 French database [44]. The content words had a mean number of 1.94 syllables (SD = 0.84, min

= 1, max = 5). These content words had a mean surface frequency of 241.19 per million (SD = 564.25). Those psychometrics are given per content word in Appendix 2.

Table 1: Demographic and neuropsychological details of the participants.

Participant	Diagnosis	Gender	Age	Education (years)	MMSE	BREF	DTLA	Aetiology and affected areas
<i>Logopenic PPA group (n = 14)</i>								
1014GR	lvPPA	F	87	8	19	11	53	
1018DD	lvPPA	F	73	12	25	18	86	
1019NT	lvPPA	M	80	15	-	-	70	
1024AY	lvPPA	F	83	7	26	15	78	Moderate cortical and subcortical atrophy
1042CG	lvPPA	M	80	7	22	17	90	
10049SM	lvPPA	F	75	17	29	17	90	Moderate atrophy in the left perisylvian region including postcentral sulcus and medial frontal areas.
10051CA	lvPPA	F	71	7	25	14	86	Hypometabolism in the left planum temporal posterior temporal areas.
10056DJ	lvPPA	M	69	17	24	9	94	Lobar degeneration left posterior part of the parietal areas.
10064IN	lvPPA	M	52	7	28	15	78	fistula occlusion
10065VN	lvPPA	F	77	7	-	-	68	
10074GJ	lvPPA	M	88	13	27	16	92	Microangiopathy. Atrophy in sub arachnoid areas and the Ventricular System. No hippocampal anomaly.
10139PM	lvPPA	M	75	12	-	-	75	
10161GJ	lvPPA	F	78	7	20	-	57	Dilatation in the Ventricular System. Atrophy associated with Bilateral atrophy in hippocampal and connected areas.
10163AV	lvPPA	F	63	9	28	17	85	
<i>Semantic PPA group (n = 5)</i>								
01002SE	svPPA	M	55	15	27	15	62	Frontal-temporal degeneration
10040LJ	svPPA	F	79		22	15	77	Frontal-temporal degeneration
10077SM	svPPA	M	81	13	30	10	83	Frontal-temporal degeneration extending to insular regions
10146RY	svPPA	F	59	17	-	-	74	
10159MN	svPPA	M	71	12	5	-	40	Frontal-temporal degeneration. Hypometabolism in left temporo-parietal
<i>Alzheimer's Disease group (n = 13)</i>								
1013CV	AD	F	82	<4	-	7	55	Hypometabolism in bilateral frontal areas, global cortical atrophy predominantly in frontal areas
1015JO	AD	F	59	8	18	11	87	Bilateral hippocampal atrophy

1016NCA	AD	M	80	15	18	14	91	
1017CD	AD	M	83	9	29	14	88	Bilateral hippocampal atrophy
1039GD	AD	M	80	17	-	-	56	
1041MN	AD	F	88	9	22	10	71	
10068NJ	AD	M	74	13	24	15	94	global sub-cortical atrophy
10070BL	AD	F	82	7	5	5	51	
10071RP	AD	M	67	17	20	16	93	
10072AJ	AD	F	87	9	21	8	96	Global dilation observed in ventricular system and strong white matter atrophy in bilateral frontal cortices
10091OM	AD	F	85	7	-	-	98	
10160PL	AD	F	83	15	21	12	89	
10162SG	AD	M	79	9	17	13	85	Bilateral hippocampal atrophy. Hypometabolism in left parietal lobe. Global cortical and subcortical atrophy. Leukoaraiosis in periventricular region.

Each participant was examined in a single session. For the diagnostic patient group sessions took place at the Institute Claude Pompidou, or at their home when this is more convenient. For control participants, sessions took place in diverse places including the individuals' home or at the lab facilities of University of Cote d'Azur. Before administration of the sentence span task, participants were given the complimentary cognitive screening tasks and their demographic information were collected with a short questionnaire. During the sentence repetition tasks, participants were instructed that the experimenter would read aloud a sentence, they should listen carefully and repeat the sentence as much as they can remember. The experimenter recorded sessions with an audio recorder and then transcribed the responses. Each sentence was only presented once, on-demand presentation repeat was not permitted. The participants' sentence repetition duration was timed based on their voice onset and offset in order for us to be able to keep track of duration across participants. However, we did not impose a time off. We quantified the following variables:

- (a) *Sentence Span* measured the maximum span length in reference to content words presented in sentences. Participants were read aloud two sentences for each span length in an increasing linear order (i.e., the order of items was not random). When a participant made one mistake in a single sentence from a span, they were allowed to continue to the next span, but their mistakes were recorded and were given half a score. If they made

two mistakes in both sentences while repeating, the task was terminated, we recorded the last span length in which at least one sentence was correctly repeated.

- (b) *Number of Content Words* was the measure of total number of correctly repeated content words (i.e., disregarding function words such as pronouns, auxiliaries etc) including all sentences across all span length conditions.
- (c) *Total Number of Words* contained all words accurately repeated including both content words and function words.
- (d) *Number of Omissions* included all types of words that are omitted in the participants' responses.
- (e) *Number of Substitutions* were the instances in which participants produced an alternative word during repeating sentences. We quantified substitution errors for all words not only for content words, but this type of error occurred virtually exclusively for the latter type of words. Self-corrections were accepted, which happened very occasionally.
- (f) *Number of Phonological Errors* represents the total number of errors in which the participants produced forms of phonological paraphasias (i.e. *l'évier* vs. *lavier*, 'the sink').

The procedures reported here were piloted with a smaller portion of the participants in this study to understand general trends [45]. Following an initial evaluation, data collection was carried out with larger number of participants. While piloting we had aimed to include all variants of PPA including the nfvPPA variant, however, during the entire data collection process (2018-2022), we were not able to recruit more than one single case of a non-fluent individual with PPA. Given the issues of generalizing outcomes from single cases, we opted for removing this individual from further analyses. Participation in this study was voluntary and all the participants gave their consent that the data can be used for scientific purposes. One session with healthy controls took about 20-25 minutes, and with diagnostic group maximum 45 minutes. The participants received no monetary remuneration. Experimental procedures reported in this study adhere to the Helsinki Declaration and its associated statements for ethical principles for medical research involving human subjects. The procedures of the overall project were approved by the University of Groningen, Faculty of Arts Research Ethics Committee [CETO, Decision No. 76006271], and locally by Research Ethics Committee of the University of Côte d'Azur [CERNI, dossier no. 2019-2].

Results

Table 2 demonstrates means performances of participant groups on our sentence repetition task. The control participants performed with a mean span of 7 ranging between 5.5 and 8, which corresponded above most individuals with PPA and AD. Results from an initial linear mixed effects regression model on sentence span data have shown that all diagnostic patient groups performed lower than the healthy controls, including lvPPA ($\beta = -1.64$, $SE = 0.26$, $t = -6.22$, $p < .001$), svPPA ($\beta = -2.09$, $SE = 0.40$, $t = -5.21$, $p < .001$), and AD groups ($\beta = -1.42$, $SE = 0.25$, $t = -5.53$, $p < .001$). Comparisons between diagnostic groups did not show any reliable differences, however. The lvPPA group performance was comparable to the AD group ($\beta = 0.22$, $SE = 0.33$, $z = 0.67$, $p = .90$), and the svPPA group ($\beta = -0.67$, $SE = 0.45$, $z = -1.48$, $p = .42$). There were no reliable differences between the svPPA and AD group performances, either ($\beta = -0.44$, $SE = 0.45$, $z = -0.98$, $p = .74$).¹

Regarding the number of content words correctly produced, the picture was somewhat mixed as svPPA variant ($\beta = -13.77$, $SE = 5.88$, $t = -2.43$, $p = 0.02$) and the AD groups ($\beta = -8.31$, $SE = 3.86$, $t = -2.15$, $p = 0.03$) performed significantly lower than the control ranges. However, the lvPPA group showed slight trend but did not differ from the controls in the number of content words produced ($\beta = -6.42$, $SE = 3.75$, $t = -1.71$, $p = 0.09$). In terms of total number of correctly repeated words, only the AD group performed less accurately than the control group ($\beta = -16.66$, $SE = 7.35$, $t = -2.26$, $p = 0.02$), whilst either the lvPPA ($\beta = -11.17$, $SE = 7.13$, $t = -1.56$, $p = 0.12$) or the svPPA variant groups ($\beta = -16.14$, $SE = 11.19$, $t = -1.44$, $p = 0.15$) did not show reliable differences from the control group level. We found no significant differences between the three diagnostic groups in their repetition of both content words and total number of words (all $ps > .31$).

Table 2: Participants' sentence repetition span task performance outcomes in means, standard deviations are given in parenthesis.

Group	Sentence Span	Number of Content words	Total number of words	Number of substitution errors	Number of omission errors	Number of phonological errors (total count)
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¹ We run a second model with the inclusion of per-million averaged frequencies per item to check whether the frequency is impacting the span scores. Our subsequent mixed effect regression model returned that surface frequency is not a significant predictor of span scores ($\beta < 0.001$, $SE = 1.52$, $t = 0.02$, $p = 0.98$).

lvPPA (n = 14)	5.57 (0.93)	53.35 (15.35)	99.57 (25.65)	4.33 (2.79)	22.35 (11.83)	1.35 (19)
svPPA (n = 5)	4.90 (1.14)	46.00 (19.91)	94.60 (44.68)	3.60 (3.13)	21.80 (14.16)	1.20 (6)
AD (n = 13)	5.34 (1.31)	51.46 (17.43)	94.07 (32.12)	4.53 (2.81)	23.00 (14.14)	0.92 (12)
Control	7.00 (0.70)	59.97 (10.09)	110.98 (19.79)	0.91 (1.74)	1.29 (3.37)	--

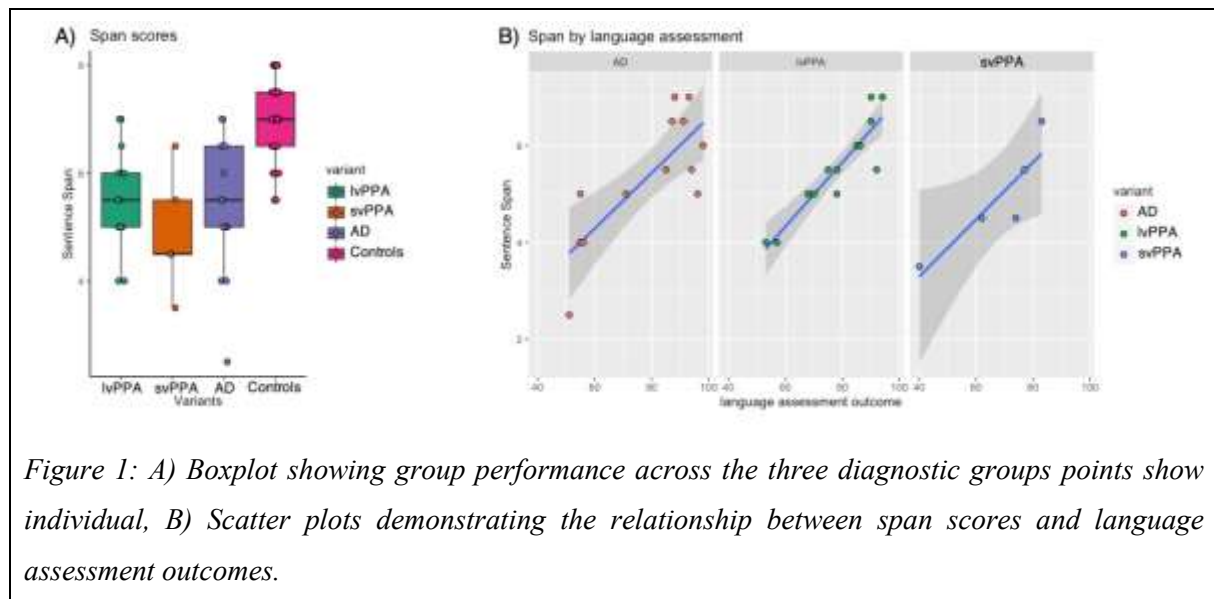


Table 3: Case-control comparisons computed per individual in the diagnostic group of participants. Control group mean sentence span is 7 (ranging between 5.5 and 8). Significant comparisons are bolded.

Logopenic PPA group			Semantic PPA group			Alzheimer's disease group		
Participant	Sentence Span	Test Statistics	Participant	Sentence Span	Test Statistics	Participant	Sentence Span	Test Statistics
1014GR	4	$t = -4.24, p < .001$	01002SE	4.5	$t = -3.53, p < .001$	1013CV	5	$t = -2.82, p = .006$
1018DD	6	$t = -1.41, p = .16$	10040LJ	5.5	$t = -2.12, p = .037$	1015JO	6.5	$t = -0.71, p = .48$
1019NT	5	$t = -2.82, p = .006$	10077SM	6.5	$t = -0.71, p = .48$	1016NCA	6.5	$t = -0.71, p = .48$
1024AY	5.5	$t = -2.12, p = .037$	10146RY	4.5	$t = -3.53, p < .001$	1017CD	7	$t = \text{null}$
1042CG	6.5	$t = -0.71, p = .48$	10159MN	3.5	$t = -4.95, p < .001$	1039GD	4	$t = -4.24, p < .001$
10049SM	7	$t = \text{null}$				1041MN	5	$t = -2.82, p = .006$
10051CA	6	$t = -1.41, p = .16$				10068NJ	5.5	$t = -2.12, p = .037$

10056DJ	7	$t = \text{null}$	10070BL	2.5	$t = -6.36,$ $p < .001$
10064IN	5	$t = -2.82, p$ $= .006$	10071RP	7	$t = \text{null}$
10065VN	5	$t = -2.82, p$ $= .006$	10072AJ	5	$t = -2.82,$ $p = .006$
10074GJ	5.5	$t = -2.12, p$ $= .037$	10091OM	6	$t = -1.41,$ $p = .16$
10139PM	5.5	$t = -2.12, p$ $= .037$	10160PL	4	$t = -4.24,$ $p < .001$
10161GJ	4	$t = -4.24, p$ $< .001$	10162SG	5.5	$t = -2.12,$ $p = .037$
10163AV	6	$t = -1.41, p$ $= .16$			

In the three diagnostic groups, we have observed an elevated number of errors during repetition as compared to the control groups. These errors included two different types: omissions where a word was completely omitted during repetition, and substitution errors in which a word was replaced (mostly with a semantically associated word). Both kinds of errors were only minimal in the control group's repetition outcomes. Outputs from a series of mixed effects regression models have shown that all three groups produced greater number of substitution errors as compared to controls (lvPPA: $\beta = 3.52$, $SE = 0.66$, $t = 5.26$, $p < .001$; svPPA: $\beta = 2.62$, $SE = 1.04$, $t = 2.50$, $p = .014$; and AD: $\beta = 0.97$, $SE = 0.29$, $t = 3.32$, $p = .001$). The diagnostic groups proved to commit a greater number of omission errors in their repetitions as compared to the control groups, who seldomly did one or two omissions. The greater number of omissions in three diagnostic groups than the control norms were also shown to be reliable by our statistical outputs (lvPPA: $\beta = 21.85$, $SE = 2.36$, $t = 8.98$, $p < .001$; svPPA: $\beta = 20.65$, $SE = 3.70$, $t = 5.58$, $p < .001$; and AD: $\beta = 21.85$, $SE = 2.51$, $t = 8.68$, $p < .001$). Pairwise comparisons revealed no significant differences across the three diagnostic groups in their amount of substitution and omission errors, however (all $ps > .82$).

It is indispensable to mention that our analysis has signalled large individual differences, even in the svPPA group of five individuals. See Figure 1B for an illustration of individual variability within each group.² Table 3 demonstrates individual sentence span scores per individual across

² An interesting point raised by an anonymous reviewer regarding variability in our data in reference to unbalanced male-to-female ratio in our diagnostic groups. We have run a set of nested models with gender as a fixed effect and as a random nested factor. The outputs have yielded that there are no critical gender differences in sentence span scores (Intercept $\beta = 6.99$; Gender $\beta = 0.42$, $SE = 0.31$, $t = 1.36$, $p = 0.17$), number of

the three diagnostic groups. In the lvPPA group 6 out of 14 individuals, in the svPPA group one individual, and in the AD group 5 out of 13 individuals proved intact in their sentence span scores as compared to the control group norms. What predicts this individual variability? One possibility is that their language abilities might be interfering with their sentence repetition performance. To be able to test whether or not potential language impairments are interfering with sentence repetition span, we have run a complementary analysis exploring the diagnostic groups' sentence span and their language assessment outcomes as measured with the DTLA. Figure 1B exhibits the linear relationship between language outcomes and sentence span scores across the three diagnostic group. Our regression analysis has indicated that in all groups, language assessment outcomes largely predicted sentence span scores (lvPPA: $\beta = 0.06$, SE = 0.008, $t = 7.65$, $p < .001$; svPPA: $\beta = 0.06$, SE = 0.01, $t = 3.27$, $p = .04$; and AD $\beta = 0.05$, SE = 0.01, $t = 4.26$, $p = .001$). This suggest that individuals who have better retained language abilities, the more likely they perform well on the sentence repetition span task.

We did a complementary analysis to quantify phonological errors in our diagnostic groups' sentence repetition outputs. Phonological errors in the control group were virtually unobserved except for a few cases where the participant self-corrected immediately. However, in the diagnostic groups, these errors were quantified to a much larger extent. The participants with lvPPA had committed a total of 19 instances of phonological error, with a mean error rate of 1.3 per individual, while the AD group had only 12, and svPPA group had 6 instances of phonological errors. Except for one participant with svPPA (i.e., 10077SM) and two participants with lvPPA (10056DJ, 10064IN) all participants with PPA had phonological errors ranging from one up to three. This type of error was rather more isolated in the AD group, only four out of 13 individuals made phonological errors. The number of phonological errors in lvPPA was statistically greater than in the AD group (Kruskal-Wallis $\chi^2 = 4.938$, $df = 1$, $p = 0.02$). There were no statistical differences between the svPPA and the lvPPA (Kruskal-Wallis $\chi^2 = 0.297$, $df = 1$, $p = 0.58$), or between the svPPA and the AD groups (Kruskal-Wallis $\chi^2 = 1.665$, $df = 1$, $p = 0.19$).

substitution errors (Intercept $\beta = 0.97$; Gender $\beta = -0.53$, SE = 0.82, $t = -0.64$, $p = 0.52$), and number of omission errors (Intercept $\beta = 1.14$; Gender $\beta = 1.88$, SE = 2.94, $t = 0.64$, $p = 0.52$). In all the three models three diagnostic variants have showed reliable differences compared to the control group, all $ps < 0.01$.

Discussion and Conclusion

The aim of this study was twofold: (i) understanding whether our three diagnostic groups (lvPPA, svPPA and AD) demonstrate greater sentence repetition difficulties than healthy ageing adults; (ii) and understanding whether the span task design would be useful in dissociating the lvPPA from other types of neurodegenerative conditions under scrutiny here (svPPA and AD type). To this end, we administered a sentence repetition task within a span task in which content words to be repeated increased as the span condition increased from three to nine content words. We have recruited groups of PPA (lvPPA = 14; svPPA = 5), AD (n = 13) and a control group (n = 61). Following the idea that sentence repetition difficulties in PPA might be associated with working memory intensive nature of verbal processing, which seems affected especially in the logopenic variant, we have explored the possibility whether individuals with the lvPPA would perform more poorly than the svPPA and the Alzheimer's disease patients. Our results showed that all the three diagnostic groups (lvPPA, svPPA, and AD) performed more poorly in all repetition span measures than the control group without showing critical pairwise group differences between those diagnostic groups. One differential impairment pattern that signalled for particular attention was found in the lvPPA group which made a relatively larger number of phonological errors than the AD group did, while no differences were observed for the svPPA group. Our expectations are therefore only partially met. It is possible to conceive that the span task is sensitive enough to distinguish impaired sentence repetition ability in neurodegenerative conditions investigated in this study. However, the picture for working memory intensive sentence repetition impairments as measured with sentence span being a reliable clinical marker for lvPPA seems far from being clear.

The control participants performed with a mean span of 7 content words on the sentence repetition span task. Immediate recall of 7 items is quite in line with Miller's *magical number seven* account for short term memory capacity [46], although modern psychologists analyse those seven spans to be comparable to 3-4 chunks of information [47,48]. It is therefore conceivable that the control participants reported in this study performed quite typically given these norms in the working memory literature. These results show that the selected sentences are able to assess short term memory capacity in relation to the number of content words. The diagnostic groups' performances were clearly below the control norms on average. The svPPA group had a mean span of 4.90 while the lvPPA group had 5.57 and the AD group had 5.34. This has suggested that the sentence span task was sensitive enough to dissociate the three

neurodegenerative conditions as compared to healthy controls. These diagnostic groups however did not differ among themselves with regard to the sentence span outcomes. Our findings are not consistent with Foxe et al. (2013) who found greater impairments in lvPPA than AD during sentence repetition while we fully support Leyton et. al (2014) who found their diagnostic groups showed affected sentence repetition but no significant group differences [13,28]. We partly support Beales et al. (2019) who found both their AD and lvPPA groups to perform poorly as compared to healthy controls without a critical pairwise difference between the two groups [31]. However, Beales et al. (2019) found people with svPPA to be performing more poorly than lvPPA and AD, which our results are not reconcilable with. Recall that lvPPA is often associated with an underlying AD pathology during the initial phases of the disease and that selective impairments in phonological short term memory might be observed in both lvPPA and AD [49]. Therefore, no critical working memory intensive sentence repetition differences in both the groups comes as no surprise. No significant difference between the svPPA and lvPPA groups' sentence repetition span is at odds with some studies [31,32]. However, this might be due to a small number of people with svPPA recruited under the current study, and we should note that there was a large heterogeneity even in such as a small number of five people with svPPA. However, it is important to mention that there were large individual differences. Eight individuals in both the lvPPA and AD groups and four individuals in the svPPA group performed more poorly showing a clear dissociation as compared to the controls. The other six individuals in lvPPA, one in svPPA, and five in the AD group were intact in repeating sentences performing within the control norms. How can this extent of individual variability be explained?

One possibility is that the participant groups may be sensitive to certain psycholinguistic features such as familiarity and typicality of stimulus characteristics. Such features have been shown to influence object naming in neurodegenerative conditions [50]. In semantic variants of frontotemporal degeneration, object naming ability is better preserved for typical and familiar items [51]. Therefore, it is a possibility that familiarity with the nouns utilized in our sentences may have resulted in such a variable pattern of sentence repetition performance. However, if our participants were influenced by an item level effect, we would have observed a greater variability across items. Particularly, in both the lvPPA and svPPA groups, individuals were able to repeat sentence stimuli up until around the span of four to five content words without much trouble (see Table 3). Furthermore, these content words used within these sentences included highly frequent and common everyday nouns (e.g., girl, teacher, door, cake

etc.) and simple transitive verbs (e.g., eat, do, close, chase). It is therefore unlikely to contemplate that the variability in our diagnostic groups' performances was due to a sheer set of psycholinguistic characteristics including familiarity, typicality and/or frequency. A second possibility we cannot rule out is that semantic characteristics of content words may have as well resulted in differential performances. In svPPA, the ability to recognise certain semantic categories is only selectively impaired, suggesting that sentence repetition difficulty in the svPPA group might be related to alterations in semantic memory. For instance, animate objects are often found to be better preserved than inanimate ones, and interestingly this impairment pattern is not influenced by psycholinguistic factors such as familiarity or frequency [52]. Although recognition of objects in a picture matching task does not directly warrant verbatim impairments in the repetition modality in aphasic syndromes, there is still a possibility that particularly the svPPA individuals tested under the current study might have difficulty recognising certain objects in auditory sentence stimulus presented to them to repeat. While it would be speculative to argue that our participants might have blended agnostic impairments³, it is clearly demonstrated that the severity of language impairments predicted the scaled sentence repetition span scores (see Figure 1B). A rather limitation under the current study is that we have not measured how far the severity of object naming and semantic category impairments in PPA influenced their sentence repetition ability. Indeed, this could have enabled us to verify whether the scores obtained, particularly by svPPA, related to an underlying impairment with the semantic content of words used as opposed to difficulty in repeating them without accessing the semantic system. Nonetheless, the data so far seem to suggest that the individuals with severely impaired language abilities overall tend to experience greater difficulty repeating sentences. It is highly possible that sentence repetition difficulty in PPA and AD is modulated with extensive short-term memory deficits that might be picked up by a span task. Note that Beales et al. (2019) found a significant correlation with forward digit span task outcomes, but not with backward digit task, and their diagnostic groups' performances on sentence repetition [31]. The authors argued that sentence repetition and digit span might be requiring equivalent demands on the working memory capacity. Although the authors do not report whether this correlation holds in each subvariants of PPA, it is obvious that our findings

³ In fact, agnostic word deafness impairments are not completely unheard of in PPA, especially when cortical atrophy strongly extends to the left superior temporal regions Otsuki, M., Soma, Y., Sato, M., Homma, A., & Tsuji, S. (1998). Slowly progressive pure word deafness. *European Neurology*, 39(3), 135-140. . At the absence of millimetric cortical atrophy data or further object recognition and comprehension data, however, it is impossible to contemplate whether some of our participants showed variability in sentence repetition due to impaired content word comprehension or a form of agnosia.

are reconcilable with the idea that repetition deficits might be predicted by memory spans. We tested this claim using a sentence span task in which the increasing number of content words were manipulated as spans. We found that a reduced sentence span is a common characteristic of the three neurodegenerative conditions alike. We therefore support Beales et al. (2019) claim that sentence repetition deficits may be modulated with working memory demands; nonetheless, our data spell cast on the idea that those working memory-intensive sentence repetition deficits reveal critical diagnostic differences between the neurodegenerative groups [31].

Two final critical issues need further attention. First, it is practicable to assume that sentence stimuli used in this study are somewhat different from previous studies, which may have resulted in certain disparities. While we used content words as critical span length, other sets of studies used sentences with meaningful words versus pseudowords [29,33,53], different lengths of syllables [28], and sentences with different syntactic constructions [30,31]. An important possibility that cannot be ruled out is that stimulus characteristics influence sentence repetition ability. It is obvious that working memory capacity is influenced by stimulus type and characteristics in visual span tasks [54]. If we follow this logic, our finding that there were no critical group differences between the diagnostic groups with regard to sentence span, the mean numbers of words and the total number of content words produced may be due to the fact that repetition span length based on content words is not sensitive enough to distinguish different neurodegenerative conditions. In span length of up to five content words, our sentences involved simple transitive verbs (catch, eat, close etc) requiring animate subjects (i.e., a girl, or a cat etc.) and either inanimate objects such as ‘cake’ and ‘door’, or animate objects such as a ‘mouse’ (see Appendix 1). However, from the span length of six content words, stimulus materials began to be complex encompassing syntactic coordination with more than one matrix clause connected with ‘but’ or ‘so’. This is suggestive that syntactic complexity seems to play a role, although we deliberately aimed to keep it low by excluding notoriously complex constructions such as embedded clauses, inversion, and passive voice. There is good evidence that different syntactically complex constructions might add additional processing difficulties during repeating sentence material, see Hohlbaum et al. (2018) for German, Macoir et al. (2021) for French PPA and Small et al. (2000) for AD patients [30,35,55]. A further point was raised by an anonymous reviewer, according to which a potential syntactic effect here is that certain items might be susceptible to attraction errors with regard to subject-verb agreement. This is based on the idea that in sentences with extended prepositional phrases (see,

for instance, Item 13: *Les chercheurs en archéologie ont découvert* ‘The researchers in archaeology have discovered’) listeners might tend to illicitly licence the verb in singular form[56]. This is not what we observed, however. Four individuals with lvPPA (1024AY, 10049SM, 10056DJ, 10068NJ) who made it until this item fully produced the verb in plural form, and many other individuals had to terminate the task before this item. We should note that illicit licencing often happens in French due to complexity of plural verb forms, nonetheless, it does not seem to us as a significant error pattern that characterised our diagnostic groups’ sentence repetition performance. Notwithstanding the lack of attraction errors, we are unable to ultimately rule out potential syntactic complexity effects on sentence repetition in our diagnostic groups. It is not much possible to tease apart whether sentence repetition ability in PPA is independent of syntactic complexity since it is very difficult to banish the impact of syntactic complexity effects while designing meaningful sentences after a considerable number of words. However, a future study might take the courage to investigate this issue within a recall task using random word strings as stimulus items to be memorized.

The second issue that needs highlighting here is that the logopenic variant of PPA might be characterised with more phonological short term memory impairments than semantic ones. We have observed similar cases of semantic renditions reported in Henry & Gorno-Tempini (2010) [5]. Two participants (1019NT and 1042CG) produced semantically appropriate alternations, such as for the phrase *Le lapin s’est échappé très vite* ‘The rabbit has escaped very quickly’ these participants repeated *Le lapin a fui (rapidement)* ‘The rabbit has run away (rapidly)’. Although, we may have expected such a strategy to reduce semantic load while repeating an increased number of content words in the sentence materials to be a global issue in lvPPA, no other people with lvPPA except for the two individuals demonstrated such a rendition strategy. Complete omissions of words were much more common. However, the number of both types of substitution and omission errors did not differ across the lvPPA, svPPA and AD groups. While the current study showed no clear diagnostic useability of sentence span with varying numbers of content words to distinguish lvPPA from AD and svPPA, it undoubtedly showed that the people with lvPPA produced an elevated number of phonological errors during repeating sentences. This finding is fully compatible with studies that characterized this disorder with a form of phonological loop deficiency [4,49]. Very typical phonetical errors included adding a word initial consonant (e.g. ‘*attraper*’ to ‘*ratrapper*’) or alternated voicing of vowels (‘*l’évier*’ to ‘*lavier*’). A strong possibility yet to be tested has to do with the vocal and acoustic features of stimulus to be repeated, including voice reaction time, silent pauses, and

prosodic parameters. These features acting as sensitive markers dissociating lvPPA has been in fact shown to be affected [57].

In conclusion, we showed that all patient groups with a neurocognitive disorder under this study (lvPPA, svPPA, and AD) exhibit a sentence repetition difficulty as compared to the healthy controls but within the diagnostic groups they had sentence repetition span outcomes that are indistinguishable from each other. This suggests that sentence repetition span is in general reduced in neurocognitive disorders, which is modulated by a reduced working memory capacity. In other words, our diagnostic group participants had severer impairments in sentence repetition as the span length increased. Nonetheless, working memory intensive sentence repetition impairment as measured with our sentence span tasks built upon number content words does not seem to be a clear sensitive marker of lvPPA distinguishing this variant from other neurocognitive disorders with a neurodegenerative pathology. We further conclude that sentence repetition difficulty in lvPPA is associated with a large number of phonological errors, which warrants more in-detail investigation regarding the nature of sentence repetition ability and capacity for phonological memory.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

SA, FM, VM, AG conceived the study, SA & FM conceptualized and prepared the task materials, AP, MGC, VM, AG, AM, JL, GS supervised the data collection process, SA analysed data and drafted the article, ALL authors revised the draft.

Funding

This project is supported by funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie Action [grant agreement no. 838602] awarded to Seçkin Arslan, and from an interdisciplinary doctoral grant from the NeuroMod Institute awarded to Alexandra Plonka.

Acknowledgments

We are grateful to our participants and their dependents for their effort in participating our study. We are also grateful to our student assistants Juliette Cheng and Tess Meyer who aided during data collection phases in this study. We are also grateful to members of Collaborations of Aphasia Trialists (CATs) Aphasia Assessment and Outcomes Working Group for their insightful discussion.

Data Availability Statement

The datasets generated for this study are available from the authors upon reasonable request.

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Supporting Information

Appendix 1: List of stimulus materials used in the sentence repetition span task with translations. Content words are bolded.

Item	Span (Total words)	Stimulus
1	3 (5)	<i>La fille mange un gâteau.</i> “The girl eats a cake ”
2	3 (5)	<i>Un étudiant fait ses devoirs.</i> “A student does his homework .”
3	4 (6)	<i>L’enseignant part et ferme la porte.</i> “The teacher leaves and closes the door .”
4	4 (7)	<i>Le chat a chassé une petite souris.</i> “The cat chased a little mouse .”
5	5 (8)	<i>Les oiseaux sont nichés sur un grand arbre vert.</i> “The birds are nestled on a tall green tree .”
6	5 (9)	<i>La mère du garçon a acheté des amandes au marché.</i> “The boy’s mother bought almonds at the market .”
7	6 (11)	<i>Une jeune fille a tenté un plongeon pendant ses vacances en juillet.</i> “A young girl attempted a dive while on vacation in July .”
8	6 (12)	<i>Le vieil homme est en retard alors il veut prendre un taxi.</i> “The old man is late so he wants to take a taxi ”
9	7 (13)	<i>L’évier de la cuisine est très bouché mais le réparateur utilise une pompe.</i> “The kitchen sink is very clogged but the repairman uses a pump .”
10	7 (14)	<i>Au restaurant la femme du professeur a mangé des nouilles asiatiques pour le déjeuner.</i> “At the restaurant the teacher’s wife ate Asian noodles for lunch .”
11	8 (16)	<i>Le lapin s’est échappé très vite dans la forêt et le chasseur n’a pas réussi à l’attraper.</i> “The rabbit escaped very quickly in the forest and the hunter failed to catch him.”
12	8 (16)	<i>Les touristes ont découvert les immenses sculptures de bronze du musée grâce à la visite guidée.</i> “ Tourists discovered the museum’s huge bronze sculptures through the guided tour .”
13	9 (17)	<i>Les chercheurs en archéologie ont découvert une grande tombe romaine dont des squelettes et des outils tranchants.</i> “ Archaeological researchers have discovered a large Roman tomb with skeletons and sharp tools .”
14	9 (18)	<i>Les océans deviendront nos ennemis si rien n’est fait pour freiner le réchauffement dû aux émissions de gaz.</i> “The oceans will become our enemies if nothing is done to curb the warming from gas emissions .”

Appendix 2: Psychometric properties of stimulus materials including lemma and surface frequencies (per million) together with number of letters and syllables for each content word used in the span task.

<i>Item</i>	<i>Word</i>	<i>Lemma</i>	<i>Lemma Frequency</i>	<i>Surface Frequency</i>	<i># Letters</i>	<i># Syllables</i>
1	<i>fille</i>	<i>Fille</i>	841,56	627,59	5	1
1	<i>gâteau</i>	<i>Gâteau</i>	55,19	42,33	6	2
1	<i>mange</i>	<i>Manger</i>	467,82	103,81	5	1
2	<i>devoirs</i>	<i>Devoir</i>	63,59	20,7	7	2
2	<i>fait</i>	<i>Faire</i>	8813,48	2751,99	4	1
2	<i>étudiant</i>	<i>Étudiant</i>	38,07	10,12	8	3
3	<i>enseignant</i>	<i>Enseignant</i>	3,94	1,63	10	3
3	<i>fermer</i>	<i>Fermer</i>	238,65	48,85	6	2
3	<i>porte</i>	<i>porte</i>	333,85	288,39	5	1
3	<i>part</i>	<i>partir</i>	1111,97	67,76	4	1
4	<i>chassé</i>	<i>chasser</i>	54,93	6,62	6	2
4	<i>chat</i>	<i>chat</i>	93	57,71	4	1
4	<i>petite</i>	<i>petit</i>	1106,8	355,66	6	2
4	<i>souris</i>	<i>souris</i>	21,94	21,94	6	2
5	<i>arbre</i>	<i>arbre</i>	81,69	49,29	5	1
5	<i>grand</i>	<i>grand</i>	638,72	338,27	5	1
5	<i>nichés</i>	<i>nicher</i>	1,52	0,02	6	2
5	<i>oiseaux</i>	<i>oiseau</i>	77,73	33,96	7	2
5	<i>vert</i>	<i>vert</i>	52,59	24,74	4	1
6	<i>acheté</i>	<i>acheter</i>	290,7	72,38	6	3
6	<i>amandes</i>	<i>amande</i>	2,19	1,13	7	2
6	<i>garçon</i>	<i>garçon</i>	251,51	188,41	6	2
6	<i>marché</i>	<i>marcher</i>	364,37	44,87	6	2
6	<i>mère</i>	<i>mère</i>	686,79	672	4	1
7	<i>fille</i>	<i>fille</i>	841,56	627,59	5	1
7	<i>jeune</i>	<i>jeune</i>	297,01	234,9	5	1
7	<i>juillet</i>	<i>juillet</i>	11,97	11,96	7	2
7	<i>plongeon</i>	<i>plongeon</i>	2,98	2,71	8	2
7	<i>tenté</i>	<i>tenter</i>	79,75	21,7	5	2
7	<i>vacances</i>	<i>vacance</i>	67,9	67,6	8	2
8	<i>homme</i>	<i>homme</i>	1123,55	781,11	5	1
8	<i>prendre</i>	<i>prendre</i>	1913,83	465,77	7	1
8	<i>retard</i>	<i>retard</i>	126,45	125,65	6	2
8	<i>taxi</i>	<i>taxi</i>	63,77	59,42	4	2
8	<i>veut</i>	<i>vouloir</i>	5249,3	701,19	4	1
8	<i>vieil</i>	<i>vieil</i>	34,69	34,69	5	1
9	<i>bouché</i>	<i>bouché</i>	2,38	1,22	6	2
9	<i>cuisine</i>	<i>cuisine</i>	87,92	85,08	7	2
9	<i>pompe</i>	<i>pompe</i>	22,92	10,51	5	1
9	<i>réparateur</i>	<i>réparateur</i>	1,04	0,95	10	4

9	<i>très</i>	<i>très</i>	1589,92	1589,92	4	1
9	<i>utilise</i>	<i>utiliser</i>	182,44	31,68	7	3
9	<i>évier</i>	<i>évier</i>	3,87	3,81	5	2
10	<i>asiatiques</i>	<i>asiatique</i>	3	0,55	10	3
10	<i>déjeuner</i>	<i>déjeuner</i>	51,34	50,32	8	3
10	<i>femme</i>	<i>femme</i>	1049,32	806,57	5	1
10	<i>nouilles</i>	<i>nouille</i>	4,37	3,35	8	1
10	<i>professeur</i>	<i>professeur</i>	98,55	90,02	10	3
10	<i>restaurant</i>	<i>restaurant</i>	50,04	44,29	10	3
10	<i>mangé</i>	<i>manger</i>	467,82	60,43	5	2
11	<i>attraper</i>	<i>attraper</i>	112,52	35,32	8	3
11	<i>chasseur</i>	<i>chasseur</i>	34,92	21,27	8	2
11	<i>forêt</i>	<i>forêt</i>	34,94	29,57	5	2
11	<i>lapin</i>	<i>lapin</i>	39,28	26,59	5	2
11	<i>réussi</i>	<i>réussir</i>	131,88	78,63	6	3
11	<i>vite</i>	<i>vite</i>	491,64	491,64	4	1
11	<i>échappé</i>	<i>échapper</i>	95,07	19,84	7	3
11	<i>très</i>	<i>très</i>	1589,92	1589,92	4	1
12	<i>bronze</i>	<i>bronze</i>	3,37	3,15	6	1
12	<i>découvert</i>	<i>découvrir</i>	124,2	46,22	9	3
12	<i>guidée</i>	<i>guider</i>	24,79	1,55	6	2
12	<i>immenses</i>	<i>immense</i>	21,56	2,55	8	2
12	<i>musée</i>	<i>muser</i>	0,44	0,17	5	2
12	<i>sculptures</i>	<i>sculpture</i>	7,12	1,64	10	2
12	<i>touristes</i>	<i>touriste</i>	14,36	10,31	9	2
12	<i>visite</i>	<i>visite</i>	99,95	86,34	6	2
13	<i>archéologie</i>	<i>archéologie</i>	1,42	1,42	11	5
13	<i>chercheurs</i>	<i>chercheur</i>	5,74	2,58	10	2
13	<i>outils</i>	<i>outil</i>	14,18	10,56	6	2
13	<i>romaine</i>	<i>romain</i>	1,99	0,34	7	2
13	<i>squelettes</i>	<i>squelette</i>	6,75	1,65	10	2
13	<i>tombe</i>	<i>tombe</i>	49,67	41,33	5	1
13	<i>tranchants</i>	<i>tranchant</i>	2,54	0,2	10	2
13	<i>découvert</i>	<i>découvrir</i>	124,2	46,22	9	3
13	<i>grande</i>	<i>grand</i>	638,72	198,25	6	1
14	<i>deviendront</i>	<i>devenir</i>	438,57	2,15	11	3
14	<i>ennemis</i>	<i>ennemi</i>	92,37	29,22	7	3
14	<i>freiner</i>	<i>freiner</i>	7,43	1,63	7	2
14	<i>gaz</i>	<i>gaz</i>	36,33	36,33	3	1
14	<i>océans</i>	<i>océan</i>	24,89	2,03	6	3
14	<i>rien</i>	<i>rien</i>	2374,91	2374,91	4	1
14	<i>réchauffement</i>	<i>réchauffement</i>	1,02	1,02	13	3
14	<i>émissions</i>	<i>émission</i>	32,31	4,56	9	3
14	<i>fait</i>	<i>faire</i>	8813,48	2751,99	4	1

Publication 5

Logogenic Primary Progressive Aphasia or Alzheimer Disease: Contribution of Acoustic Markers in Early Differential Diagnosis



Article

Logogenic Primary Progressive Aphasia or Alzheimer Disease: Contribution of Acoustic Markers in Early Differential Diagnosis

Eloïse Da Cunha, Alexandra Plonka, Seçkin Arslan, Aurélie Mouton, Tess Meyer, Philippe Robert, Fanny Meunier, Valeria Manera and Auriane Gros

Special Issue

Pathophysiology and Treatment of Neurodegenerative Aphasias

Edited by

Prof. Dr. Philippe Robert, Dr. Auriane Gros and Prof. Dr. Joel Macoir

Abstract

The logopenic variant of Primary Progressive Aphasia (lvPPA), a syndromic disorder centered on language impairment, often presents variable underlying neurodegenerative pathologies such as Alzheimer Disease (AD). Actual language assessment tests and lumbar puncture, focused on AD diagnosis, cannot precisely distinguish the symptoms, or predict their progression at onset time. We analyzed acoustic markers, aiming to discriminate lvPPA and AD as well as the influence of AD biomarkers on acoustic profiles at the beginning of the disease. We recruited people with AD ($n = 8$) and with lvPPA ($n = 8$), with cerebrospinal fluid biomarker profiles determined by lumbar puncture. The participants performed a sentence repetition task that allows assessing potential lvPPA phonological loop deficits. We found that temporal and prosodic markers significantly differentiate the lvPPA and AD group at an early stage of the disease. Biomarker and acoustic profile comparisons discriminated the two lvPPA subgroups according to their biomarkers. For lvPPA with AD biomarkers, acoustic profile equivalent to an atypical AD form with a specific alteration of the phonological loop is shown. However, lvPPA without AD biomarkers has an acoustic profile approximating the one for DLFT. Therefore, these results allow us to classify lvPPA differentially from AD based on acoustic markers from a sentence repetition task. Furthermore, our results suggest that acoustic analysis would constitute a clinically efficient alternative to refused lumbar punctures. It offers the possibility to facilitate early, specific, and accessible neurodegenerative diagnosis and may ease early care with speech therapy, preventing the progression of symptoms.

Keywords: primary progressive aphasia; logopenic variant; Alzheimer's disease; diagnosis; acoustic markers; prosody; early markers

Introduction

To preserve the autonomy of the geriatric population with neurodegenerative decline, speech therapy is the most proven and useful intervention which maintains functional communication [1]. Nonetheless, speech therapy is efficient if care is initialized at the onset time of the pathology and if it is based on a specific diagnosis. Primary Progressive Aphasia (PPA) syndrome presents a debated diagnostic classification and its links with Alzheimer's disease (AD) are still debated today [2,3]. Therefore, the imprecisions regarding the distinction between PPA and AD obstruct their differential and specific diagnosis. In this context, care is delayed and the prognosis of maintained autonomy is reduced [4].

Consequently, early specific diagnosis of neurodegenerative pathologies is crucial for adapting non-pharmacological interventions.

PPA is a neurodegenerative syndrome characterized by an isolated language impairment [5–7]. The consensual diagnosis criteria is the presence of aphasia as the primary cause of deficits in daily living activities, at the onset and in the initial phases of the disease [5]. Moreover, PPA affects more men than women, contrary to other neurodegenerative pathologies such as AD [4,8]. These clinical and demographic particularities differentiate PPA from other neuropathological diseases despite its heterogeneity [6,7,9]. The consensus classification of PPA distinguishes three subtypes under their clinical and neuropathological particularities: the non-fluent/agrammatic variant (nfvPPA), the semantic variant (svPPA) and the logopenic variant (lvPPA). Some non-classified groups persist, such as mixed forms [10–13]. In the evolution of PPA, language impairment remains the most characteristic symptom [6,11]. As it evolves, deficits can extend to other cognitive capacities such as psychiatric, neurologic and/or praxis capacities [13,14]. Most PPA cases progress to global neurodegenerative pathologies [9]. The incidence of the underlying pathology type varies according to the PPA subtype [9]. According to the literature, svPPA is the most homogeneous subtype, with on average 85.7% of frontotemporal lobar degeneration (FTLD) and 14.3% of AD [2,15]. Similarly, nfvPPA shows 86.1% FTLD, 5.6% AD, and 8.3% other pathologies such as Lewi-body dementia [2,16,17]. Finally, the major underlying pathology for lvPPA is AD with on average 55.6% of lvPPA cases, but it is, at this moment unpredictable: 35.5% of lvPPA degenerates as FTLD variants and 8.9% as other pathologies such as Lewi-body dementia [2].

Even if the underlying pathology can vary, clinical markers in lvPPA are most often associated with underlying early-onset AD [17,18]. In both pathologies, anomia and selective short term memory deficits are observed [11,18–20]. Speech output is affected by long word-finding

pauses potentially caused by lexical retrieval impairment [9,11,19,20]. In lvPPA, language impairments are often blended with episodic memory deficits, one of the first AD symptoms observed [17–19]. At an advanced stage of lvPPA, the deficit radiates to other general cognitive abilities which are often impaired in AD, such as visuospatial abilities, memory, attention, and apathy [6]. lvPPA decline is atypical from other PPA subtypes in its fast progression of language disorders and the appearance of secondary cognitive impairments [18]. Furthermore, similarities in cortical atrophy patterns are oftentimes observed in AD and lvPPA: atrophy in the posterior superior temporal and middle temporal gyri and inferior parietal lobe, associated with the phonological loop and naming functions, and posterior parietal or Perisylvian hypometabolism [9,21,22]. Neuro-anatomic alterations in lvPPA have increasing similarities with the amnesic AD neuro-anatomic alterations described in the literature [21,23].

Consequently, the clinical and neurological evolution of lvPPA is close to an atypical AD phenotype, which highly complicates differential diagnosis [22–24]. Clinical and language assessments based on lvPPA clinical criteria are not sensitive enough to distinguish these pathologies [10,25]. Some differences are noticed in clinical tests, such as non-verbal episodic memory or repetition tasks, but the difference is not sufficient to obtain a significant classification [10,26]. Currently, we succeed in precise early diagnosis of PPA subtypes and AD thanks to the association of neuro-anatomic analyses with Cerebrospinal Fluid (CSF) biomarkers [27–30]. Indeed, a decrease of β -Amyloid markers and a high tau concentration confirms AD pathology [30]. Nonetheless, 60 to 90% of lvPPA patients present β -Amyloid AD markers in their CSF [10,31]. CSF biomarkers, then, cannot be a sufficient diagnostic measure to differentiate AD and lvPPA at the onset time of cognitive decline. Nonetheless, precision on PPA classification and, specifically, the sub-classification of lvPPA and its links with an underlying AD is achievable: an amyloid-negative subtype of lvPPA ($-lvPPA$) and an amyloid-positive sub-type ($+lvPPA$) have been described according to CSF biomarkers concentration [32]. The subtype $+lvPPA$ would present an underlying onset of AD behind the lvPPA syndrome [10,25,33,34]. Neuroimaging studies support this hypothesis, showing AD neuropathologies in $+lvPPA$: a more prominent hypometabolism of the left temporoparietal region than in $-lvPPA$ [10,25,34]. Neurologic particularities in $-lvPPA$ consist of lower hypometabolism in the left temporo-parietal region. Hypometabolism is also extended to the anterior temporal and basal frontal regions in the $-lvPPA$ subtype [32]. This would explain the heterogeneity of the lvPPA group and its links with AD.

Lumbar puncture is the most effective intervention for extracting CSF and obtaining significant biomarker concentrations [29,33]. Despite its great diagnostic sensitivity and specificity, the

lumbar puncture is an invasive procedure with possible side effects [35]. It is often refused by patients during diagnosis searches because of its potential side effects [36]. An inequality of accessibility depending on place of residence and the expensive cost have been raised as obstructions to early diagnosis [29,35]. Nonetheless, CSF biomarkers, associated with clinical and neuroimage analyses, remain the most sensitive and specific diagnostic tool to discriminate AD at initial phases from other neurodegenerative pathologies [37].

Thus, the early differentiation of heterogeneous forms of lvPPA from AD has not yet been achieved. Nowadays, the presence of language impairment is one of the principal clinical markers for the diagnosis of PPA subtypes. Particularly, sentence repetition tasks are the most relevant clinical tools for discriminating lvPPA from other PPA subtypes, with different performances compared to people with AD [25,26]. Language assessment scores are not always sufficient for a sensitive and specific diagnosis [26]. Nonetheless, new technologies have led to the development of improved, more sensitive, specific and non-invasive tests [38,39]. Automated data analysis permits precise language analysis during assessment, using acoustic and vocal features [40]. Certain vocal and acoustic alterations cannot be perceived by human natural hearing but can be detected by automatic analyses, which have the potential to reveal discriminant features making the diagnosis more accurate and efficient [41,42]. Automated acoustic and vocal analysis has been described as a non-invasive representative marker of AD or PPA subtypes, distinguishing them from other neurodegenerative diseases at onset-time [41,43]. Specific temporal and acoustic features have been described for both lvPPA and AD voices [40,44]. Sentence repetition is also the most relevant acoustic feature for voice analysis and the most sensitive task focusing on language-specific selective impairment in the phonological loop in lvPPA [45].

Therefore, the aim of the present study is to identify vocal and acoustic markers discriminating lvPPA and AD and to analyze their impact in diagnosis as well as the influence of AD biomarkers on vocal and acoustic characteristics in a sentence-repetition task at an early stage of neurodegenerative decline.

Materials and Methods

Ethics

This study was approved by CPP Ile de France X (N° IDRCB: 2019-A00342-55 accepted on 11 September 2019). At the time of diagnosis, patients and relatives were informed of their inclusion in this study and could decline their participation or withdraw consent. Data was anonymized before the analyses.

Population

This prospective monocentric study recruited patients at Claude Pompidou Institute, the Research, Resources and Memory Center (CMRR) in Nice. Patients were recruited from memory consultations from October 2020 to March 2022. Patients had to correspond to the following inclusion criteria: being of age 40 or over, having been diagnosed of lvPPA or AD according to Gorno-Tempini classification and DSM-5TM criteria [11,46], speaking, reading and writing French fluently, having consulted the CMRR because of cognitive behavioral and/or motor difficulties, having French insurance coverage, having no objections to inclusion after reading the information note. The exclusion criteria for this study were: the existence of protective measures such as guardianship or curatorship, medication prescription with side effects on the central nervous system or interfering with the test execution or results, cerebrovascular disease history, psychiatric disorder history according to DSM-4TR criteria, any neurological pathology except lvPPA and AD, traumatic brain injury, untreated metabolic trouble, uncorrected hearing and vision problems and/or refusal to undergo paramedical examination such as lumbar puncture, MRI (Magnetic Resonance Imagery) and/or PET-SCAN (fluorodeoxyglucose Positron Emission Tomography scan).

The lvPPA diagnosis was determined by clinical and medical imaging data according to the criteria by Gorno-Tempini et al. [11]. The patient had to present impaired single-word retrieval in spontaneous speech and naming, and an impaired repetition of sentences and phrases. The clinical diagnosis was reached when three of the following features were related: phonologic errors in spontaneous speech and naming, spared single-word comprehension and object knowledge, spared motor speech, absence of frank agrammatism. The GréMots tests associated with the Detection Test of Language impairments in Adults (DTLA) were used to objectify these clinical characteristics [47,48]. Imaging diagnosis was based on the detection of predominant left posterior perisylvian or parietal atrophy on MRI or predominant left posterior

perisylvian or parietal hypoperfusion or hypometabolism on PET-SCANS [11,18]. In our study, the correlation of clinical and imaging diagnosis criteria validated lvPPA diagnosis. AD, considered as amnesic AD, was diagnosed by associated clinical, neuroimaging and CSF biomarkers analyses according to DSM-5TM criteria [46]. Clinical assessment corresponds to linguistic and neuropsychological tests. Imaging analyses were performed with MRI and PET-SCANS. Biomarker measures were obtained on a CSF sample by lumbar puncture.

Initially, 22 patients had met the inclusion criteria. However, 6 patients were excluded from the study because they refused to undergo the lumbar puncture. Therefore, the studied sample was composed of 8 patients with AD, and 8 patients with lvPPA, including 4 -lvPPA patients and 4 +lvPPA patients. The demographic and clinical descriptive data of the two groups and two sub-groups is summarized in Table 1. All patients were right-handed. Each patient from the AD group was matched with one patient from the lvPPA group, according to their age, educational level and cognitive level, as measured by the Minimal Mental State Examination (MMSE) score. All patients and relative caregivers only related cognitive difficulties. No behavioral or motor complaints were related.

Protocol Procedure

At their first consultation, patients orally received the necessary information for understanding the study and an informative note resuming these explanations. Then, patients signed the no-objection form at inclusion and investigators verified inclusion criteria. At the same time, paramedical examination was required for the patient to continue the study. An imaging exploration by MRI and/or PET-SCAN was performed. Patients had to undergo lumbar puncture to obtain CSF biomarker concentrations. If patients refused these additional examinations, they were excluded from the study. Then, anamnestic and descriptive data, resumed in Table 1, were collected. Anamnestic data include psychometric tests results: DTLA screening language impairment, MMSE precising cognition level, Instrumental Activities of Daily Living (IADL) scale as an autonomy score from 0 to 4, the Batterie Rapide d'Efficiency Frontale (BREF, "rapid evaluation of frontal efficiency"), screening executive functions, and categorical fluency tested on animals to evaluate lexical access and verbal working memory. To score language impairment, the practitioner administered the DTLA [48]. Investigators added a sentence repetition task called "Sentence Span Test" (SST), the protocol for which is

described on Appendix A [26]. The language assessment was audio-recorded. The assessment was held in a quiet room. The recorder was placed 10 cm in front of the patient and the microphone was oriented towards the patient’s mouth [44].

Table 1: Descriptive data of the population.

	AD	lvPPA	-lvPPA	+lvPPA	p-Value
N	8	8	4	4	
Female (%) *	62.5	62.5	50	75	1
Age range (y)	67-86	52-77	52-77	61-77	
mean age **	74.875	69.5	67.75	71.25	0.26
SD age	6.17	8.97	11.35	7.13	
Laterality (Right %) *	100	100	100	100	1
Primary Education level (%) *	25	25	0	50	1
Secondary Education level (%) *	62.5	62.5	75	50	1
Higher Education level (%) *	12.5	12.5	25	0	1
Range MMSE	21-27	20-28	20-28	20-28	
Mean MMSE **	23	23.75	23	24.5	0.71
SD MMSE	2.32	3.41	3.82	3.31	
Range DTLA score	61-98	57-94	66-94	57-88	
Mean DTLA score **	86.75	78.00	78.25	77.75	0.13
SD DTLA score	12.25	12.05	11.67	14.24	
Range BREF score	11-18	9-18	14-18	9-17	
Mean BREF score **	14.25	14.62	16.25	13.00	0.87
SD BREF score	3.23	2.95	1.48	3.16	
Range categorical fluency	4-29	18-40	24-40	18-29	
Mean categorical fluency **	19.00	29.38	34.75	24.00	0.07
SD categorical fluency	9.03	7.61	6.53	3.94	
Mean IADL score **	1.63	0.38	0.25	0.50	0.09
SD IADL score	1.49	0.70	0.43	0.87	

* χ^2 ; ** Kruskal–Wallis, p-values refer to the overall comparisons between AD and lvPPA.

Material

The recording was made on an Apple iPad, recording stereo sound with two included microphones with the parameter “Audio Quality without loss”. The SST is a memory- intensive spoken repetition task including 14 sentences. The sentence stimuli had increasing span length content of words, ranging from a span of 3 content words (e.g., *Un étudiant fait ses devoirs*; “A student does his homework”) up to 9 content words (e.g., *Les chercheurs en archéologie ont découvert une grande tombe romaine dont des squelettes et des outils tranchants*. “Researchers in archaeology have discovered a large Roman tomb including skeletons and sharp tools”). There were two sentences per span length. Within a span task design, the SST measure targets verbal working-memory capacity during sentence repetition, which is an early symptom in lvPPA and AD patients. This facilitates an early diagnosis for AD and lvPPA patients [44]. The complete sentences included in the SST are reported in Table A1 in Appendix A.

Lumbar punctures allowed the extraction of CSF and measurement of AD relative biomarkers. Measures of β 42-Amyloid peptide, total tau and phospho-tau protein concentrations were

collected [49,50]. The standard for each protein corresponds to 700–1800 pg/mL, 130–6001 pg/mL and 20–60 ng/mL, respectively.

Acoustic Analyses

Acoustic analysis was carried out on the 14 repeated sentences in the SST, detailed in Table A1 in Appendix A. Sentences were recorded as .wav files. The recordings were cut into 28 extracts corresponding to the patient’s repeated sentence with or without the sentence’s model given by the investigator. This was achieved with Audacity 3.1.3 software [51]. Acoustic analyses were implemented with PRAAT software 6.2.06 [52]. Extracted acoustic and vocal parameters were chosen because of their significant impact on AD diagnosis from controls, as demonstrated in previous studies described in the literature [53,54]. An overview and explanation of extracted acoustic features are presented in Table 2. With PRAAT software, temporal and acoustic measures were implemented. Acoustic parameters correspond to a periodicity range from 75 to 600 Hz with the autocorrelation method.

Table 2. Overview and explanation of extracted acoustic features.

Features	Explanations	Category
Vocal reaction time	Latency time before initiating sentence repetition (s). [43]	Temporal
Vowel phonation time	Mean vowel phonation duration (s). [55]	Temporal
Consonant phonation time	Distinctive mean occlusive and fricative consonant voice onset time and sounding time (s). [56]	Temporal
Phonation time deviation from model	Phonation time distance compared to model’s phonation time (calculated on vowels, occlusive and fricative consonants). [44]	Temporal
Pause ratio	Number of total pauses per second. [53]	Temporal
Non-silent pause ratio	Number of non-silent pauses, considering hesitations, autocorrections and repetitions. [53]	Temporal
Silent pause ratio	Number of silent pauses, considering voiceless segments longer than 30 ms. [53,57]	Temporal
Speech rate	Number of pulses/words/syllables/phonemes per second. [53]	Prosodic
Intensity range	Distance between maximum and minimum intensity amplitude during sentence repetition (dB).	Prosodic
Fundamental frequency (F0)	Distance between maximum and minimum fundamental frequency during sentence repetition (Hz). [58]	Prosodic
Maximum range		
Minimum F0	Lowest fundamental frequency during sentence repetition (Hz). [58]	Prosodic
Maximum F0	Highest fundamental frequency during sentence repetition (Hz). [58]	Prosodic

Statistical Analyses

Descriptive statistics were used to present demographic and clinical characteristics. Qualitative variables (gender, educational level, PET-SCAN and MRI results) were presented using percentages, and quantitative variables (psychometric scores and CSF biomarker concentrations) were described using mean, standard deviation (SD) and range. The group differences were tested with non-parametric statistical tests. The Wilcoxon– Mann–Whitney

test was used for quantitative descriptive data and the χ^2 test was used for qualitative descriptive data. The diagnostic groups showed no differences between their descriptive variables.

Concerning the sentence repetition task, descriptive analyses were first realized on psychometric data. The ratios of semantic and phonological errors and the number of content words were calculated for each sentence of each patient. Then, the mean result for each group studied was calculated. The performance score was also calculated. This corresponds to the ratio of repeated sentences without mistake or omission on content words which are highlighted in Table A1 in Appendix A. The mean performance ratio was calculated for each group: AD group, lvPPA and its sub-groups including -lvPPA and +lvPPA. Then, statistical analyses were carried out on acoustic, extracted data. This corresponds to the average results of the 14 repeated sentences for each previously extracted acoustic and temporal parameter studied in this protocol. The acoustic and temporal parameter differences were analyzed with the Wilcoxon–Mann–Whitney test. Then, variation rate was calculated on significant parameters with mean parameter values for each group.

Results

Demographic and Clinical Information

Demographic and Psychometric Information

The Characteristics and clinical information for each group are reported in Table 1. No significant differences in demographic and clinical information were found across the two groups. The AD population was older than the lvPPA population and the two groups comprised more women than men, corresponding to the pathologies' demography described in the literature [50]. They had an equivalent cognitive level as shown by the MMSE score ($p = 0.709$). As expected, the AD group had a higher language level than the lvPPA group, even though the difference in DTLA score is not significant ($p = 0.127$) [4]. The categorical fluency task shows better scores for the lvPPA population and, principally in the -lvPPA subgroup. This relates to greater impairment in the AD population for lexical access and working memory. The BREF score shows a more important alteration of executive capacities in the AD than the lvPPA group and, even more, the -lvPPA sub- group. The IADL scale shows more altered autonomy in the AD than the lvPPA group. This corresponds to the definition of AD as a global cognitive impairment pathology, contrary to lvPPA, where symptoms are specifically restricted to

language impairment at onset time. Nonetheless, no differences are significant. This confirms the difficulty of significantly differentiating these two pathologies at an early stage of neurodegeneration.

Neuroimaging and CSF Information

100% of AD patients accepted taking part in an MRI and only 37.5 of this group accepted a PET-SCAN. In the lvPPA group, 87.5% of patients accepted taking part in an MRI and 50% accepted the PET-SCAN. This includes 100% and 50% of -lvPPA patients with MRI and PET-SCAN results, respectively, and 75% and 50% of +lvPPA patients with MRI and PET-SCAN results, respectively.

In the AD population, of those who accepted the MRI imaging, the collected data revealed bilateral hippocampal atrophy from stage 1 to 3 on 6 patients' brains (75%), including two associated with cortico-sub-cortical atrophy (25%). Three patients (37.5%) also presented cortico-sub-cortical atrophy and two patients (25%) had a parietal atrophy. On AD population's PET-SCANS, parietal (75%) and temporal (25%) hypometabolism was observed. These PET-SCAN results correlate with parietal and cortico-sub-cortical atrophy on MRI observations.

In the lvPPA population with MRI results, three patients (43%) presented hippocampal atrophy from grade 1 to 4, two patients (29%) had a parietal atrophy and one patient (14%) presented cortico-sub-cortical atrophy. In the lvPPA PET-SCAN results, 10% of the population presented standard geriatric results and 90% of the population presented a temporal and/or parietal hypometabolism.

In the -lvPPA subtype, MRI results revealed one standard geriatric profile (25%), one hippocampal atrophy at stage 1 (25%), one parietal atrophy (25%) and one cortico-sub-cortical atrophy (25%). PET-SCAN results revealed standard metabolism on 25% of the population and temporo-parietal hypometabolism in 50% of the population. Temporo-parietal hypometabolism was associated with hippocampal atrophy in the -lvPPA population. In the +lvPPA subtype, two hippocampal atrophies at stage 1 and 4 (75%) and one parietal atrophy (25%) were observed. PET-SCAN results revealed parietal hypometabolism and temporo-parietal hypometabolism for 50% of the population in each case.

These observations correspond to the neuro-imaging descriptions described in the literature for lvPPA and AD [10,11,27].

CSF biomarker results presented in Table 3 reveal significant differences on the β 42-amyloid biomarker for the comparison of -lvPPA and AD as well as the comparison of the two subtypes -lvPPA and +lvPPA. The β 42-amyloid biomarker is not significant for +lvPPA and AD or for

the diagnostic groups AD and lvPPA. The tau biomarkers show no significant differences. Moreover, the opposition to LP by 27% of the total initial population reflects the difficulty of convincing patients to undergo this invasive examination in the context of neurodegenerative diagnosis searches, as described in literature [35,36].

The SST Record Associated with Temporal and Prosodic Markers, an Efficient Task for Diagnosis

Linguistic scores are reported in Table 4. The lowest linguistic scores were observed in the lvPPA group. Concerning the mean number of repeated content words, the lvPPA group presented fewer content words. Semantic errors were mostly noticed in the AD group, in contrast to phonological errors, which more present in lvPPA repetitions. The same ratios were obtained concerning CSF biomarkers: in the lvPPA group, -lvPPA repetitions contained fewer content words and +lvPPA repetitions contained more semantic errors. Statistics reveal that phonological errors had the same proportion for the two lvPPA sub-groups.

Table 3: CSF biomarkers concentration, extracted by lumbar puncture.

	β 42-Amyloid (\pm SD)	Total Tau (\pm SD)	Phospho-Tau (\pm SD)
AD	636.5 (\pm 173.64)	874.625 (\pm 234.59)	166.625 (\pm 38.28)
lvPPA	901.375 (\pm 687.29)	495.5 (\pm 447.25)	90.375 (\pm 128.46)
-lvPPA	1371.75 (\pm 747.24)	494.25 (\pm 571.69)	79.75 (\pm 170.58)
+lvPPA	431 (\pm 97.131)	496.75 (\pm 133.36)	101 (\pm 28.40)
<i>p</i> -value AD/lvPPA	0.38	0.38	0.72
<i>p</i> -value AD/+lvPPA	0.36	0.21	0.68
<i>p</i> -value AD/-lvPPA	0.008*	0.93	0.93
<i>p</i> -value +lvPPA/-lvPPA	0.05*	0.68	1

* Kruskal–Wallis, *p*-values refer to the overall comparisons between the groups cited in the 1st column.

Table 4: Mean linguistic score on the 14 SST sentences.

Diagnoses	N	Mean Content Words (\pm SD)	Mean Semantic Errors (\pm SD)	Mean Phonological Errors (\pm SD)	Mean Performance Score Ratio (\pm SD)
AD	8	4.169 (\pm 1.432)	0.161 (\pm 0.216)	0.018 (\pm 0.042)	0.857 (\pm 0.240)
lvPPA	8	4.034 (\pm 0.798)	0.299 (\pm 0.325)	0.055 (\pm 0.076)	0.786 (\pm 0.179)
+lvPPA	4	4.452 (\pm 0.855)	0.457 (\pm 0.501)	0.054 (\pm 0.099)	0.857 (\pm 0.857)
-lvPPA	4	3.643 (\pm 0.855)	0.161 (\pm 0.235)	0.054 (\pm 0.099)	0.696 (\pm 0.696)

Group and sub-group characteristics correspond to the ones described in Table 1.

Analyzing the performance scores of each group on the 14 sentence repetitions of the SST, a degree of variability in group performance for each sentence was observed. Errors began to

appear in sentence 10 for AD and in sentence 5 for lvPPA. Concerning the lvPPA subtypes, errors were observed for the two sub-groups from sentence 4. Nonetheless, -lvPPA presented the lowest mean score with only 25% of the population succeeding in repetition of the 3 last sentences. Considering the -lvPPA and the +lvPPA subgroups, a difference of performance was observed from the sixth sentence onwards. A significant distinction regarding these two subtypes could be observed from a syntactic level all along the test when considering the lvPPA and AD diagnostic groups.

Acoustic Markers of Interest for AD and lvPPA Differential Diagnosis

For the temporal markers chosen for this study, Mann–Whitney statistics revealed a significant impact of temporal parameters. Table 5 presents mean values on temporal parameters for each group in our study. A significant difference is observed on patients' reaction time to differentiate lvPPA and AD ($p = 0.016$). More precisely, lvPPA showed a mean reaction time increase of 76.79% compared to AD. The difference between the mean speech rates was not significant, considering pulses ($p = 0.186$), words ($p = 0.186$), syllables ($p = 0.215$) and phonemes ($p = 0.159$) per second.

Statistical analyses of temporal markers also revealed differences in pauses during repetition. AD patients presented a higher pauses rate than lvPPA, considering the number of total pauses, silent and non-silent pauses per second. Indeed, a significant difference was observed for the mean total pause rate ($p = 0.033$), the mean silent pause rate ($p = 0.033$) and the mean non-silent pauses rate ($p = 0.063$). AD patients showed a mean silent pause rate 64.15% higher than lvPPA patients and a mean non-silent pause rate 24.38% higher than the lvPPA group. The highest difference was found for total pause rate, with the AD patients' mean rate 185.09% higher than for the lvPPA group. Other pause parameters, such as percentage cumulated duration or mean and standard deviation of pause duration, did not reveal any significant differences. Analyses revealed significant differences between the lvPPA and AD groups on mean occlusive consonant duration distance from the model ($p = 0.042$) and on mean fricative consonant duration distance from the model ($p = 0.016$). The lvPPA mean occlusive consonant distance from the model was 26.86% higher than for AD, and the lvPPA mean fricative consonant gap was 30.84% higher than for AD. The difference between the raw mean measurement of occlusive consonants duration tends to significance ($p=0.051$) and the difference between the raw mean measurement of fricative consonants is significant ($p = 0.041$). Mean duration of consonants is longer for lvPPA than AD, with a 37.72% increase for occlusive

consonants duration and 36.75% for fricatives. Vowel phonation time showed no significant differences with raw measurements ($p = 0.356$) or duration distance from the model ($p = 0.437$).

Table 5: Mean temporal parameters for the AD and lvPPA population.

Temporal Parameters	Significance (<i>p</i> -Value)	Diagnoses	Mean (\pm SD)
Vocal reaction time (s)	AD/lvPPA (0.016) **	AD	0.779 (\pm 0.180)
	AD/-lvPPA (0.010) **	lvPPA	1.379 (\pm 0.727)
	AD/+lvPPA (0.017) **	+lvPPA	1.842 (\pm 0.751)
	-lvPPA/+lvPPA (0.096)	-lvPPA	1.916 (\pm 0.253)
Occlusive consonants duration (s)	AD/lvPPA (0.051) *	AD	0.049 (\pm 0.016)
	AD/-lvPPA (0.037) **	lvPPA	0.067 (\pm 0.017)
	AD/+lvPPA (0.097)	+lvPPA	0.101 (\pm 0.012)
	-lvPPA/+lvPPA (0.222)	-lvPPA	0.113 (\pm 0.016)
Occlusive consonant distance from model	AD/lvPPA (0.042) **	AD	1.083 (\pm 0.397)
	AD/-lvPPA (0.025) **	lvPPA	1.481 (\pm 0.389)
	AD/+lvPPA (0.156)	+lvPPA	1.288 (\pm 0.304)
	-lvPPA/+lvPPA (0.222)	-lvPPA	1.674 (\pm 0.368)
Fricative consonant duration (s)	AD/lvPPA (0.016) **	AD	0.079 (\pm 0.022)
	AD/-lvPPA (0.037) **	lvPPA	0.107 (\pm 0.015)
	AD/+lvPPA (0.097)	+lvPPA	0.101 (\pm 0.012)
	-lvPPA/+lvPPA (0.053) *	-lvPPA	0.114 (\pm 0.015)
Fricative consonant distance from model	AD/lvPPA (0.016) **	AD	0.978 (\pm 0.261)
	AD/-lvPPA (0.037) **	lvPPA	1.274 (\pm 0.155)
	AD/+lvPPA (0.235)	+lvPPA	1.223 (\pm 0.138)
	-lvPPA/+lvPPA (0.053) *	-lvPPA	1.326 (\pm 0.154)
Vowel phonation time (s)	AD/lvPPA (0.357)	AD	0.153 (\pm 0.020)
	AD/-lvPPA (0.222)	lvPPA	0.154 (\pm 0.022)
	AD/+lvPPA (0.156)	+lvPPA	0.145 (\pm 0.018)
	-lvPPA/+lvPPA (0.466)	-lvPPA	0.162 (\pm 0.022)
Vowel phonation distance from model	AD/lvPPA (0.437)	AD	1.195 (\pm 0.148)
	AD/-lvPPA (0.399)	lvPPA	1.171 (\pm 0.153)
	AD/+lvPPA (0.333)	+lvPPA	1.133 (\pm 0.156)
	-lvPPA/+lvPPA (0.466)	-lvPPA	1.208 (\pm 0.139)
Pauses/s	AD/lvPPA (0.033) **	AD	2.175 (\pm 0.565)
	AD/-lvPPA (0.037) **	lvPPA	0.763 (\pm 0.387)
	AD/+lvPPA (0.443)	+lvPPA	0.7669 (\pm 0.450)
	-lvPPA/+lvPPA (0.135)	-lvPPA	0.759 (\pm 0.309)
Silent pauses/s	AD/lvPPA (0.033) **	AD	1.148 (\pm 0.316)
	AD/-lvPPA (0.037) **	lvPPA	0.699 (\pm 0.410)
	AD/+lvPPA (0.442)	+lvPPA	0.711 (\pm 0.480)
	-lvPPA/+lvPPA (0.175)	-lvPPA	0.688 (\pm 0.325)
Non-silent pauses/s	AD/lvPPA (0.054) *	AD	0.227 (\pm 0.311)
	AD/-lvPPA (0.175)	lvPPA	0.058 (\pm 0.028)
	AD/+lvPPA (0.333)	+lvPPA	0.056 (\pm 0.031)
	-lvPPA/+lvPPA (0.074)	-lvPPA	0.059 (\pm 0.024)

(*p*-value) ** Significance according to Mann–Whitney tests; (*p*-value) * a comparison tending to significance.

From the acoustic markers studied here, Mann–Whitney statistics revealed significant differences on prosodic parameters. Table 6 presents mean values on prosodic parameters for each group in our study. Firstly, analyses revealed significant differences in periodicity variations. Mean maximum F0 ($p = 0.026$) and F0 range trend to significance on the mean F0 range ($p = 0.051$). AD patients presented a greater F0 range, with a difference of 20.62% and a higher maximum F0 increase of 17.43% in AD patients compared to lvPPA patients. To resume

the previous comparisons, the most relevant temporal parameters to distinguish lvPPA and AD patients at the onset time of the diseases are the reaction time, the pauses ratios, including non-silent and silent pauses ratios, and the occlusive and fricative consonant mean duration distances from the model. The most relevant acoustic parameters are the F0 variation and principally the mean maximum F0.

Acoustic and Temporal Characteristics according to Biomarkers

Acoustic and Temporal Differences in lvPPA Group Sub-Types According to CSF Biomarkers Variations

Mann–Whitney statistics demonstrated that none of the temporal parameters significantly differentiated –lvPPA and +lvPPA subgroups. Nonetheless, statistical analyses revealed that relevant prosodic markers could distinguish the two subgroups. The two subgroups were significantly distinguished by mean minimum F0 ($p = 0.030$). The +lvPPA subgroup presented a higher minimum F0, 23.41% higher than –lvPPA. None of the other parameters were highlighted as significant with Mann–Whitney statistics.

Comparison of Acoustic and Temporal Features, Diagnostic Groups, and Their Biomarker Profiles

According to statistical analyses, the +lvPPA subgroup was distinctive from AD in terms of temporal markers. Only one parameter shows significant differences with the AD group: the patients' mean reaction time ($p = 0.017$). The +lvPPA subgroup presents a mean reaction time 136.12% higher than the AD group. A difference trending to significance was observed on fricative consonant duration ($p = 0.053$) and its distance from model duration ($p = 0.053$). The +lvPPA subgroup has a fricative consonant mean duration and distance from the model duration 26.24% and 24.95% higher than for the AD group, respectively. None of the acoustic parameters shows a significant distinction between +lvPPA and AD. Concerning the –lvPPA group, statistical tests revealed a significant difference of patients' reaction time compared to the AD group ($p = 0.010$). Reaction time is significantly higher, by 96.32%, in the –lvPPA group. A significant distinction is also shown for fricative and occlusive ($p = 0.037$, $p = 0.037$) consonant duration and their distance from models ($p = 0.025$, $p = 0.037$). Fricative and occlusive consonants in the lvPPA group have a higher duration, 53.33% and 42.49% higher than for the AD group, respectively. Pause ratio also shows relevant differences between –lvPPA and AD, principally for total pause ratio ($p = 0.037$) and silent pause ratio ($p = 0.025$).

Both AD ratios were higher than the -lvPPA ones, with respective differences of 186.54% and 66.87%. Finally, maximum F0 significantly differentiates -lvPPA from AD ($p = 0.053$), with maximum F0 that was 13.25% higher.

To resume previous comparisons, +lvPPA can only be differentiated from AD by patients' mean reaction time, fricative consonant mean duration, and its distance from model mean duration. In parallel, -lvPPA significantly differs from AD for maximum F0. Temporal features vary for total and silent pause ratios, patients' mean reaction time and fricative and consonant durations as well as their distance from models. A summary of the distribution of significant values on acoustic parameters is represented in Figure 1.

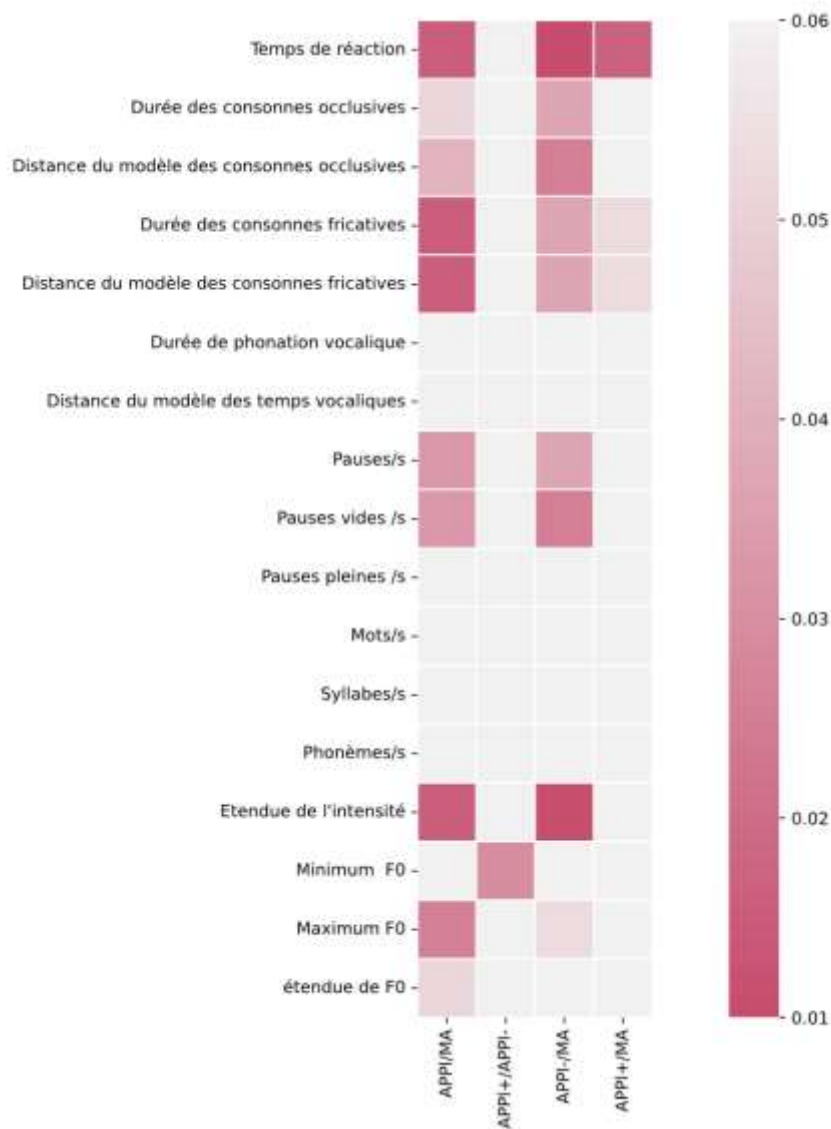


Figure 1: Distribution of significant values on acoustic parameters represented by colored gradient. Significance degree of each parameter for lvPPA and AD, +lvPPA and -lvPPA, +lvPPA and AD, -lvPPA and AD comparisons.

The figure represents a colored gradient of p-values for the significance of each acoustic parameter and each comparison according to statistical tests. It relates one acoustic parameter, named on the y-axis, with a comparison of two groups, named on the x-axis. According to the Mann–Whitney test, the difference between the two groups is considered as significant when the p-value is less than 0.05.

Table 6: Mean prosodic parameters for the AD and lvPPA population.

Prosodic Parameters Significance	(p-Value)	Diagnosis	Mean (\pm SD)
Words/s	AD/lvPPA (0.186)	AD	2.327 (\pm 0.383)
	AD/-lvPPA (0.134)	lvPPA	1.928 (\pm 0.604)
	AD/+lvPPA (0.333)	+lvPPA	2.179 (\pm 0.253)
	-lvPPA/+lvPPA (0.399)	-lvPPA	1.677 (\pm 0.735)
Syllables/s	AD/lvPPA (0.215)	AD	3.676 (\pm 0.580)
	AD/-lvPPA (0.222)	lvPPA	3.002 (\pm 0.990)
	AD/+lvPPA (0.333)	+lvPPA	3.379 (\pm 0.439)
	-lvPPA/+lvPPA (0.336)	-lvPPA	2.625 (\pm 1.219)
Phonemes/s	AD/lvPPA (0.159)	AD	7.536 (\pm 1.216)
	AD/-lvPPA (0.175)	lvPPA	6.118 (\pm 2.052)
	AD/+lvPPA (0.442)	+lvPPA	6.913 (\pm 0.896)
	-lvPPA/+lvPPA (0.276)	-lvPPA	5.324 (\pm 2.521)
Intensity range (dB)	AD/lvPPA (0.016) **	AD	35.920 (\pm 5.860)
	AD/-lvPPA (0.011) **	lvPPA	27.036 (\pm 5.249)
	AD/+lvPPA (0.097)	+lvPPA	545.932 (\pm 54.823)
	-lvPPA/+lvPPA (0.135)	-lvPPA	24.094 (\pm 4.168)
Minimum F0 (Hz)	AD/lvPPA (0.396)	AD	95.547 (\pm 17.999)
	AD/-lvPPA (0.101)	lvPPA	87.088 (\pm 15.750)
	AD/+lvPPA (0.030) **	+lvPPA	98.634 (\pm 9.661)
	-lvPPA/+lvPPA (0.222)	-lvPPA	75.542 (\pm 11.669)
Maximum F0 (Hz)	AD/lvPPA (0.026) **	AD	382.273 (\pm 91.249)
	AD/-lvPPA (0.053) *	lvPPA	325.541 (\pm 49.334)
	AD/+lvPPA (0.442)	+lvPPA	319.474 (\pm 64.704)
	-lvPPA/+lvPPA (0.074)	-lvPPA	331.605 (\pm 24.646)
F0 range (Hz)	AD/lvPPA (0.051) *	AD	271.015 (\pm 91.946)
	AD/-lvPPA (0.101)	lvPPA	224.689 (\pm 46.748)
	AD/+lvPPA (0.442)	+lvPPA	208.469 (\pm 61.490)
	-lvPPA/+lvPPA (0.102)	-lvPPA	240.91 (\pm 7.964)

(p-value) ** Significance according to Mann–Whitney tests; (p-value) * a comparison tending to significance.

Discussion and Conclusion

In the present study, we investigated the usefulness of acoustic parameters collected on a memory-intensive sentence repetition protocol with the SST to differentiate patients with lvPPA from patients with AD at onset time. We also compared their CSF biomarker profile to their acoustic profile.

The interest of acoustic parameters for accurate diagnosis between the lvPPA and AD groups was demonstrated in this study. Indeed, the temporal analyses, performed on the SST outcomes, showed significant features for discriminating the two groups. Differences were found on the mean fricative and occlusive consonant duration, with a greater duration in the lvPPA group compared to the AD group. Previous studies showed no significant variations on AD occlusive consonant voice onset time compared with healthy controls and, on the contrary, an elongation of vowel phonation duration was associated with cognitive decline [55,56]. Our results reveal an increase in consonant voice onset time in lvPPA speech, in contrast to AD. As the two groups have equivalent mean vowel mean durations, a pathological elongation of vowels in the AD group appears here as equivalent to lvPPA at onset time.

Moreover, model temporal deviation was also observed in previous studies on AD and in lvPPA comparisons to other PPA subtypes [44,59]. Our study also exposed a temporal deviation from models in the two groups, with a significant increase in deviation from model production in lvPPA occlusive and fricative consonant duration. Phonological loop alteration, a specific symptom of the lvPPA profile, would explain these specific alterations, differentiating the lvPPA from AD group by the slowing down of consonant production [60]. Consequently, the voice-onset time of consonants increases due to a phonological loop deficit [56]. Phonological loop alteration would also explain the patient reaction time augmentation observed here through an extended vocal initiation time on lvPPA repetitions.

Our results also differentiate lvPPA from AD on the base of pause rates. Pauses permit the differentiation of AD and lvPPA from healthy controls, with an increase in pause frequency [57,61]. Our study, comparing these two groups, showed an impact of total silent and non-silent pause rates on their discrimination. Differing from a previous study, the AD profile here showed the higher pause rate [62]. The greatest difference for AD was observed on silent pause rate. Indeed, AD has been described in the literature as featuring numerous silent pauses. On the

contrary, lvPPA has been described to feature non-silent pauses such as autocorrections, repetitions or voiced hesitations. Pauses were previously interpreted in the literature as a compensatory mechanism for lexico-semantic and working memory decline at an early stage of AD [57]. Thus, these temporal alterations allow for a clear differentiation between lvPPA and AD at onset time.

Prosody analyses also show a high discriminant value in our study. F0 appears here as an important acoustic marker in AD and lvPPA detection, with significant differences for F0 range and maximum F0. In our study, the AD group presented a larger F0 interval and a higher F0 on average. Fundamental frequency and its evolution have already been considered as a marker of interest for differentiating patients with AD and lvPPA from healthy controls [4,55,58]. This parameter is related to emotional prosody. F0 alteration in AD has been correlated to the decrease in F0 variations whereas, here, the AD profile presents the greatest F0 range and the highest maximum F0 [58,63]. Thus, F0 comparisons show a higher alteration in the lvPPA group compared to the AD group. In addition, the intensity amplitude range stood out as a key feature for clustering the two groups. It appears that, in our study, the AD profile had a larger intensity amplitude than the lvPPA profile. However, the literature demonstrating AD acoustic diagnostic markers include a low intensity range, inducing monotonous speech compared to healthy controls [64]. Prosody in lvPPA has also shown to exhibit alterations in a vocal sentence reading task [65]. Therefore, our results suggest a more important prosodic alteration, illustrated by low intensity and fundamental frequency, in the lvPPA group compared to the AD group in an intensive repetition task at onset time.

Considering CSF biomarkers, two lvPPA subgroups are formed: +lvPPA and -lvPPA. Here, β -Amyloid markers present a significative difference, suggesting two clinically different lvPPA populations. Moreover, CSF biomarker groups are in accordance with acoustic specificities. Each one revealed a specific acoustic profile which would permit clustering each population early according to their CSF biomarkers and clinical profiles thanks to acoustic measures.

The +lvPPA subgroup corresponds to an Alzheimer-disease-like CSF profile with positive β -Amyloid markers [25,33,34]. According to our results, +lvPPA is only different in temporal parameters: reaction time, fricative and occlusive consonant phonation time and their distance from model. These temporal parameters were higher than in AD on average. Therefore, our results suggest that +lvPPA has an acoustic profile like AD, except on temporal features. In the literature, lvPPA has been described to have specific alteration regarding the phonological loop

and lexical processing [18,60]. These cognitive functions are involved in the affected temporal parameters such as consonant production duration or reaction time [66]. Atypical AD with a primary language alteration on lexical access and sentence repetition has already been described in the literature [67]. Thus, our results raise the hypothesis that the +lvPPA acoustic profile correlates with an atypical form of AD, with first symptoms focused on language, and specifically on phonological short-term memory and lexical access alteration [66]. This is supported by the imaging description of the +lvPPA and AD groups in our study cohort.

Effectively, AD and +lvPPA have correlated neuro-imaging descriptions: the same proportion of hippocampal atrophy was observed in the +lvPPA and AD groups. This hypothesis must be verified by future studies with a greater sample of the lvPPA and AD populations including corresponding CSF biomarkers data. These results also emphasize the interest of studies on +lvPPA progression over time in order to determine an eventual convergence with specific AD with predominant language impairment.

The -lvPPA group differs in terms of similar acoustic parameters from AD as the lvPPA diagnostic group described before. Compared to AD, the -lvPPA group presents a lower maximum fundamental frequency, intensity range, and total pause and silent pause ratios. Consonant phonation and distance from the model as well as reaction time were also more altered in the -lvPPA compared to AD. These acoustic alterations were greater than in the lvPPA diagnostic group. Furthermore, the literature describes similar acoustic alterations in FTLD. FTLD silent pause rate is significantly higher compared to healthy controls [68]. An evolution of FTLD pause rate is described on the same continuum as the lvPPA pause rate increase [69]. FTLD prosody alteration is also similar: the reduction of the fundamental frequency range has been described [70]. In addition, the -lvPPA group presented the highest alteration of prosodic parameters, and prosodic alteration is correlated to frontal and parietal lobes, which are neuropathological observations associated with FTLD [65]. Consequently, the -lvPPA acoustic profile reported here correlates with FTLD acoustic characteristics presented in the literature. Nonetheless, the -lvPPA acoustic characteristics must be confirmed with a larger sample of the population. Moreover, neuroimaging characteristics of the -lvPPA group studied do not completely correspond to FTLD anatomopathology. Thus, the hypothesis correlating -lvPPA with an underlying FTLD can be verified by analyzing acoustic markers of -lvPPA with an underlying FTLD evolution over time.

Therefore, acoustic analyses comparing lvPPA and AD associated with CSF biomarker profiles allow us to reconsider the PPA classification consensus. The literature has already questioned the actual classification, analyzing PPA types of properties with automatic clustering algorithms [3,11]. Our results correlated lvPPA biomarker profiles with acoustic profiles, dividing them into two acoustic patterns. Future studies may confirm the hypothetical correlation of each acoustic profile to a specific underlying pathology.

These acoustic profiles are also coherent with MRI and PET-SCAN anatomic markers associated with each lvPPA CSF biomarker type and underlying pathology. The +lvPPA anatomopathological form presents gray matter atrophy in the temporal gyrus and parietal region associated with a parietal hypometabolism which is consistent with AD. On the contrary, -lvPPA is characterized in the literature by alterations located in the left anterior temporal region and the left inferior frontal-insula region, similarly to atrophied regions in FTLD [25,31,32]. Nonetheless, the -lvPPA population studied only presented a temporal hypometabolism on PET-SCANS which can be associated with an underlying FTLD.

Other similarities cited in the literature were not observed in this population. Nonetheless, prosodic acoustic alterations observed in the -lvPPA group are associated with the left lateral temporal lobe [65]. PET-SCAN alterations, targeting phonological loop deficits, corroborate with temporal features alterations observed in -lvPPA in the sentence repetition task [25]. Thus, the two different acoustic profiles revealed by acoustic analyses on lvPPA subgroups correspond to the two MRI neuroanatomic profiles described in the literature [31,32]. Our study thereby supports the same hypothesis of two different lvPPA subtypes differing in language, neuroanatomic alterations, CSF biomarkers and early acoustic markers. The lack of neuroanatomic deficits described in the literature in the population studied may be due to the examination being completed at an early stage of the pathology. It can be verified by an analysis of the clinical evolution of the lvPPA subgroups associated to their anatomopathological progression over time.

Moreover, this study offers new possibilities for the differential diagnosis of neurodegenerative pathologies at onset time. Until now, no significant marker has been described in the literature to specifically distinguish these two groups. Paramedical tests such as LP are not sufficiently accurate and, even more importantly, are not sufficiently accepted by patients [20,29]. Therefore, the use of discriminant acoustic features as diagnostic tools would permit a precise

differential diagnosis between lvPPA and AD. If our results are verified with a larger population, we would consider acoustic markers as effective prognostic factors for estimating a CSF biomarker profile for each patient with a suspicion of AD or PPA. Nonetheless, a larger sample of the population is necessary to confirm this preliminary study and to verify these results.

Despite this limitation, this study offers great opportunities considering the diagnosis precision in association with patient well-being. On our research continuum, the elaboration of an automated classification thanks to automatic acoustic data extraction and artificial intelligence algorithms would permit the creation of a non-invasive, early, accessible and precise diagnosis tool [45]. The precision would be ensured by the complete automatization of the system and the SST protocol by the implication of a phonological loop on its assessment [20].

Firstly, the SST, an intensive sentence repetition task, appeared as relevant for discriminating lvPPA from AD with acoustic analyses. This study confirmed the interest of an acoustic analysis of oral sentence repetition, with an increasing difficulty, as a discriminant feature for lvPPA and AD patients at onset time. The literature has already shown differences between lvPPA and AD on the SST, even if the results are not sufficiently clearcut to obtain a differential diagnosis [20]. As observed in our results, lvPPA scores were lower than AD ones considering psycholinguistic measurements. Thus, using acoustic analyses on a task targeting lvPPA deficits seems to permit a significant differentiation between the two groups in terms of acoustic analyses. Indeed, previous studies have already shown an improvement over pencil-paper assessment by using acoustic analyses to detect significant differences not achievable by natural hearing or global and duration scores [32].

Secondly, acoustic data analyses would permit a rapid screening prognosis. This acoustic prognosis would also specify a first patient's diagnosis or serve as an alternative tool when opposition to invasive tests such as LP is expressed by patients. Indeed, previous studies have reported a lack of precision of AD diagnosis and the numerous side-effects impacting the patient's well-being and motivation to take LP examination [27,28]. In addition, LP is marked by high cost and an inequity of access between patients' places of residence, as pointed out in the literature [27]. Therefore, developing associated noninvasive diagnostic instruments to complement the actual diagnosis tools would facilitate diagnosis accessibility and patients' rapid and motivated inclusion in an adapted care project. In accordance with these previous

reasons, continuing the research on a diagnostic acoustic assessment will facilitate AD and lvPPA diagnostic access.

Integrating acoustic markers in lvPPA and AD diagnosis would offer opportunities for an early and adapted care which would reduce disease evolution and encourage patients' abilities to be maintained over time. Indeed, acoustic markers would complement psychometric evaluations such as DTLA to precisely identify neuropathologies [39].

Conclusions

To conclude, acoustic markers enable the early differential diagnosis of patients with lvPPA and AD. Temporal and prosodic parameters revealed significant differences in an assessment targeting the lvPPA-specific phonological loop deficit. Acoustic markers in the SST compared to the CSF biomarker profiles also highlighted new possibilities for making PPA classification more precise. Acoustic marker analyses presented here conform with the hypothesis, stated in the literature, regarding two potential lvPPA subtypes and the possibility of classification according to MRI observations, CSF biomarkers and acoustic markers. In this regard, the lvPPA classification including CSF biomarkers, associated with our preliminary acoustic results, offers the possibility of an analysis by acoustic markers used as an accuracy test to complement actual assessment. It would serve to classify both lvPPA subtypes and AD patients. Acoustic markers would also serve as an alternative prognosis tool in cases of opposition to invasive examinations such as lumbar puncture. Finally, these new discoveries improve the comprehension of PPA syndrome and its links with other neurodegenerative pathologies.

Author Contributions:

Conceptualization, A.G. and A.M.; methodology, A.G., A.P.; validation, A.G., P.R.; formal analysis, E.D.C. and V.M.; investigation, E.D.C., T.M., AP; resources, F.M. and S.A.; data curation, E.D.C.; writing original draft preparation, E.D.C.; writing review and editing, E.D.C., A.G., A.P., V.M.; visualization, E.D.C.; supervision, A.G., V.M.; project administration, A.G., A.M. and P.R.; funding acquisition, A.G. and P.R. All authors have read and agreed to the published version of the manuscript.

Funding:

Seçkin Arslan declares support from the European Union's Horizon 2020 research and innovation program under the Marie Skłodowska-Curie Action (grant agreement No. 838602),

and Alexandra Plonka is supported by an interdisciplinary doctoral grant from the NeuroMod Institute under the auspices of the IDEX scheme of the French Government (ANR-15-IDEX-01).

Institutional Review Board Statement:

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of CPP Ile de France X (N° IDRCB: 2019-A00342-55 accepted on 11 September 2019). At the time of diagnosis, patients and relatives were informed of their inclusion in this study and could decline their participation or withdraw consent. Data were anonymized before the analyses.

Informed Consent Statement:

Informed consent was obtained from all subjects involved in the study.

Data Availability Statement:

The data reported are part of an ongoing registration program. Deidentified participant data are not available for legal and ethical reasons. Anonymized data will be made available for research purposes, upon request and specific approval of the database advisory board and ethical committee.

Acknowledgments:

This work was supported by University Côte d'Azur and NeuroMod Institute and by a grant from the Association Innovation Alzheimer. Thanks to all patients that participated in this study and to all participants.

Conflicts of Interest:

The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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Supporting Information
Appendix A

Protocol Procedure

Put the recorder on the table, 10 cm from the patient. The microphone has to be placed towards patient's mouth. Record all the assessment.

Recite the following guideline to the patient:

«Je vais vous dire des phrases, répétez-les après moi.» (“I am going to tell you sentences, repeat after me”)

Table A1: The SST protocol and its English translation.

Item	Span (Total Words)	Stimulus
1	3 (5)	<i>La fille mange un gâteau.</i> “The girl eats a cake”
2	3 (5)	<i>Un étudiant fait ses devoirs.</i> “A student does his homework.”
3	4 (6)	<i>L’enseignant part et ferme la porte.</i> “The teacher leaves and closes the door.”
4	4 (7)	<i>Le chat a chassé une PET-scanite souris.</i> “The cat chased a little mouse.”
5	5 (8)	<i>Les oiseaux sont nichés sur un grand arbre vert.</i> “The birds are nestled on a tall green tree.”
6	5 (9)	<i>La mère du garçon a acheté des amandes au marché.</i> “The boy’s mother bought almonds at the market.”
7	6 (11)	<i>Une jeune fille a tenté un plongeon pendant ses vacances en juillet.</i> “A young girl attempted a dive while on vacation in July.”
8	6 (12)	<i>Le vieil homme est en retard alors il veut prendre un taxi.</i> “The old man is late so he wants to take a taxi”
9	7 (13)	<i>L’évier de la cuisine est très bouché mais le réparateur utilise une pompe.</i> “The kitchen sink is very clogged but the repairman uses a pump.”
10	7 (14)	Au restaurant la femme du professeur a mangé des nouilles asiatiques pour le déjeuner. “At the restaurant the teacher’s wife ate Asian noodles for lunch.”
11	8 (16)	<i>Le lapin s’est échappé très vite dans la forêt et le chasseur n’a pas réussi à l’attraper.</i> “The rabbit escaped very quickly into the hood and the huntman failed to catch him.”
12	8 (16)	<i>Les touristes ont découvert les immenses sculptures de bronze du musée grâce à la visite guidée.</i> “Tourists discovered the museum’s huge bronze sculptures through the guided tour.”
13	9 (17)	<i>Les chercheurs en archéologie ont découvert une grande tombe romaine dont des squelettes et des outils tranchants.</i> “Archaeological researchers have discovered a large Roman tomb including skeletons and sharp tools.”
14	9 (18)	<i>Les océans deviendront nos ennemis si rien n’est fait pour freiner le réchauffement dû aux émissions de gaz.</i> “The oceans will become our enemies if nothing is done to curb the warming caused by gas emissions.”

Chapter 4

THE USE OF MOTOR AND LANGUAGE MARKERS AFTER COVID-19

This thesis work was led through the Covid-19 pandemic that had consequences on the nature of patients consulting in medical clinics and more specifically in memory centers. Clinical observations and research question were thus modified and enriched since Covid-19 remains a new pathology with intriguing health consequences.

Patients consulting in memory center, beyond the persistent olfactory disorders mostly reported, complained about cognitive related disorders such as concentration deficit, speech impairment or memory deficit. Usually, symptoms of patients suffering from Covid-19 generally fade out after some time, but recent studies showed that in an average of 30% of patients, cognitive sensory-motor, memory and speech or language symptoms persisted up to 7 to 12 months after Covid-19 infection, which was in correlation with our clinical observations [1–3]. These persistent symptoms are probably due to changes observed in brain structure functionally connected to the primary olfactory cortex [4]. These persistent impairments were grouped under the term of Post-Acute Covid-19 Syndrome (PACS).

Regarding the cognitive impairments described, the field of neurodegenerative diseases, specifically Alzheimer's disease (AD) in older adults, has been discussed in relation to PACS in recent literature [5]. Within the years, Remote digital assessments for preclinical AD (RAPAs) have become increasingly important in early AD screening. But since PACS patients present similar impairments than those that we find in neurodegenerative disease, it can compromise the reliability of early diagnostic markers.

The objective of this Chapter was to examine through a systematic review the affected markers in PACS patients to correlate them to already used RAPAs in AD and see if there are still relevant for a neurodegenerative early and differential diagnosis.

This study was led through the EU Joint Program – Neurodegenerative Disease Research initiative (JPND), to investigate the impact of COVID-19 on research related to neurodegenerative diseases. This work included France, Canada, and Switzerland and was funded by the French National Agency. Our working groups answered to this call focusing on COVID-19 pandemic and its impact on Alzheimer's care: an expert board has been set up based on past collaborations in this field of expertise.

The RAPAs reported in the systematic review this include olfactory, eye-tracking, graphical, speech and language, central auditory, and spatial navigation abilities assessments. In parallel of the systematic review work, an expert consensus was made whether to determine which RAPA could be compromised in AD screening after Covid-19.

In conclusion of this study, expert consensus recommends not to use olfactory AD screening assessment until complete recovery of PACS history. Moreover, we shed light on the potential use of every reported RAPA on PACS patients in daily clinical practices, developing first fragments of guidelines in managing PACS patients.

This study has been led during the third year of PhD.

In the framework of the international working group, I was specifically involved in the first part of the project, which main objective was to identify the biomarkers that are still relevant among the commonly used ones and determine new digital biomarkers for the early onset of Alzheimer's Disease in individuals who have or have not been infected by SARS-CoV2. Once these biomarkers were established, we conducted expert consensus to bring out new recommendations for the implementation of selected biomarkers in the process of early diagnosis using telehealth. This study is still ongoing.

In the framework of this study, I presented preliminary observations and results during a national conference:

- Plonka A., Vandersteen C., 25e Assises d'ORL « L'olfaction qui cache la forêt » les atteintes centrales des Covid-longs, 3 février 2023, Palais des Festivals de Cannes.

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Alzheimer's Early Detection in Post-Acute COVID-19 Syndrome: A Systematic Review and Expert Consensus on preclinical assessments

Clair Vandersteen^{1, 2, 3*}, Alexandra Plonka^{1, 4, 5, 6}, Valeria Manera^{1, 5, 6}, Kim Sawchuk⁷, Constance Lafontaine⁷, Kevin Galery⁸, Olivier Rouaud⁹, Noua Bengaied¹⁰, Cyrille Launay¹¹, Olivier Guerin^{4, 12}, Philippe Robert^{1, 4, 5}, Gilles Allali⁹, Olivier Beauchet^{13, 14}, Auriane Gros^{1, 4, 5*}

¹EA7276 Cognition Behavior Technology (CoBTek), France, ²Department of ENT surgery, Institut Universitaire de la Face et du Cou, France, ³Centre Hospitalier Universitaire de Nice, France, ⁴Centre Hospitalier Universitaire de Nice, Service Clinique Gériatrique du Cerveau et du Mouvement, France, ⁵Département d'orthophonie, UFR médecine, Université Côte d'Azur, France, ⁶Institut NeuroMod, Université Côte d'Azur, France, ⁷ACTLab, engAGE: Centre for Research on Aging, Concordia University Montreal, Canada, ⁸Research Center of the Geriatric University Institute of Montreal,, Canada, ⁹Leenaards Memory Center, Lausanne University Hospital and University of Lausanne, Switzerland, ¹⁰Federation of Quebec Alzheimer Societies, Canada, ¹¹Mc Gill University Jewish General Hospital, Canada, ¹²Université Côte d'Azur, CNRS UMR 7284/INSERM U108, Institute for Research on Cancer and Aging Nice (IRCAN), UFR de Médecine, France, ¹³Research Centre of the Geriatric University Institute of Montreal,, Canada, ¹⁴Departments of Medicine, University of Montreal, Canada

Submitted to Journal:

Frontiers in Aging Neuroscience

Specialty Section:

Alzheimer's Disease and Related Dementias

Article type:

Systematic Review Article

Manuscript ID:

1206123

Received on:

14 Apr 2023

Revised on:

17 Apr 2023

Journal website link:

www.frontiersin.org

Abstract

Introduction: The risk of developing Alzheimer's disease (AD) in older adults increasingly is being discussed in the literature on Post-Acute COVID-19 Syndrome (PACS). Remote digital Assessments for Preclinical AD (RAPAs) are becoming more important in screening for early AD, and should continue to be available for PACS patients, especially for patients at risk of AD. This systematic review examines the potential for using RAPA to identify impairments in PACS patients, scrutinizes the supporting evidence, and describes the recommendations of experts regarding their use.

Methods: We conducted a thorough search using the PubMed and Embase databases. Systematic reviews (with or without meta-analysis), narrative reviews, and observational studies that assessed patients with PACS on specific RAPAs were included. The RAPAs that were identified looked for impairments in olfactory, eye-tracking, graphical, speech and language, central auditory, or spatial navigation abilities. The recommendations' final grades were determined by evaluating the strength of the evidence and by having a consensus discussion about the results of the Delphi rounds among an international Delphi consensus panel called IMPACT, sponsored by the French National Research Agency. The consensus panel included 11 international experts from France, Switzerland, and Canada.

Results: Based on the available evidence, olfaction is the most sustained impairment found in PACS patients. However, expert consensus statements recommend that AD olfactory screening should not be used on patients with a history of PACS at this point in time. Experts recommend that olfactory screenings can only be recommended once those under study have reported full recovery. This is particularly important for the olfactory identification subdimension. The expert assessment that more long-term studies are needed after a period of full recovery, suggests that this consensus statement requires an update in a few years.

Conclusion: Based on the available evidence, olfaction could be durably impaired in PACS patients. According to expert consensus statements, AD olfactory screening is not recommended for patients with a history of PACS until complete recovery has been confirmed by PACS olfactory recovery studies, particularly for the identification sub-dimension. This consensus statement may require an update in a few years.

Introduction

On an international cohort [1], cognitive, sensory-motor, memory and speech or language symptoms persisted in an average of 30% [2–5] of patients up to 7 to 12 months after SARS-CoV-2 infection (COVID-19). These symptoms are grouped under the term of Post-Acute COVID-19 Syndrome (PACS) as defined by an OMS Delphi consensus¹). Morphological MRI changes in brain structure have also been observed for approximately 141 days after the infection [6] including primarily in global brain size and, secondarily in a decrease of the olfactory cortex thickness. Major changes in tissue damage markers in brain areas functionally connected to the primary olfactory cortex were also observed [6], which could explain why 29.8% of PACS patients complain of persistent dysosmia, or a change in the sense of smell, more than 24 months after COVID-19 [7]. The point is that much of the recent literature focuses on the emerging risk of neurodegenerative disease and more precisely on AD [8–15] after contracting COVID-19.

Worldwide, Alzheimer disease (AD) is the main neurodegenerative disease leading to dementia and its responsible for an increase in morbidity [16] affecting more than 50 million people, two-thirds living in low- and middle-income countries [16]. The prevalence of AD is estimated to triple in 2050[16]. Preclinical and prodromal AD respectively last on average for 10 and 4 years [17] before becoming dementia. The median survival rate for dementia is approximately about 3 to 6 years [18,19] after diagnosis. AD early diagnosis, followed by non-pharmacological interventions and pharmacological treatment [16], could potentially prevent the rapid cognitive decline associated with dementia. However early diagnosis remains a real challenge for clinicians as preclinical AD screening tests are still debated.

Current conventional and preclinical AD screening markers, such as neuropsychological assessments, brain morphological (MRI) or metabolic (PET) or a lumbar puncture for example [16,20], are not equally available worldwide. They are expensive, time-consuming and depend on the availability of both technical platforms and human assistance. Remote digital Assessments for Preclinical Alzheimer's disease (RAPAs) could be an alternate solution that are relatively easy-to-implement and which might reduce delays in preclinical AD diagnoses. During the COVID-19 pandemic, remote assessments became increasingly common in daily

¹ <https://apps.who.int/iris/rest/bitstreams/1376291/retrieve>

medical practice with telemedicine enabling patients to benefit from continuous remote monitoring through a variety of digital technologies, such as video conferencing tools or symptom tracking applications [21]. Remote assessments to provide cognitive assessment and plan treatment interventions allow patients to have an easier access to specialists and highly skilled healthcare professionals, even if those patients are located in remote regions in a feasible, effective and acceptable way [22,23]. Furthermore, telemedicine is a part of an intergenerational approach to technology use that included a growing number of older adults [24] during the pandemic. Telemedicine could help patients to avoid unnecessary travel and limit hospitalizations, which may be desired by some patients and reduce the costs of managing diseases. However, telemedicine is a challenging process based on a number of different factors including access and ownership of the appropriate digital tools, the ability to use these tools, the physical affordances of the devices and the mobility of the patient, as well as interactional barriers in communicating digitally with someone in a health crisis [25].

A group of AD remote and digital evaluation platform experts from France, Swiss and Canada (IMPACT project) under the leadership of the French National Research Agency, were invited to develop evidence-based recommendations and expert consensus on items related to AD early diagnosis in the post-COVID-19 era. The IMPACT project aims to: 1-review RAPAs potentially impaired in PACS patients which could become unusable in AD early screening in case PACS last a long or a lifetime; 2- describe evidence-based recommendations according to the review; 3-inform people and policy makers of the recommendations. The first and the second items were primary and secondary objectives of this work.

Materials and Methods

Search Strategy

Selection of the Remote digital Assessments for Preclinical Alzheimer's disease

An initial research stage allowed authors to identify Remote digital Assessments for Preclinical AD (RAPAs) in PubMed and Embase Databases which were easily usable, non-expansive, quick, and widely available: vocal, graphical, eye tracking, central auditive impairments, olfactory disorders, and spatial navigation abilities markers. A complete process is reported in Supplementary Material 1.

Data sources

A search request command on PubMed, Cochrane database and Embase was typed the 31/11/2022. This search included “keywords” through VOCAL “speech” OR “language” OR “language tests” OR “voice”; GRAPHICAL “Psychomotor Performance” OR “writing” OR “handwriting” OR “psychomotor performance” OR “mouse movements” OR “patterns” OR “drawing” OR “keystroke”; EYE TRACKING “eye movement” OR “eye-tracking technology” OR “saccades” OR “ocular motility”; CENTRAL AUDITIVE IMPAIRMENTS “Auditory system dysfunction » OR “central auditory function” OR “central auditory deficit”; OLFACTORY DISORDERS “Olfaction Disorders” OR “anosmia” OR “hyposmia” OR “dysosmia” OR “olfactory loss” OR “parosmia”; SPATIALIZATION “Virtual reality” OR “spatial navigation”. PACS included “long covid”, “post covid”, “post-covid”, “post-covid-19”, “long-covid-19”, “long-covid” or “post-acute covid-19 syndrome”. The search request strategy is provided in the Supplementary Figure 1.

Inclusion criteria

Types of studies

Systematic reviews with or without meta-analyses, and observational studies, only in peer-reviewed journals, were included. We excluded retrospective studies, meeting abstracts, conference presentations, book reviews, news items and corrections. Every study in English, relative to humans since 2020, was included if they were a clinical trial, a meta-analysis, a randomized controlled trial, a review, or a systematic review. Studies in languages other than English or French, older than 2020 or without abstract were not included as COVID-19 pandemic began that year. The electronic database search was supplemented by screening the reference lists of the included studies and relevant reviews.

Types of participants

Only adults (≥ 18 years old) with post-acute COVID-19 syndrome (PACS) patients were included but this term is not always called PACS but “long-COVID-19” or “post-COVID-19”. These terms were included in the search strategy protocol. Exclusion criteria were patients previously impaired with neurologic, neurodegenerative, or neuromuscular diseases; speech, voice, or language impairments; psychomotricity, writing or handwriting related diseases;

abnormal eye-movement related diseases; anterior reported hearing loss; anteriorly reported olfaction disorders or spatial navigation incapacities. All types of intervention were included.

Types of Outcomes

Outcomes measures must include one or more of the RAPA previously identified among vocal, graphical, eye tracking, central auditive impairments, olfactory disorders, or spatial navigation impairment.

Study selection and evaluation

For the first step, two reviewers (CV, AP) assessed the title/abstract of each result following inclusion and exclusion criteria. In case of conflict, a second review was scheduled with both reviewers (CV, AP) and a third one (AG) until a consensus was reached. Individual clinical research studies were evaluated in accordance with the French HAS criteria.

Quality assessment

Quality of studies reported were assessed based on a systematic review of methodological quality assessment tools [26]. Systematic reviews were assessed using AMSTAR 2 tool (Assessment of Multiple SysTemAtic Reviews) [27,28], cohort and observational studies using the Observation Study Quality Evaluation tool (OSQE) [29]. Concerning AMSTAR 2, 16 items were evaluated which 7 were critical (N°2, 4, 7, 9, 11, 13, 15). A review was assessed as high quality if none or one non-critical weakness were noticed (the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest); as moderate quality when more than one non-critical weakness was noticed (the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review); as low quality when one critical flaw with or without non-critical weaknesses were noticed (the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest); or critically low when more than one critical flaw with or without non-critical weaknesses (the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies) or multiple non-critical weaknesses were noticed (may diminish confidence in the

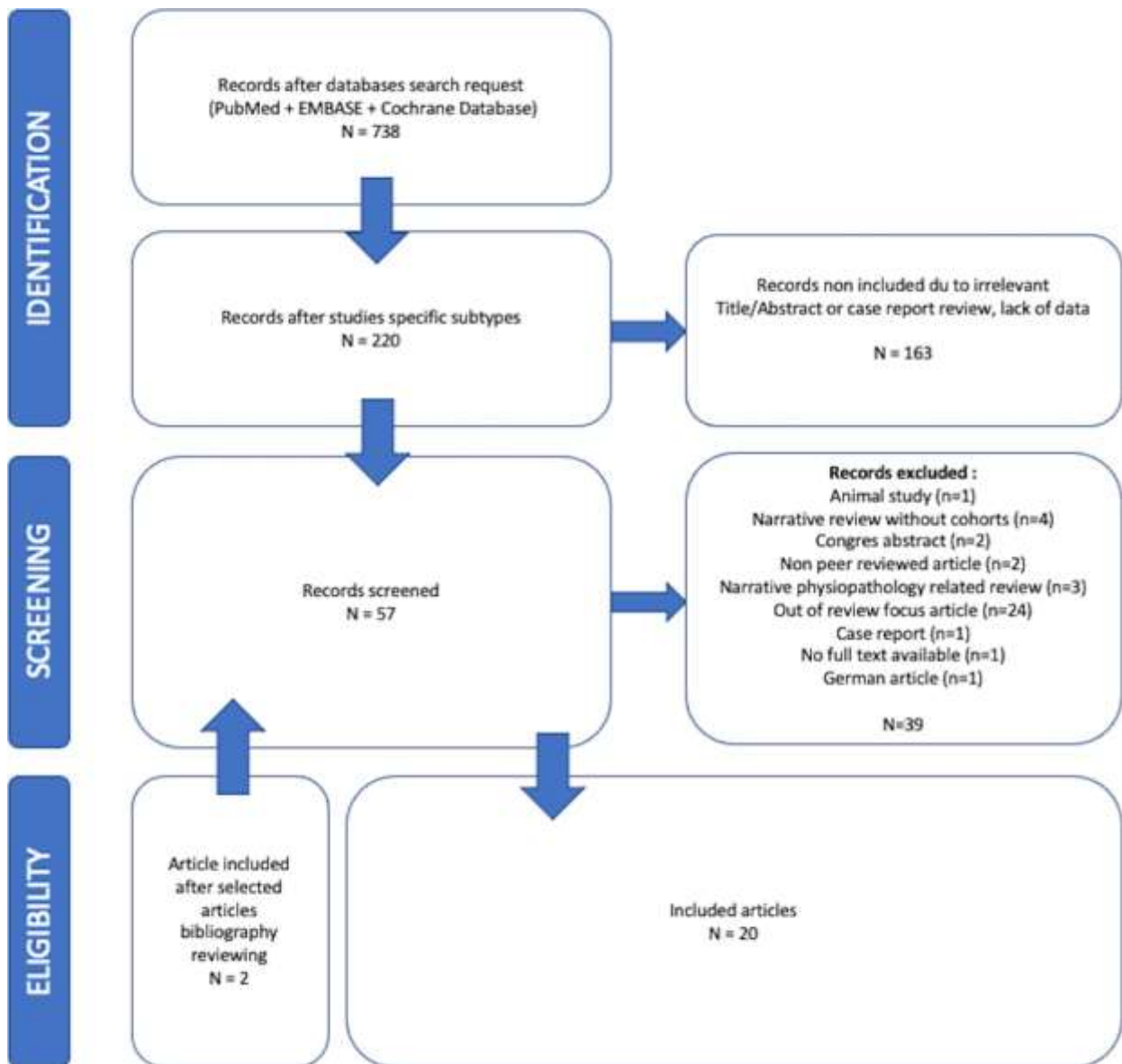
review and it may be appropriate to move the overall appraisal down from moderate to low confidence). For the OSQE evaluation tool, 16 items were evaluated with different weights explaining why authors [29] did not provide any cutoff score to discriminate good from poor quality studies, leaving to users' appreciation. Different forms were used, provided by authors in their original work [29], given depending of the observational study type. No meta-analysis was done so the risk of bias associated with the included studies was not assessed. Ethical clearance from the institutional ethical committee was not required as all the data extracted was from already published studies and no patients or the public were directly interviewed or involved in the present research.

Consensus Process

The EU Joint Program – Neurodegenerative Disease Research (JPND) initiative initiated a call for expert working groups on November 1, 2021, to investigate the impact of COVID-19 on research related to neurodegenerative diseases. Many funding organizations were requested based on the country answering to this program. France Funding company was the French National Research Agency. Our working groups answered to this call focusing on COVID-19 pandemic and its impact on Alzheimer's care: an expert board has been set up based on past collaborations in this field of expertise. Talking about digital and clinical distance evaluation platforms required bringing together other specialists in the field of digitalization and digital support explaining working with physicians (CV, OR, CyLa, OG, PR, GA, OB) neuroscientists (AP, VM, KG, NB, OG, PR, GA, OB, AG), speech therapists (AP, AG), communication and age studies experts (CoLa and KS) and a mobile media research director (KS). VM and AG developed the research topics using the population, intervention, comparator, and outcome (PICO) framework and created the initial recommendation statements. In the first round, a group of 12 experts from the IMPACT project reviewed and provided feedback on the questionnaire using a 5-point scale (ranging from "strongly agree" to "strongly disagree") [30]. Responses with a score of 1-2 were considered as indicating agreement. During the second round, the recommendation statements that did not achieve agreement were discussed further. If a consensus agreement of 75% was not reached after discussion, a third round of rating was conducted [31]. Finally, the grades of recommendation were assigned based on the strength of evidence and a consensus discussion of the results from the Delphi rounds.

Literature Search Results

Figure 1: PRISMA flowchart: Overview of the screening process



We reviewed 738 articles. 20 studies met the inclusion criteria after evaluation of titles, abstracts, and full contents of the relevant studies of which 4 were systematic reviews, 7 systematic reviews with meta-analysis, 2 narrative reviews, 6 observational cohorts and 1 case control studies. All the selection process is reported in flowchart (figure 1). The reviews and observational studies level of quality were reported in table A, B and C in Supplementary

Material. Based on AMSTAR 2 scores 69.2% (n=9), 23.1% (n=3) and 1.8% (n=1) reviews had respectively critically low, low and high quality. Based on OSQE scores, 28.6% (n=2), 14.3% (n=1), 28.6% (n=2), and 28.6% (n=2) of observational studies were respectively scored with 14, 13, 12 and 8 stars out of 16.

Demographical data

Demographics are reported in Table 1. When it was clearly reported (90%; n=18) population size ranged from 34 [32] to 178 496 [33] people within average $24\ 031 \pm 54301$ patients in reviews papers and 638 ± 1379 in cohort observational studies papers. Patients' ethnic groups were reported to be all over the world but 5 (38.5%) reviews [34–38] and 5 (71.4%) observational studies [32,39–42]. When it was clearly reported in 50% of studies (n=10), average patient ages were 40- and 50-year-old. Only 12 studies clearly reported gender impairment differences with women preferentially impaired in 6/12 studies. Definition of long-COVID-19 changed a lot in the past 2 years and so heterogeneous assessment time from COVID-19 onset was reported in table 1.

Table 1: Main demographic data included in the selected articles

Authors	Time from COVID-19 onset	N (patients)	N _{review} (studies)	Type	Age (years)	Women N(%)
Ahmad et al. 2021[43]	2 weeks to 6 months	14056	20	SR	18-60	-
Parker et al. 2021[33]	2 weeks to 6 months	178496	272	SR	17 to 93yo	-
Ser et al. 2022[39]	4 weeks to 3 months	106	-	CCS	39.4 ± 12.5	47 (44.3)
Deer et al. 2021[34]	17 days to 4,7 months	NP	59	SR/MA	12 to 73	-
Bertuccelli et al. 2022[35]	3 to 6 months	1940	25	SR	42.57 ± 7.23 to 79 ± 8 Mean = 60	873 (45)
Dirican et al. 2022[48]	23 days to 12 months	7546	20	SR/MA	53.4 ± 8.2 34 to 68.8	1671 (46.8)
Jamouille et al. 2022[36]	3 to 18 months	55	-	CS	$42,9 \pm 15,6$	40 (72.7)
De Luca et al. 2022[37]	1 month to 10,6 months	5582	16	SR	-	-
Davis et al. 2021[1]	0 to 7 months	3762	-	CS	30 to 60	2969 (78.9)
Silva Andrade et al. 2021[45]	NP	NP	62	NR	-	-
Premraj et al. 2022[38]	3 to 6 months	10530	18	SR/MA	52 ± 10	6213 (59)
Pinzon et al. 2022[49]	until 6 months	9944	36	SR/MA	17 to 81	-
Malik et al. 2022[47]	30 to 180 days	4828	12	SR/MA	58.75	2481 (45,5)

Giron Perez et al. 2022[40]	More than 3months	76	-	CS	20 to 70 Mean = 45	36 (47,4)
Xydakis et al. 2021[92]	47 days to 6 months	3691	-	NR	-	-
Fernández-de-Las-Peñas et al. 2021[46]	0 to 3 months	24225	33	SR/MA	47.8 ± 16.6	52.26
Tan et al. 2022 [44]	0 to 6 months	3699	18	SR/MA	30 to 55,8	-
Michelutti et al. 2022[41]	More than 3months	213	-	CS	53±14	151 (73)
Mendes Paranhos et al. 2022[42]	221 to 264 days	219	-	CS	18 to 60	164 (74,9)
Vandersteen et al. 2021[32]	5±2,8 months	34	-	CS	41.6±12.9	16 (47)

SR=systematic review; CCA=case control study; SM/MA=systematic review and meta-analysis; NR=narrative review; CS=cohort study

Impairments observed in the Remote digital assessments for preclinical Alzheimer's disease in Post-Acute COVID-19 patients.

The summary results of RAPAs review were reported in Table 2. We independently analyzed RAPA impairments in 20 studies and report direct or indirect impairment for each RAPA (summarized in Table 3) as RAPA could have been directly impaired (for example hand shaking in handwriting assessments) or indirectly impaired (like visual hallucinations in eye-tracking assessments). The most often-reported RAPA impairment was the olfactory function occurring in PACS patients in all but 2 studies. The second most frequently impaired biomarkers were graphical and eye-tracking ones. The third was central hearing and finally vocal and spatial navigation abilities were reported very rarely.

Table 2: Remote digital Alzheimer's disease preclinical Assessments (RAPA) impairments related to every study included in the review.

Authors	RAPA					
	Vocal	Graphical	Eye-Tracking	Central Hearing	Olfactory disorders	Spatial navigation
Ahmad et al. 2021[43]	X	X	X		X	
Parker et al. 2021[33]				X	X	
Ser et al. 2022[39]		X			X	
Deer et al. 2021[34]	X	X	X	X	X	
Bertuccelli et al. 2022[35]						X
Dirican et al. 2022[48]					X	
Jamouille et al. 2022[36]		X				
De Luca et al. 2022[37]				X	X	
Davis et al. 2021[1]	X	X	X	X	X	
Silva Andrade et al. 2021[45]	X	X	X	X	X	
Premraj et al. 2022[38]					X	

Pinzon et al. 2022[49]	X	X	X	X	X
Malik et al. 2022[47]					X
Giron Perez et al. 2022[40]					X
Xydakis et al. 2021[92]					X
Fernández-de-Las-Peñas et al. 2021[46]		X			X
Tan et al. 2022 [44]					X
Michelutti et al. 2022[41]		X			X
Mendes Paranhos et al. 2022[42]					X
Vandersteen et al. 2021[32]					X

The expert summary recommendations for the use of every RAPA in PACS are reported in Table 3

Table 3: Recommendations summary related to Remote digital Alzheimer's disease preclinical Assessments (RAPAs) evaluated in the review.

Assessed items	A - AD early diagnosis BM interest	B - AD BM specificity loss in PACS patients	C - BM interest in early diagnosis of AD in PACS patients	Level of evidence	Grade of recommendation
RAPA					
Vocal markers	4,3±0,7	3,7±0,9	3,9±0,9	II	B
Graphical markers	4,1±0,8	3,9±1	3,9±0,6	II	B
Eye-Tracking	2,7±0,7	3,3±0,7	3,3±0,9	II	B
Central Hearing	2,6±0,5	3,1±0,8	3±0,5	II	B
Olfactory disorders	4±0,9	1,6±1,4	1,4±0,7	II	B
Spatial navigation abilities	3,7±1	3,7±1,3	3,7±1,5	II	B

AD = Alzheimer disease; BM = biomarker; PACS = post-acute COVID-19 syndrome. Likert scale for items A and C are reported as 1 for not agreeing at all to 5 for completely agreeing. For item B (BM specificity loss in PACS patients), Likert scale were inverted.

Consensus Recommendations

Many RAPAs were reported as impacted in PACS patients but olfaction was the most impaired. Graphical and eye-tracking assessments were less but still reported as impacted. Consensus recommendations were discussed based on these reports.

Consensus recommendation: olfaction-related remote digital assessments for preclinical Alzheimer's disease.

Olfaction was impacted in all but 2 studies [35,36]. Direct involvement included a persistent dysosmia in 11 to 57.6% of PACS patients [1,33,40,41,43–45] related to an anosmia [38,41–44,46,47], explicitly reported in 12.8% [34], 19.3 to 21.4% [43], 32.2% [41], 44% [39] or 55.9% [32] of cases or an hyposmia [41,42] explicitly reported in 14.7% [32], 15.3% [34] or 33.1% [41] of cases. Assessment time from COVID-19 onset was extremely variable. Only two studies were over 10 to 12 months of follow up [37,48] but only De Luca et al. [37] report a 6-month recovery rate of 95.3% in a 16-studies review on PACS persistent chemosensory dysfunction. One study [32] reported olfaction subdimensions precisions related to a prevalent identification impairment significantly related to subjective olfactory recovery (VAS; $p=0.034$) compared to threshold and discrimination scores. According to WHO clinical management of COVID-19², Dirican et al. [48] did not find any difference of persistence anosmia between severe and non-severe survivors of COVID-19 with a global pooled odds ratio of 1.22 [95%CI 0.69 to 2.16] in a meta-analysis of 20 relevant observational studies. Parosmia were explicitly reported in 23.2% [1] frequently described as “smoke,” “burning,” “cigarette,” and altered “meat” smell. Phantosmia were reported in 23.2% [34]. Indirect involvement included dysgeusia [38,43,46,49], which was frequently reported associated with olfaction disorders in 19,3 to 38.5% of the studies [1,45,50]. Davis et al. [1] found no significant differences between loss of smell (35.9%, [34.4% to 37.5%]) vs. loss of taste (33.7%, [32.2% to 35.2%], $p>0.1$) in an online questionnaire observational study on 3762 PACS patients 7 months after COVID-19 onset. More precisely, parageusia and phantageusia, like qualitative olfactory dysfunction, were reported respectively in 16.4% and 9% [34] of PACS patients up to ~5 months after COVID-19 onset.

² <https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-2>

Taking into account above discussion, the expert consensus does not recommend the use of olfaction as a RAPA when patients complain of a COVID-19 PACS history (level II, grade B). Many PACS patients continue to complain of olfactory disorders 1 year after the COVID-19 onset, however, to date, not enough high-quality studies report a complete recovery amongst those undergoing either subjective testing or psychophysical olfactory testing (mainly on identification).

Consensus recommendation: graphical marker-related remote digital assessments for preclinical Alzheimer's disease.

Only one review [34] reported a study with 4% of hand muscle weakness in PACS patient that directly involve graphical markers. Many indirect symptoms were reported [1,34,36,39,43,45,49] with potential impacts on graphical capacities as pins and needles and numbness in hand (2%) [43], fatigue or muscle weakness (63%) [43]. However, even if cutaneous sensitivity and conductance parameters were significantly measured as abnormal in PACS patients reporting autonomic complaints, no nerve conduction abnormalities were noticed [39]. Many symptoms were reported that could indirectly influence graphical markers such as abnormal exteroceptive sensation (13.8%), abnormality of movements (2%), dysmetria (2.8%) [34]; muscle spasms (22%), tremors (28%), vibrating sensations (18%), tactile hallucinations (3.1%) [1]; or skeletomuscular global impairment [1,45,49] with pain [49] (27.8%), paresthesia[49] (33.3%) or movement disorders [49] (3.6%). In a cohort study, Jamouille et al. [36] reported the case of a 3 times COVID-19 infected man with anosmia, dysgeusia, severe cognitive and memory problems and alteration of cerebral perfusion on SPEC-CT: he complained about fingertips paresthesia, lateral hand tremors and sometimes, his hands opened by themselves while doing anything specific, dropping spontaneously carried objects.

Taking into account the above discussion, the expert consensus recommends to continue using graphical markers in RAPA studies. Rarely did research report hand skeletomuscular impairments that could lead to graphical marker abnormal results. No PACS studies reported kinetic results and no nerve conductivity abnormalities were reported in this review (level II, grade B).

Consensus recommendation: eye-tracking-related remote digital assessments for preclinical Alzheimer's disease.

Three studies [34,45,49] spotted ocular complications in PACS patients described as visual impairments, arterial thrombosis or ophthalmoplegia, but only one review reported a case of a 28-year-old man with thalassemia minor complaining of gaze-evoked nystagmus and intermittent diplopia on lateral gaze that persisted 10 days after hospital discharge. Five other studies [1,34,41,43,46] reported indirect potential impairment of eye-tracking tests results mainly the 6 first months after COVID-19 onset : “eyes problems” 79±17 days after COVID-19 onset[43]; visual loss 10-14 weeks after COVID-19 onset [43]; blindness in one study[34]; blurred vision (9.7% to 35.7% 7 months after COVID-19 onset)[1,34]; conjunctivitis (8.9%)[34]; diplopia (6.9%)[34] and keratoconjunctivitis (28.6%)[34]; visual hallucinations (10.4%)[1] or finally persistence of visual disturbance in 3.3 to 8%[41].

Taking into account above discussion, the experts' consensus is to continue using eye-tracking markers in RAPA studies as few studies report direct vision and/or oculomotor impairment that could lead to abnormal eye tracking assessments results (level II, grade B).

Consensus recommendation: central hearing-related remote digital assessments for preclinical Alzheimer's disease.

In this review, 4 studies [33,34,45,49] reported direct persistent hearing impairment [45] with 6.6% [34] to 15% [33] persistent sensorineural hearing loss (before 6 months) [49] without precision on the follow up and recovery. Indirect persistent hearing impairments were related to persistent tinnitus and earache (2.5 to 3.6%) [34,43], hyperacusis (34.7%), pulsatile tinnitus (19%) or tinnitus (29%) [34,49]. In a systematic review [37] reported in this work authors reported a controlled study of 27 PACS patients (Vs 20 control) 3.81 ± 2.11 months after COVID-19 onset where speech audiometry showed small but significant impairment in PACS correlated in auditory brainstem response to a lengthening of waves III-V interpeak latencies. However, in the same work [37] authors report other studies which failed to show any differences in vestibular or cochlear, even retro cochlear, function (auditory brainstem responses).

Taking into account above discussion experts consensus recommend to still use central hearing markers in RAPA studies as rare works report the possibility that PACS may cause damage to hearing system and so lead to long lasting abnormal central hearing results (level II, grade B).

Consensus recommendation: vocal and speech test-related remote digital assessments for preclinical Alzheimer's disease.

Three studies [1,34,43] in this work reported indirect impairment of speech and language in 49% of PACS patients. Seven months after the onset of COVID-19 onset, 22 % reported 22% of difficulty speaking, 47% reported difficulties finding the right word, 30% difficulties communicating verbally, 17% slurring words and 9% reported speaking unrecognizable words. Problems swallowing were reported in a 39 PACS patient cohort study, although no specifics were given [43]. Different types of aphasia were reported in an 81-cohort systematic review [34] (anomic in one study [46.3%], bilingual in one study [28.9%], expressive in one study [22.2%], receptive in one study [23.8%]) with the possibility that COVID-19 could lead to vocal and spontaneous speech impairments (flow rate, hesitations). In this work only 3 studies [1,34,45] underlined a direct speech impairment with 7 months after COVID-19 onset 38% speech and language issues [1] like slurred speech were reported for 15.8% of patients in a review of 59 PACS papers [34]. In a narrative review [45] included in this work, the authors reported the case of a 49-year-old woman with COVID-19 infection who exhibited no flu symptoms but suddenly presented speech disorder and left hemiparesis related to two small acute cerebral infarctions in the right prerolandic cortex, which is a rare complication of COVID-19. However, no follow-up data were made.

Taking into account the above discussion, the experts consensus recommends to continue to use vocal markers in RAPA studies as few works reported the possibility that COVID-19 infection may cause significant modifications to vocal performances and lead to abnormal vocal assessments results (level II, grade B).

Consensus recommendation: spatial navigation abilities test-related remote digital assessments for preclinical Alzheimer's disease.

In this review, only 2 papers [49, 51] reported PACS patients with symptoms related to spatial navigation ability impairments. The first review reported 2.6% of persistent spatial

disorientation and/or confusion in a 697 PACS patient cohort [49] of 63 ± 14.4 -year-olds on average, 6 months after hospital discharge. Moreover, in a study analyzing MoCA visuo-spatial subitems [51], the mean score of a sample of 29 non-ICU-admitted subjects, 0 to 3 months after symptoms onset, revealed impaired spatial navigational functions (2.50 ± 1.34 ; max score:4). Moreover, in the same review [51], five other studies assessed visuo-spatial abilities with visual reproduction of the Wechsler Memory Scale, the Rey-Osterrieth Complex Figure, and the Corsi Test, none of which found relevant deficits.

Taking into account the above discussion, the expert consensus is to keep using spatial navigation RAPAs, as few studies in the literature are controversial. This indicates that there is a weak possibility that COVID-19 infection may cause significant modifications to the performance of spatial navigation. (level II, grade B).

Discussion and Conclusion

This study aimed to assess the potentially impacted RAPAs in a PACS situation to assess the expert consensus or recommendations when considering PACS medical history for each RAPA. Recommendations are aimed towards physicians, neuroscientists, clinicians, or students working on AD early diagnosis to keep in mind COVID-19's potential influence on results. Clearly, PACS reporting patients may not be able to be screened for AD efficiently and special attention must be paid to the choice of early markers to use in making assessments.

A total of 20 studies met our inclusion criteria. The main finding concerns the presence of olfaction persistent impairments, which might seriously affect the validity of olfactory screening for neurodegenerative diseases. This scoping review raises two questions: First, the similarities between PACS and AD. The second is relative to the impact of PACS on RAPA targets, which could potentially hinder any AD screening due to the biased results produced by PACS outcomes.

Since the beginning of the pandemic, many authors have drawn attention to the similarity and connection between the mechanisms and risks between COVID-19 and AD. If the cerebral invasiveness of COVID-19 is still debated, then the inflammatory consequences of the COVID-19 on the brain is demonstrated. Furthermore, many arguments link COVID-19 infection and AD [8,10,14,52]. Trans endothelial mechanism is highly discussed as the main way of systemic

spreading [14] but olfactory neuroepithelium and olfactory neurons could be an alternative means of transmission [53,54]. Viruses, like HSV or EBV infection or reactivation, might play an important role in AD genesis [55] and could be self-sustained, for example by the fourth isoform of apolipoprotein E genotype (APOE4). APOE4 is a well-known AD risk factor and has been reported to facilitate HSV1 reactivation in the brain by many events such as immunosuppression, peripheral infection, or inflammation [56]. Many authors speculate on long-lasting inflammation in PACS patients with astrocytes and microglia brain activation polarized in a facilitating way (M1 phenotype) of β -amyloid and Tau phosphorylation levels increase [14,56]. Moreover, APOE4 may facilitate the infectivity of COVID-19 by regulating intracellular levels of cholesterol and increasing the S-protein binding to ACE2[14] but its PACS role and staying power is debated in clinical trials [57]. Wide ACE2 binding during COVID-19 infection could downregulate the ACE2 receptor [14] for a while, which has been reported to be decreased in post-mortem brain tissue of AD patient, and inversely is correlated to β -amyloid levels and Tau phosphorylation [58]. Finally, β -amyloid, a peptide with antimicrobial properties, may be an innate immune system actor [59] but could be theoretically and ironically be over-produced in PACS patients. Given that approximately 659 million people has so far been infected by COVID-19, more follow-up with PACS patient and more powerful, high-quality studies need to be undertaken.

Olfaction RAPAs are no longer recommended - RAPA target assessments could interfere with PACS outcomes, and as such, this type of assessment may complicate potential AD early screenings. As the experts' conclusions (Table 3) underline, olfaction could be an early AD marker. An identification impairment without any other etiology is an early symptom of phosphorylated Tau protein neurofibrillary tangles (NFTs) and β -amyloid plaques accretion in olfactory bulbs and entorhinal cortex [60], which is the main cortex gate between a smell and it's memory and one of the first brain-impaired regions in early AD [61], in the hippocamp and amygdala. Identification is impaired in PACS and reflects the olfactory subjective (visual analogic scale) and patient quality of life impairment [32]. Almost 2 years [7] after COVID-19 onset, 29.8% of PACS patients still complain of olfactory disorders (0.6% of hyposmic and 2.3% anosmic on identification psychophysical test results) with 13.4% of parosmia. Parosmias are one of the main olfactory-persistent symptoms of PACS patients [1] and are only predictive as a threshold impairment [62]. Therefore, just as we see in older patients, there will be a global olfactory score improvement but not an olfactory identification score improvement. [7,63]. Our results indicate the presence of more hyposmia, anosmia and parosmia from the time of

COVID-19 onset. As reported in this review, the lack of psychophysical olfactory tests in the included studies, are subjective assessments, and thus seem to overestimate, from a quantitative perspective, olfactory disorders for more than 40% of patients [64]. Dysgeusia was frequently reported in PACS in similar proportion to dysosmia. As retro-olfaction is often confused with taste in 50% of people [64], clinicians have to pay attention to “dysgeusia” as it could be an olfaction impairment because gustatory functions are rarely impacted during COVID-19 onset [65] and when they are, they are short-lived [66]. Lack of psychophysical olfactory testing, frequent long lasting dysosmia and risk of dysosmia misdiagnoses because of false dysgeusia in the PACS literature prevent us from specifying with precision PACS-persistent olfactory disorders and features and therefore potential long-lasting impairment identification. This is why experts recommend, for the moment, not to trust olfactory identification impairments for RAPA in PACS patient until more high-quality studies are published. Only then will researchers be able to assert if there is complete olfaction recovery.

Graphical marker RAPAs are still recommended – As the experts conclude, graphical markers are widely studied in RAPA, as AD patients report a decline in fine motor control, coordination and writing or drawing impairments that compromise daily life activities [67]. AD hand movements become slower, less fluid, and less consistent due to reduced precision in wrist and finger positioning [68]. Additionally, handwriting pressure decreases in patients with AD when cognitive tasks are performed. The differentiation of patients with healthy controls [69], but also the increase of writing time between two strokes (known as pen-up time [70]) is a key discriminator [71] between AD and Mild Cognitive Impairment (MCI) patients compared to healthy individuals when performing tasks that involve visuospatial construction, cognitive writing, or the Clock Drawing Test [72–74]. For MCI and AD screening, pooled sensitivity and specificity of kinetics are respectively 0,85 and 0,82 in a Scientific Report study [70] and allow, specifically for drawing tasks (spiral, crossed pentagons, 3D house, clock drawing test), a high specificity to screen MCI or AD patients [75]. In this research, few symptoms were reported in PACS patients that interfere with direct kinetic assessments (such as tremors, hand muscle weakness [34]) or could influence indirectly the way the patient writes or draws (such as vibrating sensations, tactile hallucinations, abnormal exteroceptive sensation or paresthesia [1,34]). The literature reports upper extremity plexopathy [76,77] in severe COVID-19 (requiring mechanical ventilation) between 1 to 3 months after infection onset. However, the responsibility of the prone position is still debated [78] and no recovery, long follow-up or specific kinetic studies have yet been performed on these neurological PACS patients. This

explains the important loss in specificity that is evaluated by experts (Table 3), who nevertheless recommend to still use this RAPA.

Speech RAPAs are still recommended - For over a decade, many authors have worked on AD - connected speech assessments [79], as confirmed by experts interest in this RAPA, especially since the development of computer-assisted voice analysis. These speech and voice assessments have focused on the lexico-semantic and discourse-pragmatic aspects, which accounts for around 80% and 77.5% of the actual research, respectively [79]. The syntactic, phonetic and phonemic and finally morphological aspects comprise, respectively, 57.5%, 55% and 35% of current studies [79]. In AD patients phonetic and phonological errors have been reported, as well as a low speech rate and increase of hesitations [80,81], lexico-semantic errors, word findings difficulties [82], and a greater number of closed classes [83] and high frequency words [84]. In this review, frequent (49% [1]) impairments of speech were reported in PACS patients with imprecise speech and language issues that could be linked more to lexico-semantic, phonetic and phonological features. In PACS patients, general [43] and verbal communication difficulties or slurring words were reported [1] as did cross lexical and semantic RAPA or different types of aphasia [34]. However, few studies reported speech specific PACS and in the 6 months after the onset of COVID-19. Although remote European (semi) automated speech analysis projects are being carried out, this sort of specific speech/acoustic measures are rarely investigated [79] in AD and never recorded in PACS. Because of these short-lasting voice PACS and without acoustic persistent issues, experts recommend to continue using speech RAPA.

Eye tracking, visual abilities, and central hearing RAPAs are still recommended - Finally, these three RAPAs were not suggested as significantly relevant by experts. Eye-tracking as RAPA is based on eyes saccades and fixation recording during specific tasks (reading, cognitive or memory test) through devices embedded-cameras (laptop, tablet, phone). Eye-tracking has been validated on AD and MCI screening 10 years ago [85,86] with a cognitive impairment diagnosis sensitivity and specificity of respectively 0,75 and 0,73 in a recent systematic review and meta-analysis [87]. In this review, only one case was reported [34] with a saccades-modifying condition. All other eye-tracking related studies pointed to potential fixation difficulties [1,34,41,43,46] in PACS patients but these were presumed to be curable for some items [34] (conjunctivitis [8.9%], keratoconjunctivitis [28.6%]). However, good vision is mandatory to be able to use new spatial navigation assessments in addition to good visuo-spatial cognitive functions. Even if VR computer-generated environments were used to assess spatial navigation,

RAPAs [88] could destabilize AD older patients. PACS were younger, and zero to few spatial navigation abilities impairments were reported. Eye-tracking has been validated in combination with virtual reality (VR) simulation [89] as a RAPA, but under some conditions there is a mismatch between the use of contemporary technologies and AD/control patients age including but under few conditions related to a mismatch between modernity and AD/controls patients age (VR induced nausea, the inability to calibrate a device, or understand the instructions). Finally, persistent visual disturbances were reported in 3.3% (n=5/151) to 8% (n=5/62) of a 213 PACS cohort observational study, 3 months after the onset of COVID-19 [41].

The last RAPA is central hearing which is the less relevant for experts. Central hearing RAPA include auditory temporal processing, dichotic tests, monaural low-redundancy speech tests and auditory discrimination and memory tests [90]. These all depend on possessing efficient sensorineural hearing, which were reported as impaired in 4 short follow-up studies [33,34,45,49] and in up to 15% of PACS patients. Moreover, central hearing assessments depend on cognitive, memory and attention abilities which could be widely impaired in respectively 70 to 90%, 70% and 50 to 90% of a 3762 PACS-patients observational cohort. Approximately 7 months after the onset of COVID-19 [1], studies report that cognitive impairments are one of the three most frequent symptoms after six months. One year after COVID-19 onset, in a non-included review, memory loss and attention abilities were still impaired in 19% and 18% of a 8591 PACS patients cohort [4]. Tinnitus and hyperacusis was reported in less than 30% of PACS patients, which could add a negative effect on hearing. Despite persistent hearing disorders reported in this review, no study reported central auditory tests on PACS patients justifying experts' recommendation to carry on using this RAPA.

This study has several limits. PACS has been gradually defined since the pandemic started until 6 October 2021 when a World Health Organization DELPHI consensus provided a clinical definition of PACS for adults and the 16 February 2023 for children and adolescents. This evolving definition explains the extreme variability of assessment times in every review reported in this work, running from 2 to 52 weeks, and mainly in the first 30 weeks after the onset of COVID-19 (Table 1). This variability in definition could have contributed to overestimating PACS sustainability and as such, the recommendations that were made at the time. Moreover, many reviews can be classified as low or critically low quality because most of them lack a meta-analysis of their data, which can result in heterogeneity, and a risk of bias assessments. Four of the six cohort observational studies received more than 75%, a full score

indicating level of quality. for the main concerns were methodological. Observational studies (level 2 HAS scientific evidence) only allowed for a presumption of scientific quality compared to level 1 studies which were, mostly here, of low quality. Finally, COVID-19 papers and as such PACS ones, have been part of a larger phenomenon which consists in an increase of COVID-19 related publications number, decrease of reviewing time and, finally, a decline in methodological quality [91].

Conclusion

This work highlights the value of using RAPAs to screen preclinical AD, including using RAPAs to screen PACS patients. However, the stratification of RAPAs is essential in the post-COVID-19 period. Graphical, eye-tracking, central hearing, and spatial navigation abilities are still usable without any concern, but olfactory function may be altered by PACS and should be avoid in a preclinical AD screening assessment. This consensus statement will require an update after few years to guarantee that treatments and recommendations continue to be supported by the latest evidence. More longitudinal studies are required to provide more evidence in the future of RAPA target modifications in PACS patients.

Data availability statement

Generated Statement: The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author contribution statement

AG, OB, GA, KS, OR, CL, NB, KG, CL, OG and PR contributed to conception and design of the study. All authors contributed to the research study. CV and AP organized the database and the first draft of the manuscript. VM and AG performed all the consensus recommendations. KS performed extensive editing. All the supervision of this project was led by AG. All authors contributed to manuscript revision, read, and approved the submitted version.

Funding

Project ERANET JPcofuND 2-WG. This research was funded in whole or in part by the French National Research Agency (ANR) under the project "ANR-22-JPW2-0002-01". With the aim of its open access publication, the author/rights holder applies an open access CC BY license to any article/manuscript accepted for publication (AAM) resulting from this submission.

Acknowledgments

We would like to thank the ERANET JPcofuND 2 and French National Research Agency for funding and the NeuroMod Institute and Académie 5 of University Cote d'Azur for their support.

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Supporting information

Supplementary Material 1

Detailed Search Request Strategy

Clair Vandersteen^{1*}†, Alexandra Plonka†, Valeria Manera, Kim Sawchuk, Constance Lafontaine, Kevin Galery, Olivier Rouaud, Noua Bengaied, Cyrille Launay, Olivier Guérin, Philippe Robert, Gilles Allali, Olivier Beauchet, Auriane Gros

*Correspondence: Corresponding Author: vandersteen.c@chu-nice.fr

Supplementary Figure

A = Early Remote digital AD preclinical assessments (RAPA) of Alzheimer disease:
("Alzheimer" OR "Alzheimer disease") AND ("biomarker" OR "biomarkers" OR "markers") AND ("early diagnosis" OR "early detection" OR "preclinical" OR "digital assessment") NOT ("biological" OR "imaging" OR "PET" OR "CSF" OR "lumbar puncture" OR "blood" OR "Parkinson")

Presence of A related in post-acute COVID-19 syndrome (PACS) patients:
(((((((LONG COVID) OR (POST COVID)) OR (POST-COVID)) OR (POST-COVID-19)) OR (LONG-COVID-19)) OR (LONG-COVID)) OR (post-acute COVID-19 syndrome)) AND ((((((((((speech) OR (language)) OR (language tests)) OR (voice)) OR ((((((((((Psychomotor Performance) OR (writing)) OR (handwriting)) OR (psychomotor performance)) OR (Keystroke)) OR (mouse movements)) OR (patterns)) OR (drawing))) OR (((eye movement) OR (eye-tracking technology)) OR (saccades)) OR (ocular motility))) OR (((Auditory system dysfunction) OR (central auditory function)) OR (central auditory deficit))) OR (((((((Olfaction Disorders) OR (anosmia)) OR (hyposmia)) OR (dysosmia)) OR (olfactory loss)) OR (parosmia))) OR ((Virtual reality) OR (spatial navigation)))

Supplementary Figure 1. Detailed Search Request Strategy for identifying papers related to Remote digital Assessments for Preclinical Alzheimer's disease potentially impacted in post-acute COVID-19 syndrome patients.

Supplementary Material 2

Complete Process of Remote digital Alzheimer's Disease preclinical assessments' identification

Introduction

The first step of this review was to identify potential promising Remote digital AD preclinical assessments (RAPA). RAPA are different from common preclinical AZ biomarkers in the way that they must be independent from material and human factors and might be significantly efficient in preclinical phase. They would be fully digitizable and easily understood by anyone on earth if you have an internet connection. It means that the local results (i.e. before web sending) must be robust and a least dependent on a few technical factors. Moreover, the human expertise required, and time-consuming effect should be low, so that the test(s) can be performed quickly by non-medical staff, or even by the patient himself.

Method

Considering these requirements, was excluded PET/TAU-PET, lumbar puncture, MRI, biological tests, or cognitive assessments, were excluded. To focus on evaluated and validated RAPA, only English review or systematic review were included in this preliminary study.

A quick but systematic review was undertaken searching on PubMed, the 15/11/2022 in the 5 last year's literature, papers related to these keywords : ("alzheimer" OR "alzheimer disease") AND ("biomarker" OR "biomarkers" OR "markers") AND ("early diagnosis" OR "early detection" OR "preclinical" OR "digital assessment") NOT ("biological" OR "imaging" OR "PET" OR "CSF" OR "lumbar puncture" OR "blood" OR "Parkinson disease").

Results and discussion

Two reviewers (CV/AP) reviewed title/abstract of 97 studies.

The first RAPA was olfactory dysfunction[1] which occurred not only in the initial AD stages (Mild Cognitive Impairment – MCI) but also prior to preclinical stages. Meta-analysis underlined that Identification olfaction subdimension is significantly impacted in MCI and proven AZ[1]. Identification olfactory related tests are recognized as screening or prognosis targets to AZ onset[2]. Despite the lack of histologic human studies data, olfactory identification impairment would be linked to TAU-neurofibrillary and amyloid- β deposition in olfactory bulb, entorhinal and hippocampal cortex leading to the inability to store and remember

smell memories[3]. Olfactory tests are easy to administrate, inexpensive (commercialized) and non-invasive.

The second RAPA concerns fine motor decline and writing or drawing related task impairment. A fine motor and coordination deterioration occurs[4] in AD patients and lead to produce slower, less smooth, less coordinated and consistent handwriting movements due to reduced ability in wrist and fingers fine positioning[5]. Moreover, “in-air” time between 2 strokes, with a tablet pencil or a directly on the screen (keystrokes[6]) also knew as flight time, is specifically discriminant for AD and MCI from healthy control with visuospatial construction tasks, cognitive writing tasks or Clock Drawing Test[7–9]. These assessments could be done on e-tablet or phone easily.

The third RAPA is related to the voice and new connected speech recording and analysing tool[10]. AD related speech and voice impairments include phonetic and phonological, lexico-semantic, morpho-syntactic, discourse and pragmatic levels impairments[11]. AD patients seems to have significant less idea density (lexico-semantic features), and less information content, index of discourse effectiveness and information units efficiency (Discourse and pragmatic features) than MCI [11]. Speech production is currently recorded during spontaneous speech, verbal fluency or picture describing tasks. Common microphone connected to a computer software allows to analyse speech, sentence and grammatical complexity, variability of word and finally speaking flow[12]. It could be hard to identify abnormalities using conventional neuropsychological tests but some authors underlined a little correlation between preclinical AD patients and subtle speech changes[13].

The fourth identified RAPA is eye tracking impairment to screen abnormal movement behaviours (saccades, fixation). Mobile versions (on iPad devices) are already developed for mild and severe cognitive impairment (Accuracy of 76%) with the same efficiency than commercial eye-tracking hardware[14]. Many authors[15–17] already used these devices to identify progressive cognitive decline with significant effectiveness.

The Fifth RAPA is central hearing impairment. Hearing loss is a well-known 8% modifiable but contributing factor to dementia[18,19]. Temporal auditory processing is associated with cognitive impairment as central auditory processing assessments (adaptive tests of temporal response (ATTR), time-compressed speech test (TCS), Dichotic Digits Test (DDT), Dichotic Sentence Identification (DSI), Speech in Noise (SPIN), and Synthetic Sentence Identification-Ipsilateral Competing Message (SSI-ICM)) has been reported to be impairment in mild cognitive impairment patients compared to a healthy control group[20]. Some authors proposed

a systematic central auditory dysfunction screening in at-risk populations to identify early AD in a low-cost way[21], specifically dichotic tests[22–24].

The last RAPA is virtual reality and spatial navigation abilities. With dedicated cognitive virtual reality based platforms development on nonspecific equipment (i-Devices for example[25,26]) accessibility and use of these tools is growing. Recently, authors reported that an entorhinal cortex-based test of virtual reality navigation was able to significantly identify early MCI patients. Serious games are probably part of the future of virtual reality assessments as reported authors who used a mobile game (Sea Hero Quest) to underline that 3D navigation ability assessed in that game was able to differentiate High-risk of AD healthy people based on genetic (APOE) and demographic risk factors.

The multifactorial nature of AD (both neurologically and clinically) and therefore of MCI, it is unlikely to be possible to produce a single biomarker of sufficient value for clinical diagnosis at this point. Efforts should be directed toward standardizing a panel of early biomarkers (including probably some of those mentioned above) capable of diagnosing MCI with sufficient sensitivity and specificity.

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Supplementary Material 3

Supplementary Tables

Table A. Quality assessment of cohort observational studies included in the review using OSQE[8] tool.

Authors	Representativeness		Independent variable: exposure, intervention, or risk factor			Dependent variable			Loss to follow-up		Miscellaneous		Optional	Total score		
	Is the sample optimal for both internal validity and representativeness?	Is the cohort really one cohort or are there sub-cohorts?	Is the assessment of the main independent variable valid?	Is the presence of the independent variable optimal?	Is the assessment of the dependent variable valid?	Was exposure unknown to assessor?	Were subjects where the outcome was present at baseline excluded?	Is follow-up sufficiently long to assess the outcome?	Is the outcome assessed continuously?	Does loss to follow-up likely introduce bias?	Did the authors use methods to properly deal with missing data?	Is there a conflict of interest?	Does the statistical analysis control for the relevant confounders?		Did the reporting of the results follow a protocol?	Are effect modifiers analyzed correctly?
Ser et al. 2022[1]	NO	YES	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	YES	YES	YES	14/16
Jamoule et al. 2022[2]	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	NO	NO	YES	13/16
Davis et al. 2021[3]	YES	YES	YES	YES	YES	YES	NO	YES	NO	NO	YES	YES	YES	YES	YES	12/16
Giron Perez et al. 2022[4]	NO	YES	YES	YES	NO	NO	NO	NO	YES	YES	YES	NO	YES	YES	NO	8/16
Michelutti et al. 2022[5]	NO	YES	YES	YES	NO	NO	NO	NO	YES	YES	YES	YES	YES	NO	NO	8/16
Vandersteen et al. 2021[6]	NO	YES	YES	YES	YES	NO	YES	NO	YES	YES	YES	YES	YES	YES	YES	12/16
Mendes Paranhos et al. 2022[7]	YES	YES	YES	YES	YES	NO	YES	NO	NO	YES	YES	YES	YES	YES	YES	12/16

Table B – Quality assessment of the only case control study included in the review using OSQE[8] tool.

Authors	Representativeness		Independent variable: exposure, intervention, or risk factor				Dependent variable		Loss to follow-up		Miscellaneous		Optional			Total score
	Is the sample optimal for both internal validity and representativeness?	Is the data collected in one population or are cases and controls selected in different populations?	Is the assessment of the main independent variable valid?	Is the presence of the independent variable optimal?	Is the assessment of the dependent variable valid?	Is the assessment of the dependent variable valid?	Do controls have a history of the disease?	Is follow-up sufficiently long to assess the outcome?	Does non-response likely introduce bias?	Is non-response similar in cases and controls?	Did the authors use methods to properly deal with missing data?	Is there a conflict of interest?	Does the statistical analysis is control for the relevant confounders?	Did the reporting of the results follow a protocol?	Are effect modifiers analyzed correctly?	
Ser et al. 2022[1]	NO	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	14/16

Table C – Quality assessment of systematic reviews included in the review using AMSTAR2[22] tool.

Authors	1. Did the research questions and inclusion criteria for the review include the components of PICO?	2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	3. Did the review authors explain their selection of the study designs for inclusion in the review?	4. Did the review authors use a comprehensive literature search strategy?	5. Did the review authors perform study selection in duplicate?	6. Did the review authors perform data extraction in duplicate??	7. Did the review authors provide a list of excluded studies and justify the exclusions?	8. Did the review authors describe the included studies in adequate detail?	9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	10. Did the review authors report on the sources of funding for the studies included in the review??	11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results??	12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	15. If they performed quantitative synthesis is did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Overall quality
Ahmad et al. 2021[9]	YES	NO	YES	NO	YES	YES	NO	YES	NO	YES	NO	NO	NO	NO	NO	YES	CRITICALLY LOW
Parkes et al. 2021[10]	YES	NO	YES	NO	NO	NO	NO	±YES	NO	NO	NO	NO	NO	NO	NO	NO	CRITICALLY LOW
Deer et al. 2021[11]	YES	YES	YES	NO	NO	NO	NO	YES	NO	YES	NO	NO	YES	NO	NO	YES	CRITICALLY LOW
Bertucci et al. 2022[12]	YES	±YES	YES	±YES	YES	YES	NO	±YES	YES	YES	NO	NO	YES	YES	NO	YES	CRITICALLY LOW
Dirican et al. 2022[13]	YES	YES	YES	±YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	YES	YES	YES	LOW
De Luca et al. 2022[14]	YES	NO	NO	±YES	YES	YES	NO	NO	NO	YES	NO	NO	NO	NO	NO	YES	CRITICALLY LOW
Silva Andrade et al. 2021[15]	YES	±YES	YES	±YES	NO	NO	YES	±YES	YES	YES	NO	YES	NO	YES	NO	YES	CRITICALLY LOW
Premraj et al. 2022[16]	YES	YES	YES	±YES	YES	YES	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	LOW
Pinzon et al. 2022[17]	YES	YES	YES	YES	YES	YES	YES	YES	YES	NO	YES	NO	NO	NO	YES	NO	CRITICALLY LOW
Malik et al. 2022[18]	YES	±YES	YES	±YES	YES	YES	YES	YES	±YES	NO	YES	NO	NO	YES	NO	YES	CRITICALLY LOW
Xydas et al. 2021[19]	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	YES	NO	YES	CRITICALLY LOW
Fernández-Las Peñas et al. 2021[20]	YES	±YES	YES	±YES	YES	YES	±YES	±YES	±YES	NO	YES	YES	NO	YES	YES	YES	HIGH
Tan et al. 2022[21]	YES	YES	YES	±YES	YES	YES	YES	±YES	YES	YES	YES	YES	YES	YES	NO	YES	LOW

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General discussion

This thesis work focuses on Primary Progressive Aphasia, from the inventory of its diagnosis to the analyses and use of new markers to improve it. Also, since the appearance of cognitive disorders after Covid-19, this work questions the use of diagnostic new markers, comparing cognitive assessments and impairments in neurodegenerative disease and Post-Acute Covid-19.

In the first chapter, we analyzed the trajectory of PPA diagnosis recorded in French Memory Clinics and Centers. We described data registered in the French Alzheimer's National Data Bank (BNA) on a period of 7 years from January 1, 2010, to December 31, 2016, and in particular the demographics and the evolution of subjects with PPA in comparison with Alzheimer's disease (AD). In general, BNA data are in correlation with the literature whether it is in terms of PPA incidence [1–3], sex ratio [4], median age at the first diagnosis being younger than in AD [5], or educational level [6]. The major difference being the age of PPA onset, older in our research than in the literature, but knowing that there might be possible bias because of the age of patients consulting in French Memory Centers.

Regarding PPA diagnosis, our study stays in correlation with the literature concerning the disease's evolution to AD, mostly in PPA Logopenic variant (lvPPA) or Frontotemporal Lobar Degeneration due to similar neuropathology [4,7,8]. But we can also question possible diagnostic errors at the beginning of the disease, according to the fact that in the BNA, there are pending diagnoses recorded or other diagnoses as AD instead of PPA at first. We demonstrated by this study, that PPA diagnosis is more delayed and more often misdiagnosed. It is still difficult to put a PPA diagnosis because of the symptomatology of the three main PPA variants and the underlying pathology, it would be thus interesting to conduct this type of analyses again, knowing that since 2016, end of our analyses, PPA criteria have been redefined [9]. Even if there are consensus on underlying pathologies like AD for lvPPA or FTLD for semantic variant of PPA (svPPA) or nonfluent/agrammatic variant (nfavPPA), there are still some questionings of the disease evolution and underlying pathology, with studies describing an AD symptomatology for svPPA patients for example [10]. It is thus fundamental to better understand the disease, to better diagnose it, predict its evolution and enhance treatment and care. In fact, there is no specific treatment for PPA, even though a recent study have proved that almost 20% of lvPPA patients having an underlying AD would be eligible for a treatment prescribed to early AD [11], but it remains preliminary, and non-pharmacological treatment as Speech and Language Therapy (SLT) are for the moment the most effective [12].

To go further in this study, we have questioned the accuracy of actual diagnostic tools, our perspective being to develop more adapted and accessible assessment tools, including early markers of the pathology using new technologies. Studies have proven that daily-living activities can be essential in PPA diagnosis and care, bringing more reliability and specificity [13,14], and that tools like tablets or smartphones are becoming more and more essential and adequate in patients diagnosis and care [15,16]. Finally, the use of new markers could bring a more specific and early diagnosis, could help to predict a pathology evolution, reducing health-care costs by going from diagnosing and treating to predicting and pre-empting [17].

This is the work led in Chapters 2 and Chapter 3, in which we analyzed graphical, gestural, speech and acoustic markers to verify which parameters are the more relevant for a more precise, early, and differential diagnosis.

Chapter's 2 first study focused on graphic parameters that we extracted from patients writing with a stylus on a touch pad. We extracted writing mean and maximum pressure from tasks divided in three tasks groups (linguistic, cognitive-non-linguistic, non-cognitive-non-linguistic), regarding previous studies that have shown that motor activity reveals language-related characteristics, due to the involvement of motor areas of the brain in writing. Studies also showed that even mild disorders can be detected using motor parameters during language production tasks, reducing thus writing pressure [18]. Our study shows differences in this writing parameter with pressure difference between PPA participants and healthy controls. PPA patients have a higher difference in the maximum pressure between a linguistic and a non-linguistic non-cognitive task than healthy controls, the cognitive load during a linguistic task being more important than in non-linguistic task for PPA patients. These results are in agreement with previous studies that showed deficits on gesture discrimination tasks clustered with linguistic tasks in PPA patients [19]. Thus, writing parameter are of interest for PPA early diagnosis.

Moreover, we wanted to verify if writing pressure can be also useful for PPA and AD, but also for PPA and Posterior Cortical Atrophy (PCA) differential diagnosis. It has been shown that kinematics in handwriting are correlated to cognitive decline [20]. In AD, writing parameters are more related to motor dysfunction with a deterioration in fine motor control and coordination than to a language impairment [21,22], and our results didn't correlate with the literature, showing a higher average pressure in the linguistic task in patients with PPA than

patients with AD. These results suggest that language disorder can also appear as a diagnostic marker in AD. We here only focused on writing pressure, but it would have been interesting to verify differences in other parameters, such as writing strokes, jerk or velocity, knowing that people with cognitive decline have a lower writing speed and pressure with longer writing times [23]. We analyzed these other writing parameters in Chapter's 2 second study, on a PCA patient case-report. Even though PCA is marked by visuospatial and visuoperceptual deficits, studies have found similarities of some of their language impairments with those found in lvPPA [24], questioning the interest of a more precise differential diagnosis, specifically at the onset. In this case, not only writing pressure was of interest, but also jerk and velocity with a reduction of these three parameters in tasks requiring a spatial component, even in linguistic tasks.

Our first study put interest only at one handwriting pressure parameter, even though other studies showed interest of velocity, jerk, and stroke in neurocognitive decline [23]. Also, we focused on PPA in general, but we wanted to go further in our analyses, knowing that lvPPA, svPPA and nfavPPA present different underlying neuropathology and different anatomical pathways of degeneration [25,26], assuming that relevant graphic parameters could be different from one PPA subtype to another. We demonstrated that there was a main effect on velocity and stroke in the three PPA variants, but more specific differences in a two-by-two comparison between PPA subtypes. We showed that velocity is of interest to distinguish lvPPA from other subtypes, which can be explained by the fact that lvPPA's underlying neuropathology is generally AD, and that velocity is a significative parameter in AD's handwriting [27,28]. Moreover, stroke parameter can also be of interest to distinguish nfavPPA subtype from other variants, with less pencil-lefts than other subtypes. In accordance with these results, we put interest on the stroke parameter in nfavPPA, to verify more specifically the gesture during the pen-up time that we cannot record on the touchpad. This study was held in the framework of Covid-19 pandemic, that accelerated the implementation of telemedicine, compelling care givers to readapt their assessments [29].

For the last study included in Chapter 2, we collected graphical markers on the touchpad and gestural markers were analyzed manually, after a video recording. The objective was to verify if these analyses can provide useful additional data for clinicians. In this purpose, we studied the total number of strokes collected by the graphical markers and the total number of strokes counted and visually annotated by the clinician. Our results showed that the nfavPPA patient performs strokes only in linguistic tasks. These pencil lifts during the linguistic writing task

could thus represent the need for nfvPPA patients to have more time for letter programming and letter representation when the pen is in up [30]. Our results suggest a relationship between language and gestural processing, as it was showed in previous studies [28], and it seems important to associate behavioral or gestural markers that could be useful for the diagnostic assessment, whether during a consultation or teleconsultation. For gesture parameter, an automated analysis would be interesting to bring more specificity and details in the annotated parameters.

Graphical and gestural markers appeared to be of interest for early and differential diagnosis, and our studies showed that writing parameters were mostly task-dependent. These markers are thus not only a sign of motor and coordination disorders, but also a sign of cognitive and, more specifically, language disorders.

In Chapter 3 we focused on language analyses. In the first study, we wanted to verify whether sentence repetition could be a discriminating task to differentiate PPA from AD. Sentence repetition is thus characteristic in lvPPA [26], but studies have resulted in mixed findings. A sentence repetition span task was created to verify if lvPPA, svPPA and AD present greater difficulties in sentence repetition and if that kind of tool, in which the number of content words increases as the span length increase, would help dissociate PPA variants from AD type dementia. Our results showed that all the three diagnostic groups (lvPPA, svPPA, and AD) performed more poorly in all repetition span measures than the control group without showing critical pairwise group differences between those diagnostic groups. One differential impairment pattern was found in the lvPPA group which made a relatively larger number of phonological errors than the AD group did, while no differences were observed for the svPPA group. Our findings are not consistent with the literature that found greater impairments in lvPPA than AD during sentence repetition, but are consistent with other studies in which PPA groups showed affected sentence repetition [31,32], but we found no difference in lvPPA and svPPA which doesn't correlate with the literature, probably due to our limited study sample. All patient groups with a neurocognitive disorder under this study (lvPPA, svPPA, and AD) present a sentence repetition difficulty as compared to the healthy controls but within the diagnostic groups they had sentence repetition span outcomes that are indistinguishable from each other. This suggests that sentence repetition span is in general reduced in neurocognitive disorders, and that this sentence span tool may not be specific enough to distinguish lvPPA from other neurocognitive disorders, but only if we consider phonological errors.

This study highlights the difficulty to distinguish lvPPA from AD, and to distinguish lvPPA symptoms, or predict their progression at onset time. Cognitive assessments verifying patients' language impairment may not be specific enough to discriminate these two pathologies. To bring more specificity to the differential diagnosis, we analyzed acoustic markers, aiming to discriminate lvPPA and AD as well as the influence of AD biomarkers on acoustic profiles at the beginning of the disease.

Even if a PPA underlying pathology can vary, clinical markers in lvPPA are mostly associated with underlying AD [33,34], resulting in common symptoms such as anomia and selective short-term memory deficits [25,35,36]. Neuroanatomic alterations in lvPPA have increasing similarities with those in AD with a similar neurological evolution [37], complicating differential diagnosis. Moreover, there is also a sub-classification of lvPPA with an amyloid-negative subtype of lvPPA (-lvPPA) and an amyloid-positive sub-type (+lvPPA) have been described according to Cerebrospinal Fluid (CSF) biomarkers concentration [38] with different disease evolution.

If language assessments are not specific enough to differentiate lvPPA from AD and to predict the disease evolution, automated acoustic and vocal analysis have been described as a non-invasive representative marker of AD, even at the onset [39]. We demonstrated that the sentence span test used in the previous study, associated with temporal and prosodic markers can be an efficient task for lvPPA diagnosis, but also for differentiating -lvPPA and +lvPPA with +lvPPA having prosodic parameters close to AD patients, making acoustic markers an alternative prognosis tool in cases of opposition to invasive examinations such as lumbar puncture.

In the first 3 Chapters, we have thus demonstrated that graphical, gestural, language and vocal analyses represent markers of interest for PPA diagnosis improvement, whether it be for an early diagnosis or a differential diagnosis. It is important to specify that this work was lead through Covid-19 pandemic. This confronted us with unknown troubles, types of patients and degenerations that raised new research questions. After first months of pandemic, patients having a post-acute Covid-19 syndrome (PACS) consulting in memory center complained about cognitive impairment, that were later confirmed by the literature [40]. These impairments questioned us on the validity of the diagnostic markers that we work on, whether PACS patients would have diagnostic markers similar to those of neurodegenerative patients.

In Chapter 4, we wanted to investigate this hypothesis, in the framework of an international working group initiated by the EU Joint Program and funded by the French National Agency, including France, Switzerland and Canada.

The purpose of this group was to investigate the impact of COVID-19 on research related to neurodegenerative diseases, focusing on COVID-19 pandemic and its impact on Alzheimer's care. Other studies have already showed persistent impairments over several months in PACS patients, including difficulty of concentrating and loss of memory [41]. The presented study constitutes a systematic review and an expert consensus on the use of preclinical assessments of AD in PACS. We identified in 20 studies Remote Digital Assessments for Preclinical AD (RAPAs) that were assessed in PACS patients including olfactory, eye-tracking, graphical, speech and language, central auditory, or spatial navigation abilities. After experts' consensus, we determined which RAPA may still be recommended in AD diagnosis after Covid-19 pandemic. Our results showed that olfaction is the most sustained impairment found in PACS patients, and experts consensus recommends that AD olfactory screening should not be used on patients with a history of PACS, until a complete recovery has been confirmed, especially in odor identification impairment that represents a common alteration between PACS patients and AD patients [42]. Eye-tracking, graphical, speech and language, central auditory, or spatial navigation abilities RAPAs are however still recommended, a statement that needs to be nuanced, according to the little hindsight we have on the pathology.

Limitations of the thesis work

This thesis work highlighted the need of improving PPA diagnosis, since we demonstrated many diagnostic deficits still present, and more specifically in France after the BNA data analysis. The need of using new diagnostic tools to improve it seems thus essential, a better understanding of the disorders and their functioning would allow an early and more adapted care and maybe even predict PPA's cognitive decline [43].

Following these findings, we investigated motor and language markers that can be used in PPA diagnosis, with an opening on future research, especially after Covid-19 pandemic and the emergence of impairments that can question the reliability of that kind of markers.

One of the major limitations of this thesis work is that in the search of relevant markers for PPA diagnosis, we only considered lvPPA, svPPA and nfvPPA, even though studies have showed the existence of other subtypes as the mixed variant or anomic only variant [9]. Our studies also

include a limited number of patients that should be increased to validate our results on a larger cohort.

Another major limitation relies on the unimodal analyses that we conducted. Indeed, one parameter can bring more specificity to a diagnosis but will never be sufficient to determine a disease. Graphic, gestural, vocal and acoustic analyses should be conducted together to be more relevant in a multimodal automatic model, such as suggested by other studies [44,45].

Finally, a major limitation is based on the little hindsight we have of PACS patients. We will have to better understand Covid-19 functioning after longitudinal studies to determine if the markers that we established are still relevant and how to analyze them if they have been modified because of the disease.

Conclusion

PPA diagnosis is often pending and misdiagnose. To improve it, we showed the interest of using new graphic, gestural, language and acoustic parameters.

Concerning graphic and gesture analyzes:

- Writing pressure is relevant for discriminating PPA from AD, and for the early PPA diagnosis. Writing velocity is relevant for discriminating lvPPA from svPPA and nfavPPA,
- Writing stroke is relevant for discriminating nfavPPA from other subtypes.
- Writing jerk or acceleration is relevant for discriminating svPPA from other subtypes.
- In the gesture analysis, stroke is also relevant for nfavPPA diagnosis.

In all these studies, relevant parameters depended on the nature of the task. Whether it was linguistic, cognitive-non-linguistic, non-cognitive-non-linguistic. Moreover, in the differential diagnosis of PCA and PPA for example, the graphic parameters were relevant in tasks involving spatialization.

Concerning language and vocal analyzes:

- A repetition task by itself is not sufficient to differentiate PPA patients from AD, even more at an early stage.
- A repetition task is relevant to differentiate PPA patients from AD if we take into account phonological errors.
- Extracting acoustic markers from sentence span repetition task is of interest for differential diagnosis of +lvPPA with AD biomarkers and -lvPPA without AD biomarkers. Fundamental frequency, empty pauses, prosody, and use of consonants are relevant acoustic markers.

Motor and language analyses can help us to better understand PPA functioning and possibly predict the syndrome's evolution. But in Covid-19 pandemic, cognitive troubles being similar to AD in PACS, we can question the reliability of these new markers, that seems, for the moment, still relevant.

The main objective of this thesis work was to determine new markers of interest for PPA diagnosis. We were able to determine significative features that lead to great future perspectives. Modeling of these different markers in one tool would be essential to use a multimodal analysis, giving a more accurate state and better understanding of a disease and its clinical impairments.

Also, the vocal features questioned the possibility of determining PPA underlying pathology without using invasive biomarkers such as lumbar puncture. These studies should be continued to get longitudinal data, essential for a better accuracy of our preliminary results.

Covid-19 pandemic brought however new clinical and research questions that have enriched this thesis work. Indeed, regarding the cognitive impairments described in PACS, we can question the reliability of neurodegenerative diagnostic markers in the future.

In conclusion, the work presented in this thesis layouts the foundations for employing graphic, gestural, vocal, and acoustic analyses to either support early and differential PPA diagnosis, bring more specificity to it, better understand its evolution, or even bring more specificity to other syndromes involving language and cognition disorders.

In parallel of this thesis work, many collaborations were made on different projects remaining around the thesis topics. Since the beginning of the pandemic, we worked on the highlighting of PACS sequelae on semantic memory related to odor loss of identification and other studies correlated to Covid-19.

At the same time, and within an international collaboration, we worked on the interest of the use of new technologies to prevent AD and related disease consequences, even more after an isolation due to the pandemic.

The publications related to these different collaborations are listed below.

- Fiorentino, J.; Payne, M.; Cancian, E.; **Plonka, A.**; Dumas, L.-É.; Chirio, D.; Demonchy, É.; Risso, K.; Askenazy-Gittard, F.; Guevara, N.; Castillo, L.; Robert, P.; Manera, V.; Vandersteen, C.; Gros, A. Correlations between Persistent Olfactory and Semantic Memory Disorders after SARS-CoV-2 Infection. *Brain Sci.* 2022, 12, 714. <https://doi.org/10.3390/brainsci12060714>
- Vandersteen, C.; Payne, M.; Dumas, L.-É.; Cancian, É.; **Plonka, A.**; D'Andréa, G.; Chirio, D.; Demonchy, É.; Risso, K.; Askenazy-Gittard, F.; Savoldelli, C.; Guevara, N.; Robert, P.; Castillo, L.; Manera, V.; Gros, A. Olfactory Training in Post-COVID-19 Persistent Olfactory Disorders: Value Normalization for Threshold but Not Identification. *J. Clin. Med.* 2022, 11, 3275. <https://doi.org/10.3390/jcm11123275>
- Vandersteen, C., Payne, M., Dumas, L.É., **Plonka, A.**, D'Andréa, G., Chirio, Demonchy, E., Risso, K., Robert, P., Fernandez, X., Askenazy-Guittard, F., Salvodelli, C., Guevara,

- N., Castillo, L. Manera, V., Gros, A. What about using sniffin' sticks 12 items test to screen post-COVID-19 olfactory disorders?. *Eur Arch Otorhinolaryngol* 279, 3477–3484 (2022). <https://doi.org/10.1007/s00405-021-07148-y>
- Vandersteen, C. Payne, M., Dumas, L-E, Metelkina-Fernandez, V., **Plonka, A.**, Chirio, D., Demonchy, E, Risso K., Askenazy-Gittard, F., Guevara, N., Castillo, L., Manera, V., Gros, A. Persistent olfactory complaints after COVID-19: a new interpretation of the psychophysical olfactory scores. *Rhinology Online*, Vol 4: 66 - 72, 2021 <http://doi.org/10.4193/RHINOL/21.010>
 - Beauchet, O., Galery, K., Lafontaine, C., Sawchuk, K., **Plonka, A.**, Gros, A., Allali, G. Frailty, e-health and prevention of late-onset Alzheimer disease and related disorders: it is time to take action. *Aging Clin Exp Res* 34, 1179–1181 (2022). <https://doi.org/10.1007/s40520-022-02122-y>

My implication and contributions in the scientific field during this thesis work were rewarded with an Academic Excellence Award given by the Fondation Université Côte d'Azur in May 2022.

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