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Doutoramento em CIÊNCIAS BIOMÉDICAS
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*"Daß die Welt meine Welt ist, das zeigt sich darin, daß die Grenzen der Sprache (der Sprache, die allein ich verstehe) die Grenzen meiner Welt bedeuten"**

Ludwig Wittgenstein
in *Tractatus Logico-Philosophicus*, 1922

*[The world is my world: this is manifest in the fact that the limits of language (of the language which alone I understand) mean the limits of my world]

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  *co-first authors

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Muito para além de quatro anos de trabalho intensivo, a presente tese representa a última etapa de um ciclo. Um ciclo repleto de alegrias e desilusões, de ganhos e de perdas, tanto no plano académico, como no plano afetivo.

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SUMMARY

Frontotemporal lobar degeneration (FTLD) is the second leading cause of early-onset (< 65 years) dementia. Some of its forms may begin by isolated language deficits, which are known as Primary Progressive Aphasia (PPA). PPA is defined as the insidious onset and progressive loss of linguistic abilities in the absence of major deficits in other areas of cognition or in activities of daily living, which are not explained by a focal brain lesion. The most recent criteria and the increasing focus on the establishment of disease-modifying therapies in FTLD, which are presently lacking, highlight the importance of neuropsychology for an early and accurate diagnosis. In light of the new classification, understanding the neuropsychology of progressive aphasias may help to early differentiate disease patterns and predict their underlying pathology. This is particularly relevant since PPA is a language-based neurodegenerative disorder that evolves to a broader cognitive decline to the point where daily-living activities will also become compromised. Thus the main objective of the present thesis was to study the contribution of neuropsychology to the identification of different clinical profiles and defining features relevant for diagnosis and management of PPA. In order to pursue the objective, four studies were conducted.

The first study approached the pathophysiology of nonfluent PPA, which remains poorly understood. Here, we compared quantitatively speech parameters in patients with nonfluent PPA versus healthy older individuals under altered auditory feedback, which has been shown to modulate normal speech output. Patients (n=15) and healthy volunteers (n=17) were recorded while reading aloud under delayed auditory feedback (DAF) with latency 0, 50 or 200 ms and under DAF at 200 ms plus 0.5 octave upward pitch shift. DAF in healthy older individuals was associated with reduced speech rate and emergence of speech sound errors, particularly at latency 200 ms. Up to a third of the healthy older group under DAF showed speech slowing and frequency of speech sound errors within the range of the nonfluent PPA cohort. Our findings suggest that (in addition to any anterior, primary language output disorder) these key features of nonfluent PPA may reflect distorted speech input signal processing, as simulated by DAF. DAF may constitute a novel candidate pathophysiological model of posterior dorsal cortical language pathway dysfunction in nfvPPA.

The objective of the second study was to test whether data mining techniques, through an unsupervised learning approach, support the three-group diagnostic model of PPA versus the existence of two main/classic groups. A series of 155 PPA patients observed in a

clinical setting and subjected to at least one neuropsychological/language assessment was studied. Several demographic, clinical and neuropsychological attributes, grouped in distinct sets, were introduced in unsupervised learning methods (*Expectation Maximization, K-Means, X-Means, Hierarchical Clustering and Consensus Clustering*). Unsupervised learning methods revealed two main groups consistently obtained throughout all the analyses (with different algorithms and different set of attributes). One group included most of the nonfluent and some logopenic PPA cases while the other was mainly composed of semantic and logopenic PPA cases. Clustering the patients in a larger number of groups ($k > 2$) revealed some clusters composed mostly by nonfluent or by semantic PPA cases. However, we could not evidence any group chiefly composed of logopenic PPA cases. Hence, findings obtained with the application of unsupervised data mining approaches do not clearly support a logopenic PPA. However further, supervised learning studies may indicate distinct results.

Behaviour changes may occur early in PPA but the frequency of these symptoms across the three variants is still controversial. In the third study, 94 consecutive PPA patients (26 nonfluent, 36 semantic, 32 logopenic) underwent language and neuropsychological assessments. The presence of behavioural changes was ascertained by semi-structured informant-based interviews using the *Blessed Dementia Rating Scale*. Eighty-two percent of the cases endorsed at least one behaviour change. Nonfluent patients presented significantly more behaviour changes and scored more often (46.2%) the item "*hobbies relinquished*" when compared to logopenic patients. These differences in behaviour symptoms probably reflect distinct underlying neurodegenerative diseases.

PPA is a neurodegenerative disorder with no effective pharmacological treatment. Cognition-based interventions are adequate alternatives, but their benefit has not been thoroughly explored. The aim of this last investigation was to study the effect of speech and language therapy (SLT) on naming ability in PPA. An open parallel prospective longitudinal study involving two centers was designed to compare patients with PPA submitted to SLT (1 h/week for 11 months, on average) with patients receiving no therapy. Twenty patients were enrolled and undertook baseline language and neuropsychological assessments; among them, 10 received SLT and 10 constituted an age- and education-matched historical control group. The primary outcome measure was the change in group mean performance on the *Snodgrass and Vanderwart Naming Test* between baseline and follow-up assessments. Intervention and control groups did not significantly differ on

demographic and clinical variables at baseline. A mixed repeated measures ANOVA revealed a significant main effect of therapy ($F(1,18) = 10.763$; $p = 0.005$) on the performance on the *Snodgrass and Vanderwart Naming Test*. Although limited by a non-randomized open study design with a historical control group, the present study suggests that SLT may have a benefit in PPA, and it should prompt a randomized, controlled, rater-blind clinical trial.

Conclusion: Despite the recent harmonization efforts, the delineation of certain PPA variants is still controversial. The present results show that neuropsychology is a key instrument not only for the clear definition of PPA subtypes but also for the study of the abnormal mechanisms and features underlying the main forms of PPA. Moreover, a neuropsychological approach to disease management seems to be feasible. Specifically, SLT emerges as an alternative and adequate approach to tackle the increasing language deficits experienced in all PPA phenotypes for some time. The emergence of promising disease-modifying therapies in the context of FTLD, in association with these cognitive-based interventions, will certainly be the future of PPA disease management.

Key-words: Primary Progressive Aphasia, nonfluent variant, semantic variant, logopenic variant, Neuropsychology

RESUMO

A Degenerescência Lobar Fronto-Temporal (DLFT) é a segunda principal causa de demência de início precoce (< 65 anos). Algumas formas desta doença iniciam-se por défices isolados da linguagem, sendo designadas por Afasia Progressiva Primária (APP). A APP é uma entidade clínica que se define pela perda progressiva dos diferentes domínios da linguagem, na ausência de quaisquer outros défices cognitivos ou funcionais e que não resulta de uma lesão focal. Dado o crescente reconhecimento de que esta síndrome apresenta diferentes manifestações clínicas, foram, recentemente, propostos critérios de diagnóstico formais para a classificação das três variantes conhecidas da APP. Esta harmonização, aliada à premente necessidade de se encontraram novas terapias farmacológicas, modificadoras do curso da doença, numa altura em que as alternativas terapêuticas a oferecer a estes doentes são limitadas, colocam em evidência o papel da neuropsicologia no diagnóstico precoce. Tal como outras doenças neurodegenerativas, a APP evolui no sentido de afetar outros domínios cognitivos e de comprometer o desempenho em atividades instrumentais e básicas de vida diária. À luz dos novos critérios de classificação, compreender as características neuropsicológicas da APP reveste-se de particular importância admitindo-se que a obtenção de perfis neuropsicológicos poderá ajudar a predizer a doença neurodegenerativa de base. Como tal, o objetivo principal da presente tese é o de estudar a neuropsicologia da APP, contribuindo para a identificação de diferentes perfis clínicos e para definição de características eventualmente relevantes para o diagnóstico, bem como para o seguimento destes doentes. Para tal, foram realizados quatros estudos:

O primeiro estudo debruçou-se sobre o estudo de aspetos patofisiológicos associados à variante não fluente, a qual permanece pouco estudada. O discurso de doentes com a variante não-fluente da APP foi comparado quantitativamente com o discurso produzido por indivíduos idosos saudáveis sujeitos a um paradigma experimental no qual se procedeu à alteração do *feedback* auditivo. Sabe-se que a modificação do *feedback* auditivo induz modificações na produção normal de discurso. Foram gravados os discursos produzidos pelos doentes (n=15) e os discursos produzidos pelos controlos saudáveis (n=17) numa tarefa de leitura em voz alta sob o efeito de *feedback* auditivo diferido (FAD) à latência de 0, 50 e 200 ms e combinando o FAD à latência de 200 ms com um aumento do tom em 0.5 oitavas. Nos indivíduos saudáveis, o FAD associou-se a uma redução do débito do discurso e à emergência de erros nos sons da fala, em particular, à latência de 200 ms. Cerca de um

terço dos indivíduos saudáveis sob o efeito de FAD evidenciaram lentificação do discurso e uma frequência de erros de produção dos sons da fala dentro do intervalo dos doentes. Estes achados sugerem que estas características típicas da variante não fluente da APP podem refletir uma perturbação do discurso secundário a uma distorção do processamento do sinal de entrada, aqui simulada pelo FAD. O FAD pode constituir um novo modelo patofisiológico da disfunção posterior da via dorsal do processamento da linguagem em doentes com APP não fluente.

O objetivo do segundo estudo foi o de testar se técnicas de *data-mining* de aprendizagem não supervisionada suportam o modelo de diagnóstico tripartido da APP ou se favorecem, apenas, a existência de dois subtipos clínicos, classicamente descritos na literatura. Uma série clínica composta por 155 doentes com o diagnóstico clínico de APP foi sujeita a pelo menos uma avaliação neuropsicológica e de linguagem. Foram definidos diferentes conjuntos de atributos ou variáveis, nomeadamente, variáveis demográficas, clínica e neuropsicológicas, os quais foram analisados através de diferentes métodos de aprendizagem não supervisionada (*Expectation Maximization, K-Means, X-Means, Hierarchical Clustering and Consensus Clustering*). Estes métodos revelaram, de forma consistente, em todas as análises, utilizando diferentes algoritmos e diferentes conjuntos de atributos, a emergência de dois grupos principais. Um desses grupos consistia, na sua maioria, em doentes não fluentes e alguns logopénicos, sendo o segundo grupo maioritariamente composto por doentes semânticos e logopénicos. O agrupamento dos casos em mais do que dois grupos ($k > 2$) revelou que os clusters obtidos eram compostos por doentes não fluentes ou semânticos. No entanto, não foi possível evidenciar um grupo exclusivamente composto por casos logopénicos. Como tal, os resultados obtidos através da aplicação de uma abordagem de análise de dados não supervisionada não apoia uma distinção clara da variante logopénica como uma entidade clinica distinta.

As alterações de comportamento podem ocorrer precocemente na APP mas a frequência com com que estes sintomas ocorrem nas suas três variantes é ainda controversa. No terceiro estudo aqui apresentado, 94 doentes consecutivos com o diagnóstico de APP (26 não fluentes, 36 semânticos e 32 logopénicos) foram submetidos a avaliação neuropsicológica e de linguagem. A presença de alterações de comportamento foi avaliada num formato de entrevista semiestruturada com os cuidadores utilizando, para tal, a Escala de Demência de Blessed. Cerca de 82% dos casos evidenciou, pelo menos, um sintoma comportamental. Os doentes não fluentes apresentaram, significativamente, mais

alterações de comportamento e pontuaram significativamente mais (46.2%) no item "*abandono dos interesses*", quando comparados com os doentes logopénicos. Estas diferenças nos sintomas comportamentais podem, com efeito, refletir doenças neurodegenerativas distintas.

Por fim, o último trabalho teve por objetivo estudar o efeito da Terapia da Fala na capacidade de nomeação em doentes com APP. Até à data, não existem tratamentos farmacológicos conhecidos para a APP. As intervenções baseadas na estimação de determinadas capacidades cognitivas parecem ser alternativa adequadas mas o seu benefício carece de um estudo sistemático, em particular, na APP. Para tal, foi desenhado um estudo longitudinal prospetivo e paralelo envolvendo dois centros para comparar um grupo de doentes com o diagnóstico clínico de APP sujeito a um programa de Terapia da Fala (sessões semanais com a duração de uma hora, durante, em média, 11 meses) com um grupo de doentes com APP que não realizaram qualquer tipo de intervenção. Foram recrutados vinte doentes, os quais realizaram uma primeira avaliação de linguagem e neuropsicológica (correspondendo ao *baseline*). Dez destes doentes receberam Terapia da Fala. Os restantes 10 doentes consistiram em controlos históricos, emparelhados por idade e escolaridade. A medida de *outcome* primária foi definida como mudança entre avaliação *baseline* e a avaliação de seguimento no desempenho médio do Teste de Nomeação de Snodgrass e Vanderwart. No *baseline*, os grupos de intervenção e de controlo não diferiram nas variáveis demográficas nem clínicas. A análise de variância (ANOVA) de medidas repetidas revelou um efeito estatisticamente significativo da terapia ($F(1,18) = 10.763$; $p = 0.005$) no desempenho médio do *Teste de Nomeação de Snodgrass e Vanderwart*. Apesar da limitação inerente à ausência de aleatorização dos doentes em cada um dos braços e da utilização de um grupo de controlo composto por doentes históricos, o presente estudo sugere que a TF pode ser benéfica na APP. Os resultados deste estudo estimulam a realização de um ensaio aleatorizado, controlado e em ocultação do avaliador.

Conclusão: Apesar dos esforços de harmonização da classificação da APP, a delineação desta entidade clinica do ponto de vista neuropsicológico, bem como das suas variantes clínicas, continua a ser controversa. Os resultados apresentados na presente dissertação demonstram que a neuropsicologia é um instrumento útil e muito relevante não só na caracterização das diferentes formas de apresentação desta síndrome, como também para o estudo dos mecanismos de doença alterados em cada uma das variantes. Além disso, a

Terapia da Fala emerge igualmente como uma alternativa adequada para lidar com as dificuldades de linguagem crescentes e que são comuns a todas as variantes. A emergência, num futuro próximo, de terapias modificadoras do curso da doença, quer na APP em particular, quer na DLFT em geral, aliadas a intervenções não farmacológicas, parecem ser prometedoras.

Palavras-chave: Afasia Progressiva Primária, variante não fluente, variante semântica, variante logopénica, Neuropsicologia

CONTENTS

LIST OF ABBREVIATIONS

^{11}C-PiB	^{11}C-Pittsburgh compound B
^{18}F-FDG	2-[fluorine-18]-fluoro-2-deoxy-d-glucose
3R	Three-repeat isoform
4R	Four-repeat isoform
aMCI	amnestic Mild Cognitive Impairment
Aβ	Beta-amyloid protein
AAF	Altered auditory feedback
AD	Alzheimer's Disease
AGD	argyrophilic grain disease
ALS	Amyotrophic Lateral Sclerosis
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AoS	Apraxia of Speech
APOE	Apolipoprotein E gene
ATL	Anterior temporal lobe
BDRS	Blessed Dementia Rating Scale
bvFTD	behavioural variant Frontotemporal Dementia
CBD	Corticobasal Degeneration
CBS	Corticobasal Syndrome
CHMP2B	chromatin-modifying protein 2B
CJD	Creutzfeld-Jakob Disease
CSF	Cerebrospinal fluid
DAF	Delayed auditory feedback
DN	dystrophic neurites
DTi	diffusion tensor imaging
FTD	Frontotemporal Dementia
FTLD	Frontotemporal Lobar Degeneration
FTLD-U	ubiquitin positive Frontotemporal Lobar Degeneration
FUS	fused in sarcoma
GM	grey matter
GRN	Progranulin
LPA	Logopenic Progressive Aphasia
lvPPA	logopenic variant Primary Progressive Aphasia
MAPT	microtubule associated protein tau
MCI	Mild Cognitive Impairment
MND-ALS	Motor Neuron Disease – Amyotrophic Lateral Sclerosis
MSTD	multiple system tauopathy with dementia
NCI	neuronal cytoplasmic inclusions
nfvPPA	nonfluent Primary Progressive Aphasia
NII	neuronal intranuclear inclusions
NTFs	intracellular neurofibrillary tangles
PET	Positron emission tomography
PiD	Pick's Disease
PNFA	Progressive Nonfluent Aphasia
PPA	Primary Progressive Aphasia
PPAoS	Primary Progressive Apraxia of Speech
PPA-G	Primary Progressive Aphasia with agrammatism
PPA – L	logopenic Primary Progressive Aphasia
PPA - M	mixed Primary Progressive Aphasia
PPA – S	semantic Primary Progressive Aphasia
PSP	Progressive Supranuclear Palsy
PSPS	Progressive Supranuclear Palsy Syndrome
SD	Semantic Dementia
SLT	Speech and Language Therapy
STP	superior temporal plane
svPPA	semantic variant Primary Progressive Aphasia
TARDBP	TAR DNA-binding protein

TDP-43	transactive response DNA-binding protein with molecular weight 43 kDa
VCP	valosin-containing protein
VIF	Variance Inflation Factor
WAB	Western Aphasia Battery
WAIS	Wechsler Adult Intelligence Scale
WM	white matter
wpm	words per minute

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I. GENERAL INTRODUCTION

Communication can be defined as the sharing of information by means of a symbol system in order to express a particular idea. It is present in many animal species and facilitates complex social relationships and interactions. Human language is a unique system of communication. It involves the use of arbitrary signs and symbols, reliant on phonology and rules of syntax to express lexical or semantic meaning (i.e. using words) (Mesulam, Rogalski, et al., 2014; Schaefer & Hebben, 2014).

Aphasia can be defined as an acquired selective impairment of language components (phonology, morphology, syntax, semantics, pragmatics), modalities (speaking, reading, writing, signing) and functions (expression and comprehension) that results from a brain lesion to the areas and structures involved in language processing, located in the language-dominant hemisphere (Papathanasiou & Coppens, 2013). Such definition should be differentiated from those language disturbances arising from neurodevelopmental conditions like mental retardation, hearing impairment, autism, malformation of vocal apparatus or emotional disturbances. It should also be differentiated from the developmental disorders of language (occurring in the absence of any of the above mentioned causal disabilities), known as *specific language impairments* (Bishop, 2009), which predispose children to fail in the acquisition and use of normal language at or near the expected age, typically in the context of otherwise normal development (Tallal, Sainburg, & Jernigan, 1991). Finally, aphasia should also be differentiated from dementia.

Aphasia can manifest itself in different signs and symptoms, depending on the size and location of the lesion. Thus, describing a specific type of aphasia and its features helps to identify a particular brain lesion location and possibly suggest a specific brain pathology or a specific locus of dysfunction (Ellis & Young, 1988; Damásio, 1992). Paul Broca, in the 19th Century, established the important connection between speech production and the inferior frontal gyrus of the left cerebral hemisphere (Broca, 1863) and Carl Wernicke, related sensory aphasia (i.e. loss of memory for words) to the left temporal lobe (Wernicke, 1874). Both discoveries represent the first framework for anatomically and functionally differentiating types of language dysfunction. Moreover, Wernicke was the first author to formulate a theory of how different brain regions responsible for expressive and receptive functions interact with each other. His ideas were further developed by Lichteim and re-addressed by Geschwind (Geschwind, 1965a, 1965b), creating the so called *Wernicke-Lichteim-Geschwind* model. According to this model, different brain centers are

interconnected and a lesion in a specific brain area/center or in the pathways connecting different centers may result in a more or less well-defined aphasic syndrome. In addition, Geschwind observed that the anatomical disconnection of a white matter tract connecting the posterior portion of the superior temporal lobe to the inferior frontal lobe (i.e. arcuate fasciculus) caused a different type of aphasia from those described by Broca and Wernicke a century before (i.e. conduction aphasia). He also proposed that damage to the concept center, or the connections between this and others, explained the features of two other aphasic conditions: motor and sensory transcortical aphasia (Geschwind, 1970, 1972). These findings, together with the extensive work of Harold Goodglass and Edith Kaplan on the neuropsychological characterization of the fluency of aphasic patients and on the development of the most widely known comprehensive, multifactorial battery to evaluate a broad range of language dysfunctions that often underlie the various aphasic syndromes, the *Boston Diagnostic Aphasia Examination* – BDAE (Goodglass & Kaplan, 1972), led to delineation of the so called "*classical aphasia syndromes*": Broca's, Wernicke's, Conduction, Anomic, Transcortical Motor, Transcortical Sensory, Mixed Transcortical and Global aphasias.

According to a more contemporary conceptualization, which was largely based on functional imaging studies (Wylie & Regner, 2014), language and its organization are considered to be mediated by an asymmetrically distributed large scale network. The network components are located in the perisylvian cortex and surrounding parts of the frontal, parietal and temporal lobes of the language dominant (usually left) hemisphere of the brain (Hickok & Poeppel, 2007; Saur et al., 2008; Xiang, Fonteijn, Norris, & Hagoort, 2010; Wilson et al., 2011; Schwartz, Faseyitan, Kim & Coslett, 2012). These components can be divided into dorsal (involved in the phonological encoding, fluency, and grammatical structure) and ventral (playing an important role on the lexical-semantic processing) pathways, conforming to the so-called "*dual stream model*" (Hickok & Poeppel, 2004; Saur et al., 2008). The major contribution from these recent models has been the refinement of functional anatomical localization and specification of language sub processes not taken into account in the previous classical approach.

Research into language has traditionally and largely concentrated on aphasias caused by focal brain damage, in particular, cerebrovascular disease. In recent years, interest has shifted to encompass language disorders appearing in the context of progressive neurodegenerative brain disorders. These diseases represent an opportunity to

study the neural components of the large-scale language network and how this network is selectively vulnerable to the deleterious effects of neurodegeneration. The present thesis will, hence, focus on the role of neuropsychology in the study of language-based neurodegenerative diseases, called Primary Progressive Aphasias (PPA).

PPA is a group of clinical syndromes characterized by a progressive, isolated deterioration of language abilities, during, at least, a two-year period, in the absence of marked impairment in other cognitive and behavioural domains, which result from the neurodegeneration of the language dominant cerebral hemisphere (Mesulam, 1982, 1987, 2001). A historical perspective of the concept, and the formal definition and pathological characterization of this clinical entity will be reviewed in Chapter II-2.1 and 2.2, respectively.

A neuropsychological approach to PPA is important for several reasons. First of all, neuropsychology conveys an important diagnostic purpose. Due to its progressive nature, PPA evolves to the point where the remaining areas of cognition begin to deteriorate, and instrumental activities of daily living (ADLs) become increasingly compromised. At this point, patients are considered to have entered a dementia phase that is sometimes called "*aphasic dementia*" or "*PPA plus*" (Rogalski & Mesulam, 2009). This phase may occur many years after or within a relatively short time frame from diagnosis. Here, neuropsychological assessment will aim to exclude the presence of concurrent dementia (or prominent deficits in cognitive domains other than language) for the diagnosis of PPA to be made. This is not a straightforward task, even for neuropsychologists with vast experience in assessing patients with dementia. The majority of neuropsychological tests imply verbal instructions and require verbal responses, which puts every aphasic patient in disadvantage. For instance, lower performances on verbal episodic memory tasks may be observed but they may reflect word retrieval deficits rather than a true memory problem. As such, non-verbal tests are preferred instead. However, the application of any neuropsychological test (either verbal or non-verbal) can be virtually compromised in cases presenting with a severe form of aphasia. In the impossibility to obtain a quantitative neuropsychological profile, diagnosis is largely based on the information of functional status, which can only be obtained with the caregiver. Functional scales, which assess the autonomy on instrumental and basic ADLs (e.g. *Blessed Dementia Rating Scale*, *Instrumental Activities of Daily Living*, *Disability Assessment for Dementia*, among others) (Blessed, Tomlison, & Roth, 1968; Lawton & Brody, 1969; Gélinas, Gauthier, McIntyre,

& Gauthier, 1999) may constitute, in these cases, crucial information to establish the diagnosis.

Once the diagnosis of PPA is made, one must characterize the pattern of deficits observed. PPA is a devastating condition that evolves to compromise the ability to communicate even the most simple thoughts and needs. The very mild word-finding deficits and anomia that characterize the early stages of the disease are followed by the revealing of core language deficits, which may persist for years until they give rise to a more generalized language disruption. Neuropsychology has, then, a second important role, which is the identification of the language abilities that are impaired or otherwise preserved to define a neuropsychological profile. The dynamic nature of the aphasia in PPA, together with the emergence of subtle dissociations of language functions that are less likely to arise in patients with stroke aphasia, soon led clinicians and researchers to consider PPA cases heterogeneous enough not to fit into the classic aphasic syndromes (Mesulam, Rogalski, et al., 2014). Accordingly, a whole different terminology to these cases was formally proposed (Gorno-Tempini et al., 2011). The distinctive clinical, imaging and pathological signatures of each PPA variant will be subject of a detailed revision in the Chapter II-2.3 of the present thesis.

The importance of neuropsychology to understand different aspects of PPA is reflected in a series of original studies joined together in Chapter IV of this thesis.

As previously stated, the definition of a neuropsychological profile implies a thorough assessment of all linguistic abilities. These should include the analysis of spontaneous speech (how the message is generated, its content, grammar and motor programming features), confrontation naming, single-word and sentence comprehension, object/people knowledge, word and sentence repetition, reading, writing and spelling, sentence generation/completion and motor assessment (e.g. repetition of syllables) (Rohrer et al., 2008; Gorno-Tempini et al., 2011). Sensitive cognitive tests are needed to identify subclasses of patients based on these features. In fact, the last years have seen an effort to create such measures. Some batteries, like the *Western Aphasia Battery* (WAB) revised, have been proposed for the differentiation of PPA variants with high accuracy (Kertesz, McMonagle, Blair, Davidson, & Munoz, 2005; Kertesz, 2007; Kertesz, Jesso, Harciarek, Blair, & McMonagle, 2010). The creation of new batteries (e.g. *Sydney Language Battery*) (Savage et al., 2013) or the development of novel linguistic measures like the *Northwestern Anagram Test* (which assesses the grammaticality of sentence production by

asking the patient to assemble single printed words to create sentences describing pictures) (Weintraub, Mesulam, Wieneke, Rogalski, & Thompson, 2009) have also shown to be adequate to differentiate subtypes. Moreover, the same authors developed an empirical quantitative template resulting from the combination of performance on this novel task and a single-word comprehension measure (e.g. *Peabody Picture Vocabulary Test*). This template accurately classified patients, even at very mild stages, and showed good correlation with cortical atrophy patterns, hence displaying biological validity (Mesulam et al., 2009; Mesulam, Wieneke, Thompson, Rogalski, & Weintraub, 2012). Another classification approach, based on four key speech and language variables (*motor speech disorders*, *agrammatism*, *single-word comprehension* and *sentence repetition*) has also been proposed. This algorithm classified correctly 45 of 47 (96%) of patients regarding PPA variants and showed high concordance with the gold standard expert clinical diagnosis, based on the International Consensus Criteria (Leyton et al., 2011). Despite all this development in the field of cognitive testing, classification currently remains problematic and unclassified cases are relatively frequent (Wicklund et al., 2014). From our experience, some PPA cases at very early stages can hardly be classified. In others, the severity of language deficits may also prevent an accurate diagnosis into one of the variants. Others even never reach a plausible diagnosis, which leads us to think that the current classification model should be subjected to further refinements in order to include, for instance, other disease profiles. These caveats will be addressed in the Study 2 of the Chapter IV, conducted to test the applicability of sophisticated data driven analysis to extensive neuropsychological data to test the current classification model of PPA.

In an era marked by the search for disease-modifying drugs specifically created to tackle neurodegeneration even at pre-symptomatic stages (Rohrer et al., 2015), the emergence of pathological in-vivo biomarkers (such as the new imaging techniques using Aβ and tau ligands) are certainly relevant for an accurate clinical diagnosis. However, the use of neuropsychology to characterize a global cognitive profile, aside the linguistic pattern, typical of each PPA variant, may improve clinical classification and identify signatures of disease progression. As previously stated, neurodegeneration selectively targets specific regions of the cerebral cortex. Even within areas of prominent cortical atrophy, some neuronal populations are affected and others might be preserved, which creates a pattern of distorted neural network connectivity, distinct from the entire loss of function seen in vascular aphasia (Sonty et al., 2007; Mesulam, Rogalski, et al., 2014).

Neuropsychology has thus an important role in testing novel paradigms of disruption of selective neural networks. In this context, Study 1 of the Chapter IV consists of an experimental investigation primarily conducted in healthy individuals to test the hypothesis of disruption of the dorsal language pathway in a subgroup of PPA patients. The results of this study shed light on the probable disrupted mechanisms underlying specific clinical features. On the other hand, Study 3 of the Chapter IV will revise the state of the art concerning the presence of behavioural changes in PPA as a relevant clinical feature implicated in the differential diagnosis among PPA variants that may correspond to Alzheimer's disease (AD) or Frontotemporal Lobar Degeneration (FTLD) pathologies.

Research has now taken us to the stage where neuropsychology allows the description of different patterns of impairment and retained abilities. This assumption suggests that different profiles and, most of all, different stages of disease require different types of management (Maxim & Bryan, 2006). Cognitive interventions, such as Speech and Language Therapy (SLT) are aimed at improving cognitive and functional abilities and quality of life for patients and for their caregivers, in a time where a pharmacological treatment is still unavailable. Even here, neuropsychology is relevant to manage communication disabilities, since an accurate and specific diagnosis is the foundation from which a treatment strategy should evolve. Understanding of which language capabilities and other cognition functions are retained, as well as those which show breakdown, is essential to plan an intervention in the individual patient, and to identify the most adequate outcome measures for clinical trials, in the expectation that the resources given to the patient can be translated into everyday function, hopefully improving quality of life. As such, the Study 4 of the Chapter IV will focus on the impact of a SLT program on PPA patients and its implications on disease management.

The findings of these original studies illustrate the relevance of neuropsychology to understand different aspects of PPA, and have implications for future research which will be discussed in the Chapter V of the present thesis.

II. LITERATURE REVIEW

Maruta, C. (2015). The musician entrapped in the aphasic mind: The tragic story of Maurice Ravel. (*submitted*).

Maruta, C. (2015). Primary Progressive Aphasia: A literature review. *(manuscript in preparation).*

The candidate made substantial contribution to the conception and design of the present works, drafted and revised critically the manuscripts for important intellectual content.

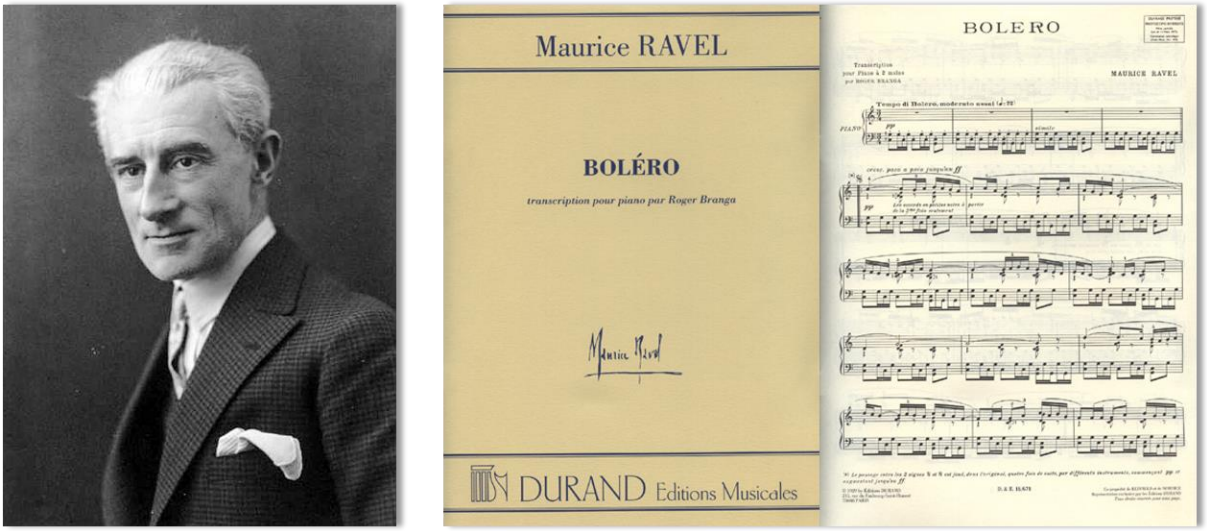
1. The musician entrapped in the aphasic mind: The tragic story of Maurice Ravel

Joseph-Maurice Ravel (1875 – 1937) was a French composer known especially for his melodies, masterful orchestration, richly evocative harmonies and inventive instrumental textures and effects (Cytowic, 1976). Along with Claude Debussy, he became one of the most prominent figures associated with the Impressionist movement in music. While celebrated for his musical legacy, he also represents a fascinating neurological case-study.

His condition is stated to have begun in 1927, when he was 52 years old, by a progressive deterioration of writing and subsequent word-finding problems. Interestingly, these symptoms emerged one year before the completion of his masterpiece *Boléro* and the *Piano Concerto for the Left Hand* (the latter being commissioned by the Austrian pianist Paul Wittgenstein). *Boléro* is one of those compositions that is hardly forgotten once heard (Figure A). Much of its impressiveness is certainly the result of how it was written: by alternating between two main melodic themes, repeating the pair eight times with increasing volume and layers of instrumentation. On explaining the idea for the piece, Ravel stated that his intention was "(…) *to repeat it a number of times on different orchestral levels but without any development* (…)" thus having "(…) *no music in it* (…)" (Ravel, 1927; *sic.* Burnett, 1987). In the last decade, some authors have argued that this musical technique was already revealing signs of his disease because it appeared to present a compulsive, structured, even perseverative nature (Amaducci, Grassi, & Boller, 2002). In fact, despite the extraordinary complexity of this piece, it is sufficiently different from other earlier compositions to raise the question whether something was already going wrong with Ravel's brain. Yet, this is a matter still in debate, especially because other pieces that followed the creation of *Boléro* do not seem to show such a pattern (Warren, 2003).

Ravel became aware of his inability to make familiar gestures during the summer of 1933. However, the signs of this ideomotor apraxia were, in fact, present earlier in the course of the disease as they were accompanied initially by tremor of hand, and manifested by blunders in writing, erasures and slowing of gestures. To his horror, the ability to write both in verbal and musical terms became largely compromised: he found increasing difficulty in putting his musical thoughts on paper, coping became impossible and he could no longer play the piano.

Figure A. Maurice Ravel in 1925 and *Boléro* music sheet



Sources: Bibliothèque nationale de France; http://www.diarezzo.de

His last creative work, *Ronsard à son Âme*, is known to have been written down to Ravel's "(…) *laborious dictation* (…)" (*sic.* Henson, 1988) in 1933. The following year he wrote, with major difficulties, his last letter and signed for the last time his own name. By that time, he also "(…) *scarcely attempted to speak* (…)" (*sic.* Henson, 1988), which suggests that his speech production was already very disturbed at this stage, almost near mutism. Despite the growing spoken and written language impairments, Ravel was able to recognize through audition his productions and whether musical instruments were out of tune, indicating that at least auditory perception was preserved (Warren, 2003). In short, Ravel's intact affectivity, aesthetic sensitivity and musical thinking contrasted with his extreme difficulty in expressing such dimensions, which made it impossible for him to produce music. Like a writer who no longer can translate his ideas and images into words, Ravel could no longer translate the patterns which were his music into symbols: he was agraphic for music. In his own words *"(...) this opera is here, in my head, I hear it, but I will never write it (...) I can no longer write my music. (...)*" (*sic.* Amaducci et al., 2002).

In his clinical notes, Théophile Alajouanine, his neurologist between 1933 and 1936, concluded that Ravel's slowly progressive apraxia and aphasia pointed towards a cerebral atrophy with prominent involvement of the left hemisphere. Since an autopsy was never performed, one can only speculate that Ravel's disease was compatible with

Frontotemporal Lobar Degeneration (FTLD), probably overlapping Pick's disease (PiD) or a Corticobasal Degeneration (CBD) (Baeck, 1996; Amaducci et al., 2002). Until his death in 1937, at the age of 62, due to complications resulting from an attempt of neurosurgical treatment (a right sided craniotomy), he remained socially active, making us think that he never actually reached a dementia stage.

2. Primary Progressive Aphasia (PPA)

2.1. Historical perspective

In 1892, Arnold Pick first described a patient with a history of gradually progressive speech disturbance associated with atrophy of the left temporo-polar region and posterior two thirds of the frontal lobe, in the context of a progressive social disorder characterized by disinhibited, socially inappropriate behaviour (Pick, 1892). In Pick's description, the language disturbance resembled that of a transcortical sensory aphasia, and this case became known as the first description of Semantic Dementia (SD) (Kertesz & Harciarek, 2014). However, the first case reporting a progressive difficulty limited to language, with declining speech fluency but unremarkable memory, social, or visuospatial abilities was provided one year later by Paul Sérieux. His paper described a woman who presented a progressive loss of spoken word comprehension and in whom "(…) *la mémoire et l'intelligence de la maladie étaient suffisament conservées (...)*". Her brain was later examined by Déjerine who observed a bi-temporal cortical atrophy and neuronal loss (Sérieux, 1893). Additional sporadic cases of slowly progressive focal neuropsychological deficits due to probable brain atrophy in relatively young patients (sometimes in the late forties) started to emerge in the literature (Déjerine & Sérieux, 1897; Pick, 1904, 1906; Rosenfeld, 1909; Ernst, Dalby, & Dalby, 1970; Wechsler, 1977; Mitsuyama, Tobo, & Itoi, 1978; Anderson & Barlow, 1980). However, it was only in the early eighties of the 20th century that a syndrome of progressive aphasia in the absence of dementia was again brought to clinical attention, by the hand of Marsel Mesulam.

In a case-series published in 1982, he described six right-handed patients, who in the *presenium* experienced the insidious onset and gradual progression of an aphasic disorder. In all but one, the language disturbance resembled an anomic aphasia, mostly characterized by a slow, laboured speech, containing several word-finding pauses with

spared repetition and comprehension. The pattern of fluctuating fluency without frank agrammatism of classic vascular nonfluent aphasia led Mesulam to coin the term "*logopenia*" [derived from the Greek 'λόγος'(*logos*), meaning "*word*" and 'πενία' (*penia*), which means "*deficiency*"] as a clinical state intermediate between nonfluent and fluent aphasia (Mesulam, 2007). One patient had pure-word deafness. Activities of daily living were essentially well preserved and patients showed good judgment and insight into their difficulties. In four of these patients, the gradual deterioration culminated in behavioural changes and a more generalized state of dementia may have emerged in the other two, but only after seven or more years of disease evolution. Atrophy involving the left perisylvian region was described in all these patients (Mesulam, 1982). Mesulam introduced the concept of "s*lowly progressive aphasia without generalized dementia*" to refer to this clinical picture: "*slowly*" as opposed to the progressive but relatively faster course of certain brain tumours; "*progressive*" as opposed to aphasia resulting from an acute stroke event; "*without generalized dementia*" in order to differentiate it from typical Alzheimer's Disease (AD), a memory-based dementia (Mesulam, 2007).

By the time Mesulam published his paper, some skeptical opinions regarding the true existence of such a condition rose in the scientific milieu (Foster & Chase, 1983). However, several similar cases followed Mesulam's paper (Foster, Patronas, DeLaPaz, & et al., 1982; Wechsler, Verity, Rosenschein, Fried, & Scheibel, 1982; Heath, Kennedy, & Kapur, 1983; Kirshner, Webb, Kelly, & Wells, 1984; Morris, Cole, Banker, & Wright, 1984; Assal, Favre, & Regli, 1985; Maeda, Ono, Shimizu, & Iizuka, 1988; Sapin, Anderson, & Pulaski, 1989), being decisive to the delineation of the clinical picture of "Primary Progressive Aphasia" (PPA) (Mesulam, 1987).

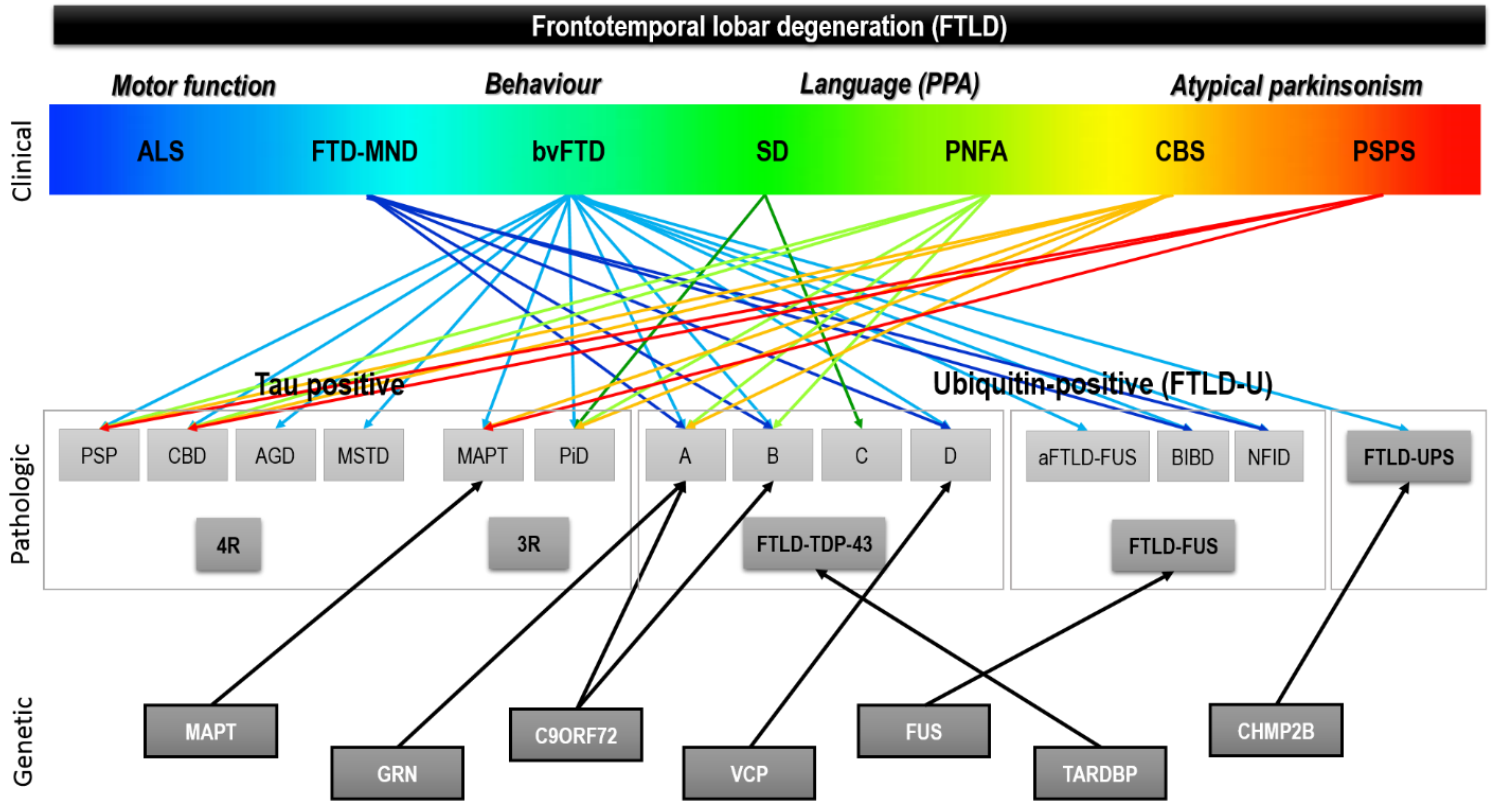
2.2. PPA under the Frontemporal Lobar Degeneration spectrum

PPA is a clinical syndrome led by a progressive, relatively selected language impairment, variably affecting word-finding, object naming, syntax, phonology, morphology, spelling or word comprehension, without an identifiable cause other neurodegeneration (ruling out other possible causes for the language deficit, such as stroke or brain tumours) (Mesulam, 2001, 2003) (Appendix 1). This aphasic disorder should be the most prominent deficit (i.e. *primary)* at symptom onset and in the initial phases of the disease, and should be solely responsible for impaired activities of daily living for, at least, one to two years. This temporal criterion was originally introduced to exclude rapidly

progressive dementias like Creutzfeld-Jacob Disease (CJD) with an aphasic onset, or other dementia syndromes where language deficits emerge in the context of equally prominent amnestic, behavioural or visuospatial deficits (Mesulam, 2001). Despite this rule, it has been acknowledged that establishing an exact onset of a neurodegenerative disease is not straightforward and the two-year rule should be interpreted with caution (Mesulam, 2007). Recommendations state that a differential diagnosis should be made between a *primary* vs a *secondary* form of progressive aphasia that typically arises in other dementia syndromes with other initial prominent deficits (e.g. memory, visuospatial skills, behaviour, praxis or motor functions). In this case, and according to Mesulam's criteria, such patients should not be diagnosed with PPA but classified as having a progressive aphasia in conjunction with the dominant syndrome (Mesulam, Rogalski, et al., 2014). In fact, memory for recent events, reasoning, visuospatial and social skills are relatively well preserved in PPA, at least, during the initial stages (Wicklund, Johnson, & Weintraub, 2004). Prominent behavioural disturbances should also be absent in order to make a root diagnosis of PPA (Mesulam, 2001).

PPA is the result of a selective/focal degeneration of the left language-dominant cerebral hemisphere. In the majority of cases, this is attributable to a spectrum of disease processes grouped under the umbrella term of Frontotemporal Lobar Degeneration (FTLD). FTLD encompasses a group of clinical, pathological and genetically heterogeneous disorders, which are outlined in Figure B. Three major clinical subtypes associated with degeneration of the frontal and temporal lobes can be distinguished based on the early and predominant symptoms and signs. The first is characterized by an early and progressive decline in social behaviour and personal conduct, with disinhibition, apathy, loss of sympathy, perseverative and stereotyped behaviours (behavioural variant of Frontotemporal Dementia - bvFTD) (Neary et al., 1998; Rascovsky et al., 2011). The second are the language variants of FTLD, which can be further divided into nonfluent (also referred to as Progressive Nonfluent Aphasia - PNFA) and semantic variants (also referred to as Semantic Dementia - SD) (Neary et al., 1998). Both are categorized as PPA. The third are the overlap syndromes, which include parkinsonian syndromes like Corticobasal Syndrome (CBS) (Armstrong et al., 2013) and Progressive Supranuclear Palsy Syndrome (PSPS) (Litvan et al., 2003) and motor neurone-disease, in particular, amyotrophic lateral sclerosis (MND – ALS) (Brooks, 1994).

Figure B. Clinical, pathologic and genetic frontotemporal lobar degeneration (FTLD) spectrum



Legend: aFTLD – atypical frontotemporal lobar degeneration with ubiquitinated inclusions; AGD - argyrophilic grain disease; ALS – amyotrophic lateral sclerosis; BIBD – basophilic inclusion body disease; bvFTD – behavioral variant frontotemporal dementia; C9ORF72 - chromosome 9 open reading frame 72; CBD – corticobasal degeneration; CBS – corticobasal syndrome; CHMP2B – charged multivesicular body protein 2B; FTD-MND – frontotemporal dementia with motor neuron disease; FTLD-TDP-43 – frontotemporal lobar degeneration with transactive response DNA-binding protein with molecular weight 43 kDa; FTLD-UPS – frontotemporal lobar degeneration with proteins of the ubiquitin proteasome system; FUS – fused in sarcoma; GRN – progranulin; MAPT – microtubule associated protein tau; MSTD - multiple system tauopathy with dementia; NFID – neuronal intermediate filament inclusion disease; PNFA – progressive nonfluent aphasia; SD – semantic dementia; PiD – Pick's disease; PSP – progressive supranuclear palsy; PSPS – progressive supranuclear palsy syndrome; TARDBP - TAR DNA-binding protein; VCP – valosin containing protein.

Note: *Diagram based on* Rohrer & Rosen (2013), Laforce (2013) *and* Villemagne, Fodero-Tavoletti, Masters, & Rowe (2015)

Apart from the sporadic cases, between 30% and 50% of patients with FTLD have a strong positive family history of the disease (Seelaar et al., 2008) but only 10 to 30% of family pedigrees show an autosomal dominant inheritance pattern (Riedl, Mackenzie, Förstl, Kurz, & Diehl-Schmid, 2014). In a recent study, 36% of the overall PPA series had a family history and only 5 (5%) had a genetic mutation detected (Flanagan et al., 2015). Common mutations associated with FTLD are found in microtubule associated protein tau (MAPT) gene (Heutink et al., 1997; Hutton et al., 1998) and progranulin (GRN) genes (Baker et al., 2006), both located in the chromosome 17. The latter has already been associated with PPA phenotypes although the H1/H1 haplotype on chromosome 17 coding for tau also appears to be associated with PPA (Sobrido et al., 2003). More recently, an abnormal expansion of a GGGGCC hexanucleotide repeat in a noncoding region of chromosome 9 open reading frame 72 (C9orf72) gene was identified as a common pathogenic mutation linking familial FTLD with ALS (Renton et al., 2011). Other less common mutations include cases of inclusion body myopathy with Paget's disease of the bone, caused by mutations involving the valosin-containing protein (VCP) gene on chromosome 9 (Watts et al., 2004; Forman et al., 2006), chromatin-modifying protein 2B (CHMP2B) gene on chromosome 3 (Skibinski et al., 2005), a mutation of TARDBP on chromosome 1 (Chiò et al., 2010), and a mutation involving cases with ubiquitin inclusions consisting of an accumulation of proteins encoded by the fused in sarcoma (FUS) gene located on the chromosome 16 (Yang, Warraich, Nicholson, & Blair, 2010). FUS and frontotemporal dementia with parkinsonism linked to chromosome 17 pathology are not commonly reported in PPA (Lashley et al., 2011).

With respect to FTLD spectrum pathology, it can be broadly separated into three major types of abnormal accumulation of proteins. Tauopathies, characterized by the accumulation of hyperphosphorylated microtubule-associated protein tau in neurons and glia (FTLD-tau) (Andreadis, Brown, & Kosik, 1992; Mackenzie et al., 2010), typically present in cases of familial FTLD caused by MAPT mutations (Morris et al., 1984), and cases with the neuropathology of PiD, PSP, CBD, argyrophilic grain disease (AGD), multiple system tauopathy with dementia (MSTD) and frontotemporal dementia with parkinsonism linked to chromosome 17 (Mackenzie et al., 2010). In addition, the biochemical form of tau is known to vary among different conditions and three-repeat (3R) and four-repeat (4R) isoforms have been identified (Dickson, Kouri, Murray, & Josephs, 2011). Ubiquitin-positive, tau-negative inclusions (FTLD-U) are the second major subtype of FTLD, the most common being the transactive response DNA-binding protein with

molecular weight 43 kDa (TDP-43) (Neumann et al., 2006; Sampathu et al., 2006). The majority of ALS cases present this pathological changes which provide further evidence for the continuum between this clinical entity and FTLD (Neumann et al., 2006; Kwong, Neumann, Sampathu, Lee, & Trojanowski, 2007). Four different FTLD-TDP subtypes have been conceptually harmonized (Mackenzie et al., 2011): Type A includes cases with moderate to numerous TDP43-immunoreactive neuronal cytoplasmic inclusions (NCI) and short dystrophic neurites (DN) predominantly in the upper cortical layers II/III; type B refers to cases with moderate to numerous TDP43 immunoreactive NCI and sparse DN across all cortical layers; type C is assigned to cases in which long DN are present predominantly in the upper cortices and NCI; and type D, corresponding to cases with numerous lentiform neuronal intranuclear inclusions (NII). This nomenclature is helpful to predict syndromic presentation. Specifically in PPA, the subtypes of FTLD pathological change typically observed include TDP-43 types A, B and C (Harris & Jones, 2014) and PiD, CBD and PSP. Finally, some FTLD-U TDP-43 negative cases present with an abnormal accumulation of FUS protein (Neumann et al., 2009; Urwin et al., 2010). This group include atypical FTLD with ubiquitinated inclusions (aFTLD-U) (Mackenzie, Foti, Woulfe, & Hurwitz, 2008), neuronal intermediate filament inclusion disease (NIFID) (Bigio, Lipton, White, Dickson, & Hirano, 2003) and basophilic inclusion body disease (BIBD) (Mackenzie et al., 2010). The distribution of overall pathological deposits in PPA has been found to be asymmetrical, with the left hemisphere more severely affected (Harris & Jones, 2014; Mesulam, Weintraub et al., 2014).

Some forms of PPA have also been associated with Alzheimer's disease (AD) pathology (Rabinovici et al., 2008; Grossman, 2010; Gorno-Tempini et al., 2011), which is characterized by amyloid β (Aβ) plaques and intracellular neurofibrillary tangles (NTFs) comprising hyperphosphorilated tau (Braak & Braak, 1991). When Alzheimer pathology is detected, the neurofibrillary tangles show lower entorhinal-to-neocortical ratios and greater leftward asymmetry in PPA than in the typical amnestic dementia of AD (Mesulam, 2013). Cases with focal spongiform degeneration (Kirshner, Tanridag, Thurman, & Whetsell, 1987), particularly CJD (Shuttleworth, Yates, & Paltan-Ortiz, 1985; Yamanouchi, Budka, & Vass, 1986) involving the left peri-sylvian cortex are also part of the literature concerning the underlying pathology in PPA.

2.3. Classification of PPA

Epidemiological data of PPA are presently very limited. Autopsy-based studies have estimated that 20 to 40% of autopsy-proven FTLD cases have PPA (Hodges et al., 2004; Kertesz, McMonagle, Blair, Davidson, & Munoz, 2005; Grossman et al., 2007; Grossman et al., 2008; Grossman, 2010). As such, prevalence of PPA in the general population can only be extrapolated from FTLD studies, which estimate a prevalence ranging from 1.1 to 15.0 per 100000 inhabitants (Ratnavalli, Brayne, Dawson, & Hodges, 2002; Grossman, 2010, 2014) and an incidence of about 0.88–1.4 per 100000 inhabitants (Grossman, 2014). The average age of onset is about 58 years old (Johnson et al., 2005), although younger and older cases are not uncommon. Survival is about seven years on average (Roberson et al., 2005). There are no known risk factors for PPA. Yet, gender has been indicated as a potential factor modulating PPA, with women on average presenting greater impairment than men at the same stage of the disease and declining at a faster rate when compared to their male counterparts (Rogalski, Rademaker, & Weintraub, 2007). Also, developmental dyslexia has been reported as co-occurring in higher frequency in PPA (Rogalski, Johnson, Weintraub, & Mesulam, 2008; Rogalski et al., 2014).

The majority of PPA patients present initially with word-finding difficulty and anomia, which evolve to different patterns of language disturbance. In 1982, and despite not having proposed a classification for his PPA cases, Mesulam acknowledged the heterogeneity of their language symptoms both at onset and evolution. Neary's criteria represent the first attempt to delineate two main disease variants, PNFA and SD (Appendix 1). This classification, by focusing on the reduced speech fluency evidenced by PNFA patients (in a similar way to Broca's aphasia) and deterioration of the semantic knowledge and comprehension deficits in the context of a fluent speech in SD (resembling Wernicke's aphasia), led to a generalization of the dichotomy fluent vs non fluent aphasia in a similar fashion that has been classically used to describe the aphasia syndromes of vascular aetiology. The increasing observation of a subset of patients with clinical features that did not fit into one of the previous variants, led to the suggestion of a third clinical variant, which was termed logopenic progressive aphasia (LPA) (Gorno-Tempini et al., 2004; Henry & Gorno-Tempini, 2010). In 2011, in an effort to guarantee uniformity of case reporting and comparability of research results, a International Consensus Criteria have recognized the existence of three PPA variants, the diagnosis of which can be made upon

three-levels of evidence, namely, clinical, imaging and probability of underlying pathology (Gorno-Tempini et al., 2011): a) nonfluent/agrammatic variant PPA, b) semantic variant PPA, and c) logopenic variant PPA.

2.3.1. Nonfluent variant

Non-fluent variant PPA (nfvPPA), also known as "*Progressive Nonfluent Aphasia*" (PNFA) (Grossman et al., 1996; Neary et al., 1998) or "*PPA with agrammatism*" (PPA-G) (Mesulam et al., 2009) was the initial type of PPA described in Mesulam's seminal report. Its clinical hallmark is the presence of a slower, effortful speech, characterized by an average rate of about 45 words per minute (wpm), which is less than one third the speech rate of healthy subjects (Ash et al., 2006, 2009). It incorporates shorter words than normal subjects (Fraser et al., 2012) and presents speech-sound errors (Ash et al., 2013). In a stepwise linear regression analysis, Gunawardena and colleagues found that the presence of simplified grammatical structures alone predicted speech fluency in this variant (Gunawardena et al., 2010). In fact, one of the canonical hallmarks of this variant is a grammatical production deficit (*agrammatism*), observed as simplification of grammatical forms with fewer sentences containing subordinate clauses or the passive voice (e.g. "*an apple was eaten by John")* (Wilson, Henry, et al., 2010), significant shortage of verbs (Hillis, Tuffiash, & Caramazza, 2002; Hillis, Sangjin, & Ken, 2004), omission of required determinants or other grammatical morphemes (e.g. "*the*", "*and*", "*of*"), inappropriate subject-verb agreement/inflections (e.g. "*painting <u>are</u> a hobby of mine*") (Ash et al., 2009), and words may be incorrectly inserted in the grammatical structure of a sentence (Grossman et al., 2012). All of these features contribute to reduced mean length of utterance (MLU) (with lengthy pauses within and between utterances) and reduced frequency of grammatically complex utterances (Ash et al., 2009), which become increasingly frequent with disease progression, to the point where patients can only produce single-word utterances or, at the extreme, reach a state of mutism. Distortion of prosody is another clinical characteristic of nfvPPA speech. Prosody is the pattern of pitch contours spanning words and sentences that help to provide emphasis and revealing the emotional content of speech (Grossman, 2012). Nonfluent PPA cases presenting prosodic disturbances as the initial feature have been called "*foreign accent syndrome*" because the patient's speech is affected in such a way that it is perceived by listeners as foreign (Luzzi et al., 2008; Paolini et al., 2013).

Apart from the agrammatism, nfvPPA cases may also reveal apraxia of speech (AoS), which consists of a disturbance of the articulatory planning (Ogar, Slama, Dronkers, Amici, & Gorno-Tempini, 2005). They present slowness of speech rate, articulatory distortions, distorted sound substitutions and segmentation of syllables in multisyllabic words or across words. In addition, these patients find difficulty repeating strings of syllables particularly those requiring the ability to coordinate complex articulatory movements (e.g. "*pa ta ka… pa ta ka...*") (Ogar, Dronkers, Brambati, Miller, & Gorno-Tempini, 2007). Articulatory groping, stuttering over the first-consonants and trial-and-error articulatory movements are also frequently evident. AoS can co-occur with orofacial or limb apraxia in nfvPPA (Rohrer, Rossor, & Warren, 2010a) or as a component of more widespread degenerative syndromes such as CBS and PSPS (Josephs et al., 2006; Rohrer, Rossor, et al., 2010a). Nonetheless, AoS can occur in the absence of other speech, language or motor dysfunction. According to Mesulam's criteria, apraxic speech alone is not sufficient to fulfil the diagnosis of PPA (Mesulam, 2001; Mesulam, Rogalski, et al., 2014). That's why recently it has been argued that AoS in isolation may represent a clinically distinct neurodegenerative syndrome, with specific features ("*Primary Progressive Apraxia of Speech*"; PPAoS) (Josephs et al., 2012; Duffy, Strand, & Josephs, 2014; Duffy et al., 2015). Further evidence supports this distinction. A recent hierarchical cluster analysis based on speech and language features revealed that it is possible to separate sub-variants under nfvPPA which are characterized by isolated agrammatism, pure motor speech disorder or mixed agrammatism and AoS. This evidence highlights the substantial variability under this clinical phenotype (Leyton, Ballard, Piguet, & Hodges, 2014). Dysarthria can also occur in nfvPPA (Gorno-Tempini et al., 2004; Josephs et al., 2012; Silveri et al., 2014) and may present hypokinetic features (e.g. monopitch, reduced stress, or speech festination) or spastic features (strained, harsh vocal quality, bursts of loudness, low pitch, slowed rate and imprecise articulation) (Caso, Mandelli, et al., 2014).

Naming abilities are relatively preserved, with average performances on confrontation naming when compared to other variants and controls (Gorno-Tempini et al., 2004). However, naming of actions may be significantly more impaired than naming of nouns (Hillis et al., 2004; Cotelli et al., 2006; Silveri et al., 2014) being affected by both lexico-semantic and syntactic attributes (Marcotte et al., 2014) and reflecting the affection of the fronto-parieto-subcortical circuits involved in action knowledge and action representation (Cotelli et al., 2006). Another study suggested that patients with AoS may

have relatively better confrontation naming than those without speech apraxia (Rohrer, Rossor et al., 2010a). Phonemic/phonological errors may occur in this task (Budd et al., 2010). Repetition of longer sentences, multisyllabic and phonologically similar words or even short words and sentences is also impaired (Kertesz & Harciarek, 2014; Leyton, Savage, et al., 2014).

The comprehension of single words is well preserved (Gorno-Tempini et al., 2011). In fact, semantic deficits are not characteristic of nfvPPA and even with disease progression patients may maintain relatively preserved comprehension. The presence of semantic errors in naming and speech is virtually present in all PPA variants and nfvPPA is no exception. Nonfluent PPA patients may produce semantic errors or struggle to provide an accurate description of the meaning of single words but this is the result of the programming involved in speech production (that limits verbal output) rather than a semantic access problem (Budd et al., 2010). In fact, nfvPPA show significantly better performance than svPPA patients in tasks that require to point to a target item named by the examiner among an array of several pictures presented in random location (Hodges, Martinos, Woollams, Patterson, & Adlam, 2008). Syntactic comprehension, on the other hand, especially for difficult morphosyntactic constructions that involve third person singular present agreement (e.g. "*she wakes up early*"), embedded clauses (e.g. "*This is the book* [*that I bought yesterday*]") and cleft sentences (e.g. "*It was from John that she heard the news")* is impaired (Deleon et al., 2012; Charles et al., 2014). For instance these patients reveal difficulty in pointing to one of several pictures based on a sentence (Wilson, Dronkers, et al., 2010). A significant number of agrammatic errors are also evident in written production (Graham, Patterson, & Hodges, 2004). Nonfluent PPA patients also have difficulty in anagram tasks that require the subject to order a series of printed words into a grammatically complex sentence describing a picture (Weintraub, Mesulam, Wieneke, Rogalski, & Thompson, 2009). Both syntax comprehension tasks (e.g. Token Test) and written description of pictures are often useful in detecting early signs of grammatical errors and help differentiate nfvPPA with agrammatism from a more speech apraxic clinical picture (Weintraub et al., 2009; Kertesz & Harciarek, 2014). With respect to reading abilities, in general they tend to arise with the aphasia evolution, with patients having a mild difficulty in reading written words aloud resulting from phonemic problems.

Cognitive deficits in nfvPPA are not limited to language. Executive functions are particularly affected, with worse performance in letter fluency compared to category

fluency tasks (Libon et al., 2007; Hodges et al., 2008; Grossman, 2012), inhibitory control (Gunawardena et al., 2010) and both digit span forward and backwards tasks (more pronounced in the latter when compared to bvFTD and svPPA) (Lu et al., 2013), indicating a more general auditory verbal short-term memory impairment (Hodges et al., 2008; Grossman, 2012). Nonfluent PPA also shows the worst performance on praxis testing compared to the other two variants (Gorno-Tempini et al., 2004). Visuoconstructional praxis may be more imapired than in svPPA (Hodges et al., 2008). Nonfluent PPA also shows disturbance at the emotional processing level, with difficulty in decoding emotional prosody in language (Shany-Ur & Rankin, 2011) and a selective difficulty in facial emotion recognition particularly for negative emotions (e.g. fear), when compared with lvPPA (Piguet, Leyton, Gleeson, Hoon, & Hodges, 2015). Yet, performance tends to improve with the intensity of those emotions (Kumfor et al., 2011). Rather than an explicit emotion processing deficit, nfvPPA patients seem to present a more implicit deficit, related to inability to feel the emotions. This has been suggested in a recent study that showed that these patients present reduced autonomic responses (skin conductance response and heart rate) when observing and evaluating affective pictures that contrasted with better performance on the explicit judgment of positive vs negative attributes of those emotions compared to AD patients and controls (Balconi et al., 2015). With regard to behavioural changes, nfvPPA patients usually do not display severe changes at an early stage apart from mild apathy, agitation and depression (Marra et al., 2007; Rohrer & Warren, 2010), with increasing severity and emergence of some disinhibition-like behaviours (such as aggression) later in the course of the disease (Marczinski, Davidson, & Kertesz, 2004).

Nonfluent PPA is usually accompanied by mild extrapyramidal signs (Kremen, Mendez, Tsai, & Teng, 2011). If unilateral rigidity, dystonia, myoclonus, limb apraxia features are present, nfvPPA may overlap with CBD; when vertical gaze and axial rigidity are prominent, it may be associated with PSPS (Kertesz, Martinez-Lage, Davidson, & Munoz, 2000). More rarely, nfvPPA can be associated with asymmetrical idiopathic Parkinson's disease, with bradykinesia, rigidity and rest tremor (Graff-Radford, Duffy, Strand, & Josephs, 2012; Doherty, Rohrer, Lees, Holton, & Warren, 2013) and other atypical parkinsonian syndromes (multisystem atrophy and olivopontocerebellar atrophy) (Silveri et al., 2014). Nonfluent PPA can also occur in the context of a pyramidal motor system disorder, suggesting ALS, with bulbar and limb weakness, muscle wasting,

fasciculations, abnormal myotactic reflexes and positive Babinski response (Lomen-Hoerth, Anderson, & Miller, 2002).

Cross-sectional imaging studies highlight a pattern of cortical brain atrophy that typically involves the left inferior frontal region, adjacent frontal operculum (*pars opercularis*) and anterior insula, extending more dorsally into the left prefrontal regions and ventrally into superior portions of the left anterior temporal lobe (Gorno-Tempini et al., 2004; Gorno-Tempini et al., 2011). When AoS is prominent, premotor and supplementary motor cortex can be affected (Gorno-Tempini et al., 2004; Josephs et al., 2012). Grey matter (GM) damage is also seen in striatal regions (Gorno-Tempini et al., 2006), which correlates with a reduced striatal tracer uptake seen in nfvPPA prior to the emergence of clinical parkinsonian features, corroborating a nigrostriatal degeneration hypothesis (Gil-Navarro, Lomeña et al., 2013). It has also been suggested that this left fronto-insular-striatal represent a speech production network responsible for the fluency deficits typical of this variant (Wilson, Henry, et al., 2010). Severe white matter (WM) damage is observed in tracts connecting all these regions only in nfvPPA, highlighting their specific role in speech production processes and their involvement in the motoric aspects of fluency, as these pathways are relatively preserved in the other two variants of PPA (Mandelli et al., 2014). WM disease may also account for by the breakdown of three large scale networks for language expression (Grossman et al., 2012). WM damage is seen mostly in the dorsal language pathways (the so-called "*dorsal stream*"), i.e. the subcomponents of the left superior longitudinal fasciculus, particularly the arcuate fasciculus linking frontal brain regions with language areas in the posterior-superior temporal lobe (Galantucci et al., 2011; Agosta et al., 2012; Grossman, 2012; Josephs et al., 2012; Mahoney, Malone, et al., 2013; Schwindt et al., 2013; Zhang et al., 2013) which has been associated with impaired production of grammatically well-formed sentences (Wilson et al., 2010; Wilson et al., 2011; Grossman et al., 2012). This projection may also play a role in auditory-motor associations important for speech fluency (Hickok & Poeppel, 2007). Other tracts that have been shown abnormalities in projections mediating connectivity in the "*ventral stream*", including the inferior frontal-occipital and uncinate fasciculi coursing through the external capsule to superior temporal regions, which has been associated with reduced MLU and difficulty in processing grammatically well-formed sentences (Charles et al., 2014). This fronto-occipital pathway may support lexical representations that include the major grammatical category of words in sentences (Hickok

& Poeppel, 2007). An interruption of a bilateral frontal network mediated by projections to the fornix and anterior corpus callosum has also been described in nfvPPA (Agosta et al., 2012; Grossman, 2012; Schwindt et al., 2013). Other areas eventually become affected, as shown by recent longitudinal imaging studies, indicating that the frontal lobe shows the fastest rate of atrophy over time, followed by temporal (more pronounced on the left) and parietal lobes (more pronounced on the right) and some subcortical structures including the caudate (Gorno-Tempini et al., 2004; Rohrer, Warren, Modat, et al., 2009; Rohrer, Clarkson, et al., 2012; Lu et al., 2013).

Familial forms of nfvPPA have been described and linked to PGRN mutations (Mesulam et al., 2007; Rademakers et al., 2007; Benussi et al., 2009; Caso et al., 2012; Pires et al., 2013; Caso, Agosta, et al., 2014). Other family-inherited nfvPPA phenotypes can result from MAPT mutations (Pickering-Brown et al., 2008; Villa et al., 2011). A rare MAPT sequence variant (p.A152T) was reported in two cases with nfvPPA diagnosis, one of which with clinical elements suggestive of PSP (Lee et al., 2013). C9orf72 repeat expansion has been less systematically reported in these patients (Gijselinck et al., 2012; Mahoney et al., 2012; Snowden et al., 2012). More recently, nfvPPA has been associated with a pathogenic Presenilin 1 P264L mutation, which is usually present in typical amnestic AD (Mahoney, Downey, et al., 2013). According to a clinicopathological study with a sample of 52 paints, Harris and colleagues found that 75% of the nfvPPA cases had FTLD spectrum pathology (Harris et al., 2013). In terms of pathological signatures, about 50% of nfvPPA cases have FTLD – tau and about 20% have FTLD-TDP 43 type A pathology (Mesulam, Wicklund, Johnson, et al., 2008; Harris & Jones, 2014). Recently in vivo signatures for both pathologies have been proposed, with AoS being the most frequent manifestation of nfvPPA caused by FTLD–tau (with hypokinetic dysarthria, later development of extrapyramidal signs and more WM frontal damage). On the other hand, TDP-43 pathology has been described in patients with early mutism, severe buccofacial apraxia, spastic dysarthria and greater inferior frontal GM atrophy (Caso, Mandelli et al., 2014).

2.3.2. Semantic variant

Semantic cognition refers to a collection of higher cortical functions that allow us to encode, store and use general knowledge about the world, such as the meaning of words and objects, in order to generate flexible and sophisticated verbal and nonverbal behaviour

(Tulving, 1972; Jefferies & Lambon Ralph, 2006). In her seminal study, Elizabeth Warrington described three patients in whom a reduced comprehension both for verbal (words) and visual (objects) material suggested the breakdown of the semantic/conceptual knowledge (Warrington, 1975). An explicit connection between PPA and Warrington's report was not made until 1989, when Snowden and colleagues used, for the first time, the term "*Semantic Dementia*" (SD) (Snowden, Goulding, & Neary, 1989) to describe three patients selected on the basis of their language deficits, which were quite similar to Warrington's cases. These patients contrasted with those described by Mesulam in 1982 and a subsequent publication focusing on the clinical, neuropsychological, behavioural and radiological findings of another series of five SD cases (Hodges, Patterson, Oxbury, & Funnell, 1992) represented the first attempt to differentiate both clinical presentations. The following decades saw SD being referred to as "*Gogi* ("*word meaning*" in Japanese) *Aphasia*" (Tanabe et al., 1992), "*Primary Progressive Semantic Aphasia*" (Kertesz, Davidson, & McCabe, 1998), "*Temporal Variant FTD*" (Bozeat, Gregory, Ralph, & Hodges, 2000), "*Fluent PPA*" (Clark, Charuvastra, Miller, Shapira, & Mendez, 2005; Adlam, Patterson, Rogers, et al., 2006), "*Semantic PPA*" (PPA-S) (Mesulam et al., 2009) and, more recently, "*Semantic Variant PPA*" (svPPA) (Gorno-Tempini et al., 2011).

The comprehensive description made by Hodges and colleagues was extensive enough to remain currently accurate, highlighting the relative homogeneity within this PPA variant as opposed to the remaining subtypes. The two canonical hallmarks of svPPA are word retreival difficulty (anomia) both in speech and confrontation naming (which is significantly worse than the word-finding difficulties seen in nfvPPA or in lvPPA) and impaired single-word comprehension (Hodges & Patterson, 1996; Gorno-Tempini et al, 2004; Gorno-Tempini et al., 2011). Not only is the semantic patient unable to name an object (e.g. "*chair*" or "*cup*") but also finds difficult to access the verbal concept associated with it, reflecting an impaired knowledge of the word meaning. According to some authors, the emergence of the question "*what is a…?*" during the neuropsychological assessment represents an early useful pathognomonic feature in the differential diagnosis versus other PPA subtypes (Kertesz, Jesso, Harciarek, Blair, & McMonagle, 2010; Warren, Rohrer, & Rossor, 2013).

Semantic PPA patients present with a fluent, well-articulated, phonologically and syntactically preserved speech (Kavé, Heinik, & Biran, 2012; Wilson, DeMarco, et al., 2014). Patients typically use general terms (e.g. "*thing*"), increase the use of high

frequency, superordinate category names (e.g. "*animal*" for "*dog*"), show a reduction of lower frequency/familiarity nouns (e.g. "*giraffe*") and overuse closed class words, demonstrative (e.g. "*this*" or "*that*") and interrogative pronouns ("*Wh*" words), which denotes uncertainty or approximate expressions in the use of nouns (Bird, Lambon Ralph, Patterson, & Hodges, 2000; Ash et al., 2006; Hodges & Patterson, 2007; Wilson, Hnery, et al., 2010; Fraser et al., 2012; Ash et al., 2013; Hoffman, Meteyard, & Patterson, 2014; Meteyard, Quain, & Patterson, 2014). Other consequences of this loss of words include semantically related word substitutions (semantic paraphasias; e.g. "*cat*" for "*dog*" or "*apple*" for "*banana*"), and circumlocutions with more or less substantive content (Knibb & Hodges, 2005). The profound anomia and reliance on high frequency lexical items have implications for the kind of syntactic constructions that can be used. In fact, svPPA patients tend to produce fewer complex auxiliary forms and to overuse high frequency inflections (e.g."*ing*"), which creates simpler syntactic constructions (Meteyard et al., 2014). All of these features give their speech an "empty" tone (Neary et al., 1998). Verbs are also more accurately produced than nouns (Thompson, Lukic, King, Mesulam, & Weintraub, 2012), although their use has been suggested to be affected by semantic complexity, with svPPA patients showing greater impairment in production of semantically heavier than of semantically lighter verbs, when compared to nfvPPA patients (Marcotte et al., 2014). As the disease progresses, speech becomes filled with clichés and semantic jargon, profoundly uninformative, irrelevant to the questions being asked or the topic discussed. Pragmatic disturbances contribute to the peculiarity of the speech of svPPA patients, which is characterized by garrulous, excessive and frequently disinhibited output, stereotypic thematic perseverations, not-stop-to-listen behaviour and laughing. With time and despite the maintained fluency, the increasing lexical-semantic problems affects even high-familiarity, typical words, verbs become affected as well and the length of patients' connected speech decreases, leading eventually to mutism (Knibb & Hodges, 2005; Ash et al., 2006; Kertesz et al., 2010).

With respect to the single-word comprehension deficit, it can be more subtle and remain unnoticed until a formal assessment is performed because it is often masked under a highly fluent speech. It is usually observed when the patient is requested to provide the meaning of words or to match a spoken word to an object/picture, especially low-frequency words (Hodges et al., 2008). The patient makes a vague, inaccurate, over-generalized description (similar to the semantically impoverished responses in picture

naming) or fails to produce a description at all (e.g. "*don't know*"). A phenomenon called "*alienation du mot*" (Knibb & Hodges, 2005), in which the patient repeats the word as if it were the first time he hears it while claiming he knows what it means but he can't remember, is commonly observed in these patients. Single-word comprehension is particularly impaired for nouns compared to verbs (Thompson et al., 2012), and interestingly svPPA patients perform normally in comprehension of complex syntactic/grammatical structures (within the limits of single-word comprehension). Repetition of multisyllabic words and sentences is often spared (Gorno-Tempini et al., 2004; Hodges et al., 2008; Kertesz & Harciarek, 2014; Leyton, Savage, et al., 2014). However, some patients may make phonological errors in repetition and may be less accurate in repeating lists of words they can't understand (Jefferies, Patterson, & Ralph, 2008), which highlights a probable role of the semantic system in maintaining the integrity of phonological word forms (McCarthy & Warrington, 2015).

The presence of dissociations between different domains of knowledge has already been acknowledged in the past. Proper names (for people and landmarks) tend to be severely affected and among common names, living entities may be more affected than non-living entities (Papagno, Capasso, & Miceli, 2009). In addition, svPPA patients may have relatively preserved comprehension for abstract compared to concrete concepts (Grossman & Ash, 2004; Papagno et al., 2009; Catricalà, Della Rosa, Plebani, Vigliocco, & Cappa, 2014) in an opposite direction observed in typical AD, where semantic deficits tend to affect more the understanding of abstract than concrete concepts. Even within abstract concepts, svPPA tend to show a pattern of dissociation, with poorer performance on tasks assessing category-specific abstract domains, such as social relations (Catricalà et al., 2014). Verbal concepts show a similar pattern, with motion (concrete) verbs being more affected than cognitive (abstract) verbs (Yi, Moore, & Grossman, 2007).

As previously stated, both naming and single-word comprehension are particularly affected for low-familiarity items (Hodges & Patterson, 2007). In addition, in a recent experiment designed to study the effect of word class (verb/noun), word regularity (regular/irregular) and word frequency (high/low) on inflectional morphology (the part of grammar that marks words for grammatical features such as tense, aspect, mood, polarity, person, number, gender and case) across the three PPA variants, Wilson and colleagues confirmed the more pronounced impact of the lexical-semantic deficit on svPPA not only for low-frequency but also irregular words, with a significant higher proportion of over-

regularization errors (Wilson, Brandt, et al., 2014). The difficulty processing irregular words (those that have uncommon phoneme-grapheme relationships and/or spellings) is more likely to be observed in reading and writing tasks. Semantic PPA patients present a particular difficulty in reading aloud irregular words, making mispronunciation and regularization errors (e.g. "*dufnut*" for "*doughnut*"), a phenomenon known as *surface dyslexia* (Fushimi, Komori, Ikeda, Lambon Ralph, & Patterson, 2009). Dual-route models for reading and writing processing (Yamada, Imai, & Ikebe, 1990; Behrmann & Bub, 1992; Coltheart, Curtis, Atkins, & Haller, 1993; Zorzi, Houghton, & Butterworth, 1998) are helpful to understand this clinical feature. Written language processing is accomplished by two distinct but interactive cognitive procedures: a lexical (or lexical-semantic) and a sub-lexical (phonological) route. Reading and spelling by the lexical-semantic route relies on a three-step procedure, from the orthographic input lexicon to the cognitive system and to the phonological output lexicon (a store of the phonological forms of known familiar, exceptional, and irregular words and their pronunciations), responsible for the activation of word-specific orthographic and phonological memory representations. These representations are then linked to their corresponding conceptual representations stored in the semantic system (involved in associating the visual form of the word to its meaning). This procedure is only suitable with words whose orthography is stored at lexical level: i.e. the lexical route is responsible for processing all familiar words whether they are regular or irregular in terms of the letters-sound relationships (i.e. whole-word route) (McCarthy & Warrington, 2015).

The occurrence of surface dyslexia in svPPA points to a disturbance in the lexical route, which is assumed to result from damage to the orthographic input lexicon (Coltheart, Tree, & Saunders, 2010) or, more substantially, the access to semantic knowledge (Woollams, Ralph, Plaut, & Patterson, 2007). As a consequence, only the phonological route is available. This sub-lexical route allows for the correct reading of non-words and regular words through the application of a plain grapheme-phoneme conversion. When these rules are applied to irregular words, they are read as if they were regular. The patient identifies the words' constituents (letters, graphemes, phonemes) and generalizes the knowledge of how these parts are associated with each other in a phoneme-grapheme relationship. This creates a phonologically incorrect representation, the word is mispronounced and regularization errors occur. Writing parallels reading: patients display a preserved execution of writing, without apraxia or grammatical errors, but the spelling of

irregular words is often incorrect, though almost always phonologically plausible (*surface dysgraphia*) (Caine, Breen, & Patterson, 2009).

Neary's criteria considered equally important and necessary the presence of a semantic fluent aphasia and visual semantic deficits (associative agnosia, which is a difficulty in recognizing/identifying objects, and prosopagnosia, difficulty in recognizing familiar faces) for the diagnosis of SD, indicating that semantic processing deficits extend to non-verbal domains (Neary et al., 1998). The presence of visual semantic deficits has created considerable confusion regarding the status of SD as a relatively independent syndrome from PPA, and this discussion persisted in the literature until 2011. The question has always been whether SD overlapped the accepted definition of svPPA. Strictly speaking, SD does not conform a pure aphasic syndrome and, as such, it does not fit in the diagnostic criteria for PPA (Mesulam, 2001). PPA diagnosis, therefore, encompasses only a subset of SD patients, namely, those in whom an aphasic disorder characterized by a fluent aphasia and impaired single-word comprehension constitute the most salient aspect of the clinical picture (Mesulam, 2003; Mesulam et al., 2009). The presence of both aphasia and agnosia would constitute, on these terms, a more generalized state of dementia, ruling out a PPA diagnosis. Interestingly, the majority of SD patients share many features with svPPA, particularly at the verbal level, with the primary semantic impairment predominantly seen in naming and single-word comprehension. Nonetheless, some authors argue that a pure svPPA can hardly be identified since in the majority of patients deficits are not restricted to language and deficits in object knowledge are seen in other stimulus modalities (Adlam et al., 2006). Moreover, a recent study assessed the impact of the 2011 diagnostic criteria on prior clinical diagnosis and found that about 87% of SD cases met criteria for svPPA, which further confirms the overlap between the two syndromes (Chare et al., 2014). SD and svPPA may represent a continuum of the same disorder, with SD probably being a more advanced stage of svPPA (Gorno-Tempini et al., 2011), with key impairment lying not only on verbal grounds but on a mutimodal selective deterioration of the semantic memory, which spreads to non-verbal domains as well (Kertesz et al., 2010; Silveri et al., 2014). In fact, svPPA can be defined as a multimodal disorder of the meaning: the difficulty lies on assigning an identity (i.e. recognizing the significance) to stimuli that are perceived normally. This is likely due to degradation within a single, central network of conceptual knowledge (Bozeat, Lambon Ralph, Patterson, Garrard, & Hodges, 2000). The deficit affect object recognition or the association of the sensory

percept with its meaning (associative agnosia), while perceptual encoding and discrimination are relatively spared. This can be elicited in semantic association tasks such as the *Pyramids and Palm Trees Test* (Howard & Patterson, 1992) and word-picture matching test like the *Peabody Picture Vocabulary Test* (Dunn, 1965), where patients with svPPA display significantly worse performance when compared to normal subjects (Mandelli et al., 2014; Marcotte et al., 2014). Factors such as object/features familiarity and typicality modulate significantly the pattern of recognition, consisting of important predictors of performance (Bozeat, Lambon Ralph, Patterson, & Hodges, 2002; Adlam et al., 2006). Semantic variant PPA patients recognize superordinate categories better than prototypes and tend towards typicalization errors and reduced number of distinctive features for concepts in both living and nonliving categories (e.g. they may draw from memory a duck, but with four legs and a tail) (Bozeat et al., 2003). Visual modality is the primary non-verbal domain to be affected, although other non-verbal modalities may follow. Patients show difficulty in recognizing objects and faces, including recognition of negative facial emotions (Kumfor et al., 2011; Kamminga et al., 2014), processing flavour and odour (Luzzi et al., 2007; Rami, Loy, Hailstone, & Warren, 2007; Piwnica-Worms, Omar, Hailstone, & Warren, 2010; Omar, Mahoney, Buckley, & Warren, 2013), nonverbal auditory information in accents (Fletcher et al., 2013) or other meaning nonverbal environmental sounds (Warrington, 1975; Bozeat, Lambon Ralph, et al., 2000; Adlam et al., 2006; Goll et al., 2010). The ability to discriminate colours tends to be relatively preserved (Robinson & Cipolotti, 2001; Gorno-Tempini et al., 2004), but the ability to group different colours into categories, to name secondary colours and perception of colours located in the spectral midpoints between red, blue and green are disturbed (Rogers, Graham, & Patterson, 2015). Semantic PPA patients also have difficulty in matching objects to function and matching to action, while not showing deficits in matching to recipient (Bozeat et al., 2002; Adlam et al., 2006). Impaired recognition of the arithmetic signs, difficulty in arithmetic facts and procedural errors in calculation are also among the deficits experienced by svPPA patients (Luzzi, Cafazzo, Silvestrini, & Provinciali, 2013). Agnosia for tactile stimuli has also been described in svPPA (Coccia, Bartolini, Luzzi, Provinciali, & Ralph, 2004).

With respect to the remaining areas of cognition in svPPA, and consistent with their primary semantic breakdown, these patients perform significantly worse than bvFTD and nfvPPA patients on measures of semantic knowledge and retrieval, categorical/semantic

verbal fluency, verbal abstraction and verbal recognition (Hodges & Patterson, 1996; Gorno-Tempini et al., 2004; Lu et al., 2013). Overall, cognitive functions that do not rely on language or conceptual knowledge are relatively spared, such as executive functioning and attentional abilities (Iaccarino et al., 2015). Phonemic fluency is considered to be normal (Marczinski & Kertesz, 2006), although with contradictory findings (Adlam et al., 2006). Semantic PPA presents a remarkable anterograde episodic memory for everyday life events (Scahill, Hodges, & Graham, 2005; Adlam, Patterson, & Hodges, 2009), with recent autobiographical memory relatively preserved in comparison with remote epochs (Irish et al., 2011). A recent study showed that svPPA patients have some nonverbal episodic memory for novel action sequences, even after a 24h delay, and that new anterograde memory can to some extent be established without significant support from semantic memory (Adlam, de Haan, Hodges, & Patterson, 2013), though semantic deficits invariably affect performance on verbal learning tasks that require semantic processing input (McCarthy & Warrington, 2015). Non-verbal topographical memory for buildings, landscapes and outdoor scenes is also within the normal range (Cipolotti & Maguire, 2003), as well as route learning (Luzzi et al., 2014). This particular feature may be useful for the diagnostic differentiation between SD and AD which present, by contrast, with prominent deficits in topographical memory early in the disease course. Measures of working memory, non-verbal reasoning, visuospatial and motor abilities are not affected in svPPA (Hodges et al., 1992; Adlam et al., 2006).

Typically, a pattern of behaviour changes accompanies svPPA (Lu et al., 2013), mainly characterized by decreased empathy, disinhibition and changes in diet/food preferences (with some cases presenting mild Klüver-Bucy syndrome, with compulsive food intake) (Hodges et al., 1992; Rohrer & Warren, 2010; Kamminga et al., 2014). Obsessive-compulsive behaviours have also been reported (Sabbe & Vandenbulcke, 2014) as patients frequently become preoccupied by a narrow range of activities which they pursue obsessively. They develop a preference for a fixed routine, develop complex behavioural rituals and may clock watch constantly (Snowden, 1999). Some authors have suggested that increasingly self-centered behaviours may be the result of a more global deficit of social cognition (the cognitive process that is engaged to understand or interpret the self in relation to others and the environment) (Forbes & Grafman, 2010) rather than semantic disruption per se (Duval et al., 2012). Anosognosia has also been reported in svPPA, but one recent study suggested that it may be secondary to difficulty evaluating

language content which, in turn, affects the ability to reflect upon current and past language skills, producing under-awareness of language deficits, when compared to their nfvPPA counterparts (Savage, Piguet, & Hodges, 2015).

Neurological examination is usually unremarkable, even with disease progression (Gorno-Tempini et al., 2004; Silveri et al., 2014). In very rare cases, extrapyramidal or amyotrophic neurological features may emerge (Hodges & Patterson, 2007; Kremen et al., 2011; Östberg & Bogdanović, 2011). Symptoms of autonomic dysregulation have recently been reported in FTLD: similarly to bvFTD patients, svPPA patients show an increased prevalence of weakness, fatigue and pain around the neck and shoulders, which may originate orthostatic hypotension. This group also reported increased symptoms of constipation, excessive fullness after a small meal, reduced tolerance to cold and tiredness during the day (Ahmed et al., 2014; Jones, 2011).

The bilateral anterior temporal lobe (ATL) has been extensively implicated as playing an important role in semantic memory (Tulving, 1972; Patterson, Nestor, & Rogers, 2007; Simmons & Martin, 2009) and atrophy of this region is the imaging signature of svPPA. This phenotype shows a highly consistent neuroanatomical profile characterized by selective, bilateral but asymmetric (usually greater in the left than in the right hemisphere) atrophy and hypometabolism in the anterior inferior, medial and superior portions of the temporal lobe with typically "*knife blade*" atrophy at the poles (but relatively normal cortex in more posterior temporal and peri-Sylvian regions) (Hodges et al., 1992; Mummery et al., 2000; Davies, Graham, Xuereb, Williams, & Hodges, 2004; Gorno-Tempini et al., 2004; Hodges & Patterson, 2007; Rohrer et al., 2009; Warren et al., 2013). Atrophy tends to spread to the more inferior temporal lobe involving the fusiform gyrus and mesial/limbic temporal structures, including the hippocampus, anterior thalamus, anterior and posterior cingulate (Brambati, Rankin, Narvid, et al., 2009; Rohrer et al., 2009; Faria, Sebastian, Newhart, Mori, & Hillis, 2014; Iaccarino et al., 2015). All these regions and structures are known to play an important role on the consolidation of episodic memories. A recent study found that, within the Papez's circuit, the mamillary bodies and the posterior parts of the hippocampus (body/tail) are unaffected in svPPA, which may explain the relative sparing of episodic memory in this subtype (Tan et al., 2014). Longitudinal imaging studies reveal in addition that the fastest rate of atrophy occurs in temporal lobes, followed by frontal, parietal and, to a lesser extent, the occipital lobes (Rohrer, Clarkson, et al., 2012). The atrophy also spreads to more posterior regions of the

temporal lobe (in keeping with the increasing comprehension deficits), as well as the orbitofrontal cortex and insula, with expansion of the anterior and posterior lateral ventricles (Brambati et al., 2009; Rohrer et al., 2009; Lu et al., 2013). Some svPPA patients have the same areas affected in the right anterior temporal lobe, clinically presenting with a prominent progressive prosopagnosia (Hodges, 2001; Thompson, Patterson, & Hodges, 2003; Snowden, Thompson, & Neary, 2004; Josephs, Whitwell, Vemuri, et al., 2008; Gefen et al., 2013). Despite the predominant visual deficits, right-sided svPPA also has some degree of verbal semantic impairment akin to that seen in the left-temporal variant (Kertesz & Harciarek, 2014). At the same time, the right-sided variant usually presents with behavioural changes at onset (Hodges & Patterson, 2007), posing a problem to the differential diagnosis with bvFTD (Kamminga et al., 2014). This pattern of behavioural changes is accounted for by studies correlating right hemisphere atrophy with more behavioural disturbances (Josephs, Whitwell, Vemuri et al., 2008; Irish, Hodges, & Piguet, 2014). Evidence suggests that the mean rate of atrophy is significantly greater in the right temporal lobe over time. As svPPA evolves, atrophy of the right temporal lobe overtakes the left temporal, which is consistent with the later development of visual agnosia and more pronounced behavioral deficits in left-sided variant svPPA (Gorno-Tempini et al., 2004; Hodges & Patterson, 2007; Rohrer et al., 2008). A post-mortem study indicated that the distribution of atrophy is asymmetric (Davies, Halliday, Xuereb, Kril, & Hodges, 2009), which provides evidence to consider both left and right-temporal variants as lying on an anatomical continuum.

Diffusion tensor imaging (DTI) studies also show important damage to the left frontotemporal WM tracts, greater in the left ventral pathway (inferior longitudinal and uncinate fasciculus), the dorsal tracts (entire left superior longitudinal fasciculus, particularly the arcuate fasciculus, but also corpus callosum (and the splenial fibers projecting to the superior temporal gyrus), left external capsula, cingulum and fornix (Agosta et al., 2010; Whitwell et al., 2010; Acosta-Carbonero et al., 2011; Mahoney, Malone et al., 2013; Zhang et al., 2013). Some studies have also shown abnormalities in other tracts including the left inferior fronto-occipital fasciculus (Borroni et al., 2007; Agosta et al., 2010, 2013; Ash et al., 2013; Powers et al., 2013). Functional imaging studies show, at the same time, a distributed pattern of functional connectivity abnormalities where a reduced nodal degree is seen in the inferior and ventral temporal regions and occipital cortices, extending into the medial and ventral frontal cortex

bilaterally, left amygdala and/or hippocampus, and basal ganglia (left caudate nucleus). These findings account for the cross-modality of the semantic deficit and provide a basis for disruption of the "modality specific" visual cortical origin of the ventral processing pathway (Agosta et al., 2014).

Concerning the underlying pathology, FTLD-TDP 43 is the main pathological change seen in svPPA (Grossman et al., 2007; Nestor et al., 2007), particularly type C histological features (Kertesz et al., 2005; Knibb, Xuereb, Patterson, & Hodges, 2006; Hodges & Patterson, 2007; Snowden, Neary, & Mann, 2007; Grossman et al., 2008; Grossman 2010; Harris et al., 2013a; Mesulam, Weintraub, et al., 2014). Some cases have underlying taupathies, mainly PiD (Hodges et al., 2004). In a study reporting neuropathological findings in 36 svPPA cases, AD pathology was identified in nine of them (Josephs, Whitwell, Duffy, et al., 2008). Mutations of the MAPT gene often are associated with the svPPA phenotype (Pickering-Brown et al., 2008; Bessi et al., 2010; Grossman, 2014). Only a few single cases with semantic disorders have been reported in association with GRN mutations (Le Ber et al., 2008) and a recent single case study associated the clinical phenotype of svPPA to a novel GRN mutation variant [g.2897 C>T (p.Thr409Met)] in a patient with strong family history of dementia (Cerami et al., 2013). Less frequently, cases with a semantic phenotype have been linked to a C9orf72 repeat expansion (Galimberti et al., 2013).

2.3.3. Logopenic variant

The term "*logopenia*", associated with PPA from the very beginning (Mesulam, 1982), was re-introduced more specifically to label those PPA patients who did not show the pattern of language dysfunction typical of the two previous variants (Weintraub, Rubin, & Mesulam, 1990; Gorno-Tempini et al., 2004; Gorno-Tempini et al., 2008; Henry & Gorno-Tempini et al., 2010). This entity is known as "*logopenic progressive aphasia*" (LPA) (Gorno-Tempini et al., 2004) or "*logopenic variant primary progressive aphasia*" (lvPPA) (Gorno-Tempini et al., 2011).

Logopenic PPA refers to a subset of patients presenting with deficits in single-word retrieval (i.e. in word-finding), phonological paraphasias (linguistic-based errors that reflect a disorder of the selection and ordering of phonological components of the target word), both in spontaneous speech and in confrontation naming, and impaired repetition of phrases and sentences (Gorno-Tempini et al., 2011; Leyton, Savage, et al., 2014).

Repetition of shorter words is usually normal, although phonological errors may occur with multisyllabic words (e.g. "*hippopotamus*") (Leyton & Hodges, 2013).

The dynamic contours of lvPPA speech make classification quite challenging, particularly for those with little expertize in assessing such patients. Speech can be fluent in short segments but is often interrupted by less fluent utterances that emerge due to the frequent word-finding pauses, circumlocutions, simplifications, substitutions, hesitations and false starts, which occur more frequently after determinants preceding content words (Teichmann, Kas, et al., 2013). This occurs as part of the disruption of a mechanism involved in producing content words in spontaneous connected speech (Ash et al., 2013) and conveys an impression of non-fluency to the listener (Mesulam, Rogaski, et al., 2014). This is probably the reason why these cases have been included under the label of nfvPPA for decades prior to the delineation of lvPPA as a clinical separate syndrome. In fact, the speech rate tends to fall between nfvPPA and svPPA (Gorno-Tempini et al., 2004; Wilson, Henry, et al., 2010). Despite the reduced fluency, speech does not show the agrammatic, articulatory or prosody deficits that are likely to occur in nfvPPA (Gorno-Tempini et al., 2004; Rohrer, Rossor, & Warren, 2010b; Gorno-Tempini et al., 2011; Teichmann, Kas, et al., 2013; Silveri et al., 2014). Moreover, lvPPA patients do not produce telegraphic speech with missing function words and morphemes (Wilson, Henry et al., 2010). Both lvPPA and nfvPPA speeches can be differentiated at an acoustic level, in particular, by measures of vowel duration in a multisyllabic word repetition task. Performance on this task has been correlated with the presence of apraxia of speech [with a high agreement (> 80%) of expert judgments] and with cortical brain atrophy in critical areas for speech motor planning and programming, typically present in nfvPPA (Ballard et al., 2014).

The sentence repetition deficit, in which the patient omits words or replaces them with similar ones (e.g. when repeating the sentence "*They sold the house and both moved to the farm*", the lvPPA patient may show one of these two responses: "*They sold the house…*" or "*They sold the house and <u>went</u> to the farm*"), and the occurrence of phonological errors both in speech and naming points towards a more generalized phonological short-term memory impairment (Gorno-Tempini et al., 2008, 2011). According to Baddeley's model of working memory (Baddeley & Hitch, 1974; Baddeley, 1983, 1986, 2000), a central executive (which acts as supervisory system) controls the flow of information from and to three *slave systems*: the *visuo-spatial sketchpad* (which deals with visuospatial information), the episodic buffer (dedicated to linking information across

domains to form integrated units of visual, spatial, and verbal information with time) and the *phonological loop.* The *phonological loop* is specialized in the retention of verbal information over short periods of time. It comprises both a phonological store, that holds for seconds memory traces of auditory (verbal) or visual (written) input and their temporal order in an acoustic or phonological form, and an articulatory loop or rehearsal process, which maintains decaying representations in the phonological store through repetition of words or other speech elements, analogous to subvocal speech. Gorno-Tempini and colleagues studied six lvPPA patients who underwent a series of experimental tasks aimed to assess the phonological component of working memory. These tasks included auditory and visual span tasks with digits, letters and words. Results showed that patients performed normally on the immediate recall of individual digits and pairs of digits but were severely impaired in sequences of more than three digits, independently of the modality of the input. Moreover, patients could only repeat one long word and this effect of word length was particularly evident in the auditory modality. These findings hence suggested that the core cognitive deficits in lvPPA are secondary to a breakdown of the phonological loop (Gorno-Tempini et al., 2008; Leyton, Savage, et al., 2014). Impairment in the functioning of the phonological loop is also likely to disrupt the processing and syntactic comprehension of sentences (Baddeley & Wilson, 1988; Vallar & Papagno, 2002), which is more influenced by the length and frequency of a sentence than its grammatical complexity (Gorno-Tempini et al., 2008; Magnin et al., 2013). Single-word comprehension, on the other hand, is relatively intact (Rohrer et al., 2013), although some recent studies report single-word comprehension performances below average in a proportion of lvPPA patients (Teichmann, Kas, et al., 2013). Object knowledge is also usually preserved, despite the fact that some of these patients may show lower performance on semantic association tasks. Both findings can be argued to be the result of the widespread of the atrophy to more anterior parts of the temporal lobe. Logopenic PPA patients have difficulty in inflecting nonwords as well as low-frequency irregular words, due to their lexical deficits (Wilson, Brandt, et al., 2014) which are, nonetheless, less severe than in svPPA patients (Wilson, Henry, et al., 2010). With regard to written language, they present a selective deficit in nondoword reading, reflecting a phonological/deep dyslexia (Brambati, Ogar, Neuhaus, Miller, & Gorno-Tempini, 2009; Rohrer, Ridgeway, et al., 2010; Leyton & Hodges, 2013). Spelling deficits have also been described in this variant (Sepelyak et al., 2011).

The remaining neuropsychological profile of lvPPA is characterized chiefly by additional dominant parietal lobe deficits occurring alone or in combination. These include poor arithmetic abilities/dyscalculia (Rohrer, Ridgway, et al., 2010; Magnin et al., 2013; Rohrer et al., 2013) and limb apraxia (although less severe than nfvPPA) (Rohrer, Ridgway, et al., 2010; Adeli, Whitwell, Duffy, Strand, & Josephs, 2013; Teichmann, Kas, et al., 2013). Phonemic and category fluency are also affected in lvPPA (Magnin et al., 2013; Teichman, Kas, et al., 2013) and patients perform significantly worse than AD patients on both forward and backward conditions of the Digit Span task, but with a better visuospatial than verbal span (Foxe, Irish, Hodges, & Piguet, 2013). In addition, lvPPA patients are more impaired on measures of scanning and visuomotor tracking, divided attention, cognitive flexibility, episodic memory, orientation and visuospatial/visuoconstrutive abilities (Gorno-Tempini et al., 2004; Wicklund, Rademaker, Johnson, Weitner, & Weintraub, 2007; Gorno-Tempini et al., 2008; Rabinovici et al., 2008; Rohrer, Ridgway, et al., 2010; Wilson, Dronkers, et al., 2010; Galantucci et al., 2011; Machulda et al., 2013; Miller et al., 2013; Teichmann, Kas, et al., 2013; Flanagan, Tu, Ahmed, Hodges, & Hornberger, 2014; Piguet et al., 2015). Behavioural changes can be present, with more negative-type behaviors such as apathy and depression, but also anxiety, irritability and agitation (Rosen et al., 2006; Rohrer & Warren, 2010). Disease progression usually involves worsening of anomia, sentence repetition and sentence comprehension but consistent with the spread of imaging changes also deficits in single-word comprehension, single word repetition and verbal memory (Rohrer et al., 2013). Also in this variant a rapid and generalized cognitive decline that involves nonverbal domains to reach a dementia diagnosis within 12 months is reported (Leyton, Hsieh, Mioshi, & Hodges, 2013). Yet, atypical lvPPA forms have been described, with mild aphasia and other neuropsychological impairments and longer disease duration, possibly representing a slowly progressive variant of lvPPA (Machulda et al., 2013). A high frequency of learning disabilities (e.g. dyslexia) was found to be selectively present in the logopenic group compared with semantic and non-fluent populations (Miller et al., 2013).

Imaging studies often show a pattern of asymmetrical atrophy and hypometabolism predominantly in the left posterior temporal lobe (superior and middle temporal gyri), inferior parietal areas and temporoparietal junction, including Brodmann area 37, and medial temporal lobe, but also including left posterior cingulate regions, with additional involvement of precuneus and posterior frontal lobe (Gorno-Tempini et al., 2004; Rohrer,

Rossor, et al., 2010b; Gorno-Tempini et al., 2011; Rogalski, Cobia, & Harrison, 2011; Madhavan et al., 2013; Teichmann, Kas, et al., 2013). The trajectory of atrophy in lvPPA seems to be the most heterogeneous of the three variants. Over time, disease remains asymmetrical, with increasing involvement of more anterior areas in the left hemisphere (temporal, frontal, caudate), and mirroring of the earlier affected left hemisphere regions in the right hemisphere, at an atrophy rate of around 2% a year (Rohrer et al., 2013). This may explain the emergence of significant semantic deficits during the course of the disease (Funayama et al., 2013; Silveri et al., 2014).

White matter disease is observed bilaterally in the corona radiata, inferior longitudinal fasciculus, and inferior fronto-occipital fasciculus and corpus callosum. Left superior longitudinal fasciculus and left uncinate fasciculus tracts also demonstrated reduced fractional anisotropy and these changes have been correlated with poorer performance on category fluency and naming tasks (Mahoney, Malone, et al., 2013; Powers et al., 2013). The temporoparietal component of the dorsal pathway is also affected (Galantucci et al., 2011). The reduced connectivity in the left temporal language network and inferior parietal and prefrontal regions of the left working memory network provided further evidence for the hypothesis of an overall auditory-verbal short term memory deficit underlying the language deficit in lvPPA (Baldo & Dronkers, 2006; Whitwell et al., 2015).

The underlying pathology associated with lvPPA is highly heterogeneous. The majority of clinopathological post-mortem studies link lvPPA syndrome to AD pathology, but the proportion of patients presenting this histopathological features at autopsy varies among studies (between 46 and 77%) (Grossman, 2010; Harris et al., 2013; Chare et al., 2014; Mesulam, Weintraub, et al., 2014).

Measures of the cerebrospinal fluid (CSF) $A\beta_{1\text{-}42}$, total tau protein and phosporylated tau have also been identified as abnormal in lvPPA cases, in a similar fashion to typical AD, highlighting, once again, the pathological relationship between both syndromes (Santangelo et al., 2015). Another study even suggested a more pronounced involvement of tauopathy in lvPPA due to AD with increasing levels of tau and a more important neuronal death in this variant when compared to amnestic Mild Cognitive Impairment (aMCI) (Magnin et al., 2014). Other *in vivo* studies, using molecular imaging techniques such as position emission tomography (PET) with the ^{11}C-Pittsburgh compound B (^{11}C-PiB), a fluorescent derivate of thioflavin T that binds to fibrillary Aβ and allows for its quantification (Klunk et al., 2004), have also shown that the majority of lvPPA cases

have Aβ typically seen in AD pathology (Rabinovici et al., 2008; Leyton et al., 2011). NFT density was observed to be significantly higher in left temporoparietal cortices in lvPPA compared to AD, with no differences observed in hippocampus (Josephs, Dickson, et al., 2013). In addition, the presence of phonological errors in spontaneous speech has been recently identified as marker of lvPPA and predictor of AD pathology. In fact, a cluster analysis with 14 lvPPA patients and 18 nfvPPA patients, led to the identification of a cluster characterized by high PiB retention, the presence of phonological errors and cortical thinning on the left superior temporal gyrus (Leyton, Ballard, et al., 2014).

One interesting finding is that the uptake pattern may not be the same in all patients, as about 50% show an unsual Aβ distribution to the occipital lobe, which is associated with a distinct clinical profile, characterized by a worse performance on several cognitive domains (calculation, executive and visuospatial abilities), a similar aphasia severity and longer disease duration when compared to those with typical patterns of PiB uptake (Whitwell et al., 2013). Further studies, including PET with fluorine-18 fluorodeoxyglucose ([^{18}F]FDG) (Newberg, Alavi, & Reivich, 2002) and using the novel ^{18}F-florbetapir compound (Wong et al., 2010) have confirmed that reduced activity and AD histopathological changes deposition can be located in more posterior, left parieto-temporo-occiptal regions in lvPPA (García-Azorín et al., 2014). Interestingly, another atypical, non-amnestic form of AD, Posterior Cortical Atrophy (PCA) (McKahnn et al., 2011), shows a language impairment with prominent word-retrieval deficits, reduced phonemic fluency and slowed speech rate, which resembles the language profile of lvPPA (Crutch, Lehman, Warren, & Rohrer, 2013; Magnin et al., 2013).

Taken together, these findings highlight the clinical heterogeneity associated with lvPPA: cases with pure aphasia seem to be distinct from those with aphasia embedded in the context of more widespread cognitive deficits but with language being the predominant symptom. The discussion around lvPPA gets even more complex if we consider that not all lvPPA cases have AD-compatible biomarkers (Teichmann, Kas, et al., 2013; Josephs, Duffy, Strand, Machulda, Vemuri, et al., 2014). In fact, a proportion of lvPPA cases with FTLD pathology have also been described, accounting for between 40 and 50% of lvPPA cases, and including TDP-43 type A, FTLD-tau and FTLD-U (Grossman, 2010; Harris et al., 2013; Mesulam, Weintraub, et al., 2014). There may be a continuum between lvPPA and CBS, as asymptomatic dopaminergic depletion has been reported in four of a series of twenty lvPPA patients (Magnin et al., 2013). A smaller number of patients present with a

mixture of other pathological findings, which include dementia with Lewy bodies, cerebrovascular disease and CJD (Martory et al., 2012; Harris et al., 2013; Johnson et al., 2013; Teichmann, Migliaccio, Kas, & Dubois, 2013). As far as genetics is concerned, an increased occurrence of APOE e4 haplotype is often associated with lvPPA and an increasing risk of Aβ deposition in this variant as assessed by PiB-PET (Rohrer, Rossor, et al., 2010b; Josephs, Duffy, Strand, Machulda, Senjem, et al., 2014). Logopenic PPA may present with GRN mutations as well (Rohrer, Crutch, Warrington, & Warren, 2010; Josephs, Duffy, Strand, Machulda, Vemuri, et al., 2014). A single case of lvPPA with C9orf72 is also reported in the literature (Saint-Aubert et al., 2014).

Although three clinical subtypes of PPA have been delineated, doubts still persist as there is a considerable overlap between these and other syndromes that can be accompanied by language deficits.

III. OBJECTIVES AND OUTLINE OF THE THESIS

The present thesis aims to study the neuropsychological features of PPA, contributing to the identification of different clinical profiles by tackling the neuropsychological heterogeneity of the disease and defining features eventually relevant for diagnosis. For this purpose, we will present four chapters, each of which being an independent study, with its own specific objectives. Three of them will be presented here in the form of original manuscripts and one as a book chapter. The presentation of each study was adapted in order to fit into the format of the present thesis.

The objective of the first study is to understand the pathophysiology of nfvPPA by comparing quantitatively the speech output produced by healthy older individuals under altered auditory feedback and by patients with nfvPPA.

The second study aims to test the existence of the three-group diagnostic model of PPA using advanced data-mining methods applied to neuropsychological data.

The objective of the third study is to examine behaviour changes across the three PPA variants.

Finally, the objective of the fourth study is to examine the effect of speech and language therapy on naming ability in PPA.

IV. STUDIES

STUDY 1

Delayed auditory feedback simulates features of nonfluent primary progressive aphasia

Maruta C*, Makhmood S*, Downey LE, Golden HL, Fletcher PD, Witoonpanich P, Rohrer JD, Warren JD (2014). Delayed auditory feedback simulates features of nonfluent primary progressive aphasia. *Journal of Neurological Sciences*; 347(1-2): 345-8.

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The candidate made substantial contribution to the analysis and interpretation of the data, drafted and revised critically the manuscript for important content.

1. Introduction

During normal speech production, auditory feedback provides sensory information that is used to fine-tune vocal motor output: where access to this feedback is limited (as in the speech of hearing impaired individuals), speech distortions tend to emerge. In experimental settings, synthetically altered auditory feedback (AAF) has been shown to modulate speech output when applied to a speaker's air-conducted voice (Howell, 1990). Two forms of AAF, namely delayed auditory feedback (DAF) (Goldiamond, Atkinson, & Bilger, 1962) and frequency altered feedback (Unger, Glück, & Cholewa, 2012) have been most extensively studied. Individuals with intrinsically normal speech fluency often show loss of fluency, distorted prosody or articulatory errors under AAF (Chon, Kraft, Zhang, Loucks, & Ambrose, 2013), whereas AAF has been used therapeutically in stutterers (Andrews, Howie, Dozsa, & Guitar, 1982; Lincoln, Packman, & Onslow, 2006). Functional brain imaging studies have demonstrated a distributed cortical substrate for AAF in bilateral posterior superior temporal and inferior parietal areas that form part of the dorsal cortical stream for processing speech and other sounds (Hashimoto & Sakai, 2003; Takaso, Eisner, Wise, & Scott, 2010). While a number of detailed accounts of dorsal cortical auditory pathway function have been proposed (Hickok & Poeppel, 2004; Warren, Wise, & Warren, 2005; Rauschecker & Scott, 2009; Hickok, Houde, & Rong, 2011; Specht, 2014), these generally emphasize intimate sensorimotor linkages between speech perception and production. More particularly, perceptual control of speech production may engage a mechanism in the posterior superior temporal plane (STP) that links auditory vocal representations with articulatory gestures via the dorsal language pathway (Warren et al., 2005).

Progressive nonfluent aphasia (the nonfluent/agrammatic variant of primary progressive aphasia, nfvPPA) is a canonical neurodegenerative syndrome characterized by slow, effortful, hesitant speech marred by errors of grammar and articulation (Rohrer, Rossor, et al., 2010b; Gorno-Tempini et al., 2011; Grossman, 2012). It is generally considered a disorder of language output programming, though the pathophysiology of nfvPPA is incompletely understood. Neuroanatomically, nvfPPA is linked to damage in peri-sylvian cortical regions associated with the dorsal language pathway (Sonty et al., 2007; Agosta et al., 2012; Mahoney, Malone, et al., 2013). The speech disturbance in nfvPPA bears certain similarities to that induced in healthy individuals by AAF: in particular, slowing of speech rate, dysprosody and emergence of articulatory errors.

Moreover, patients with nfvPPA have additional deficits in processing complex sounds, including prosody, accents, pitch patterns, voices and environmental noises (Goll et al., 2010, 2011; Hailstone et al., 2011, 2012; Rohrer, Sauter, Scott, Rossor, & Warren, 2012), aligning this syndrome with the wider spectrum of progressive aphasia syndromes (Uttner et al., 2006). This suggests that AAF and nfvPPA might disrupt language network function by at least partly convergent pathophysiological mechanisms, whereby disordered processing of vocal sensory input contributes to impaired speech output via the dorsal language pathway. AAF techniques have been used to assess mechanisms and to rehabilitate dysarthria and dysphasia in stroke, Parkinson's disease and various other neurodegenerative disorders (Boller, Vrtunski, Kim, & Mack, 1978; Hanson & Metter, 1980; Chapin, Blumstein, Meissner, & Boller, 1981; Downie, Low, & Lindsay, 1981; Van Nuffelen, De Bodt, Vanderwegen, Van de Heyning, & Wuyts, 2010) but have not been applied previously in nfvPPA. Here, we compared quantitatively the speech produced by healthy older individuals under AAF and by patients with nfvPPA. We hypothesized that healthy participants under AAF would show slowing of speech rate and emergence of speech sound errors similar to those exhibited by patients with nfvPPA.

2. Material and methods

2.1. Participants

The healthy participant group (n = 17; nine males, mean age 67 years, range 50–78 years) comprised older native English speakers with no previous history of developmental dysfluency, stuttering or hearing deficits. Patients with nfvPPA (n = 15; 12 males, mean age 77 years, range 66–84 years) were recruited consecutively from a specialist cognitive disorders clinic; all fulfilled current consensus criteria for nfvPPA (Gorno-Tempini et al., 2011) and general neuropsychological performance profiles corroborated the syndromic diagnosis in all cases (Rohrer, Rossor, et al., 2010b). The nfvPPA and healthy participant groups did not differ in gender composition ($\chi 2 = 0.467$; $p = 0.545$), however the nfvPPA group was on average significantly older than the healthy participants (Mann–Whitney U = 134.000; $p = 0.03$).

Ethical approval for the study was obtained from the Local Research Ethics Committee, and all participants gave written informed research consent.

2.2. Experimental procedures

The "*Grandfather Passage*"(Van Riper, 1963) (Figure 1.1) was chosen as a standardized, representative inventory of English phonemes. Three AAF conditions were created using a commercially available software package, Fluency Coach® (http://www.fluencycoach.com/). A short-latency DAF condition was set at 50 ms, corresponding approximately to the minimum delay at which modulation of fluency has been shown in studies of stuttering (Kalinowski & Stuart, 1996); a long-latency DAF condition was set at 200 ms, corresponding approximately to the duration of a syllable in conversational spoken English and associated with maximal fluency disruption in previous work (Stuart, Kalinowski, Rastatter, & Lynch, 2002); and a combined AAF condition was set at 200 ms plus an upward pitch shift of 0.5 octaves.

Figure 1.1. *The Grandfather Passage* (Van Riper, 1963)

The Grandfather Passage

You wished to know all about my grandfather. Well, he is nearly ninety-three years old; he dresses himself in an ancient black frock coat, usually minus several buttons; yet he still thinks as swiftly as ever. A long, flowing beard clings to his chin, giving those who observe him a pronounced feeling of utmost respect. When he speaks, his voice is just a bit cracked and quivers a trifle. Twice each day he plays skilfully and with zest upon our small organ. Except in the winter when the ooze or snow or ice prevents, he slowly takes a short walk in the open air each day. We have often urged him to walk more and smoke less, but he always answers, "Banana Oil!" Grandfather likes to be modern in his language.

The AAF conditions were administered to healthy participants via Sennheiser® (HD265 Linear) headphones at a comfortable listening level (at least 70 dB) in a quiet room. Participants were instructed to read the passage aloud as naturally as possible. Speech samples were recorded as digital wave files using Goldwave® software onto a laptop computer with a built-in microphone, for analysis off-line. Before recording commenced, healthy participants were first familiarized with the AAF procedure and set-up. The order of presentation of AAF conditions was randomized between participants,

however the baseline (no AAF) condition was always administered last, to reduce any rehearsal effects; participants were blind to condition order.

Speech wave files were initially edited manually to remove any extraneous noise sources or pauses. Mean speech rate for each AAF condition in the healthy participant group and for the nfvPPA group was calculated as the mean number of words produced per second, as determined using a customized programme in MATLAB®. The mean total number of errors for each AAF condition in the healthy participant group and for the nfvPPA group was determined from an acoustic analysis of the speech recordings: errors were further subclassified according to whether they were speech sound errors (syllable duplications, omissions or misarticulations), or grammatical errors (errors of morphology or syntax).

2.3. Statistical and qualitative analyses

Statistical analyses were performed using SPSSv17®. Multivariate analyses of variance (MANOVAs) were used to assess the effect of group membership (healthy vs nfvPPA) on behavioural performance in each AAF condition. Age, gender and reverse digit span (an index of auditory working memory potentially relevant to monitoring of speech output under AAF) were incorporated as covariates in group comparisons. MANOVAs were also performed to assess the effect of DAF condition (independent variable: baseline, short-latency DAF, long-latency DAF) on behavioural performance of healthy participants (dependent variables: speech rate, total errors, duplications, misarticulations, omissions); post hoc pair-wise comparisons between conditions using Bonferroni's correction were carried out if significant overall correlations were found. For all tests, results were considered statistically significant at a threshold $p<0.05$.

In addition, in order to qualitatively assess the confusability of healthy individuals' speech under AAF with speech produced by patients with nfvPPA, speech samples from the nfvPPA group and the healthy group under DAF were classified according to group membership by an experienced cognitive neurologist blinded to group membership.

3. Results

3.1. Group data on reading task

For the reading aloud task, the healthy participant group showed a significantly faster mean speech rate than the nfvPPA group at baseline ($F(1,27) = 57.7$, $p<0.0001$) and this difference remained (but was attenuated) under the short-latency DAF ($F(1,27) = 17.9$, $p<0.0001$), long-latency DAF ($F(1,27) = 8.77$, $p = 0.006$) and combined AAF ($F(1,27) = 6.34$, $p = 0.018$) conditions. The mean total error score and scores for error subcategories did not differ significantly between the healthy participant and nfvPPA groups at baseline nor under any of the AAF conditions; this was likely attributable to the wide variation in error scores within the nfvPPA group (see Figure 2). In both the healthy participant and nfvPPA groups, the most frequent speech sound error types were phonemic duplications and misarticulations.

Significant main effects of DAF condition on speech rate ($F(2,43) = 29.95$, $p<0.0001$), total error score ($F(2,43) = 10.35$, $p<0.0001$) and duplication ($F(2,43) = 8.05$, $p= 0.001$) and misarticulation ($F(2,43) = 6.63$, $p = 0.003$) error scores were found. Speech rate was significantly slower on short-latency and long-latency DAF than on baseline ($p<0.0001$). Duplication errors were significantly more frequent in the long-latency DAF condition than at baseline or in the short-latency DAF condition ($p<0.05$) and misarticulation errors were significantly more frequent in the long-latency DAF condition than at baseline ($p = 0.002$).

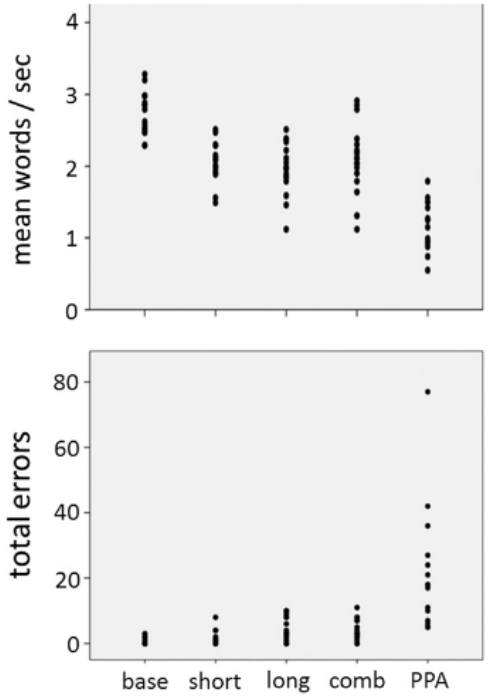
3.2. Individual data: healthy individuals acquiring speech features of nfvPPA under AAF

A proportion of healthy individuals (Figure 1.2) showed slowing of mean speech rate and total error rates within the range of patients with nfvPPA. The proportion of healthy participants acquiring these characteristics rose with increasing DAF latency: at a DAF latency of 200 ms, 4/17(24%) of healthy participants developed a mean speech rate within the nfvPPA range and 6/17 (35%) developed a total error score within the nfvPPA range. Main effects of gender and age on error rates were observed: healthy male participants produced significantly more duplication errors than healthy female participants overall ($F(1,43) = 5.88$, $p = 0.020$), and healthy participants made significantly more frequent misarticulation errors with advancing age ($F(1,43) = 7.83$, $p = 0.008$).

When speech samples from the nfvPPA group and the healthy participant group under DAF (latency 200 ms) were classified (nfvPPA or healthy) by an experienced cognitive neurologist blinded to group membership, 2/17 (12%) of healthy participant

speech samples were misclassified as nfvPPA while all nfvPPA samples were classified correctly.

Figure 1.2. Plots of individual raw scores for mean speech rate and total error scores for healthy older participants under each AAF condition and for patients with nonfluent primary progressive aphasia on reading aloud.



Legend: The error score is the raw number of errors made over the whole passage; base - healthy individuals baseline (no altered feedback); short – short latency delayed auditory feedback = 50 ms; long – long latency delayed auditory feedback = 200ms; comb – combined 200 ms delay plus frequency altered (0.5 octave upward) auditory feedback; PPA, nonfluent primary progressive aphasia.

4. Discussion

Here we have shown that AAF, in particular, increasing DAF latency, is associated with significant deterioration in the rate and quality of speech output in healthy older individuals. These findings corroborate previous evidence in younger individuals concerning the effects of DAF latency on speech output (Stuart et al., 2002; Takaso et al., 2010; Chon et al., 2013). Our data further demonstrate that DAF can induce two cardinal features of nfvPPA, slowing of speech rate and speech sound errors, in a substantial proportion (up to a third) of healthy older individuals. The findings imply that an anterior,

primary language output disorder is not essential to produce these key features of nfvPPA - disordered processing of speech input signals (as simulated by DAF) can itself do this.

The question arises as to whether the effects of AAF we have demonstrated were essentially nonspecific and any similarity to nfvPPA therefore purely incidental. We consider this unlikely: in susceptible individuals, the profile of speech sound errors produced was qualitatively as well as quantitatively similar to the profile in nfvPPA, duplications and misarticulations being over-represented in relation to omissions. Moreover, the effects of AAF in healthy individuals here were driven largely by DAF (i.e., manipulation of feedback latency) with little added effect from frequency manipulation. Taken together, this circumstantial evidence argues that DAF was exerting a relatively specific pathophysiological effect and that this effect may have accessed a broadly similar mechanism to the disease process in nfvPPA. The effects of DAF on speech rate and error frequency were strongest at a latency of 200 ms on this reading task. This pattern would be anticipated if DAF principally disrupted the sequential transcoding of phonemes into an 'automatic' or obligatory motor speech output: i.e., if DAF acts at the level of the dorsal cortical language pathway (Warren et al., 2005). This putative action on the dorsal language pathway would align the DAF paradigm with neuropsychological and structural and functional neuroimaging evidence implicating the dorsal pathway in the pathogenesis of nfvPPA (Sonty et al., 2007; Goll et al., 2010; 2011; Hailstone et al., 2011, 2012; Agosta et al., 2012; Rohrer, Sauter, et al., 2012; Mahoney, Malone, et al., 2013).

Accounts of language breakdown in nfvPPA have tended to emphasize the role of anterior brain regions with a primary role in motor speech programming. However, recent work has highlighted more general deficiencies of complex sound analysis in the progressive aphasias that are not primarily motor, or indeed, specifically verbal (Uttner et al., 2006; Goll et al., 2010, 2011; Hailstone et al., 2011, 2012; Rohrer, Sauter, et al., 2012). This accords both with neuroimaging evidence implicating a distributed brain network and long dorsal white matter tracts in the pathogenesis of nfvPPA (Sonty, et al., 2007; Agosta et al., 2012; Mahoney, Malone, et al., 2013) and with the concept that the dorsal language and auditory cortical pathways behave as a functional unit with progressive transcoding of information along these pathways (Warren et al., 2005). We do not, of course, argue here for a unitary mechanism of nfvPPA: rather, DAF may be modelling a key component of nfvPPA that has been relatively under-recognized, namely, disordered sensori-motor integration that impacts on motor speech output via the dorsal language pathway. In this

model, DAF may simply be acting to simulate the effect of 'noisy' processing in the dorsal pathway; however, the disease process in nfvPPA might parallel the effects of DAF more closely if, for example, a net reduction of processing speed in damaged cortex disrupts the scheduling of auditory-motor transformations in the dorsal pathway and thereby interferes with feedback controls on speech output (Warren et al., 2005; Rauschecker & Scott, 2009). The dynamic nature of DAF may be particularly relevant in an era of increasing interest in pathophysiologically motivated, reversible models of brain damage, notably transcranial magnetic stimulation (Trebbastoni, Raccah, de Lena, Zangen, & Inghilleri, 2013).

The determinants of individual susceptibility to DAF remain largely unknown. In this and in previous studies, age and gender were identified as important modulatory factors (Corey & Cuddapah, 2008; Chon et al., 2013). Normal ageing is associated with a generalized slowing of cognitive processing speed (Salthouse, 1996), which might lead to a correspondingly reduced capacity for tracking alterations of incoming speech signals. This reduction of temporal flexibility might interact with ageing associated reorganization of neural networks mediating speech production (Sörös, Bose, Sokoloff, Graham, & Stuss, 2011) and executive filtering of auditory inputs (Alain & Woods, 1999). The particular susceptibility of males to DAF may reflect auditory cortical structural and electrophysiological gender differences (Brun et al., 2009; Swink & Stuart, 2012); these gender effects may modulate auditory-motor integration, and may also contribute to the higher incidence of developmental speech impairments in males (Yairi & Ambrose, 2005). Individual susceptibility factors might be exploited in applying DAF in neurodegenerative disease settings: it might, for example, be feasible particularly in older male individuals to use DAF as a speech output 'stress test' in the early stages of progressive aphasia, or to assist in monitoring the impact of therapeutic interventions.

This study should be regarded as preliminary, with several limitations that suggest directions for future work. Larger cohorts are required to substantiate these findings and allow stratification according to specific DAF parameters and individual DAF susceptibility factors, in particular the effects of normal ageing. It will be important to assess the effects of DAF directly in cohorts of patients with progressive aphasia. Future studies should explore the potential of AAF to track the evolution of disease longitudinally across the heterogeneous progressive aphasia spectrum, including the logopenic variant which may be integrally linked to dorsal cortical language pathway dysfunction (Grossman, 2012; Rohrer, Sauter, et al., 2012; Mahoney, Malone, et al., 2013; Trebbastoni

et al., 2013). The validity of DAF as a pathophysiological model of nfvPPA could be assessed using functional neuroanatomical techniques in parallel cohorts of patients and healthy individuals under DAF: this would help to define the underlying brain mechanism, with the prediction that DAF shifts neural network activity associated with speech production in the healthy brain toward the profile of nfvPPA. It would also be of interest to track adaptation to DAF shown by healthy individuals (Katz & Lackner, 1977): the brain mechanisms that support such plasticity might help compensate (or fail to compensate) the effects of brain damage in nfvPPA. We hope that the present data will stimulate further systematic exploration of AAF and related pathophysiological models of progressive aphasia.

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STUDY 2

Classification of primary progressive aphasia: Do unsupervised data-mining methods support a logopenic variant?

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The candidate made substantial contribution to the study concept and design, collection, analysis and interpretation of the data, drafted and revised critically the manuscript for important content.

1. Introduction

Despite recent effort to establish a diagnostic consensus (Gorno-Tempini et al., 2011), uncertainties persist regarding the classification of PPA into nonfluent, semantic and logopenic variants. In fact, some cases can hardly be classified into one of the three syndromes, as shown in studies reporting a considerable variability in non-classification rates (between about 10 and 41% of cases) (Mesulam, Wieneke, Thompson, Rogalski, & Weintraub, 2012; Sajjadi, Patterson, Arnold, Watson, & Nestor, 2012; Gil-Navarro et al., 2013; Harris et al., 2013a; Wicklund et al., 2014). At the same time, some research groups argue for the existence of other PPA subtypes, either representing subsets of patients from specific variants (Josephs, Duffy, et al., 2013; Machulda et al., 2013), or "mixed" phenotypes, that is, cases displaying core features of more than one variant (e.g. deficits both in grammar and single-word comprehension) (Mesulam et al., 2009, 2012; Sajjadi, Patterson, & Nestor, 2014). On the other hand, lvPPA was the last clinical syndrome to be described and, with the exception of sentence repetition, the diagnosis is largely based on the exclusion of the two other variants (absence of single-word comprehension deficits and motor speech disorders). The lack of specific and distinctive features in this group may sometimes lead to erroneous classification and delayed diagnosis (Hu, McMillian, Libon, & et al., 2010; Leyton et al., 2011), especially because this group tends to incorporate patients with heterogeneous underlying pathologies (Harris et al., 2013). In a prospective study with 46 PPA patients assessed with a standard neuropsychology test battery and with samples of connected speech, a principal component analysis clearly identified 2 main groups (a semantic and an agrammatic factor) but did not suggest evidence for a third discrete logopenic syndrome. In fact, a substantial proportion of patients did not show either semantic or nonfluent/agrammatic features but could not be classified as logopenic. This raises the question whether logopenic diagnostic features may be insufficiently specific to separate this group from the other syndromes (Sajjadi et al., 2012).

Distinguishing different disease presentations in PPA from a neuropsychological standpoint is important to effectively tackle the progression and conversion to dementia, improve diagnostic accuracy and lead to adequate pharmacological intervention. Sophisticated data-mining approaches to analyze large datasets are gaining relevance in neurodegenerative diseases research, since traditional statistical analyses have difficulty dealing with the large quantities of clinical, neuropsychological, genetic and imaging data. Furthermore, machine learning methods are well suited to deal with high dimensional data,

to adequately handle missing values and to help solve dataset imbalance problems. They are currently being applied to evaluate AD risk in large multicentric datasets such as the Alzheimer's Disease Neuroimaging Initiative (ADNI) project (Casanova et al., 2013). Moreover, our group has shown that these methods can improve accuracy, sensitivity and specificity of classification and predictions based on neuropsychological testing in Mild Cognitive Impairment (MCI) and AD patients (Maroco et al., 2011; Lemos et al., 2012). With regard to PPA, the applicability of these methods is constrained by sample sizes, as most previous studies have enrolled small number of patients (the largest including 84 patients) (Wicklund et al., 2014). The present study aims to test the three-groups diagnostic model of PPA *versus* the existence of two main/classic groups, as well as detect the existence of additional disease presentation patterns, by using several unsupervised learning algorithms in a clinical series of 155 PPA patients.

2. Methods

2.1. Participants

Participants were referred to language/neuropsychological assessment at two clinical institutions in Lisbon (Language Research Laboratory, Faculty of Medicine of Lisbon and *Memoclínica*), between 1983 and 2012. The study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee.

2.2. Inclusion criteria

Patients were included if they were right-handed Portuguese native speakers and fulfilled the diagnostic criteria for PPA (Mesulam, 2001, 2003): a) most prominent clinical feature is difficulty with language (word-finding deficits, paraphasias, effortful speech, grammatical and/or comprehension deficits); b) activities of daily living are maintained except those related to language; c) aphasia is the most prominent deficit at symptom onset and for the initial stages of the disease; d) absence of prominent episodic memory, visual memory, visuospatial impairment or behavioural changes during the initial stages of the illness; f) aphasia is not better accounted for by other non-degenerative diseases of the nervous system (e.g. stroke or tumor) or by a psychiatric illness.

2.3. Exclusion criteria

Patients were excluded if they had at least one of the following:

a) Presence of dementia according to the DSM-IV-TR (APA, 2001) or significant impairment on instrumental activities of daily living (score ≥ 3 points on the first eight items of the *Blessed Dementia Rating Scale* (BDRS) (Blessed et al., 1968; Ribeiro, de Mendonça, Guerreiro, 2006)
b) Presence of neurological disorder (stroke, brain tumor, brain trauma, epilepsy) able to induce language or other cognitive impairments
c) Uncontrolled systemic illness with cerebral impact (hypertension, metabolic, endocrine, toxic and infectious disease)
d) History of alcohol abuse or recurrent substance abuse or dependence
e) Presence of mental retardation
f) Presence of severe auditory or visual impairment able to compromise the application of language/neuropsychological tests

2.4. Procedures

All patients underwent at least one language/neuropsychological examination, which was consistently performed by the same senior neuropsychologist (M.G.). In a few cases, the language assessment was also carried out by an experienced Speech Therapist. All assessments followed a standard protocol, comprising several test batteries and scales:

Language assessment

- *Lisbon Battery for the Assessment of Aphasia* (Damásio, 1973; Castro-Caldas, 1979; Ferro, 1986): Aphasia severity rating scale; description of the *Cookie Theft* picture for analysis of spontaneous speech; visual confrontation naming; object identification; comprehension of oral commands; word and sentence repetition; text reading and comprehension; spontaneous writing and writing of words and sentences by copy or by dictation.
- *Snodgrass and Vanderwart Naming Test* (Snodgrass & Vanderwart, 1980)
- *Token Test* (22-item short-version) (De Renzi & Vignolo, 1962)
- Verbal (semantic and phonological) fluency (Lezak, Howieson, Bigler, & Tranel, 2012)

- *Vocabulary* subtest from *Wechsler Adult Intelligence Scale* (WAIS) (Wechsler, 1955)

Neuropsychological assessment

Some neuropsychological tests with a verbal component (e.g. verbal memory) could not be considered for analysis due to interference from language deficits already present in some cases at the time of evaluation. Nonverbal tests were preferred instead to evaluate different cognitive domains:

- *Lisbon Battery for the Evaluation of Dementia* (BLAD) (Garcia, 1984), which includes the following tests: cancellation task; motor and graphomotor initiatives; digit span; personal, spatial and temporal orientation; buccofacial and limb praxis (ideomotor and ideative) testing by oral command, imitation and manipulation of objects; written/mental calculation; clock drawing test, copy of a cube and of geometrical drawings; visual memory; Raven's coloured progressive matrices – Ab series; right-left orientation.
- *Trail Making Test* (TMT) (Reitan, 1958)
- *Blessed Dementia Rating Scale* (BDRS) (Blessed et al., 1968)

Z-scores were calculated after the equation [z = (x-mean)/SD)] according to age/education norms for the Portuguese population (Guerreiro, 1998). Impairment was calssified if a subject scored more than 1.5 SD below the mean for age/education. Neuropsychological diagnosis and further classification into one of the three subtypes (Gorno-Tempini et al., 2011) was based on the consensus between two neuropsychologists (M.G. and C.M.), using the neuropsychological and language profiles (*gold-standard*) (Appendix 1).

2.5. Statistical analysis

Demographic, clinical and neuropsychological data were analyzed using a one-way ANOVA for numerical data, with post-hoc analysis with Bonferroni correction, and Pearson χ^2 test for nominal data, using *IBM SPSS Statistics* software (V. 20). Differences were considered statistically significant at $p<0.05$.

2.6. Data mining settings

The original dataset comprised 155 patients, 104 (67%) of which were clinically classified into one of the three PPA subtypes (*classifiable patients*; 31 nfvPPA, 35 svPPA, 38 lvPPA). The remaining 51 cases (33%) were considered unclassifiable (*unclassifiable patients*; unPPA). Since we were interested in testing the existence of three PPA variants under optimal conditions, that is, in a group of typical cases of each variant, we decided to define a subgroup of prototypical patients (*model patients*; n=36, distributed as 14 nfvPPA, 12 svPPA, 10 lvPPA). This group included patients whose classification was performed with a high degree of confidence by clinical experts (good representatives of each subtype).

Data pre-processing

Variables for which >30% of values were missing were removed. We imputed missing values using the average value or mode (whether the attribute was numerical or nominal, respectively) for algorithms that cannot deal with missing values (*EM*, for instance) or for algorithms which we considered favourable to handle missing values *a priori* (*K-Means* and *X-Means*). Data imputation was not performed in algorithms which were prepared to handle missing values (e.g. *Hierarchical Clustering*). Variables based on Z-scores were categorized as "*no alteration*", "*mild impairment*", "*moderate impairment*" and "*severe impairment*" classes, based on the deviation of values from the mean for age/education. Numerical and ordinal variables were normalized following the *min-max normalization* (Mirkin, 2013).

Variable selection

Four variable datasets were defined, based on distinct domains:

a) *Total set of variables*, divided into demographic (patient identification, gender, age at symptom onset, age at first assessment, education), clinical (PPA classification, first symptoms, family history of dementia, personal medical history) and neuropsychological variables (performance on each language /neuropsychological test) (154 variables). Due to the large number of variables constituting this dataset, it was only used in a few exploratory analyses.

b) *Language variables*, including scores on several language tests and measures (96 variables).

c) *Model variables*, variables found necessary and sufficient to classify the subgroup of "model patients" (46 variables).

d) *Operational criteria variables*. This set of variables was a group of nine qualitative language dimensions operationally defined after the core features specified in the working consensus research guidelines and already used by other authors (Leyton et al., 2011): "*motor speech disorder*", "*agrammatism*", "*word retrieval problems in spontaneous speech*", "*naming*", "*single-word repetition*", "*single-word comprehension*", "*sentence repetition*", "*sentence comprehension*", "*paraphasias in spontaneous speech*". The severity of impairment on each attribute was graded from 0 – absent, 1 – subtle or questionable, 2 – mild but definitely present, to 3 – moderate to severe. This subset of attributes was only tested on the *"model patients"* subgroup.

Unsupervised Learning

Unsupervised learning corresponds to a data-mining approach whose main purpose is grouping cases according to their characteristics. As such, unlike supervised learning, these algorithms do not use the target class (PPA variant in our study) to group the patients (Vercellis, 2009). Clustering was the unsupervised learning method used in this study. Clustering models divide the cases of a dataset (patients in our study) into a given number of homogeneous groups of cases (clusters), such that cases belonging to one group are similar to one another and dissimilar from cases included in other groups (Vercellis, 2009; Mirkin, 2013). This is usually performed by defining appropriate metrics related to the notions of distance and similarity between pairs of observations. We used clustering methods to identify groups of patients without clinical supervision and then verify if the predefined PPA variants matched the automatically discovered groups (confirm whether patients from different PPA variants are separated or placed together in different groups). In addition, we investigated the potential existence of other groups apart from the three canonical PPA variants (nfvPPA, lvPPA, svPPA) operationally defined in the literature (Gorno-Tempini et al., 2011).

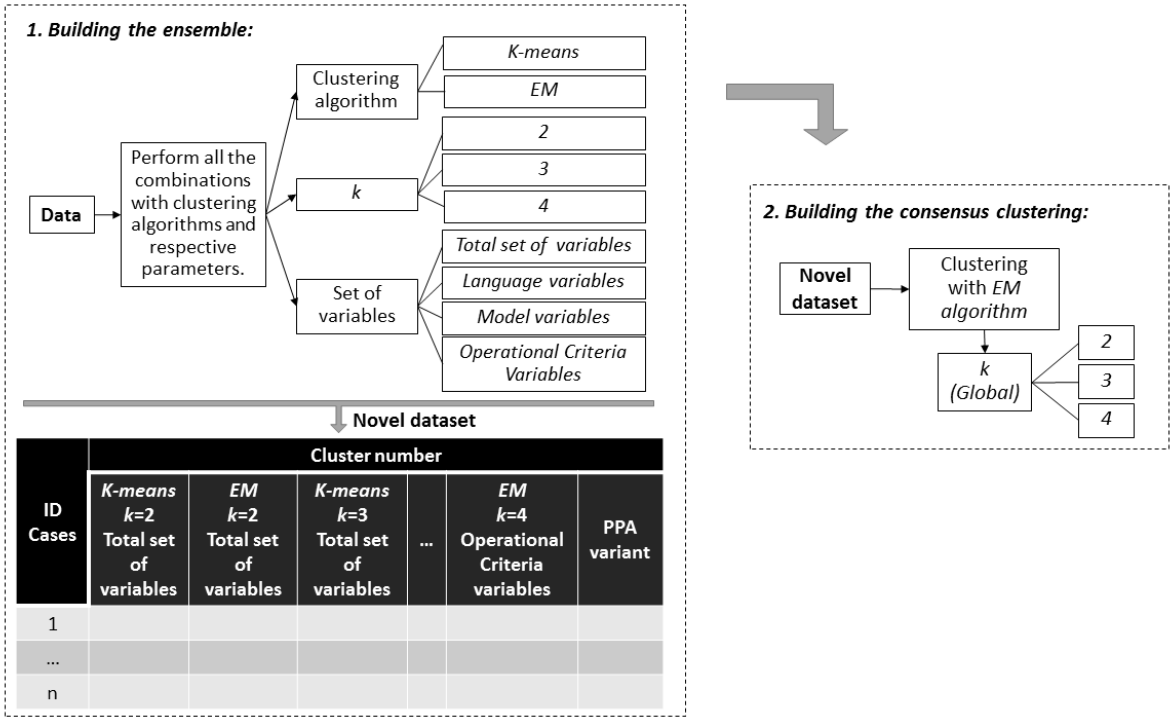
We used several clustering approaches, namely the *Partitional Clustering* algorithms *K-Means* (Mirkin, 2013) (which produces *k* non-overlapping clusters or

centroids where each case belongs to the cluster with the nearest mean) and *Expectation Maximization* (*EM)* (Han & Kamber, 2006) (which groups data using a finite mixture density model of *k* probability distributions or clusters) applied through *Waikato Environment for Knowledge Analysis software* (WEKA® version 3.7.1, 2004). Different values for the number of clusters (*k* = 2, 3, and 4) were predefined *a priori* with the purpose of testing the possible existence of more (or fewer) than three PPA classes or possible groups corresponding to intersections. In addition, we used the *X-Means* algorithm (Pelleg & More, 2000) (a variant of *K-Means* which estimates the number of clusters (*k*) by optimizing Bayesian Information Criteria) through WEKA® software.

Hierarchical Clustering was also performed. In this case, a fixed number of clusters is not defined *a priori*. Instead, clusters are represented in a hierarchy based on their similarity, creating a dendrogram (Han & Kember, 2006). Then, clusters are yielded by choosing specific cutting levels in the dendogram. We used the complete linkage method to determine distances between groups of patients. Analyses were performed using *Matlab*®.

Since, in some cases, individual clustering algorithms may not be capable of correctly finding the underlying structure for all datasets, we additionally followed a *Consensus Clustering* approach (Pons & Schulcloper, 2011). The goal was to identify stable clusters, given that clusters discovered by several algorithms tend to be more reliable. *Consensus Clustering* consists of producing a single clustering (consensus) by combining different clustering results on the same data, resulting from: *1)* runs of the same algorithm with different parameters, *2)* runs of different algorithms with the same set of patients and variables, and *3)* runs of the same algorithm with different sets of variables. As illustrated in Figure 2.1, in the present study, the methodology consisted of a first step, in which the clustering ensemble was built by running alternatively *K-Means* and *EM* several times with the parameter *k* set as 2, 3 and 4, and alternating the set of variables used in each analysis (total set of variables, language, model and operational criteria variables). A new dataset was generated, where columns depicted the cluster assigned to each case, according to different clustering algorithms and/or type of variables used in the analyses (as shown in the lower part of Figure 2.1). In a second step, the *EM* clustering algorithm combined the clustering results from the first step to generate a representative consensus clustering, reaching a global parameter *k* (*k* global). This task was performed with WEKA® software.

Figure 2.1. Diagram illustrating the two-step approach designed to obtain the Consensus Clustering



Legend: The procedure consists of two steps: 1) <u>*Building the ensemble*</u>, where algorithms *K-Means* and *EM are run alternately* several times with the parameter *k* set as 2, 3 and 4, and alternating the set of variables used in each analysis (total set of variables, language, model and operational criteria variables). The dataset created by this procedure (novel dataset) presents columns depicting the cluster assigned to each case (according to different clustering algorithms and/or type of variables used in the analyses); 2) <u>*Building the consensus clustering*</u>, where *Expectation Maximization* algorithm is run in the novel dataset, reaching a global clustering parameter *k* (*k* global)

In each analysis, results were evaluated by identifying which patients (along with their previous clinical PPA class assignment) composed each cluster found, in order to inspect how well the PPA classes were divided into distinct clusters. Moreover, we analyzed which clusters were more stable and consistent (groups that remained essentially unalterable whenever the parameter *k*/set of variables changed).

3. Results

Demographic data on the 155 cases with PPA (20% nfvPPA, 23% svPPA and 24% lvPPA variants clinically classifiable and 33% unPPA) are shown in Table 2.1. Patients

with nfvPPA had significantly longer evolution times between onset and the first assessment when compared to the other variants or unclassifiable patients.

Table 2.1. Demographic characteristics

	nfvPPA (n=31)	**svPPA** (n=36)	**lvPPA** (n=37)	**unPPA** (n=51)	**Statistics**	**Differences**
Gender (F:M)	18:15	18:18	26:13	26:21	χ^2=3.712 p=0.294	n.s.
Age at onset (yrs)	66.6(6.9)	64.2(7.4)	68.3(9.1)	68.8(9.0)	F=2.398 p=0.071	n.s.
Age at 1st assessment (yrs)	69.7(6.8)	66.2(7.4)	69.9(8.8)	70.6(8.9)	F=2.230 p=0.087	n.s.
Education (yrs)	7.2(4.1)	7.9(4.4)	7.5(4.3)	9.1(4.9)	F=1.390 p=0.248	n.s.
Time from onset to 1st assessment (months)	**37.3(29.7)**	22.1(13.2)	23.7(11.4)	23.0(14.8)	**F=5.228 p=0.002**	**nfvPPA > svPPA, lvPPA, unPPA**
CDR-SB[a]	1.3(0.7)	1.6(1.1)	1.6(1.1)	-	F=0.027 p=0.974	n.s.

Legend: [a]The figures in the table are mean values, the figures in parentheses are standard deviations; bolded values represent statistically significant differences; CDR-SB – Clinical Dementia Rating – Sum of Boxes; F – female; lvPPA – logopenic variant Primary Progressive Aphasia; M – male; nfvPPA – nonfluent variant Primary Progressive Aphasia; svPPA – semantic variant Primary Progressive Aphasia; unPPA – unclassifiable Primary Progressive Aphasia; yrs – years

Regarding the language/neuropsychological evaluation, and consistent with the diagnostic criteria, svPPA patients showed the lowest performance on *Snodgrass & Vanderwart Naming Test*, object identification and vocabulary when compared to the other variants (Table 2.2).

As expected, nfvPPA group was the one that showed a significant higher frequency of speech production deficits (agrammatism, articulation deficits and stuttering like dysfluencies) when compared to the other groups. Furthermore, nfvPPA patients had a high frequency of hesitations in speech production, as lvPPA patients did. Patients with lvPPA and nfvPPA patients were significantly impaired on sentence repetition, and nfvPPA patients also showed significantly lower scores on measures of executive function,

Table 2.2. Neuropsychological data of the sample

	nfvPPA (n=31)	**svPPA** (n=36)	**lvPPA** (n=37)	**unPPA** (n=51)	**Statistics**	**Differences**
Language measures:						
Speech production						
Presence of agrammatism (Y:N)	**13:12**	7:27	7:29	3:41	**χ^2=19.451 *p*<0.001**	**nfvPPA < svPPA, lvPPA, unPPA**
Presence of articulation deficits (Y:N)	**13:13**	0:37	3:34	1:44	**χ^2=46.112 *p*<0.001**	**nfvPPA < svPPA, lvPPA, unPPA**
Presence of hesitations (Y:N)	**10:13**	2:33	**14:21**	7:37	**χ^2=17.647 *p*=0.001**	**lvPPA, nfvPPA < svPPA, unPPA**
Presence of stuttering-like dysfluencies (Y:N)	**11:14**	1:34	6:29	2:41	**χ^2=24.948 *p*<0.001**	**nfvPPA < svPPA, lvPPA, unPPA**
Aphasia Severity Scale (/6)	**2.9(1.3)**	4.21(0.8)	4.0(0.9)	4.5(0.7)	**F=18.264 *p*<0.001**	**nfvPPA < svPPA, lvPPA, unPPA**
Object Naming (% correct)	71.3(32.4)	60.7(33.0)	75.6(29.11)	**92.0(16.0)**	**F=8.321 *p*<0.001**	**unPPA > nfvPPA, svPPA**
SVNT (% correct)	81.5(19.9)	**52.6(23.0)**	78.8(16.5)	82.3(19.7)	**F=11.971 *p*<0.001**	**svPPA < nfvPPA, lvPPA, unPPA**
Object Identification (% correct)	98.9(3.8)	**95.4(9.3)**	99.6(2.2)	99.5(3.0)	**F=4.691 *p*=0.004**	**svPPA < lvPPA, unPPA**
Repetition						
Words (/30)	**27.6(6.1)**	30.0(0.2)	28.9(2.8)	30.0(0.1)	**F=4.514 *p*=0.005**	**nfvPPA < svPPA, unPPA**
Sentences (/14)	**4.0(3.4)**	8.0(3.5)	**4.6(2.1)**	9.3(2.4)	**F=25.490 *p*<0.001**	**nfvPPA, lvPPA < svPPA, unPPA**
Comprehension						
Oral Commands (/8)	**7.2(1.0)**	7.3(1.3)	7.6(0.5)	7.8(0.3)	**F=3.692 *p*=0.014**	**nfvPPA < unPPA**
Token Test (/22)	**10.7(4.8)**	14.0(5.2)	12.0(4.3)	15.1(3.8)	**F=6.174 *p*=0.001**	**nfvPPA < svPPA, unPPA lvPPA < unPPA**
Presence of Alexia (Y:N)	18:12	10:20	12:22	**4:35**	**χ^2=19.073 *p*<0.001**	**unPPA < nfvPPA, svPPA, lvPPA**
Presence of Agraphia (Y:N)	24:8	11:25	17:21	**10:33**	**χ^2=22.610 *p*<0.001**	**unPPA, svPPA < nfvPPA, lvPPA**
Vocabulary (% correct)	66.1(19.7)	**62.2(28.1)**	77.8(24.3)	90.2(10.2)	**F=3.960 *p*=0.015**	**svPPA < nfvPPA, lvPPA, unPPA**
General cognitive measures:						
Letter Cancelation (A's)						
Time to complete (seconds)	57.1(24.2)	49.9(21.8)	56.7(26.1)	53.4(19.2)	F=0.681 *p*=0.565	n.s.
No. of letters cancelled (/16)	13.9(3.1)	15.0(1.6)	14.8(1.7)	15.2(1.4)	F=2.550 *p*=0.059	n.s.
TMT – A						
Time to complete (seconds)	104.6(31.9)	65.8(38.8)	97.9(46.8)	103.7(35.2)	F=2.349 *p*=0.087	n.s.
No. connections (/24)	23.4(1.8)	23.2(2.2)	23.4(0.8)	22.9(4.1)	F=0.095 *p*=0.963	n.s.
No. errors	0.6(1.2)	0.6(1.6)	0.7(0.8)	0.7(1.6)	F=0.010 *p*=0.999	n.s.

TMT – B						
Time to complete (seconds)	273.5(43.3)	173.0(81.5)	238.30(73.1)	238.7(83.0)	F=2.756 *p*=0.055	n.s.
No. connections (/24)	15.0(9.8)	23.0(2.6)	14.6(10.2)	18.0(8.6)	F=1.904 *p*=0.145	n.s.
No. errors	1.7(1.1)	1.0(1.6)	2.0(1.5)	2.3(5.9)	F=0.223 *p*=0.880	n.s.
Digit Forward[l]	**3.7(1.6)**	4.8(1.4)	4.1(0.9)	4.7(1.1)	**F=4.939 *p*=0.003**	**nfvPPA < svPPA, unPPA**
Digit Backwards	**2.0(1.4)**	2.9(1.2)	2.8(0.9)	3.0(0.9)	**F=5.687 *p*=0.001**	**nfvPPA < svPPA, unPPA**
Category Fluency (Food)	7.0(4.1)	8.8(5.4)	9.0(4.5)	10.2(4.5)	F=2.214 *p*=0.090	n.s.
Motor Initiative (/3)	**1.9(1.1)**	2.5(0.9)	2.2(0.7)	2.5(0.8)	**F=2.956 *p*=0.035**	**nfvPPA < unPPA**
Graphomotor Iniative (/2)	1.2(0.7)	1.6(0.6)	1.5(0.6)	1.5(0.5)	F=2.584 *p*=0.056	n.s.
WMS-III Visual Memory – Designs B and C (/28)	10.7(8.1)	14.5(7.3)	13.5(6.0)	15.1(6.4)	F=1.773 *p*=0.158	n.s.
Praxis (/12)	**11.0(1.4)**	11.9(0.4)	11.8(0.6)	11.7(1.0)	**F=6.237 *p*=0.001**	**nfvPPA < svPPA,lvPPA, unPPA**
Copy of Cube (/3)	**1.9(1.1)**	2.2(0.8)	2.6(0.7)	2.1(0.9)	**F=2.743 *p*=0.046**	**nfvPPA < lvPPA**
Clock Drawing Test (/3)	**1.5(0.9)**	2.2(0.8)	1.9(0.8)	2.3(0.8)	**F=4.781 *p*=0.003**	**nfvPPA < svPPA, unPPA**
Calculation (/14)	**7.5(5.2)**	9.7(4.5)	9.1(4.1)	10.9(3.7)	**F=4.145 *p*=0.008**	**nfvPPA < unPPA**
CPM (Ab series; /12)	6.1(3.1)	7.5(2.8)	6.7(2.6)	7.0(2.5)	F=1.438 *p*=0.235	n.s.
Right-left orientation (/6)	**4.9(1.9)**	5.6(1.0)	5.5(1.0)	5.7(0.8)	**F=2.860 *p*=0.040**	**nfvPPA < unPPA**
BDRS						
Total (/28)	3.2(1.6)	2.9(1.9)	2.4(1.7)	2.9(2.0)	F=1.088 *p*=0.357	n.s.
ADL's (/8)	0.8(0.7)	1.0(0.8)	0.9(0.8)	0.8(0.6)	F=0.460 *p*=0.711	n.s.

Legend: The figures in the table are raw mean values, the figures in parentheses are raw standard deviations; bold values represent statistically significant differences; ADL's – Activities of daily living; BDRS – Blessed Dementia Rating Scale; CPM – Coloured Progressive Matrices; F – One-way ANOVA parametric test; lvPPA – logopenic variant Primary Progressive Aphasia; nfvPPA – nonfluent variant Primary Progressive Aphasia; N – no; n.s. – non-significant; p – p-value; SVNT – Snodgrass & Vanderwart Naming Test; svPPA – semantic variant Primary Progressive Aphasia; TMT – Trail Making Test; unPPA – unclassifiable Primary Progressive Aphasia; WMS – III – Wechsler Memory Scale Third Edition; Y – yes; χ^2 - Chi-Square Test.

praxis, calculation and visuoconstructive abilities, when compared to the two other variants and unclassifiable patients (Table 2.2).

3.1. Partitional Clustering

In order to perform analyses as thoroughly and extensively as possible, the different clustering approaches were applied across sets of variables (total, language, model and operational criteria variables) and to the different groups of cases (all available patients, classifiable patients and model patients).

In general, clustering with standard algorithms (in particular, *K-Means* and *EM*) and with different predefined number of clusters (k = 2, 3, or 4) produced clusters composed by cases coming from all PPA subtypes. This was initially observed with the entire set of patients (classifiable and unclassifiable). Moreover, unclassifiable patients did not form a separate group. Instead they emerged within groups containing svPPA, lvPPA or nfvPPA cases. Since the main goal of this analysis was to infer whether the automated procedure was able to separate the patients according to their clinically predefined variant, we decided to discard the unclassifiable cases for the subsequent analyses, thus removing noise from the dataset.

Overall, considering only the classifiable or model patients, clustering with *K-Means* and *EM* also produced clusters composed of a mixture of PPA subtypes. This means that the gold-standard (clinical judgment) was not concordant with the clusters generated. Table 2.3 (*left hand side panels*) shows clustering results when k was set to 3, based on the hypothesis that three groups would emerge, each representing the three major PPA phenotypes. Clustering the classifiable patients with the total set of variables (Table 2.3, *first panel*) produced a group with a mixture of 6 lvPPA, 12nfvPPA and 6 svPPA cases (Cluster $\mathbf{C0_{k3}}$), a group with 13 lvPPA, 12 nfvPPA and 8 svPPA cases (Cluster $\mathbf{C1_{k3}}$), and finally a group of 19 lvPPA, 7 nfvPPA and 21 svPPA cases (Cluster $\mathbf{C2_{k3}}$). With regard to the model patients (with the same set of variables) the results were slightly better given the emergence of a small but isolated nfvPPA group (Table 2.3, *second panel,* cluster $\mathbf{C0_{k3}}$). However, the majority of lvPPA and svPPA cases were still grouped together within the same cluster (Table 2.3, *second panel,* cluster $\mathbf{C1_{k3}}$). Beyond that, the remaining majority of nfvPPA cases were also grouped with some lvPPA and svPPA cases (Table 2.3, *second panel,* cluster $\mathbf{C2_{k3}}$). Results were similar after grouping the classifiable patients with a more specific language set of variables (Table 2.3, *third panel*).

After applying *K-Means* to model patients with the dataset of model variables, a single cluster composed only of nfvPPA cases was again evident, containing now the majority of nfvPPA cases (Table 2.3, *fourth panel,* Cluster $\mathbf{C2_{k3}}$), while the other subtypes scattered among the remaining clusters. Thus, this reduced set of variables allowed for a clearer isolation of nfvPPA cases. It is worth noting that none of the other two clusters showed a preponderance of lvPPA over the other PPA subtypes.

Table 2.3. Clustering results when ***k*=3** (*left hand side*): dataset with the total set of variables for all classifiable patients (*first panel*), model patients (*second panel*) and language variables for all classifiable patients (*third panel*), using *EM*, and model variables for model patients, using *K-Means* (*fourth panel*); Clustering results when ***k*=4** (*right hand side*): dataset with language variables for all classifiable patients using *EM* (*fifth panel*); data set with operational criteria variables for model patients, using *K-Means* (*sixth panel*)

		***EM* (*k*=3)**									***K-Means* (*k*=3)**			***EM* (*k*=4)**				***K-Means* (*k*=4)**			
		Total set of variables						*Language variables*			*Model variables*			*Language variables*				*Operational criteria variables*			
		1st panel			*2nd panel*			*3rd panel*			*4th panel*			*5th panel*				*6th panel*			
		All Classifiable patients			*Model patients*			*All Classifiable patients*			*Model patients*			*All classifiable patients*				*Model patients*			
		C0k3	**C1k3**	**C2k3**	**C0k3**	**C1k3**	**C2k3**	**C0k3**	**C1k3**	**C2k3**	**C0k3**	**C1k3**	**C2k3**	**C0k4**	**C1k4**	**C2k4**	**C3k4**	**C0k4**	**C1k4**	**C2k4**	**C3k4**
Clinical Classification	*lvPPA*	6	13	19	0	6	4	17	18	3	5	5	0	13	20	2	3	6	0	4	0
	nfPPA	12	12	7	4	1	9	15	5	11	1	3	10	5	13	12	1	6	6	2	0
	svPPA	6	8	21	0	10	2	9	20	6	6	6	0	20	5	0	10	0	0	3	9

Legend: Figures in each cell represent number of cases; C – cluster; EM – Expectation Maximization; k – clustering parameter; lvPPA – logopenic variant primary progressive aphasia; nfvPPA – nonfluent variant primary progressive aphasia; No. – Number; svPPA – semantic variant primary progressive aphasia

The outcome produced by the application of *EM*, when *k* was increased to 4 to the dataset of language variables and all classifiable patients, included a small cluster of mainly svPPA cases (Table 2.3, *fifth panel*, cluster **C3$_{k4}$**) and another group of 12 nfvPPA cases (Table 2.3, *fifth panel*, cluster **C2$_{k4}$**). The other two clusters were primarily constituted by mixtures of svPPA plus lvPPA (Table 2.3, *fifth panel*, cluster **C0$_{k4}$**) and nfvPPA/lvPPA patients (Table 2.3, *fifth panel*, cluster **C1$_{k4}$**). That is, even for large values of *k*, no group comprising almost exclusively lvPPA cases was found, since these cases were spread over the remaining groups. Notwithstanding, the identification of a really isolated semantic cluster was only achieved with model patients and using the operational criteria variables (Table 2.3, *sixth panel*, cluster **C3$_{k4}$**). Within this analysis, a single cluster composed only by nfvPPA cases was again observed (Table 2.3., *sixth panel*, cluster **C1$_{k4}$**). The remaining clusters (Table 2.3, *sixth panel*, clusters **C0$_{k4}$** and **C2$_{k4}$**) constituted, once again, mixtures of lvPPA with nfvPPA and svPPA patients, respectively.

Due to the aforementioned inconsistency between automated clustering and gold-standard with *k*=3 (expected number of clusters) and 4, we decided to perform a detailed evaluation of the emergent clusters in order to discover any distribution pattern of PPA cases and/or to find the true number of clusters detected by this method.

This algorithm produced successively two clusters in all the datasets which suggests that the ideal number of clusters found for the datasets in this study was two. In fact, setting *k*=2 generated two clusters whose composition was very consistent along the analyses, independently of the algorithms, set of features or set of patients used (Table 2.4). In model patients, EM (*k*=2) revealed the emergence of a nfvPPA cluster when applied to the dataset of model variables (Table 2.4, *first panel*, cluster **C0$_{k2}$**) or a majority of nfvPPA with some lvPPA cases, when applied to the datasets of language (Table 2.4., *second panel*, **C0$_{k2}$**), total (Table 2.4, *third panel*, **C0$_{k2}$**) or operational criteria variables (Table 2.4, *fourth panel*, **C0$_{k2}$**). The second cluster obtained with the same datasets of variables was, in turn, mostly composed by svPPA and lvPPA cases (Table 2.4, *first, second, third and fourth panel*s, cluster **C1$_{k2}$**). Basically, nfvPPA and svPPA cases were easily separated into two different groups while lvPPA cases could be found in both groups, although more frequently clustered with svPPA rather than with nfvPPA patients. A similar pattern of results was observed with all classifiable patients either using model (Table 2.4, *fifth panel*) or language variables (Table 2.4, *sixth panel*).

Table 2.4. Clustering results when ***k*=2**: dataset with model patients and the set of model (*first panel*), language variables (*second panel*), total set (*third panel*) or operational criteria variables (*fourth panel*), dataset with classifiable patients and the set of model (*fifth panel*) or language variables (*sixth panel*), using *EM*.

		***EM* (*k*=2)**											
		Model patients								*All Classifiable patients*			
		1st Panel		*2nd Panel*		*3rd Panel*		*4th Panel*		*5th Panel*		*6th Panel*	
		Model variables		*Language variables*		*Total set of variables*		*Operational criteria variables*		*Model variables*		*Language variables*	
		$C0_{k2}$	**$C1_{k2}$**	**$C0_{k2}$**	**$C1_{k2}$**	**$C0_{k2}$**	**$C1_{k2}$**	**$C0_{k2}$**	**$C1_{k2}$**	**$C0_{k2}$**	**$C1_{k2}$**	**$C0_{k2}$**	**$C1_{k2}$**
Clinical classification	*lvPPA*	0	10	3	7	3	7	6	4	30	8	3	35
	nfvPPA	11	3	12	1	10	4	12	2	13	18	17	14
	svPPA	0	12	0	12	1	11	2	10	28	7	4	31

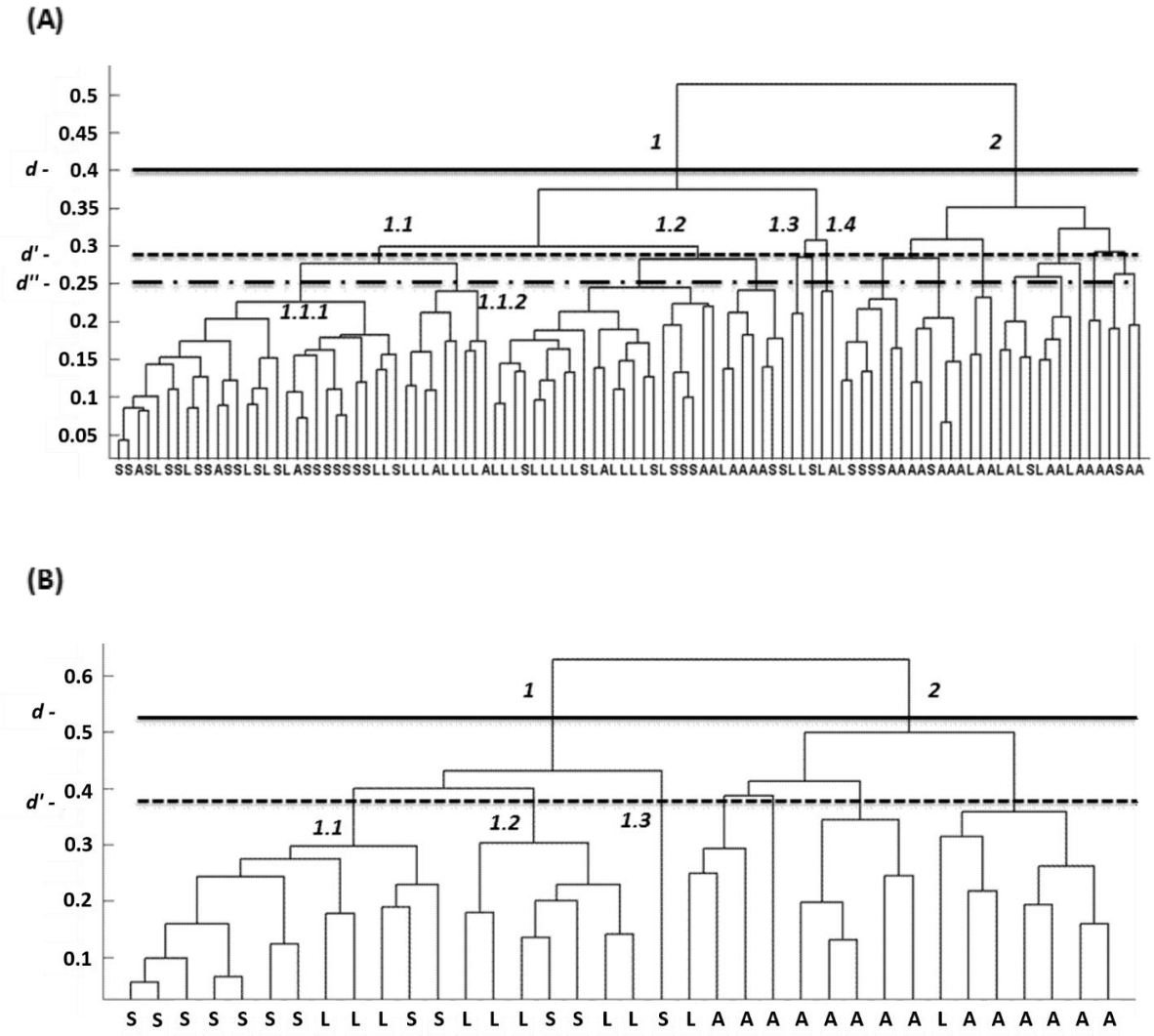
Legend: Figures in each cell represent number of cases; C – cluster; EM – Expectation Maximization; k – clustering parameter; lvPPA – logopenic variant Primary Progressive Aphasia; nfvPPA – nonfluent variant Primary Progressive Aphasia; No. – Number; svPPA – semantic variant Primary Progressive Aphasia

3.2. Hierarchical Clustering

The results obtained with *Hierarchical Clustering* showed the formation of two main groups, both in the dataset of classifiable patients with the total set of variables (Figure 2.2A) and in the dataset of model patients with model variables (Figure 2.2B). By inspection of the dendrogram for all the classifiable patients with the total set of variables (Figure 2.2A), with a cut at a distance close to around $d = 0.4$, cluster 1 aggregated most of the svPPA and lvPPA patients (32 lvPPA, 13 nfvPPA and 28 svPPA cases) whereas cluster 2 included the majority of the nfvPPA cases (18 nfvPP plus 7 svPPA and 6 lvPPA cases). The procedure of cutting the dendrogram at a lower level ($d' = 0.28$) to inspect sub-clusters within the main clusters was again performed. Sub-cluster 1.1 comprised 14 lvPPA, 5 nfvPPA and 19 svPPA patients while sub-cluster 1.2 included 15 lvPPA, 7 nfvPPA and 8 svPPA cases. The remaining sub-clusters comprised 3 lvPPA, 1 nfvPPA (sub-cluster 1.3) and 1 svPPA (sub-cluster 1.4) cases. It was only at a deeper level of the dendrogram ($d'' = 0.25$) that it was possible to isolate a majority of svPPA patients (7 lvPPA, 4 nfvPPA and 19 svPPA).

In a similar fashion, the dendrogram for model patients with model variables (Figure 2.2B), revealed the emergence of two main clusters (with a cut at a distance close to $d = 0.5$): one with a mixture of 8 lvPPA and 12 svPPA cases (Figure 2.2B, cluster 1) and another with 14 nfvPPA and 2 lvPPA cases (Figure 2.2B, cluster 2). Since cluster 1 included the majority of svPPA and lvPPA, we decided to explore its corresponding sub-clusters (at a lower level of the dendrogram; $d' = 0.35$). Results showed that sub-cluster 1.1 aggregated 9 svPPA patients and only 3 lvPPA cases. The sub-cluster 1.2 included 5 lvPPA and 3 svPPA cases. Therefore, at a lower level of the dendrogram, it was still not possible to separate svPPA from lvPPA patients.

Figure 2.2. Dendrograms obtained by applying hierarchical clustering to: **(A)** all classified patients with the total variables, and **(B)** model patients with the model variables.



Legend: The continuous black line indicates one potential cut to get 2 clusters; the fragmented black lines indicate potential cuts to get sub-clusters; the y-axis represents distances; the x-axis represents patients' PPA classification: A = nfvPPA; S = svPPA; L = lvPPA

3.3. Consensus Clustering

The results obtained through *Consensus Clustering* showed that, when *k* (global) = 3, the emergent clusters did not allow a clear separation of the PPA variants according to their predefined classification. Despite this fact, usually one of these clusters was composed mainly by patients from a unique PPA variant (typically nfvPPA). When *k* (global) = 2, the composition of the two emergent clusters was similar to the ones obtained

with the algorithms *K-Means* and *EM* in isolation, that is, one group yielded lvPPA and svPPA cases while another comprised mainly nfvPPA and some lvPPA cases. Increasing *k* (global) did not improve the results as lvPPA and svPPA cases remained inseparable and the remaining clusters were represented by intersections from various subtypes, thus confirming the results found with both *Partitional* and *Hierarchical Clustering*.

4. Discussion

The aim of the present study was to test whether data mining techniques, through an unsupervised learning approach, supported the three-group diagnostic model of PPA (according to recent published criteria) versus the existence of some other number of groups. Running the algorithms (with *k* set as 3) revealed that the composition of the groups obtained and the gold-standard did not match, meaning that clustering algorithms were unable to detect the three PPA variants proposed in the literature. We also intended to evaluate how many distinct groups of patients were present in the clinical series. Results with clustering techniques consistently revealed the emergence of two main groups (even with cases with high confidence in diagnosis) that stayed largely unchangeable independently of the algorithms used and of the set of quantitative or qualitative variables analyzed. Although those groups tended to include a mixture of all PPA variants (in particular with all classifiable patients), it is worth noting that one group comprised mainly svPPA and lvPPA cases whereas the other included the majority of nfvPPA and some lvPPA cases. Unclassifiable patients did not form an individual group. Instead, they belonged in the majority to the cluster comprising mainly svPPA and lvPPA cases. When data were clustered in two groups, there was a clear separation of most of the svPPA and nfvPPA cases. Still, lvPPA remained undoubtedly the most difficult class to individualize, being frequently grouped together with svPPA cases and with some nfvPPA cases as well. The variant that was most easily separated was nfvPPA. In fact, the detachment of most of the svPPA and lvPPA cases was only feasible for larger values of predefined number of clusters (*k*) or in deeper levels of the dendrogram (*Hierarchical Clustering*).

Based on the analysis of connected speech samples, Sajjadi and colleagues (Sajjadi et al., 2012) have previously used a factor analysis to examine if the three recent defined subtypes would emerge in a group of 46 consecutive PPA patients. They found a four-factor solution, where the two first factors accounted together for 42% of the total variance. The first factor clustered semantic measures (single-word comprehension, nonverbal

associative knowledge, picture naming and irregular word reading), whereas the second one clustered grammatical features, namely, sentence repetition, apraxia of speech and mean length of utterance. None of the remaining factors resembled a canonical logopenic profile. The authors suggest that lvPPA can hardly be considered an independent entity, since many patients that do not present semantic or agrammatic/nonfluent features not necessarily display linguistic/neuropsychological characteristics of so-called lvPPA (Sajjadi et al., 2012). This clearly reveals that separation of the three PPA variants is not trivial and the difficulty in substantiating the criteria of Gorno-Tempini and colleagues (Gorno-Tempini et al., 2011). Our results, by using a more sophisticated and extensive data-driven analysis in a larger sample, confirm previous findings and highlight the current debate around the classification of PPA syndromes.

For many years clinicians and researchers have considered PPA solely in the context of FTLD as PNFA and SD, with criteria defined by Neary and colleagues (Neary et al., 1998). The third lvPPA variant represents a relatively recent construct, although its description was already implicit in Mesulam's seminal report (Mesulam, 1982). Logopenic PPA was only formally described in 2004 (Gorno-Tempini et al., 2004) based on imaging findings (later correlated with clinical data) which contrasted with the mainly clinically-based descriptions underlying the definition of PNFA and SD. Furthermore, the lvPPA variant represents a heterogeneous entity whose diagnosis is based predominantly on the absence of core features of the other variants (absence of semantic impairment and of apraxia of speech/agrammatism) which leads to the inclusion in the same group patients with probably distinct clinical features.

In this study, lvPPA patients were difficult to dissociate from the other cases and some of them were closer to svPPA patients, whereas others were closer to nfvPPA patients. This highlights the substantial variability of the lvPPA syndrome and its mixed nature: many lvPPA patients may display a relatively effortful speech which resembles that of patients with nfvPPA. On the other hand, their naming difficulties may make them look similar to svPPA patients (Rascovsky & Grossman, 2013), particularly at very early stages. Furthermore, these cases may vary in the extent of damage to the ventral language pathway which can manifest as variable semantic impairment, which further complicates classification (Harciarek & Kertesz, 2011).

One could argue that language/neuropsychological attributes used to assess patients in this study might not have been sufficient to discriminate logopenic patients from the

other two variants. In fact, the recent consensus guidelines point the language areas that should be subjected to a thorough assessment but do not give information on specific tests or the cut-off points to use. Furthermore, one of the problems associated with retrospective studies is that tests tend to change overtime as new instruments are introduced to assessment batteries. As a consequence, quantitative scores on those measures are lacking for many cases, which will influence analysis based solely upon quantitative performance. Nonetheless, other studies have failed to classify a significant proportion of PPA patients even though they used different batteries (Sajjadi et al., 2012; Sajjadi et al., 2014; Wicklund et al., 2014). The use of qualitative measures of impairment on main language areas affected in each PPA subtype did not seem to improve this situation as a full discrimination was still not feasible.

About one third of our cases could not be classified into one of the subtypes, showing once again the limitation associated with the current criteria. Although the study of the unclassifiable cases was not the primary objective of this study, this finding is consistent with previous reports (Wicklund et al., 2014). Some of these "difficult" cases have even been reported to remain unclassifiable for some time (Mesulam et al., 2012). This situation gets worse when disease evolution is taken into account, as patients' linguistic profiles tend to lose their specificity, making it harder even for clinical experts to classify a patient into one of the variants. The majority of our unclassifiable cases present word retrieval and naming deficits, without definite semantic or agrammatic features. Since they do not display repetition deficits as well, they cannot be strictly classified as logopenic according to 2011 criteria, being left without a classification. Mesulam & Weintraub (Mesulam & Weintraub, 2014) recently addressed this issue, suggesting that "impairment of repetition" should be considered an ancillary rather than a core feature in order to include more patients into this group. Only then they should be subdivided as having or not having deficits in repetition. Mixed phenotypes tend also to be considered unclassifiable. Once again, the same authors highlight the need to consider a fourth "mixed" variant, leading to a decrement of the number of the unclassifiable cases (Mesulam & Weintraub, 2014).

It is interesting to note that that nfvPPA cases had longer evolution times compared to svPPA, lvPPA and unclassifiable cases. This may be due to the nature of language deficits presented by these patients: in cases where agrammatism is the most salient feature, this aspect can stay undetectable by patients and relatives and may only be

identified by a thorough assessment. In most cases, patients seek medical help when their speech becomes profoundly disturbed, marked by several dysfluencies and at a time when apraxic symptoms are often quite evident. In addition, the differences in evolution times may be accounted for by differences in the speed of the underlying neurodegenerative processes known to be associated to each variant.

As strengths of the present work, we highlight the use of a robust clinical sample, larger than those reported so far in the literature, the exhaustive nature of the analyses in terms of type of algorithms, sets of variables and sub-groups of patients used. Nonetheless, some limitations should be acknowledged as well. First of all, this is a retrospective study and, for that reason, data considered nowadays essential for diagnosis might not have been obtained. This might represent a cause for misclassification in some cases and the impossibility of reaching a diagnosis into subtypes in others. Secondly, imaging and pathological data were not considered in the analyses. The inclusion of biomarkers beyond language and neuropsychological tests might improve clustering analysis. Furthermore, from a computational standpoint, the number of patients under study may be considered small for an unsupervised learning study (disproportion between the number of patients and variables). Indeed, in data mining studies a larger cardinality of examples may lead to a more accurate outcome. This caveat could be attenuated through multicentric studies, in which several series of PPA patients from centres of expertise would be included. Furthermore, future work should focus on supervised machine learning, in order to help a more accurate classification of patients and the identification of different profiles.

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STUDY 3

Behaviour symptoms in primary progressive aphasia variants

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The candidate made substantial contribution to the study concept and design, collection, analysis and interpretation of the data, drafted and revised critically the manuscript for important content.

1. Introduction

Although not initially recognized (Weintraub et al., 1990) and even used as exclusionary criteria for PPA diagnosis, behaviour/personality changes are often reported as early features in PPA (Mesulam, 2001; Gorno-Tempini et al., 2011). They may appear simultaneously (Rohrer & Warren, 2010; Fatemi et al., 2011) or slightly after the emergence of language symptoms (Kertesz, Davidson, & Munoz, 1999). An overlap between PPA and bvFTD is often observed with disease progression (Marczinski et al., 2004). Depression (Medina & Weintraub, 2007; Banks & Weintraub, 2008; Rohrer & Warren, 2010; Fatemi et al., 2011), apathy, anxiety, agitation, irritability (Banks & Weintraub, 2008; Rohrer & Warren 2010; Fatemi et al., 2011), abnormal appetite/eating disorders (Rohrer & Warren, 2010; Fatemi et al., 2011), lack of insight (Banks & Weintraub, 2008) and disinhibition (Rohrer & Warren, 2010) have been reported as major behaviour changes in PPA patients. Previous studies have essentially focused on comparing the behaviour profile of patients with svPPA with that of bvFTD patients (Snowden et al., 2001; Liu et al., 2004). However, the findings regarding behavioural changes across the three PPA variants have been contradictory: some studies report that svPPA is the variant with the most frequent and severe behaviour problems when compared to other subtypes (Rosen et al., 2006), whereas others suggest that there are no differences between variants in terms of frequency and severity of the behaviour changes, but different trends may be identified (Rohrer & Warren, 2010).

Identifying behaviour symptoms should be important for diagnosis since they are more likely to occur in frequency and severity in the context of FTLD than AD (Rascovsky et al., 2011; Konstantinopoulou, Aretouli, Ioannidis, Karacostas, & Kosmidis, 2013). The identification of patterns of behaviour change associated with specific PPA profiles might contribute to a more accurate diagnosis of the PPA syndromes and, as a consequence, help in differential diagnosis by predicting the underlying disease process. Furthermore, early detection of behaviour changes should be important for disease management, therapeutic decisions and global outcome. Hence, the aim of the present chapter is to examine the changes in behaviour assessed using the behaviour/personality part of the *Blessed Dementia Rating Scale* ($BDRS_{Behaviour}$) across the three PPA variants in a consecutive clinical series. We hypothesize that the type of variant would be associated with changes in behaviour, specifically that patients with nfvPPA and svPPA, which are related to FTLD

pathology, show more behaviour changes than patients with lvPPA that is frequently caused by AD.

2. Methods

2.1. Participants

Participants were right-handed patients who fulfilled diagnostic criteria for PPA referred to a language/neuropsychological assessment in one of two clinical institutions in Lisbon. The study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee.

2.2. Inclusion criteria

The inclusion criterion was the diagnosis of PPA, according to the following criteria (Mesulam, 2001; Gorno-Tempini et al., 2001): a) most prominent clinical feature is difficulty with language (word-finding deficits, paraphasias, effortful speech, grammatical and/or comprehension deficits); b) activities of daily living are maintained except those related to language; c) aphasia is the most prominent deficit at symptom onset and for the initial stages of the disease; d) absence of prominent initial episodic memory, visual memory, visuospatial impairment or behaviour changes during the initial stages of the illness; f) aphasia is not better accounted for by other non-degenerative diseases of the nervous system (e.g. stroke or tumor) or by a psychiatric illness.

2.3. Exclusion criteria

Patients were excluded if they had, at least, one of the following:

a) Dementia according to the DSM-IV-TR (APA, 2001)
b) A neurologic disorder (stroke, brain tumor, brain trauma, epilepsy) able to induce language or other cognitive deficits
c) Uncontrolled systemic illness with cerebral impact (hypertension, metabolic, endocrine, toxic and infectious disease)
d) History of alcohol abuse or recurrent substance abuse or dependence
e) Presence of mental retardation

f) Presence of severe auditory or visual impairment able to compromise the application of language/neuropsychological tests

2.4. Procedures

All patients underwent a language/neuropsychological examination, which was consistently performed by the same senior neuropsychologist (M.G.). Despite the fact that some patients had more than one assessment, in the present study we only considered data obtained in the first assessment. The language protocol consisted of the following tests and batteries: a) *Lisbon Battery for the Assessment of Aphasia* (Damásio, 1973; Castro-Caldas, 1979; Ferro, 1986), which comprises the *Aphasia Severity Rating Scale* (where lower values correspond to higher severity); description of the *Cookie Theft* picture (for analysis of spontaneous speech); object naming; object identification; comprehension of oral commands; word and sentence repetition; text reading and comprehension (to assess the presence of alexia); spontaneous writing and writing of words and sentences by copy or by dictation (to assess the presence of agraphia), b) *Snodgrass and Vanderwart Naming Test* (Snodgrass & Vanderwart, 1980), c) *Token Test* (De Renzi & Vignolo, 1962), d) *Verbal (semantic and phonological) fluency* (Lezak et al., 2012), e) *Vocabulary subtest of the* WAIS (Wechsler, 1955). With respect to the neuropsychological assessment, nonverbal tests were usually preferred to evaluate different cognitive domains since the language deficits could interfere with the application and interpretation of verbal tests/performances. As such, the neuropsychological protocol comprised: a) *Lisbon Battery for the Evaluation of Dementia* (BLAD) (Garcia, 1984) (cancellation task; motor and graphomotor initiatives; Digit Span; personal, spatial and temporal orientation; buccofacial, ideomotor and ideational limb praxis testing by oral command, imitation and manipulation of objects; written/mental calculation; clock drawing test, copy of a cube and of geometrical drawings; visual memory; Raven Coloured Progressive Matrices – Ab series; right-left orientation), b) *Trail Making Test* (TMT) (Reitan, 1958).

2.5. Diagnosis of PPA subtypes

Classification into PPA variants followed the international consensus working criteria (Gorno-Tempini et al., 2011) and was made based on a consensus between two

neuropsychologists (M.G. and C.M.), using the language and neuropsychological profiles (Appendix 1).

2.6. Assessment of behaviour/personality changes

The presence of changes in personality was assessed by the BDRS (Blessed et al., 1968), which is a brief clinical rating scale assessing functional capacity for activities of daily living and changes in personality over the preceding six months based on an interview with a close informant (relative or friend). It consists of 22 items that measure changes in performance of everyday activities ($BDRS_{ADL's}$ - eight items; e.g. *performing household tasks, using money, remember short lists of items, finding the way indoors and around familiar streets, grasping situations, recalling recent events, and dwelling in the past*), changes in self-care habits ($BDRS_{Habits}$ – three items; i.e. *eating, dressing and continence*) and changes in personality, interests and drives ($BDRS_{Behaviour}$ - eleven items). The latter part of the scale was considered the primary outcome measure in the present study. It inquires about the presence or the absence of the following behaviour symptoms: "*increased rigidity"*, "*increased egocentricity"*, "*coarsening of affect"*, "*impairment of regard of feelings for others", "impairment of emotional control", "diminished emotional responsiveness", "hilarity in inappropriate situations", "sexual misdemeanor", "hobbies relinquished", "growing apathy"* and *"purposeless hyperactivity"*. Overall scores on BDRS range from 0 to 28, where higher scores indicate greater decline.

2.7. Statistical analysis

All analyses were conducted using *IBM SPSS Statistics* software (V. 20). Differences were considered statistically significant at $p<0.05$.

Demographic, clinical and neuropsychological numerical variables were compared among groups using One-way Analysis of Variance (one-way ANOVA) for independent samples (with pair-wise Bonferroni's post-hoc tests). The Pearson Chi-Square test was used for categorical variables. A two-tailed z-test for proportions (with Bonferroni correction) was used to compare column proportions across the three groups.

The primary analysis compared the ratings of $BDRS_{Behaviour}$ among the three PPA variants using Analysis of Covariance (ANCOVA). Secondary analyses included the comparison among the groups on $BDRS_{ADL's}$ and $BDRS_{Habits}$ ratings. Since both age at

symptom onset and age at the time of assessment were significantly different among groups, they should be controlled for in the analysis. However, multicolinearity analyses revealed that the Variance Inflation Factor (VIF) was above 10 for these independent variables (*Age at symptom onset*, Tolerance = 0.040, *VIF* = 25.227; *age at first assessment*, Tolerance = 0.040, *VIF* = 25.227), meaning that they were highly collinear. As such, we opted to introduce age at the time of assessment in the model as a covariate, but leave out age at symptom onset. Post-hoc pair-wise comparisons between groups using Bonferroni's correction were carried out if significant overall differences were found.

The frequencies of behaviour symptoms in the overall sample and in each sub-group were also analyzed. For each symptom separately, Pearson Chi-Square tests were used to compare the proportion of patients with behaviour changes among the three diagnostic groups. A two-tailed z-test for proportions (with Bonferroni correction) was used to compare column proportions across the three groups.

3. Results

Our sample was initially composed by 158 PPA cases. However, and in line with the classification caveats frequently reported in PPA studies (Banks & Weintraub, 2008), a proportion of cases (27.8%) was not considered reliably classifiable so we opted to exclude them from further analyses. As such, 94 PPA patients were included in the present study.

Demographic and cognitive data for the whole sample and according to the PPA variants are shown in Table 3.1. Patients with lvPPA were significantly older than semantic patients at symptom onset and at assessment. Regarding the language measures, nonfluent/agrammatic PPA patients had significantly higher scores on the aphasia severity scale when compared to the other two variants (Table 3.1). Consistent with the diagnostic criteria, svPPA patients showed the lowest performance on *Snodgrass & Vanderwart Naming Test* and object identification when compared to the other two variants. This variant also showed a lower performance than the lvPPA group on vocabulary. As expected, the nfvPPA group showed a significantly higher frequency of speech production deficits (agrammatism, articulation deficits and stuttering dysfluencies) when compared to the other groups. Patients with nfvPPA and lvPPA both had a high frequency of hesitations in speech production. Patients with lvPPA and with nfvPPA were significantly more impaired on sentence repetition, and nfvPPA patients were significantly more impaired in writing abilities (Table 3.1).

Table 3.1. Demographic data and performance in selected language tests in patients with nonfluent, semantic and logopenic primary progressive aphasia variants

	Total n=94	**nfvPPA** n=26	**svPPA** n=36	**lvPPA** n=32	**Statistics**	***p-value***	***Post-hoc***
Gender (F:M)	45:49	10:16	16:20	19:13	χ^2=2.789	0.248	n.s.
Age at onset (years)	67.1(7.8)	67.1(7.4)	64.5(7.0)	**70.4(8.0)**	**F=5.116**	**0.008**	**lvPPA>svPPA***
Age at assessment (years)	69.4(7.7)	70.0(7.3)	66.5(7.2)	**72.0(7.8)**	**F=4.847**	**0.010**	**lvPPA>svPPA***
Education (years)	8.2(4.5)	8.4(4.4)	8.3(4.6)	8.1(4.6)	F=0.018	0.982	n.s.
Presence of agrammatism (Y:N)	26:60	**13:8**	7:27	6:25	**χ^2=13.226**	**0.001**	**nfvPPA<svPPA, lvPPA†**
Presence of articulation deficits (Y:N)	12:78	**9:14**	0:36	3:28	**χ^2=19.143**	**<0.001**	**nfvPPA<svPPA, lvPPA†**
Presence of hesitations (Y:N)	28:59	**11:11**	1:33	**16:15**	**χ^2=21.882**	**<0.001**	**lvPPA, nfvPPA<svPPA†**
Presence of stuttering-like dysfluencies (Y:N)	18:70	**11:11**	1:34	6:25	**χ^2=18.488**	**<0.001**	**nfvPPA<svPPA, lvPPA†**
Aphasia severity rating scale (/6)	3.8(1.0)	**3.2(1.1)**	4.1(0.7)	3.9(0.8)	**F=6.925**	**0.002**	**nfvPPA<svPPA, lvPPA***
Object Naming (% correct)	72.6(28.3)	78.0(24.7)	**62.8(32.1)**	78.9(24.0)	**F=3.472**	**0.035**	**svPPA<nfvPPA, lvPPA***
SVNT (% correct)	68.8(23.7)	82.7(19.5)	**54.7(24.0)**	76.6(17.2)	**F=10.636**	**<0.001**	**svPPA<nfvPPA, lvPPA***
Object Identification (% correct)	97.9(6.1)	99.5(1.8)	**95.3(9.2)**	99.5(2.5)	**F=4.846**	**0.010**	**svPPA<nfvPPA, lvPPA***
Word repetition words (/30)	29.5(1.7)	29.0(2.8)	29.9(0.3)	29.6(1.1)	F=2.331	0.103	n.s.
Sentence repetition (/14)	5.9(3.6)	**4.5(3.6)**	7.8(4.0)	4.8(1.8)	**F=8.448**	**<0.001**	**nfvPPA, lvPPA<svPPA***
Comprehension of oral comands (/8)	7.5(1.0)	7.4(0.9)	7.4(1.3)	7.6(0.6)	F=0.380	0.685	n.s.
Token Test (/22)	12.5(5.1)	10.7(4.6)	13.9(5.8)	12.4(4.2)	F=2.598	0.081	n.s.
Presence of alexia (Y:N)	39:44	15:11	14:17	10:16	χ^2=4.369	0.358	n.s.
Presence of agraphia (Y:N)	49:43	**20:6**	14:22	15:15	**χ^2=10.261**	**0.036**	**nfvPPA<svPPA, lvPPA†**
Vocabulary (% correct)	62.7(24.2)	68.1(18.7)	**53.8(23.5)**	77.2(23.4)	**F=3.512**	**0.042**	**svPPA<lvPPA***

Legend: *Bonferroni's post-hoc test; **† two-tailed z-test;** Figures represent mean values, the figures in curve brackets represent standard deviations; bold values represent statistically significant results at p<0.05; nfvPPA – nonfluent variant primary progressive aphasia; svPPA – semantic variant primary progressive aphasia; lvPPA – logopenic variant primary progressive aphasia; F – One-way ANOVA; SVNT – Snodgrass & Vanderwart Naming Test; Y – Yes; N – No; n – number; n.s. – non significant χ^2 - Chi-Square Test

Table 3.2. Blessed Dementia Rating Scale scores and frequency (%) of each symptom for nonfluent, semantic and logopenic primary progressive aphasia variants

		Total n=94	**nfvPPA** n=26	**svPPA** n=36	**lvPPA** n=32	**Statistics**	***p-value***	***Post-hoc***
$BDRS_{Behaviour}$ (/11)[a] (mean±SD)		1.9(1.4)	**2.3(1.4)**	1.9(1.5)	**1.4(1.1)**	**F=3.412**	**0.037**	**nfvPPA>lvPPA***
Item 1	*Increased rigidity (%)*	26.6	30.8	27.8	21.9	χ^2= 0.623	0.732	n.s.
Item 2	*Increased egocentricity (%)*	8.5	7.7	11.1	6.3	χ^2=0.545	0.761	n.s.
Item 3	*Impairment of regard of feeling for others (%)*	7.4	7.7	8.3	6.3	χ^2=0.110	0.947	n.s.
Item 4	*Coarsening of affect (%)*	13.8	15.4	19.4	3.1	χ^2=2.548	0.280	n.s.
Item 5	*Impairment of emotional control (%)*	37.2	38.5	38.9	34.4	χ^2=0.171	0.918	n.s.
Item 6	*Hilarity in inappropriate situations (%)*	3.2	3.8	5.6	0	χ^2=1.742	0.418	n.s.
Item 7	*Diminished emotional responsiveness (%)*	5.3	7.7	2.8	3.1	χ^2=0.807	0.668	n.s.
Item 8	*Sexual misdemeanor (%)*	0	0	0	0	-	-	-
Item 9	*Hobbies relinquished (%)*	29.8	**46.2**	30.6	**12.5**	**χ^2=6.409**	**0.041**	**nfvPPA>lvPPA††**
Item 10	*Growing apathy (%)*	54.3	65.4	41.7	50.0	χ^2=3.934	0.140	n.s.
Item 11	*Purposeless hyperactivity (%)*	3.2	7.7	2.8	0	χ^2=2.780	0.249	n.s.
$BDRS_{Total}$ (/28)[b] (mean±SD)		2.8(1.8)	3.4(1.6)	2.8(1.9)	2.3(1.6)	F=2.591	0.080	n.s.
$BDRS_{ADL's}$ (/8)[c] (mean±SD)		0.9(0.8)	0.8(0.7)	0.9(0.8)	0.9(0.8)	F=0.517	0.598	n.s.
$BDRS_{Habits}$ (/9)[d†] (mean±SD)		0.1(0.3)	0.2(0.6)	0.0(0.0)	0.0(0.2)	-	-	-

Legend: *Bonferroni's post-hoc test; †very few cases (n=4) scored on this part of BDRS so the statistical test was not conducted; †† two-tailed z-test; The figures associated with each part of the BDRS represent mean values with the respective standard deviations in curved brackets; the figures associated with each $BDRS_{Behaviour}$ item represent the frequency of patients (as percentage) scoring each item in the sample as whole and in each PPA subtype; age at the time of the assessment was entered in model as covariate; bold values represent statistically significant results at $p<0.05$; BDRS – Blessed Dementia Rating Scale; ADL's – activities of daily living; nfvPPA – nonfluent variant primary progressive aphasia; svPPA – semantic variant primary progressive aphasia; lvPPA – logopenic variant primary progressive aphasia; F – One-way ANCOVA; n – number; n.s. – non significant

[a]possible score range from 0 to 11, with higher scores indicating behaviour impairment; [b]possible score range from 0 to 28, with higher scores indicating greater impairment; [c]possible score range from 0 to 8, with higher scores indicating greater impairment on instrumental activities of daily living; [d]possible score range from 0 to 9, with higher scores indicating greater impairment on basic activities of daily living.

To assess differences in ratings of the behaviour part of the BDRS ($BDRS_{Behaviour}$) among the three PPA variants, univariate ANCOVA was performed (Table 3.2). After controlling for age at the time of assessment, a significant main effect of PPA group on $BDRS_{Behaviour}$ ratings was found (F=3.412, df=2,94, p=0.037; Table 3.2). Pair-wise comparisons with Bonferroni's correction revealed that nfvPPA scored significantly more on $BDRS_{Behaviour}$ when compared to lvPPA patients. No significant differences were found among the three PPA variants regarding $BDRS_{Total}$ and $BDRS_{ADL's}$. Only four patients scored on the $BDRS_{Habits}$ subscale, so the analysis was not performed for this part of the scale.

In the PPA series as a whole, about 82% of the patients endorsed at least one $BDRS_{Behaviour}$ symptom. When each symptom was taken in isolation, the most prevalent symptoms were "*growing apathy"* (54.3%), followed by "*impairment of emotional control*" (37.2%), "*hobbies relinquished*" (28.7%) and "*increased rigidity"* (26.6%) (Table 3.2). There was a statistically significant difference in the frequency of the symptom "*hobbies relinquished*" among the three PPA patient groups (χ^2=8.031, df=2, p=0.018). The proportion of nfvPPA patients endorsing this symptom was significantly higher when compared to lvPPA patients (z = 2.852, p=0.004) (Table 3.2).

4. Discussion

The aim of the present study was to examine the changes in behaviour across the three PPA variants. The main result was that nfvPPA patients showed more behaviour changes than lvPPA patients.

Previous studies have reported contradictory findings regarding the frequency and type of behaviour changes among PPA variants. A study aiming to characterize the behaviour abnormalities that occur in svPPA in comparison with the remaining variants and other dementia syndromes (AD and bvFTD) showed that svPPA presented the most severe behaviour problems, in a similar fashion to bvFTD, while nfvPPA and lvPPA had less behavioural disturbance, in particular significantly less disinhibition and aberrant motor behaviours (Rosen et al., 2006). In contrast, a more recent study found that the frequency and severity of behaviour changes was not significantly different among the three PPA variants, however distinctive patterns could be observed, with disinhibition-like

behaviours occurring more frequently in svPPA, and apathy and irritability prevailing in nfvPPA and lvPPA (Rohrer & Warren, 2010).

Identifying a pattern of behaviour changes associated with specific variants could be relevant to predict the underlying brain dysfunction and pathology. In the present study, we found a higher frequency of significant behaviour symptoms in nfvPPA patients. The nfvPPA variant is commonly associated with atrophy of the frontal region of the left hemisphere, and can extend more dorsally into left prefrontal regions (Rogalski, Cobia, Harrison, et al., 2011). A similar pattern is also observed in bvFTD (Perry et al., 2006), where progressive behaviour deterioration is the clinical hallmark of the disease (Rascovsky et al., 2011). Conversely, in the present study, patients with lvPPA presented fewer behaviour symptoms. Logopenic variant PPA has been linked to AD pathology (Leyton et al., 2011) and this variant may represent an atypical presentation of AD (Rohrer, Rossor, & Warren, 2012). Neuropsychiatric and personality changes such as apathy, depression, aggression and agitation occur in early AD (Lyketsos et al., 2011) but they are less striking when compared to bvFTD (as the frontal and anterior medial temporal areas are relatively spared in AD) and do not represent the primary feature of the disease (McKhann et al., 2011). It should be noted that we did not find a higher frequency of behaviour symptoms in svPPA, which is also included within the FTLD pathological spectrum and involves focal degeneration of the anterior temporal lobes. Previous studies suggested that svPPA patients may display more neuropsychiatric symptoms when compared to the remaining variants, with a pattern of disinhibition-like behaviours that qualitatively resembles that of bvFTD (although less severe) (Bozeat, Gregory, et al., 2000; Rosen et al., 2006; Rohrer & Warren, 2010). The discrepancy between these previous studies and the present results regarding the frequency of behaviour symptoms in svPPA might arise from differences in the instruments used to assess behaviour changes, as further discussed below.

Remarkably, as much as 82% of the overall clinical series presented at least one behaviour symptom, which is in line with previous studies reporting high prevalence rates of behaviour changes (around 90%) (Banks & Weintraub, 2008) in PPA. Such evidence supports the notion that behaviour changes are a common feature in patients who meet diagnostic criteria for PPA. When symptoms are taken in isolation, "*growing apathy*" was present in more than 50% of our cases. In a case-control study which sought to examine if neuropsychiatric symptoms occur over and above expected in the normal population,

apathy was also the most significant distinguishing feature between PPA patients and controls (Fatemi et al., 2011). The second symptom frequently endorsed in our PPA series was "*hobbies relinquished*". The abandonment of previous hobbies and interests may constitute a more direct implication of the language disorder (Fatemi et al., 2011). In fact, the presence of a language impairment interferes with many everyday activities: the patient struggles to maintain social interactions (withdrawing him/herself from conversation, hence increasing isolation) and to perform verbally mediated activities (reading for instance). Interestingly, we found that the frequency of this symptom is significantly higher in nfvPPA patients. This could be accounted for by the presence of neurological signs and/or limb apraxia, known to accompany the syndromes of nfvPPA (Grossman, 2012), which would further complicate task performance.

Strenghts of the present work are the use of a large clinical sample composed by consecutive cases with PPA, and the use of a standardized instrument which was consistently applied to all patients' informants. The BDRS is a well-validated instrument designed to monitor progression to dementia (Stern, Mayeux, Sano, et al., 1987; Morris, Heyman, Mohs, et al., 1989). It is easy to administer, provides replicable results, and has high reliability and validity, with scores correlating well with the cerebral changes of primary degenerative dementia (Blazer, 2009). In addition, it has been considered a key instrument to assess functionality in activities of daily living and behaviour in AD (Waldemar et al., 2000), being a sensitive and specific screening test for dementia with a good correlation with neuropsychological test performance (Erkinjuntti, Hokkanen, Sulkava, & Palo, 1988). In terms of limitations, we should note that some behaviour symptoms, usually addressed by domain-specific scales such as the *Frontal Behaviour Inventory* (FBI) or the *Neuropsychiatry Inventory* (NPI), are not tackled by BDRS. This may explain why we found a lower frequency of behavioural symptoms in svPPA as compared to previous studies, since the occurrence, for instance, of eating disorders, previously reported in patients with svPPA, either using FBI or NPI (Bozeat, Gregory, et al., 2000; Rosen et al., 2006), is not directly assessed by BDRS. Another limitation of the present study is that some cases had to be excluded from analysis due inability to reach a more definite syndromic diagnosis (Mesulam et al., 2012; Wicklund et al., 2014). A final limitation is the lack of imaging and autopsy-proven pathological data to be correlated with behavior findings.

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STUDY 4

Speech therapy in primary progressive aphasia: A pilot study

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The candidate made substantial contribution to the analysis and interpretation of the data, drafted and revised critically the manuscript for important content.

1. Introduction

PPA is a very disabling disorder for which there is, at present, no available treatment. A few pharmacological trials (using bromocriptine, galantamine, and memantine) conducted so far have enrolled small numbers of patients and produced inconclusive results (Reed, Johnson, Thompson, Weintraub, & Mesulam, 2004; Kertesz et al., 2008; Boxer et al., 2009; Johnson et al., 2010), and there have been no trials with other therapies. Taking into account this discouraging perspective, the implementation of non-pharmacological procedures, specifically designed to compensate for progressive language deficits, may seem a feasible alternative.

There is evidence from other neurodegenerative conditions that cognition-based interventions may be effective in maintaining or improving cognitive function and perhaps delay progression to dementia. A Cochrane collaboration study recently reviewed 36 trials on the effect of cognitive stimulation on mild cognitive impairment, revealing some beneficial effect of this type of intervention on measures of immediate and delayed recall, when comparing groups subjected to intervention and groups with no stimulation (Martin, Clare, Altgassen, Cameron, & Zehnder, 2011). Similar results have also been reported in patients with mild dementia (Woods, Aguirre, Spector, & Orrell, 2012).

Speech and language therapy (SLT) has been extensively used in patients with aphasia of different etiologies and has been shown to be effective (Leal, Farrajota, Fonseca, Guerreiro, & Castro-Caldas, 1993; Robey, 1994; Mazzoni et al., 1995; Robey, 1998; Basso & Macis, 2011). It aims to maximize the subject's communicative abilities. A recent meta-analysis (Kelly, Brady, & Enderby, 2010) identified 30 controlled trials of speech therapy, performed between 1969 and 2009, showing beneficial effects in a variety of language measures (spontaneous speech, gestural use, aphasia severity, expressive written language, and comprehension). Functional neuroimaging studies have confirmed these results by showing neural reorganization following SLT (Léger et al., 2002; Peck et al., 2004).

Because PPA affects mostly language, it is reasonable to presume that SLT might be effective in this condition given the fact that other behavioral interventions have proved to be useful in degenerative diseases. To date, case reports and single-subject experimental research have been presented (Louis et al., 2001; Henry, Beeson, & Rapcsak, 2008; Beeson et al., 2011); however, the scarce number of participants and the absence of a control intervention in the majority of the studies limit the significance of the results. Attempts to

introduce other approaches based on training with a text-to-speech alternative communication device or sign language were also reported (Pattee, Von Berg, & Ghezzi, 2006), but again the generalization of these preliminary encouraging results appears difficult.

The aim of our study was to find out whether a SLT program can mitigate language decline in PPA, by comparing a group exposed to this intervention with a historical control group of PPA patients who did not undergo any stimulation. Specifically, we tested the hypothesis that patients subjected to speech therapy would show significantly less decline over time in expressive language measure, namely naming ability, as compared to the control group. If positive results were found, they would encourage carrying out a formal randomized controlled trial to establish the efficacy of SLT in PPA. This intervention would hopefully assist in the maintenance or even transitory amelioration of patients' linguistic skills, promoting their ability to communicate and their quality of life.

2. Materials and Methods

2.1. Participants

Participants were patients referred for language/neuropsychological assessments at the two participating clinical institutions in Lisbon and who fulfilled the diagnostic criteria for PPA (Gorno-Tempini et al., 2011). The intervention group comprised 10 patients who underwent speech therapy sessions at the institution (Memory Clinic) that offered the patients the possibility of being enrolled in a SLT program. The controls were 10 age- (± 2 years) and education- (± 3 years) matched PPA patients consecutively selected from the clinical institutions' databases (Memory Clinic and Laboratory of Language Research) if they had at least two language/neuropsychological assessments and were not subjected to SLT. The study was approved by the local ethics committee.

2.2. Inclusion Criteria

All patients fulfilled the following criteria:

- The presence of PPA, according to the criteria recently proposed by Gorno-Tempini and colleagues (Gorno-Tempini et al., 2011): a) Insidious onset and gradual progressive impairment of language production, object naming, syntax, or word comprehension, apparent during conversation or through speech and

language assessments; b) Activities of daily living are maintained except those related to language (e.g. using the telephone); c) Prominent, isolated language deficit at symptom onset, during the initial phase of the disease and at time of examination; d) absence of prominent episodic and nonverbal memory loss and visuospatial impairment during the initial stages of the illness; e) other cognitive functions may be affected later on, but language remains the most impaired domain throughout the course of the illness; f) absence of prominent behavioral disturbances at the time of diagnosis; g) the pattern of deficits is not better accounted for by other non-degenerative diseases of the nervous system (e.g. stroke or tumor), as ascertained by neuroimaging, or medical disorders; h) cognitive disturbance is not better accounted for by a psychiatric diagnosis;

- Right-handedness;
- Native Portuguese speakers;
- Complete language/neuropsychological assessments.

2.3. Exclusion Criteria

- Presence of dementia, according to DSM-IV-TR criteria (APA, 2001);
- Other neurological or psychiatric disorders that might induce language or other cognitive deficits (e.g. stroke, brain tumor, traumatic brain injury, epilepsy, severe and uncontrolled medical illness, namely, hypertension, metabolic, endocrine, toxic or infectious disease).

2.4. Procedures

In all cases, clinical history was evaluated, and they underwent neurological examination and a detailed cognitive assessment which comprised language and neuropsychological evaluations. An experienced neuropsychologist (M.G.) performed the neuropsychological assessment. The test battery consisted of the nonverbal subtests of the *Lisbon Battery for the Assessment of Dementia* (BLAD) (Garcia, 1984). Since results in many neuropsychological tests are somewhat difficult to interpret in patients with PPA, due to test reliance on verbal directions, verbal stimuli, and/or verbal responses, nonverbal tests were preferred to evaluate different cognitive domains (sustained attention, motor and graphomotor initiative, visuoconstructive abilities, visual memory, and matrix reasoning).

Activities of daily living and behavioral changes were also assessed during the interview with the caregivers.

Language Assessment

At the baseline evaluation, patients were assessed by a speech therapist (L.F.) using a comprehensive language test battery (*Lisbon Aphasia Examination Battery*, BAAL (Damásio, 1973; Castro-Caldas, 1979; Ferro, 1986) that included the following instruments: (a) picture description (*Goodglass and Kaplan's cookie theft*) (Goodglass & Kaplan, 1972) for analysis of spontaneous speech; (b) visual object naming (BAAL); (c) *Snodgrass and Vanderwart Naming Test* (Snodgrass & Vanderwart, 1980); (d) a short 22-item version of the *Token Test* (De Renzi & Vignolo, 1962); (e) object identification and comprehension of oral commands (BAAL); (f) word and sentence repetition (BAAL); (g) text reading and comprehension (BAAL); (h) writing sentences to dictation (BAAL), and (h) spontaneous writing of a text. A global language measure, the Aphasia Quotient (AQ), was calculated for all patients by adding the scores (as percentages) of 4 BAAL subtests (fluency, object naming, repetition, and comprehension of oral commands) and dividing the sum by four (Ferro & Kertesz, 1983). Classification into PPA subtypes (agrammatic, semantic, and logopenic) followed specific criteria outlined by Gorno-Tempini and colleagues (Gorno-Tempini et al., 2011) (Appendix 1).

Speech Therapy Intervention

SLT comprised 60-min weekly sessions conducted by a trained speech therapist with experience in PPA (L.F.). The main goal of this intervention was the improvement of the patient's ability to communicate by verbal means with others in everyday life through a stimulation approach (Schuell, Carroll, & Street, 1955). This method is considered an individualized multimodality stimulation approach (Duffy & Coelho, 2001). Improvement in comprehension and expression of both spoken and written language was targeted through different exercises such as picture naming, description of pictured actions, complex auditory-verbal comprehension, reading and writing, facilitation of expression of feelings and opinions, and enhancement of conversational skills. The patient's attention is directed to the content he/she wants to express (Wepman, 1976). These exercises were completed during sessions with the speech therapist. Depending on the patient's education

level, motivation, and aphasia severity, about 5–10 of these exercises were given as homework. Conversational success, with the focus on functional outcome (Simmons-Mackie, 2001; Holland & Fridriksson, 2011), was also explored and stimulated by the use of other communication strategies (speaking, writing, drawing or gesturing). Thus, authentic opportunities are provided to patients to develop effective strategies for overcoming potential obstacles to communication. The main goal was always the exchange of ideas in a naturalistic and interactive manner in a supported conversation (Kagan, 1999). The main conversational topics usually included everyday life stories, recent news, episodes of soap operas and sports, restaurants, shops, family/friends, social life, and emotions. This was accomplished through picture description about personal safety, nonsense/unreal and decision-making situations. Tasks also included description and organization of sequences.

2.5. Primary Outcome Measure

The primary outcome measure was the mean change in *Snodgrass and Vanderwart Naming Test* scores before and after the intervention. This test assesses the ability to visually name 128 black and white picture drawings (Snodgrass & Vanderwart, 1980). Picture naming has been reported as the measure most positively affected by speech therapy in stroke aphasic patients (Bhogal, Teasell, & Speechley, 2003; Best et al., 2011), and impairment of word finding (leading to anomia during visual confrontation naming) is the single most prominent deficit in PPA (Mesulam, 2001). The remaining language measures (*Token Test*, object naming, word repetition, comprehension of oral commands, and object identification) were considered as secondary outcome measures.

2.6. Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics (version 19.0, SPSS, Chicago, Ill., USA). A significance level of 0.05 was used in the analyses. Since the variables displayed normal distribution and homogeneity of variances ($p > 0.05$), demographic and clinical numerical variables were compared in both groups using the parametric independent samples Student's t test. The Pearson χ^2 test was used for categorical variables. A mixed repeated measures analysis of variance (ANOVA) was performed to evaluate the effect of speech therapy on primary as well as secondary

outcome measures, using the initial and the follow-up evaluations as the within-subjects condition, and the presence or absence of intervention as the between-subjects condition. Since both the severity of aphasic changes at baseline and the time elapsed could decisively influence the outcome, the initial AQ and the evolution time between baseline and follow-up were entered as covariates in the analysis.

3. Results

Table 4.1 shows the demographic and clinical data of both the intervention and the control group. Overall, more men participated in the study (70%). There were no statistically significant differences in the demographic and clinical data of the two groups. The SLT group and the control group did not significantly differ concerning aphasia severity as assessed by the AQ (p = 0.720; Table 4.1). No significant differences were found in the mean scores of the *Snodgrass and Vanderwart Naming Test* at the baseline assessment between patients who underwent SLT (110.8 ± 18.2) and controls (87.7 ± 23.2; t (18) = 1.402; p = 0.178).

Table 4.1. Demographic and clinical results in speech therapy and control groups

		SLT (N=10)	**Control** (N=10)	**Statistics***	***p***
PPA Variant *(A:S:L)*		2:2:6	0:6:4	-	-
Gender *(F:M)*		4:6	2:8	χ^2=0.952	0.329
Education *[years; mean(sd)]*		11.4 (3.8)	8.1 (3.8)	t=1.991	0.062
Age *[years; mean(sd)]*	*At symptom onset*	65.6 (7.9)	64.6 (7.5)	t=0.292	0.774
	At baseline	68.0 (7.8)	66.2 (7.7)	t=0.518	0.611
Evolution times from baseline to follow-up *[months; mean(sd)]*		11.1 (9.3)	14.9 (11.4)	t=-0.817	0.424
Aphasia Quotient *[%; mean(sd)]*		85.9 (7.8)	87.1 (7.2)	t=0.364	0.720
Number of sessions *[mean(sd)]*		37.1(20.2)	-	-	-

Legend: SLT – Speech and Language Therapy; A – agrammatic; S – semantic; L – logopenic; t – t-Student independent samples test; χ^2 – Chi-Square Test

Table 4.2. Effect of the Speech and Language Therapy on primary and secondary outcome variables

	SLT (N=10)		**Control** (N=10)		**Repeated Measures ANOVA**									
					Evolution*		**Therapy****		**Evolution x Therapy**		**Evolution x Evolution times**		**Evolution x Initial A.Q.**	
	Baseline Mean(sd)	*Follow-up Mean(sd)*	*Baseline Mean(sd)*	*Follow-up Mean(sd)*	**F**	***p***	**F**	***p***	**F**	***p***	**F**	***p***	**F**	***p***
SVNT	100.8(18.2)	90.7(31.6)	87.7(23.2)	61.7(26.0)	1.037	0.324	**10.763**	**0.005**	2.772	0.115	**6.583**	**0.021**	0.857	0.368
Object Naming	12.9(3.6)	11.8(5.0)	13.7(2.6)	11.5(4.4)	0.934	0.352	0.090	0.769	0.009	0.927	**10.458**	**0.007**	0.759	0.400
Comprehension of oral commands	7.8(0.4)	7.0(1.3)	7.8(0.6)	7.2(0.9)	0.563	0.467	0.208	0.656	0.117	0.739	2.417	0.146	0.550	0.473
Token Test	15.4(3.7)	12.8(4.6)	15.4(4.2)	15.5(3.7)	3.008	0.105	0.157	0.698	3.910	0.068	**9.418**	**0.008**	3.761	0.073
Object Identification	16(0)	15.3(1.9)	16.0(0)	15.8(0.4)	0.184	0.680	0.208	0.660	0.208	0.660	0.245	0.634	0.173	0.689
Word Repetition	29.9(0.3)	29.6(1.0)	30.0(0)	30.0(0)	0.293	0.596	2.230	0.156	1.241	0.283	1.166	0.297	0.338	0.570

Legend: SLT – Speech and Language Therapy; A.Q. – Aphasia Quotient; SVNT – Snodgrass & Vanderwart Naming Test; ANOVA – Analysis of Variance; * Within subjects condition; ** Between subjects condition

3.1. Effect of Speech Therapy

The intervention group received on average 37.1 speech therapy sessions during 11.1 months (Table 4.1). As shown in table 2 , a mixed repeated measures ANOVA was conducted to assess whether there were statistical differences in the primary outcome measure with regard to evolution (baseline vs. follow-up) and therapy (with vs. without speech therapy). After controlling for evolution times and the initial AQ, a significant main effect of therapy (p = 0.005) was found on the primary variable, the performance on the *Snodgrass and Vanderwart Naming Test* (Table 4.2), meaning that patients subjected to SLT declined less than controls. The interaction between evolution and therapy was not significant (p = 0.083); however, significant interactions were found between evolution and evolution times for the primary (p = 0.021) and secondary outcome measures (*Token Test*, p = 0.008; Table 4.2), reflecting a more pronounced decline for longer follow-ups.

4. Discussion

The present study suggests that there is a tendency for a less severe decline of language, in particular concerning naming ability, in PPA patients subjected to SLT when compared with a control group that did not undergo SLT. We found that patients subjected to SLT declined significantly less in the primary variable, the *Snodgrass and Vanderwart Naming Test*. An effect of language rehabilitation on picture naming has been previously reported, but only based on single cases. Louis and colleagues (Louis et al., 2001) addressed the impact of intensive training on phonological skills in 3 PPA patients over a 42-day training period. The authors found that, in spite of global worsening of language abilities over intervention, some language functions (fluency, written comprehension, repetition, reading, and reduction of phonemic paraphasias) either remained stable or improved. Another study (Henry et al., 2008) followed 2 individuals with progressive language impairment and a stroke aphasia patient in a daily 90-min semantically based intensive treatment to improve lexical retrieval, over 16 days. Results indicated that all patients showed improved lexical retrieval on a generative naming task for specific categories trained during intervention. However, only 1 of the PPA patients and the stroke aphasia patient maintained improved performance on follow-up at 3 weeks and 4 months after treatment. The same research group reported similar results with the therapy of a logopenic PPA patient who performed follow-up assessment at 3 weeks, 4 and 6 months

after intervention. This patient also showed an improvement in naming on the training task, which generalized towards an improvement in standardized measures of confrontation naming (Beeson et al., 2011).

It must be emphasized that it would be particularly important to find effective non pharmacological approaches to treat PPA, since no pharmacological treatments are currently available. A few clinical trials testing different drugs can be found in the literature, but they reported inconsistent results. The study of the effect of bromocriptine on the performance of various language tasks revealed that it did not produce significant effects on language measures during a 15-week double-blind cross-over study, when comparing PPA and placebo groups (Reed et al., 2004). Another open-label study, this time with galantamine, in a sample of 36 behavioral frontotemporal dementia and PPA patients showed a non-significant trend for efficacy in the aphasic subgroup, suggesting that aphasia scores were more stable in the treatment than in the placebo group (Kertesz et al., 2008). A similar open-label study with memantine (Boxer et al., 2009) reported a relative stability on the ADAS-Cog over the 52 weeks of the study in progressive nonfluent aphasia patients, whereas patients with semantic dementia declined. Finally, a more recent double-blind, placebo-controlled trial showed a slight positive effect of this same drug, consisting of a smaller decline on the WAB aphasia quotient in the groups administered the drug than in the placebo group (Johnson et al., 2010).

Considering cognitive therapy for neurodegenerative disorders in a broader context, it has certainly been difficult to find unequivocal benefits of such interventions, for example, in mild cognitive impairment and mild dementia (Martin et al., 2011; Woods et al., 2012). However, the study of a specific form of cognitive intervention (speech therapy) in a homogenous group presenting a limited cognitive dysfunction (language impairment) may be particularly advantageous to reveal beneficial effects on cognitive performance. If we consider that the majority of techniques used in cognitive rehabilitation are designed to stimulate a broader range of impaired and/or preserved cognitive functions, the use of SLT in PPA patients might be representative of the possible impact of rehabilitation in neurodegenerative diseases.

As strengths of our study we underline the use of a sample followed longitudinally, the inclusion of a matched control group, and the fact that language intervention was always conducted by the same speech therapist, allowing the use of a consistent treatment structure (though adapted to each case).

We also acknowledge several limitations of the present work in the context of a pilot study undertaken to prompt future prospective trials. First of all, allocation to the treatment or the control group was not randomized, even though patients in both groups were age- and education-matched. This constitutes an important limitation, since the groups might differ in other variables relevant for the primary outcome measure that were not controlled for. However, we feel there was no clear allocation bias in the sense that patients more likely to benefit would have been directed to SLT. In fact, patients were offered the possibility of entering a SLT program at one institution, and this program was not available at the other institution. Thus, the allocation was essentially dependent on the clinical center and not on patients' characteristics, although it can be argued that socioeconomical status might have driven the choice of the center. Another limitation of the present study was a considerable variability of follow-up times in the intervention and control groups. This is partially due to the retrospective nature of the analysis that did not adhere to a formal assessment protocol at predetermined follow-up intervals, and to the historical nature of the control sample. A final limitation is that, due to the lack of a control intervention, the benefit of the language therapy might, at least partially, reflect nonspecific effects of contact with the speech therapist.

Future interesting directions in this area might be to consider the use of functional magnetic resonance imaging to observe possible changes in brain activation patterns over time as a result of speech therapy, as previously reported in stroke patients (Peck et al., 2004; Meinzer et al., 2013). On the other hand, a particular intervention might not equally impact on each syndrome, so that future prospective trials should take into account the specific PPA subtypes. Finally, future studies should not be confined to specific language measures, but address the possible impact of speech therapy on broader functional communication abilities, which are extensively stimulated during training sessions and might have important functional benefits. Language deficits can be extremely disabling as they disrupt the ability to express even basic thoughts and needs. The majority of aphasic patients are unable to maintain their previous job and suffer from a reduction of their social contacts, causing great problems at individual, social, and socio-economic levels (Fonseca, Farrajota, Leal, & Castro-Caldas, 1993). In the therapy context, the patient learns new strategies to use in everyday life that improve his/her capacity to communicate with others and interact with the environment, allowing engagement in many language-based activities (e.g. making appointments, schedules, and using the telephone). As a consequence, the

linguistic processes which are failing are further stimulated (Pulvermüller & Berthier, 2008). In fact, some studies suggest that therapy can have an impact on patients' views of their communicative activities and life participation by increasing their activity ratings, especially those that require active communication (Best et al., 2011). The use of functional communication scales such as the ASHA Functional Assessment of Communication Skills for Adults (ASHA FACS) (Frattali, Thompson, Holland, Wohl, & Ferketic, 1995) in future trials would provide more ecologically valid measures for everyday communication.

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V. DISCUSSION, FINAL CONCLUSIONS AND FUTURE WORK

PPA is a devastating progressive disorder that occurs as part of neurodegeneration of a large-scale distributed neuronal network for language. Almost every PPA patient has his/her own peculiarities and the systematic study of this condition over the past years has led to the identification of different disease presentations, in a close connection with the recent discoveries in the field of imaging, genetic and pathologic biomarkers. In a broader sense, neuropsychology has always played a vital role in the diagnosis and characterization of neurodegenerative diseases. In a time where an accurate diagnosis can be reached *in-vivo* through the use of advanced biochemical methods to assess the cerebrospinal fluid, as well as sophisticated brain imaging techniques with specific ligands to Aβ or tau, both reflecting underlying pathology, and orienting to precise treatment, the value of neuropsychology may be placed in question. A major concern that certainly arises after detection of any brain change is whether this has any functional importance. However, these changes are not necessarily uniform and many individuals will manifest impairments in cognitive areas that are more severe than expected by their current stage of illness. Moreover, given the lack of clear prediction of cognition and functioning from cortical degenerative changes in late life (Iacono et al., 2009) there will be considerable need to perform cognitive assessments following more sophisticated methods to ascertain the level of cognitive and functional impairment in a given individual. Similarly, serial neuropsychological assessments will likely provide better (and less expensive) information about gradual changes in cognitive functioning and potential for future outcome than other diagnostic tools, hence adding critical information to neurological and neuroimaging assessments.

The present thesis sought to study the neuropsychological aspects of PPA, contributing to the identification of different clinical profiles by tackling the neuropsychological heterogeneity of the disease and defining features relevant for diagnosis. For this purpose, we presented evidence (through the format of original investigations) that give support to neuropsychology as a crucial tool for the understanding and management of PPA.

From a diagnostic standpoint, neuropsychological assessment is key for deciding whether a progressive language disorder occurs in the context of generalized cognitive impairment or if it represents the only leading cognitive deficit (PPA), taking into account

the measurement of behavioural abilities and disabilities. Still under the diagnosis field, a second important step lies on the delineation of a neuropsychological profile in PPA in line with the International Consensus Criteria (Gorno-Tempini et al., 2011). If it is true that PPA patients have been traditionally considered under the spectrum of FTLD and the majority of them do in fact lie under this complex, further evidence shows that some cases represent atypical forms of other neurodegenerative diseases, the most frequent being AD. In Chapter II of the thesis an extensive revision on the three PPA variants (nfvPPA, svPPA and lvPPA) focused on their specific clinical distinctions and how each clinical profile correlates with specific patterns of brain atrophy and genetic and pathological changes. Despite the widely accepted classification, controversies still persist. We focused on this issue by testing the existence of this three-group diagnostic model of PPA using advanced data-mining methods applied to neuropsychological data (Chapter IV, Study 2). The main conclusion was that even using sophisticated unsupervised learning techniques does not clearly support a distinction of a series of PPA cases into three PPA variants. Results pointed to the existence of two main clinical phenotypes (even in prototypical patients), svPPA and nfvPPA, the lvPPA cases being spread over those groups and never emerging as a single separate variant. These findings align with the growing body of literature suggesting that an accurate classification of PPA is still not completely feasible and supports evidence on the heterogeneity of the syndromes of progressive aphasia, particularly with respect to lvPPA.

Another important role of neuropsychology is allowing for the study of the abnormal mechanisms and features underlying the main forms of PPA. We tested a novel pathophysiological model of nfvPPA through an AAF experimental paradigm (Chapter IV, Study 1). This study showed that healthy older individuals under increasing DAF present qualitative and quantitative speech outputs near to those exhibited by nfvPPA patients. These findings suggest that DAF simulates a distorted speech input signal processing and indicate how it affects motor speech production (sensorimotor integration) through partial disruption of the dorsal language pathway, a phenomenon not yet systematically addressed in this PPA variant. In fact, the delineation of experimental behavioural designs to test models of pathophysiological dysfunctions raise new theoretical implications for understanding the core features of each variant.

At the same time, and from a more clinical standpoint, it is being increasingly acknowledged that the presence of behavioural ancillary features may further characterize

each PPA variant. Changes in personality/behaviour represent a specific clinical marker of typical frontal lobe syndromes. Such symptoms are often reported by caregivers, may be the cause of major distress and often an adequate management is mandatory. I focused on the occurrence of behavioural changes in PPA and its variants, by reviewing the state of the art and by presenting some of the data acquired in our clinical series (Chapter IV, Study 3). Indeed, in our PPA series, nfvPPA patients presented more behaviour changes than lvPPA patients, probably reflecting distinct underlying neurodegenerative diseases, FTLD and AD respectively. The introduction of a neuropsychiatric assessment, together with the performance on neuropsychological tests, may enhance the clinical diagnosis and help with the classification of PPA into subtypes.

The last contribution of neuropsychology that we emphasized within this thesis was its role in the field of disease management (Chapter IV, Study 4). Here, we aimed to assess the effect of speech and language therapy in the mitigation of language deficits in PPA. The results suggested that the implementation of a non-pharmacological, language-based intervention in PPA might attenuate the progression of some language deficits, particularly, naming deficits. Moreover, the results obtained should prompt further studies using randomized, controlled, rater-blind procedures to ascertain the effective role of speech therapy in PPA and on each specific variant.

The lack of pharmacological agents that target the pathological changes in PPA represents a major challenge currently for clinicians dealing with PPA patients. The field of FTLD has undergone major developments and it is expected that within the next years new drugs will be tested. In the meantime, the ability to identify those PPA patients with AD pathology (through certain in-vivo biomarkers) may constitute an argument in favor of treating them symptomatically with known AD drugs or including them in clinical trials designed to tackle AD at its mild stages. Even within this scenario, little is known about how different PPA and typical amnestic AD are in terms of molecular disease mechanisms and how such differences impact on drug efficacy. Neuropsychology may help bridge this gap by providing evidence on the beneficial effect of other therapies in communication in PPA. The last few years have seen an effort to apply electronic augmentative/alternative communication devices to overcome communication problems displayed by aphasic patients, including PPA. Many companies have made available in the technological market several applications to be used through tablets or iPads® that stimulate specific linguistic skills. Despite this evolution, limitations still persist as these devices may not be entirely

suitable for patients presenting certain visual, motor or other cognitive impairments, and are not specifically designed to address the needs of PPA patients. Future research should then focus on the development of technology specifically designed to address novel technological means to facilitate communication between the patient and the environment.

Since Mesulam's seminal paper, PPA has undergone intensive study and became a major research field. Nonetheless, the debate whether PPA constitutes an isolated entity or is part of the characteristics of several diseases persists to the present day. Independently of the subtype considered, it is known that all PPA patients will eventually develop a generalized form of dementia. In fact, the single most important study on the subject indicated that the incidence of generalised dementia in PPA would probably approach 50% over several years (Westbury & Bub, 1997). However, little is known about the natural history of PPA and its variants. Knowing if different disease profiles are associated with distinct evolution patterns has important implications in terms of disease management as well. As such, future work should aim to identify the clinical and neuropsychological predictors of future conversion of PPA to dementia and determine whether the main variants differ in terms of survival. In addition, future work should also include other indicators of disease progression and loss of patient autonomy (e.g. loss of all communication, inability to walk unassisted, inability to eat by oneself, institutionalization, and death). In fact, different disease presentations are likely to have their own natural history. The accurate identification of prognostic factors and setting the time estimated from diagnosis to dementia or other milestones will provide the definition of subgroups of patients based on disease prognosis. Moreover, it will identify patients with an adequate interval to treat and to try to change disease course. In this case, disability milestones will be key outcome measures in future pharmacological trials. In addition, natural history studies are essential to provide the patient and caregivers with estimations of progression to disability milestones that allows long-term care planning soon after diagnosis in order to enhance quality of life (particularly, at a time where the patient is functioning relatively well).

The advances in structural, functional and molecular brain imaging have been essential for the definition of the functional and biological neural mechanisms underlying FTLD in general. The future may see the development of new radioisotopes that target pathological differentiation (e.g. taupathies versus proteinopathies) between patients with the same clinical phenotype. In addition, it is mandatory that future research tackles how

differences in pathological processes are responsible for selectively affecting specific neural circuits. Genetics have also gone an extensive development (with some mutations still awaiting to be identified) but further studies are needed to answer the question of how the same pathogenic mutation affect differently members of a same family, producing distinct clinical phenotypes (Pires et al., 2013). The clinical characterization of this plethora of disease patterns is an important role of neuropsychology. Finally, an interesting line of investigation should be the study of how determinant factors such as language of origin (for instance, in terms of its architectural structure or grammar) and cultural background may account for the variability seen in PPA presentation, fo example, in terms of the relative ease by which specific language deficits (some of them essential for a classification into PPA subtypes) can be elicited.

We have come a long way since the description of the first signs of Ravel's condition, as we now hold knowledge of the neural basis of language and progressive aphasias. Science, in its own thorough, systematic manner (akin to Ravel's own style) has been able to decipher his affliction. That is to say, it has translated into words what this condition represented, giving us a glimpse of the musician's aphasic mind, and ultimately speaking for him. However, while listening to his remarkable masterpieces, one can only believe that his tremendous geniality could have never truly been lost or "trapped" by his aphasic mind, as it lingers in the memory of those who keep experiencing his creations.

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APPENDIX 1

Diagnostic Criteria

A. Primary Progressive Aphasia (Mesulam 2001; Gorno-Tempini et al., 2011)

Inclusion: criteria 1-3 must be answered positively

1. Most prominent clinical feature is difficulty with language
2. These deficits are the principal cause of impaired daily living activities
3. Aphasia should be the most prominent deficit at symptom onset and for the initial phases of the disease

Exclusion: criteria 1-4 must be answered negatively for a PPA diagnosis

1. Patterns of deficits is better accounted for by other nondegenerative nervous system or medical disorders
2. Cognitive disturbance is better accounted for by a psychiatric diagnosis
3. Prominent initial episodic memory, visual memory, and visuoperceptual impairments
4. Prominent, initial behavioral disturbance

B. Progressive Nonfluent Aphasia and nonfluent/agrammatic variant Primary Progressive Aphasia

PROGRESSIVE NONFLUENT APHASIA
(Neary et al., 1998)

Disorder of expressive language is the dominant feature initially and throughout the disease course. Other aspects of cognition are intact or relatively well preserved.

I. *Core diagnostic features*

A. Insidious onset and gradual progression
B. Nonfluent spontaneous speech with at least one of the following: agrammatism, phonemic paraphasias, anomia

II. *Supportive diagnostic features*

A. *Speech and language*
1. Stuttering or oral apraxia
2. Impaired repetition
3. Alexia, agraphia
4. Early preservation of word meaning
5. Late mutism

B. *Behavior*
1. Early preservation of social skills
2. Late behavioral changes similar to FTD

C. *Physical signs:* late contralateral primitive reflexes, akinesia, rigidity, and tremor

D. Investigations
1. *Neuropsychology:* nonfluent aphasia in the absence of severe amnesia or perceptuospatial disorder
2. *Electroencefalography:* normal or minor asymmetric slowing
3. *Brain imaging (structural and/or functional):* asymmetric abnormality predominantly affecting dominant (usually left) hemisphere

NONFLUENT/AGRAMMATIC VARIANT PPA
(Gorno-Tempini et al. 2011)

I. *Clinical diagnosis on nonfluent/agrammatic variant PPA*

At least one of the following core features must be present:
1. Agrammatism in language production
2. Effortful, halting speech with inconsistent speech sound errors and distortions (apraxia of speech)

At least 2 of 3 of the following other features must be present:
1. Impaired comprehension of syntactically complex sentences
2. Spared single-word comprehension
3. Spared object knowledge

II. *Imaging-supported nonfluent/agrammatic variant diagnosis*

Both of the following criteria must be present:
1. Clinical diagnosis of nonfluent/agrammatic variant PPA
2. Imaging must show one or more of the following results:
a. Predominant left posterior fronto-insular atrophy on MRI
b.Predominant left posterior fronto-insular hypoperfusion or hypometabolism on SPECT or PET

III. *Nonfluent/agrammatic variant PPA with definite pathology*

Clinical diagnosis (criterion 1below) and either criterion 2 or 3 must be present:
1. Clinical diagnosis of nonfluent/agrammatic variant PPA
2. Histopathologic evidence of a specific neurodegenerative pathology (e.g. FTLD-tau, FTLD-TDP, AD, other)
3. Presence of a known pathogenic mutation

C. Semantic Dementia and semantic variant Primary Progressive Aphasia

SEMANTIC DEMENTIA
(Neary et al., 1998)

Semantic disorder (impaired understanding of word meaning and/or object identification) is the dominant feature initially and throughout the disease course. Other aspects of cognition, including autobiographic memory, are intact or relatively well preserved.

I. *Core diagnostic features*

A. Insidious onset and gradual progression
B. Language disorder characterized by
- **1.** Progressive, fluent, empty spontaneous speech
- **2.** loss of word meaning, manifest by impaired naming and comprehension
- **3.** semantic paraphasias *and/or*

C. Perceptual disorder characterized by
- **1.** Prosopagnosia: impaired recognition of identity of familiar faces *and/or*
- **2.** Associative agnosia: impaired recognition of object identity

D. Preserved perceptual matching and drawing reproduction
E. Preserved single-word repetition
F. Preserved ability to read aloud and write to dictation orthographically regular words

II. *Supportive diagnostic features*

A. *Speech and language*
- **1.** Press of speech
- **2.** Idiosyncratic word usage
- **3.** Absence of phonemic paraphasias
- **4.** Surface dyslexia and dysgraphia
- **5.** Preserved calculation

SEMANTIC VARIANT PPA
(Gorno-Tempini et al. 2011)

I. *Clinical diagnosis of semantic variant PPA*

Both of the following core features must be present:
- **1.** Impaired confrontation naming
- **2.** Impaired single-word comprehension

At least 3 of the following other diagnostic features must be present:
- **1.** Impaired object knowledge, particularly for low-frequency or low-familiarity items
- **2.** surface dyslexia and dysgraphia
- **3.** spared repetition
- **4.** spared speech production (grammar and motor speech)

II. *Imaging-supported semantic variant PPA*

Both of the following criteria must be present:
- **1.** Clinical diagnosis of semantic variant PPA
- **2.** Imaging must show one or more of the following results:
  - **a.** Predominant anterior temporal lobe atrophy
  - **b.** Predominant anterior temporal hipoperfusion or hypometabolism on SPECT or PET

III. *Semantic variant PPA with definite pathology*

Clinical diagnosis (criterion 1 below) and either criterion 2 or 3 must be present:
- **1.** Clinical diagnosis of semantic variant PPA
- **2.** Histopathologic evidence of a specific neurodegenerative disease (e.g., FTLD-tau, , FTLD-TDP, AD, other)
- **3.** Presence of a known pathogenic mutation

B. *Behavior*
- **1.** Loss of sympathy and empathy
- **2.** Narrowed preoccupations
- **3.** Parsimony

C. *Physical signs*
- **1.** Absent or late primitive reflexes
- **2.** Akinesia, rigidity an tremor

D. *Investigations*

E. *Neuropsyhcology:*
- **1.** Profound semantic loss, manifest in failure of word comprehension and naming and/or face and object recognition
- **2.** Preserved phonology and syntax, and elementary perceptual processing, spatial skills, and day-to-day memorizing

F. *Electroencephalography*: normal

G. *Brain imaging (structural and/or functional):* predominant anterior temporal abnormality (symmetric or asymmetric)

D. Logopenic variant Primary Progressive Aphasia

LOGOPENIC VARIANT PPA
(Gorno-Tempini et al. 2011)

I. *Clinical diagnosis of logopenic variant PPA*

Both of the following core features must be present:
- **1.** Impaired single-word retrieval in spontaneous speech and naming
- **2.** Impaired repetition of sentences and phrases

At least 3 of the following other features must be present:
- **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

II. *Imaging-supported semantic variant PPA*

Both criteria must be present:
- **1.** Clinical diagnosis of logopenic variant PPA
- **2.** Imaging must show at least one of the following results:
  - **a.** Predominant left posterior perisylvian or parietal atrophy on MRI
  - **b.** Predominant left posterior perisylvian or parietal hypoperfusion or hypometabolism on SPECT or PET

III. *Logopenic variant PPA with definite pathology*

Clinical diagnosis (criterion 1 below) and either criterion 2 or 3 must be present:
- **1.** Clinical diagnosis of logopenic variant PPA
- **2.** Histopathologic evidence of a specific neurodegenerative disease (e.g., AD, FTLD-tau, , FTLD-TDP, other)
- **3.** Presence of a known pathogenic mutation

APPENDIX 2

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Short communication

Delayed auditory feedback simulates features of nonfluent primary progressive aphasia

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ABSTRACT

The pathophysiology of nonfluent primary progressive aphasia (nfvPPA) remains poorly understood. Here, we compared quantitatively speech parameters in patients with nfvPPA versus healthy older individuals under altered auditory feedback, which has been shown to modulate normal speech output. Patients (n = 15) and healthy volunteers (n = 17) were recorded while reading aloud under delayed auditory feedback [DAF] with latency 0, 50 or 200 ms and under DAF at 200 ms plus 0.5 octave upward pitch shift. DAF in healthy older individuals was associated with reduced speech rate and emergence of speech sound errors, particularly at latency 200 ms. Up to a third of the healthy older group under DAF showed speech slowing and frequency of speech sound errors within the range of the nfvPPA cohort. Our findings suggest that (in addition to any anterior, primary language output disorder) these key features of nfvPPA may reflect distorted speech input signal processing, as simulated by DAF. DAF may constitute a novel candidate pathophysiological model of posterior dorsal cortical language pathway dysfunction in nfvPPA.

1. Introduction

During normal speech production, auditory feedback provides sensory information that is used to fine-tune vocal motor output: where access to this feedback is limited (as in the speech of hearing impaired individuals), speech distortions tend to emerge. In experimental settings, synthetically altered auditory feedback (AAF) has been shown to modulate speech output when applied to a speaker's air-conducted voice [21]. Two forms of AAF, namely delayed auditory feedback (DAF; [10]) and frequency altered feedback [37] have been most extensively studied. Individuals with intrinsically normal speech fluency often show loss of fluency, distorted prosody or articulatory errors under AAF [7], whereas AAF has been used therapeutically in stutterers [3,24]. Functional brain imaging studies have demonstrated a distributed cortical substrate for AAF in bilateral posterior superior temporal and inferior parietal areas that form part of the dorsal cortical stream for processing speech and other sounds [18,35]. While a number of detailed accounts of dorsal cortical auditory pathway function have been proposed [19,20,26,32,41], these generally emphasise intimate sensorimotor linkages between speech perception and production. More particularly, perceptual control of speech production may engage a mechanism in the posterior superior temporal plane (STP) that links auditory vocal representations with articulatory gestures via the dorsal language pathway [41].

Progressive non-fluent aphasia (the nonfluent/agrammatic variant of primary progressive aphasia, nfvPPA) is a canonical neurodegenerative syndrome characterised by slow, effortful, hesitant speech marred by errors of grammar and articulation [13,14,27]. It is generally considered a disorder of language output programming, though the pathophysiology of nfvPPA is incompletely understood. Neuroanatomically, nvfPPA is linked to damage in peri-Sylvian cortical regions associated with the dorsal language pathway [1,25,30]. The speech disturbance in nfvPPA bears certain similarities to that induced in healthy individuals by AAF: in particular, slowing of speech rate, dysprosody and emergence of articulatory errors. Moreover, patients with nfvPPA have additional deficits in processing complex sounds, including prosody, accents, pitch patterns, voices and environmental noises [11,12,15,16,28], aligning this syndrome with the wider spectrum of progressive aphasia syndromes [38]. This suggests that AAF and nfvPPA might disrupt language network function by at least partly convergent pathophysiological mechanisms, whereby disordered processing of vocal sensory input contributes to impaired speech output via the dorsal language pathway. AAF techniques have been used to assess mechanisms and to rehabilitate dysarthria and dysphasia in stroke, Parkinson's disease and various other neurodegenerative disorders [4,6,9,17,39] but have not been applied

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previously in nfvPPA. Here, we compared quantitatively the speech produced by healthy older individuals under AAF and by patients with nfvPPA. We hypothesised that healthy participants under AAF would show slowing of speech rate and emergence of speech sound errors similar to those exhibited by patients with nfvPPA.

2. Material and methods

2.1. Participants

The healthy participant group (n = 17; nine males, mean age 67 years, range 50–78 years) comprised older native English speakers with no previous history of developmental dysfluency, stuttering or hearing deficits. Patients with nfvPPA (n = 15; 12 males, mean age 77 years, range 66–84 years) were recruited consecutively from a specialist cognitive disorders clinic; all fulfilled current consensus criteria for nfvPPA [13] and general neuropsychological performance profiles corroborated the syndromic diagnosis in all cases [27]. The nfvPPA and healthy participant groups did not differ in gender composition ($\chi^2 = 0.467$; $p = 0.545$), however the nfvPPA group was on average significantly older than the healthy participants (Mann–Whitney $U = 134.000$; $p = 0.03$).

Ethical approval for the study was obtained from the Local Research Ethics Committee, and all participants gave written informed research consent.

2.2. Experimental procedures

The "Grandfather Passage" ([40]; Supplementary Fig. S1) was chosen as a standardised, representative inventory of English phonemes. Three AAF conditions were created using a commercially available software package, Fluency Coach® (http://www.fluencycoach.com/). A short-latency DAF condition was set at 50 ms, corresponding approximately to the minimum delay at which modulation of fluency has been shown in studies of stuttering [22]; a long-latency DAF condition was set at 200 ms, corresponding approximately to the duration of a syllable in conversational spoken English and associated with maximal fluency disruption in previous work [33]; and a combined AAF condition was set at 200 ms plus an upward pitch shift of 0.5 octaves.

The AAF conditions were administered to healthy participants via Sennheiser® (HD265 Linear) headphones at a comfortable listening level (at least 70 dB) in a quiet room. Participants were instructed to read the passage aloud as naturally as possible. Speech samples were recorded as digital wavefiles using Goldwave® software onto a laptop computer with a built-in microphone, for analysis off-line. Before recording commenced, healthy participants were first familiarised with the AAF procedure and set-up. The order of presentation of AAF conditions was randomised between participants, however the baseline (no AAF) condition was always administered last, to reduce any rehearsal effects; participants were blind to condition order.

Speech wavefiles were initially edited manually to remove any extraneous noise sources or pauses. Mean speech rate for each AAF condition in the healthy participant group and for the nfvPPA group was calculated as the mean number of words produced per second, as determined using a customised programme in MATLAB®. The mean total number of errors for each AAF condition in the healthy participant group and for the nfvPPA group was determined from an acoustic analysis of the speech recordings: errors were further subclassified according to whether they were speech sound errors (syllable duplications, omissions or misarticulations), or grammatical errors (errors of morphology or syntax).

2.3. Statistical and qualitative analyses

Statistical analyses were performed using SPSSv17®. Multivariate analyses of variance (MANOVAs) were used to assess the effect of group membership (healthy vs nfvPPA) on behavioural performance in each AAF condition. Age, gender and reverse digit span (an index of auditory working memory potentially relevant to monitoring of speech output under AAF) were incorporated as covariates in group comparisons. MANOVAs were also performed to assess the effect of DAF condition (independent variable: baseline, short-latency DAF, long-latency DAF) on behavioural performance of healthy participants (dependent variables: speech rate, total errors, duplications, misarticulations, omissions); post hoc pair-wise comparisons between conditions using Bonferroni's correction were carried out if significant overall correlations were found. For all tests, results were considered statistically significant at a threshold $p < 0.05$.

In addition, in order to qualitatively assess the confusability of healthy individuals' speech under AAF with speech produced by patients with nfvPPA, speech samples from the nfvPPA group and the healthy group under DAF were classified according to group membership by an experienced cognitive neurologist (PW) blinded to group membership.

3. Results

3.1. Group data on reading task

For the reading aloud task, the healthy participant group showed a significantly faster mean speech rate than the nfvPPA group at baseline ($F(1,27) = 57.7$, $p < 0.0001$) and this difference remained (but was attenuated) under the short-latency DAF ($F(1,27) = 17.9$, $p < 0.0001$), long-latency DAF ($F(1,27) = 8.77$, $p = 0.006$) and combined AAF ($F(1,27) = 6.34$, $p = 0.018$) conditions. The mean total error score and scores for error subcategories did not differ significantly between the healthy participant and nfvPPA groups at baseline nor under any of the AAF conditions; this was likely attributable to the wide variation in error scores within the nfvPPA group (see Fig. 1). In both the healthy participant and nfvPPA groups, the most frequent speech sound error types were phonemic duplications and misarticulations.

Significant main effects of DAF condition on speech rate ($F(2,43) = 29.95$, $p < 0.0001$), total error score ($F(2,43) = 10.35$, $p < 0.0001$) and duplication ($F(2,43) = 8.05$, $p = 0.001$) and misarticulation ($F(2,43) = 6.63$, $p = 0.003$) error scores were found. Speech rate was significantly slower on short-latency and long-latency DAF than on baseline ($p < 0.0001$). Duplication errors were significantly more frequent in the long-latency DAF condition than at baseline or in the short-latency DAF condition ($p < 0.05$) and misarticulation errors were significantly more frequent in the long-latency DAF condition than at baseline ($p = 0.002$).

3.2. Individual data: healthy individuals acquiring speech features of nfvPPA under AAF

A proportion of healthy individuals (Fig. 1) showed slowing of mean speech rate and total error rates within the range of patients with nfvPPA. The proportion of healthy participants acquiring these characteristics rose with increasing DAF latency: at a DAF latency of 200 ms, 4/17 (24%) of healthy participants developed a mean speech rate within the nfvPPA range and 6/17 (35%) developed a total error score within the nfvPPA range. Main effects of gender and age on error rates were observed: healthy male participants produced significantly more duplication errors than healthy female participants overall ($F(1,43) = 5.88$, $p = 0.020$), and healthy participants made significantly more frequent misarticulation errors with advancing age ($F(1,43) = 7.83$, $p = 0.008$).

When speech samples from the nfvPPA group and the healthy participant group under DAF (latency 200 ms) were classified (nfvPPA or healthy) by an experienced cognitive neurologist blinded to group membership, 2/17 (12%) of healthy participant speech samples were misclassified as nfvPPA while all nfvPPA samples were classified correctly.

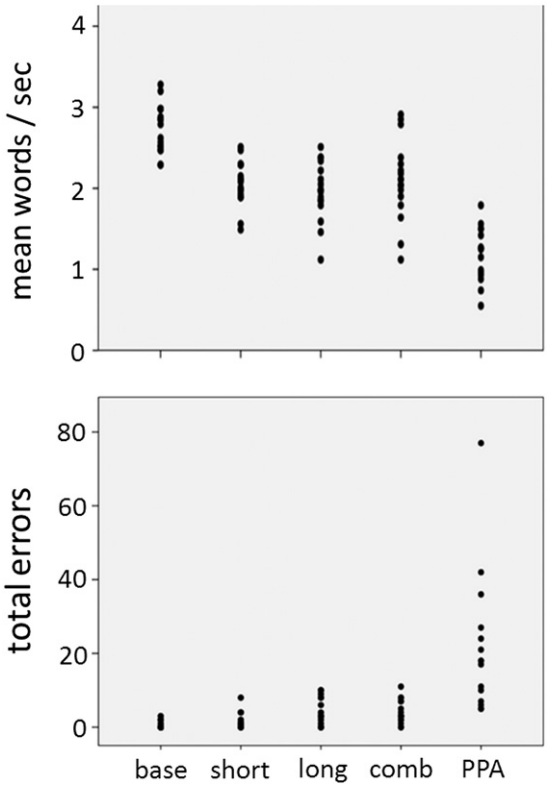

Fig. 1. Plots of individual raw scores for mean speech rate and total error scores for healthy older participants under each AAF condition and for patients with nonfluent primary progressive aphasia on reading aloud. The error score is the raw number of errors made over the whole passage. Key: base, healthy individuals baseline (no altered auditory feedback); short, short latency delayed auditory feedback = 50 ms; long, long latency delayed auditory feedback = 200 ms; comb, combined 200 ms delay plus frequency altered (0.5 octave upward) auditory feedback; PPA, nonfluent primary progressive aphasia.

4. Discussion

Here we have shown that AAF, in particular, increasing DAF latency, is associated with significant deterioration in the rate and quality of speech output in healthy older individuals. These findings corroborate previous evidence in younger individuals concerning the effects of DAF latency on speech output [7,33,35]. Our data further demonstrate that DAF can induce two cardinal features of nfvPPA, slowing of speech rate and speech sound errors, in a substantial proportion (up to a third) of healthy older individuals. The findings imply that an anterior, primary language output disorder is not essential to produce these key features of nfvPPA — disordered processing of speech input signals (as simulated by DAF) can itself do this.

The question arises as to whether the effects of AAF we have demonstrated were essentially nonspecific and any similarity to nfvPPA therefore purely incidental. We consider this unlikely: in susceptible individuals, the profile of speech sound errors produced was qualitatively as well as quantitatively similar to the profile in nfvPPA, duplications and misarticulations being over-represented in relation to omissions. Moreover, the effects of AAF in healthy individuals here were driven largely by DAF (i.e., manipulation of feedback latency) with little added effect from frequency manipulation. Taken together, this circumstantial evidence argues that DAF was exerting a relatively specific pathophysiological effect and that this effect may have accessed a broadly similar mechanism to the disease process in nfvPPA. The effects of DAF on speech rate and error frequency were strongest at a latency of 200 ms on this reading task. This pattern would be anticipated if DAF principally disrupted the sequential transcoding of phonemes into an 'automatic' or obligatory motor speech output: i.e., if DAF acts at the level of the dorsal cortical language pathway [41]. This putative action on the dorsal language pathway would align the DAF paradigm with neuropsychological and structural and functional neuroimaging evidence implicating the dorsal pathway in the pathogenesis of nfvPPA [1,11,12,15,16,25,28,30].

Accounts of language breakdown in nfvPPA have tended to emphasise the role of anterior brain regions with a primary role in motor speech programming. However, recent work has highlighted more general deficiencies of complex sound analysis in the progressive aphasias that are not primarily motor, or indeed, specifically verbal [11,12,15,16,28,38]. This accords both with neuroimaging evidence implicating a distributed brain network and long dorsal white matter tracts in the pathogenesis of nfvPPA [1,25,30] and with the concept that the dorsal language and auditory cortical pathways behave as a functional unit with progressive transcoding of information along these pathways [41]. We do not, of course, argue here for a unitary mechanism of nfvPPA: rather, DAF may be modelling a key component of nfvPPA that has been relatively under-recognised, namely, disordered sensori-motor integration that impacts on motor speech output via the dorsal language pathway. In this model, DAF may simply be acting to simulate the effect of 'noisy' processing in the dorsal pathway; however, the disease process in nfvPPA might parallel the effects of DAF more closely if, for example, a net reduction of processing speed in damaged cortex disrupts the scheduling of auditory-motor transformations in the dorsal pathway and thereby interferes with feedback controls on speech output [26,41]. The dynamic nature of DAF may be particularly relevant in an era of increasing interest in pathophysiologically motivated, reversible models of brain damage, notably transcranial magnetic stimulation [36].

The determinants of individual susceptibility to DAF remain largely unknown. In this and in previous studies, age and gender were identified as important modulatory factors [7,8]. Normal ageing is associated with a generalised slowing of cognitive processing speed [29], which might lead to a correspondingly reduced capacity for tracking alterations of incoming speech signals. This reduction of temporal flexibility might interact with ageing-associated reorganisation of neural networks mediating speech production [31] and executive filtering of auditory inputs [2]. The particular susceptibility of males to DAF may reflect auditory cortical structural and electrophysiological gender differences [5,34]; these gender effects may modulate auditory-motor integration, and may also contribute to the higher incidence of developmental speech impairments in males [42]. Individual susceptibility factors might be exploited in applying DAF in neurodegenerative disease settings: it might, for example, be feasible particularly in older male individuals to use DAF as a speech output 'stress test' in the early stages of progressive aphasia, or to assist in monitoring the impact of therapeutic interventions.

This study should be regarded as preliminary, with several limitations that suggest directions for future work. Larger cohorts are required to substantiate these findings and allow stratification according to specific DAF parameters and individual DAF susceptibility factors, in particular the effects of normal ageing. It will be important to assess the effects of DAF directly in cohorts of patients with progressive aphasia. Future studies should explore the potential of AAF to track the evolution of disease longitudinally across the heterogeneous progressive aphasia spectrum, including the logopenic variant which may be integrally linked to dorsal cortical language pathway dysfunction [14,25,27,36]. The validity of DAF as a pathophysiological model of nfvPPA could be assessed using functional neuroanatomical techniques in parallel cohorts of patients and healthy individuals under DAF: this would help to define the underlying brain mechanism, with the prediction that DAF shifts neural network activity associated with speech production in the healthy brain toward the profile of nfvPPA. It would also be of interest to track adaptation to DAF shown by healthy individuals [23]: the brain mechanisms that support such plasticity might help compensate (or fail to compensate) the effects of brain damage in nfvPPA. We hope that the present data will stimulate further systematic exploration of AAF and related pathophysiological models of progressive aphasia.

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ORIGINAL ARTICLE

Classification of primary progressive aphasia

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Abstract

Our objective was to test whether data mining techniques, through an unsupervised learning approach, support the three-group diagnostic model of primary progressive aphasia (PPA) versus the existence of two main/classic groups. A series of 155 PPA patients observed in a clinical setting and subjected to at least one neuropsychological/language assessment was studied. Several demographic, clinical and neuropsychological attributes, grouped in distinct sets, were introduced in unsupervised learning methods (Expectation Maximization, K-Means, X-Means, Hierarchical Clustering and Consensus Clustering). Results demonstrated that unsupervised learning methods revealed two main groups consistently obtained throughout all the analyses (with different algorithms and different set of attributes). One group included most of the agrammatic/non-fluent and some logopenic cases while the other was mainly composed of semantic and logopenic cases. Clustering the patients in a larger number of groups ($k > 2$) revealed some clusters composed mostly of non-fluent or of semantic cases. However, we could not evidence any group chiefly composed of logopenic cases. In conclusion, unsupervised data mining approaches do not support a clear distinction of logopenic PPA as a separate variant.

Key words: *Primary progressive aphasia, logopenic variant (lvPPA), non-fluent variant (nfvPPA), semantic variant (svPPA), data mining*

Introduction

Primary progressive aphasia (PPA) is a clinical syndrome defined by the presence of a language disorder affecting word-finding, object naming, syntax, phonology, morphology, spelling or word comprehension in the context of a neurodegenerative disease localized to the language-dominant (usually left) hemisphere (1,2). The language impairment should be the most salient feature during, at least, a two-year period, as memory for recent events, reasoning, visuospatial and social skills are relatively well preserved during the initial stages of the disease (3). During the course of PPA, other cognitive deficits can emerge, although aphasia remains the most severe impairment (1), invariably evolving to mutism (4).

PPA has been primarily considered a form of presentation of frontotemporal lobar degeneration (FTLD), a clinically, pathologically and genetically heterogeneous condition representing several distinct disorders (that include progressive decline in personality/behaviour or language) associated with circumscribed neurodegeneration of the frontal and anterior temporal lobes (5). In this context, two main language presentation patterns have been traditionally accepted. Progressive non-fluent aphasia (PNFA) (6,7) defines patients with an effortful, non-fluent speech (less than one-third the speech rate of healthy subjects) (8,9) with speech sound errors and distortions attributable to apraxia of speech. These patients also often have grammatical deficits in language production and impaired syntactic comprehension. Semantic dementia (SD) (10–12), in contrast, is characterized by a fluent, well-articulated and grammatically correct speech, but profoundly anomic and/or circumlocutory, giving the listener the subjective feeling of being 'empty'. Another core feature of SD is the single-word comprehension deficit that results from a progressive breakdown of semantic memory (13) affecting other non-verbal areas, such as visual information (recognition of

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familiar faces or objects), odours and flavours (14) or non-verbal environmental sounds (15) with disease progression.

The extensive clinical description and distinction between PNFA and SD led many authors to argue that they reflected an oversimplification of the clinical presentations of primary progressive aphasia. However, a subset of patients seemed not to fit this dichotomic classification and a third clinical variant, associated with a different underlying pathology (in particular, Alzheimer's disease (AD)), was empirically described and termed logopenic progressive aphasia (4,16). This new phenotype includes patients with a slow, hesitant speech with word-finding pauses, anomia and phonemic paraphasias, and syntactically simple but grammatically correct sentences, without motor speech disturbances. A length-dependent repetition deficit is also characteristic of this variant, presumably accounted for by a more general phonological short-term memory deficit (17). Recently, clinical, imaging and pathological criteria have been formally defined for three distinct variants of PPA (18): agrammatic/non-fluent (nfvPPA), semantic (svPPA) and logopenic progressive aphasia (lvPPA). This clinical classification has been supported by several imaging, genetic and pathological studies (18–24).

Despite this effort, uncertainties persist regarding classification of PPA. Some cases can hardly be classified into one of the three syndromes, as shown in studies reporting a considerable variability in non-classification rates (between about 10 and 41% of cases) (19,25–28). At the same time, some research groups argue for the existence of other PPA subtypes, either representing subsets of patients from specific variants (29,30), or 'mixed' phenotypes, i.e. cases displaying core features specific to more than one variant (e.g. deficits both in grammar and single-word comprehension) (25,31,32). On the other hand, lvPPA was the last clinical syndrome to be described and, with the exception of sentence repetition, the diagnosis is largely based on the exclusion of the two other variants (absence of single-word comprehension deficits and motor speech disorders). The lack of specific and distinctive features in this group may sometimes lead to an erroneous classification and delay diagnosis (33,34), especially because this group tends to incorporate patients with heterogeneous underlying pathologies (27). In a prospective study with 46 PPA patients assessed with a standard neuropsychology test battery and with samples of connected speech, a principal component analysis clearly identified two main groups (a semantic and an agrammatic factor) but did not suggest evidence for a third discrete logopenic syndrome. A substantial proportion of patients did not show either semantic or non-fluent/agrammatic features but could not be classified as logopenic. This raises the question whether logopenic diagnostic features may be insufficiently specific to separate this group from the other syndromes (26).

Distinguishing different disease presentations in PPA from a neuropsychological standpoint is important to effectively tackle the progression and conversion to dementia, improve diagnostic accuracy and lead to adequate pharmacological intervention. Sophisticated data-mining approaches to analyse large datasets are gaining relevance in neurodegenerative diseases research, since traditional statistical analyses have difficulty dealing with the large amounts of clinical, neuropsychological, genetic and imaging data. Furthermore, machine learning methods are well suited to deal with high dimensional data, to adequately handle missing values and to help solving dataset imbalance problems. They are currently being applied to evaluate AD risk assessment in large multicentric datasets such as the Alzheimer's Disease Neuroimaging Initiative (ADNI) project (35). Moreover, our group has shown that these methods can improve accuracy, sensitivity and specificity of classification and predictions through neuropsychological testing in Mild Cognitive Impairment (MCI) and AD (36,37) patients. With regard to PPA, the applicability of these methods is certainly constrained by sample sizes, as most studies have enrolled small numbers of patients (the largest including 84 patients (28)). The present study aims to test the three-groups diagnostic model of PPA versus the existence of two main/classic groups, as well as detect the existence of additional disease presentation patterns, by using several unsupervised and learning algorithms in a clinical series of 155 PPA patients.

Methods

Participants

Participants were referred to language/neuropsychological assessment at two clinical institutions in Lisbon (Language Research Laboratory, Faculty of Medicine of Lisbon and Memoclínica), between 1983 and 2012. The study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee.

Inclusion criteria

Patients were included if they were right-handed Portuguese native speakers and fulfilled the diagnostic criteria for PPA (1,2): 1) most prominent clinical feature is difficulty with language (word-finding deficits, paraphasias, effortful speech, grammatical and/or comprehension deficits); 2) activities of daily living are maintained except those related to language; 3) aphasia is the most prominent deficit at symptom onset and for the initial stages of the disease; 4) absence of prominent initial episodic memory, visual memory, visuospatial impairment or behavioural changes during the initial stages of the illness;

and 5) aphasia is not better accounted for by other non-degenerative diseases of the nervous system (e.g. stroke or tumour) or by a psychiatric illness.

Exclusion criteria

Patients were excluded if they had, at least, one of the following: 1) presence of dementia according to the DSM-IV-TR (38) or significant impairment on instrumental activities of daily living (score ≥ 3 points on the first eight items of the Blessed Dementia Rating Scale (BDRS)) (39,40); 2) presence of neurological disorder (stroke, brain tumour, brain trauma, epilepsy) able to induce language or other cognitive impairments: 3) uncontrolled systemic illness with cerebral impact (hypertension, metabolic, endocrine, toxic and infectious disease); 4) history of alcohol abuse or recurrent substance abuse or dependence; 5) presence of mental retardation; and 5) presence of severe auditory or visual impairment able to compromise the application of language/neuropsychological tests.

Procedures

All patients underwent at least one language/neuropsychological examination, which was consistently performed by the same senior neuropsychologist (MG). In a few cases, the language assessment was also carried out by an experienced speech therapist. All assessments followed a standard protocol, comprising several test batteries and scales:

Language assessment.

- Battery for the Assessment of Aphasia of Lisbon (41–43): Aphasia severity rating scale; description of the Cookie Theft picture for analysis of spontaneous speech; visual confrontation naming; object identification; comprehension of oral commands; word and sentence repetition; text reading and comprehension; spontaneous writing and writing of words and sentences by copy or by dictation.
- Snodgrass & Vanderwart Naming Test (44)
- Token Test (22-item short-version) (45)
- Verbal (semantic and phonological) fluency (46)
- Vocabulary subtest from Wechsler Adult Intelligence Scale (WAIS) (47)

Neuropsychological assessment. Some neuropsychological tests with a verbal component (e.g. verbal memory) could not be considered for analysis due to the interference of language deficits already present in some cases at the evaluation moment. Nonverbal tests were preferred instead to evaluate different cognitive domains:

- Battery of Lisbon for the Evaluation of Dementia (BLAD) (48), which includes the following tests: cancellation task; motor and graphomotor initiatives; digit span; personal, spatial and temporal orientation; buccofacial and limb praxis (ideomotor and ideative) testing by oral command, imitation and manipulation of objects; written/mental calculation; clock drawing test, copy of a cube and of geometrical drawings; visual memory; Raven's coloured progressive matrices – Ab series; right-left orientation.
- Trail Making Test (TMT) (49)
- Blessed Dementia Rating Scale (BDRS) (39)

Z-scores were calculated after the equation [z = (x-mean)/SD)] according to age/education norms for the Portuguese population (50). Impairment was considered if a subject scored more than 1.5 SD below the mean for age/education. Neuropsychological diagnosis and further classification into one of the three subtypes (18) was based on the consensus between two neuropsychologists (MG and CM), using the neuropsychological and language profiles (gold standard) (Table I).

Statistical analysis

Demographic, clinical and neuropsychological data were analysed using a one-way ANOVA for numerical data, with post hoc analysis with Bonferroni correction, and Pearson's χ^2 test for nominal data, using IBM SPSS Statistics software (v. 20). Differences were considered statistically significant at $p < 0.05$.

Data mining settings

The original dataset comprised 155 patients, 104 (67%) of which were clinically classified into one of the three PPA subtypes (classifiable patients; 31 nfvPPA, 35 svPPA, 38 lvPPA). The remaining 51 cases (33%) were considered unclassifiable (unclassifiable patients; unPPA). Since we were interested in testing the true existence of three PPA variants under optimal conditions, i.e. in a group of typical cases of each variant, we decided to define a subgroup of prototypical patients (model patients; $n = 36$, distributed as 14 nfvPPA, 12 svPPA, 10 lvPPA). This group included patients whose classification was performed with a high degree of confidence by clinical experts (good representatives of each subtype).

Data pre-processing. Variables whose percentage of missing values was superior to 30% were removed. We imputed missing values beforehand using the average value or mode (whether the attribute was numerical or nominal, respectively) for algorithms that cannot deal with missing values (e.g. EM) or for algorithms for which we considered it favourable to handle missing values a priori (K-Means and X-Means). Data imputation was not performed in algorithms that are constructed to handle missing values (e.g. Hierarchical Clustering). Variables using Z-scores were categorized into 'no alterations', 'mild impairment', 'moderate impairment' and 'severe

Table I. International clinical recommendations for classification of PPA (Gorno-Tempini et al., 2011).

	Core features	Ancillary features
Non-fluent/agrammatic variant (nfvPPA)	■ Agrammatism in language production ■ Effortful, halting speech with inconsistent speech sound errors and distortions (apraxia of speech)	■ Impaired comprehension of syntactically complex sentences ■ Absence of single-word comprehension or object knowledge impairments
Semantic variant (svPPA)	■ Impaired confrontation naming ■ Impaired single-word comprehension	■ Impaired object knowledge, particularly for low frequency or low-familiarity items ■ Surface dyslexia or dysgraphia ■ Absence of repetition or motor speech production deficits
Logopenic variant (lvPPA)	■ Impaired single-word retrieval in spontaneous speech and naming ■ Impaired repetition of sentences and phrases	■ Speech (phonologic) errors in spontaneous speech and naming ■ Absence of single-word comprehension, object knowledge or motor speech / agrammatism impairments

impairment' classes, based on the deviation of values from the mean for age/education. Numerical and ordinal variables were normalized following the min-max normalization (51).

Variable selection. Four variable datasets were defined, based on distinct domains:

1) Total set of variables, divided into demographic (patient identification, gender, age at symptom onset, age at first assessment, education), clinical (PPA classification, first symptoms, family history of dementia, personal medical history) and neuropsychological variables (performance on each language /neuropsychological test) (154 variables). Due to the large number of variables constituting this dataset, it was only used in a few exploratory analyses.
2) Language variables, including scores on several language tests and measures (96 variables).
3) Model variables, variables found necessary and sufficient to classify the subgroup of 'model patients' (46 variables).
4) Operational criteria variables. This set of variables was a group of nine qualitative language dimensions operationally defined after the core features specified in the working consensus research guidelines and already defined by other authors (21): 'motor speech disorder', 'agrammatism', 'word retrieval problems in spontaneous speech', 'naming', 'single-word repetition', 'single-word comprehension', 'sentence repetition', 'sentence comprehension', 'paraphasias in spontaneous speech'. The severity of impairment on each attribute was graded from 0 – absent, 1 – subtle or questionable, 2 – mild but definitely present, to 3 – moderate to severe. This subset of attributes was only tested on the 'model patients' subgroup.

Unsupervised learning. Unsupervised learning corresponds to a data-mining approach whose main purpose is grouping cases according to their characteristics. As such, unlike supervised learning, these algorithms do not use the target class (PPA variant in our study) to group the patients (52). Clustering was the unsupervised learning method used in this study. Clustering models divide the cases of a dataset (patients in our study) into a given number of homogeneous groups of cases (clusters), so that cases belonging to one group are similar to one another and dissimilar from cases included in other groups (51,52). This is usually performed by defining appropriate metrics related to the notions of distance and similarity between pairs of observations. We used clustering methods to identify groups of patients without clinical supervision and then verify if the predefined PPA variants matched the automatically discovered groups (confirm whether patients from different PPA variants are separated and placed together in different groups). In addition, we investigated the potential existence of other groups apart from the three canonical PPA variants (nfvPPA, lvPPA, svPPA) operationally defined in the literature (18).

We used several clustering approaches, namely the Partitional Clustering algorithms K-Means (51) (which produces k non-overlapping clusters or centroids where each case belongs to the cluster with the nearest mean) and Expectation Maximization (EM) (53) (which groups data using a finite mixture density model of k probability distributions or clusters) applied through Waikato Environment for Knowledge Analysis software (WEKA® version 3.7.1, 2004). Different values for the number of clusters (k = 2, 3, and 4) were predefined a priori with the purpose of testing the possible existence of more (or less) than three PPA classes or possible groups corresponding to intersections. In addition, we used the X-Means algorithm (54) (a variant of K-Means which estimates the number of clusters (k) by optimizing the Bayesian Information Criteria) through WEKA® software.

Hierarchical Clustering was also performed. In this case, a fixed number of clusters is not defined a priori. Instead, clusters are represented in a hierarchy based on their similarity, creating a dendogram (53). Subsequently, clusters are yielded by choosing specific cutting levels in the dendogram. We used the

complete linkage method to determine the distance between groups of patients. Analyses were performed using Matlab®.

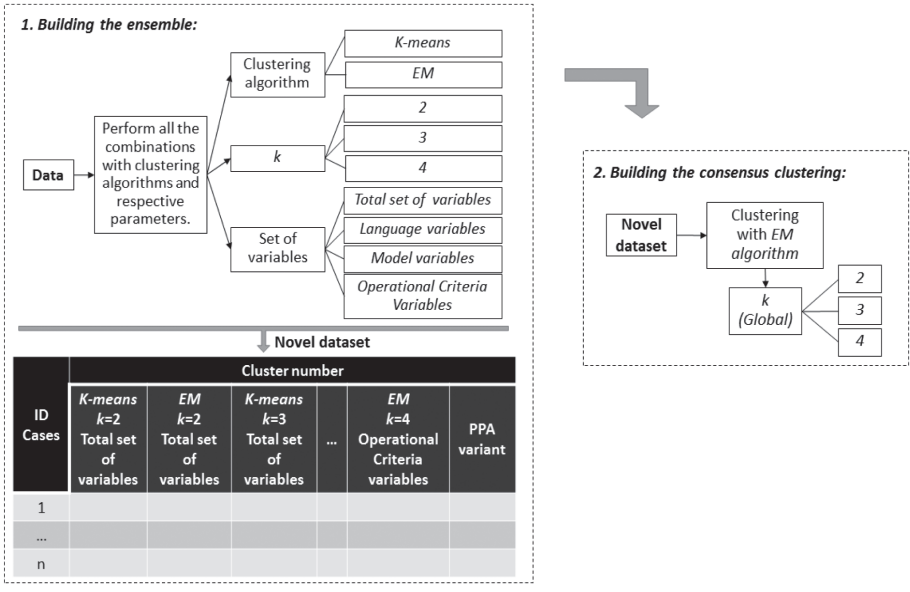
Since, in some cases, individual clustering algorithms may not be capable of correctly finding the underlying structure for all datasets, we additionally followed a Consensus Clustering approach (55). The goal was to identify stable clusters, given that clusters discovered by several algorithms tend to be more reliable. Consensus Clustering consists of producing a single clustering (consensus) by combining different clustering results on the same data, resulting from: 1) runs of the same algorithm with different parameters; 2) runs of different algorithms with the same set of patients and variables; and 3) runs of the same algorithm with different sets of variables. As illustrated in Figure 1, in the present study, the methodology consisted of a first step, in which the clustering ensemble was built by running alternatively K-Means and EM several times with the parameter k set as 2, 3 and 4, and alternating the set of variables used in each analysis (total set of variables, language, model and operational criteria variables). A new dataset was generated where columns depicted the cluster assigned to each case, according to different clustering algorithms and/or type of variables used in the analyses (as shown in the lower part of Figure 1). In a second step, the EM clustering algorithm combined the clustering results from the first step to generate a representative consensus clustering, reaching a global parameter k (k global). This task was performed with WEKA® software.

In each analysis, results were evaluated by identifying which patients (along with their previously clinical PPA class assignment) composed each cluster found, in order to inspect how well the PPA classes were divided into distinct clusters. Moreover, we analysed which clusters were more stable and consistent (groups that remained essentially unalterable whenever the parameter k/set of variables changed).

Results

Demographic data on the 155 cases with PPA (20% nfvPPA, 23% svPPA and 24% lvPPA variants clinically classifiable and 33% unPPA) are shown in Table II. Patients with nfvPPA had significantly longer evolution times between onset and the first assessment compared to the other variants or unclassifiable patients.

Regarding the language/neuropsychological evaluation, and consistent with the diagnostic criteria, svPPA patients showed the lowest performance on Snodgrass & Vanderwart Naming Test, object identification and vocabulary compared to the other variants (Table III). As expected, nfvPPA group was the one that showed a significantly higher frequency of speech production deficits (agrammatism, articulation deficits and stuttering-like dysfluencies) compared to the other groups. Furthermore, nfvPPA patients had a high frequency of hesitations in speech production, as lvPPA patients did. Patients with lvPPA and nfvPPA patients were significantly impaired on sentence repetition, and nfvPPA patients also showed significantly lower scores on measures of executive function, praxis, calculation and visuoconstructive abilities, compared to the two other variants and unclassifiable patients (Table III).



Note: The procedure consists of two steps: 1) Building the ensemble, where algorithms K-Means and EM are run alternately several times with the parameter k set as 2, 3 and 4, and alternating the set of variables used in each analysis (total set of variables, language, model and operational criteria variables). The dataset created by this procedure (novel dataset) presents columns depicting the cluster assigned to each case (according to different clustering algorithms and/or type of variables used in the analyses); 2) Building the consensus clustering, where Expectation Maximization algorithm is run in the novel dataset, reaching a global clustering parameter k (k global).

Figure 1. Diagram illustrating the two-step approach designed to obtain the Consensus Clustering.

Table II. Demographic characteristics.

	nfvPPA ($n=31$)	svPPA ($n=36$)	lvPPA ($n=37$)	unPPA ($n=151$)	Statistics	Differences
Gender (F:M)	18:15	18:18	26:13	26:21	$\chi^2=3.712$ $p=0.294$	n.s.
Age at onset (yrs)	66.6(6.9)	64.2(7.4)	68.3(9.1)	68.8(9.0)	$F=2.398$ $p=0.071$	n.s.
Age at 1st assessment (yrs)	69.7(6.8)	66.2(7.4)	69.9(8.8)	70.6(8.9)	$F=2.230$ $p=0.087$	n.s.
Education (yrs)	7.2(4.1)	7.9(4.4)	7.5(4.3)	9.1(4.9)	$F=1.390$ $p=0.248$	n.s.
Time from onset to 1st assessment (months)	**37.3(29.7)**	22.1(13.2)	23.7(11.4)	23.0(14.8)	**$F=5.228$ $p=0.002$**	nfvPPA > svPPA, lvPPA, unPPA
CDR-SB[a]	1.3(0.7)	1.6(1.1)	1.6(1.1)	-	$F=0.027$ $p=0.974$	n.s.

[a]The figures in the table are mean values, the figures in parentheses are standard deviations; bolded values represent statistically significant differences.
CDR-SB Clinical Dementia Rating – sum of boxes; F: female; lvPPA: logopenic variant primary progressive aphasia; M: male; nfvPPA: non-fluent variant primary progressive aphasia; svPPA: semantic variant primary progressive aphasia; unPPA: unclassifiable primary progressive aphasia; yrs: years.

Partitional Clustering

In order to perform analyses as thorough and extensive as possible, the different clustering approaches were applied to the different sets of variables (total, language, model and operational criteria variables) and to the different groups of cases (all available patients, classifiable patients and model patients).

In general, clustering with standard algorithms (in particular, K-Means and EM) and with different predefined number of clusters (k = 2, 3, or 4) produced clusters composed of cases coming from all PPA subtypes. This was initially observed with the entire set of patients (classifiable and unclassifiable). Moreover, unclassifiable patients did not form a

Table III. Neuropsychological data of the sample.

	nfvPPA ($n=31$)	svPPA ($n=36$)	lvPPA ($n=37$)	unPPA ($n=51$)	Statistics	Differences
Language measures:						
Speech production						
Presence of agrammatism (Y:N)	**13:12**	7:27	7:29	3:41	**$\chi^2=19.451$ $p<0.001$**	nfvPPA < svPPA, lvPPA, unPPA
Presence of articulation deficits *(Y:N)*	**13:13**	0:37	3:34	1:44	**$\chi^2=46.112$ $p<0.001$**	nfvPPA < svPPA, lvPPA, unPPA
Presence of hesitations (Y:N)	**10:13**	2:33	**14:21**	7:37	**$\chi^2=17.647$ $p=0.001$**	lvPPA, nfvPPA < svPPA, unPPA
Presence of stuttering-like dysfluencies (Y:N)	**11:14**	1:34	6:29	2:41	$\chi^2=24.948$ **$p<0.001$**	nfvPPA < svPPA, lvPPA, unPPA
Aphasia Severity Scale (/6)	**2.9(1.3)**	4.21(0.8)	4.0(0.9)	4.5(0.7)	**$F=18.264$ $p<0.001$**	nfvPPA < svPPA, lvPPA, unPPA
Object Naming (% correct)	71.3(32.4)	60.7(33.0)	75.6(29.11)	**92.0(16.0)**	**$F=8.321$ $p<0.001$**	unPPA > nfvPPA, svPPA
SVNT (% correct)	81.5(19.9)	**52.6(23.0)**	78.8(16.5)	82.3(19.7)	**$F=11.971$ $p<0.001$**	svPPA < nfvPPA, lvPPA, unPPA
Object Identification (% correct)	98.9(3.8)	**95.4(9.3)**	99.6(2.2)	99.5(3.0)	**$F=4.691$ $p=0.004$**	svPPA < lvPPA, unPPA
Repetition						
Words (/30)	**27.6(6.1)**	30.0(0.2)	28.9(2.8)	30.0(0.1)	**$F=4.514$ $p=0.005$**	nfvPPA < svPPA, unPPA
Sentences (/14)	**4.0(3.4)**	8.0(3.5)	**4.6(2.1)**	9.3(2.4)	**$F=25.490$ $p<0.001$**	nfvPPA, lvPPA < svPPA, unPPA
Comprehension						
Oral Commands (/8)	**7.2(1.0)**	7.3(1.3)	7.6(0.5)	7.8(0.3)	**$F=3.692$ $p=0.014$**	nfvPPA < unPPA
Token Test (/22)	**10.7(4.8)**	14.0(5.2)	12.0(4.3)	15.1(3.8)	**$F=6.174$ $p=0.001$**	nfvPPA < svPPA, unPPA lvPPA < unPPA
Presence of Alexia (Y:N)	18:12	10:20	12:22	**4:35**	**$\chi^2=19.073$ $p<0.001$**	unPPA < nfvPPA, svPPA, lvPPA

(Continued)

Table III. (*Continued*)

	nfvPPA ($n=31$)	svPPA ($n=36$)	lvPPA ($n=37$)	unPPA ($n=51$)	Statistics	Differences
Presence of Agrafia (Y:N)	24:8	11:25	17:21	**10:33**	**$\chi^2=22.610$ $p<0.001$**	unPPA, svPPA < nfvPPA, lvPPA
Vocabulary (% correct)	66.1(19.7)	**62.2(28.1)**	77.8(24.3)	90.2(10.2)	**$F=3.960$ $p=0.015$**	svPPA < nfvPPA, lvPPA, unPPA
General cognitive measures:						
Letter Cancellation (As)						
Time to complete (seconds)	57.1(24.2)	49.9(21.8)	56.7(26.1)	53.4(19.2)	$F=0.681$ $p=0.565$	n.s.
No. of letters cancelled (/16)	13.9(3.1)	15.0(1.6)	14.8(1.7)	15.2(1.4)	$F=2.550$ $p=0.059$	n.s.
TMT – A						
Time to complete (seconds)	104.6(31.9)	65.8(38.8)	97.9(46.8)	103.7(35.2)	$F=2.349$ $p=0.087$	n.s.
No. connections (/24)	23.4(1.8)	23.2(2.2)	23.4(0.8)	22.9(4.1)	$F=0.095$ $p=0.963$	n.s.
No. errors	0.6(1.2)	0.6(1.6)	0.7(0.8)	0.7(1.6)	$F=0.010$ $p=0.999$	n.s.
TMT – B						
Time to complete (seconds)	273.5(43.3)	173.0(81.5)	238.30(73.1)	238.7(83.0)	$F=2.756$ $p=0.055$	n.s.
No. connections (/24)	15.0(9.8)	23.0(2.6)	14.6(10.2)	18.0(8.6)	$F=1.904$ $p=0.145$	n.s.
No. errors	1.7(1.1)	1.0(1.6)	2.0(1.5)	2.3(5.9)	$F=0.223$ $p=0.880$	n.s.
Digit Forward[1]	**3.7(1.6)**	4.8(1.4)	4.1(0.9)	4.7(1.1)	**$F=4.939$ $p=0.003$**	nfvPPA < svPPA, unPPA
Digit Backwards	**2.0(1.4)**	2.9(1.2)	2.8(0.9)	3.0(0.9)	**$F=5.687$ $p=0.001$**	nfvPPA < svPPA, unPPA
Category Fluency (Food)	7.0(4.1)	8.8(5.4)	9.0(4.5)	10.2(4.5)	$F=2.214$ $p=0.090$	n.s.
Motor Initiative (/3)	**1.9(1.1)**	2.5(0.9)	2.2(0.7)	2.5(0.8)	**$F=2.956$ $p=0.035$**	nfvPPA < unPPA
Graphomotor Iniative (/2)	1.2(0.7)	1.6(0.6)	1.5(0.6)	1.5(0.5)	$F=2.584$ $p=0.056$	n.s.
WMS-III Visual Memory – Designs B and C (/28)	10.7(8.1)	14.5(7.3)	13.5(6.0)	15.1(6.4)	$F=1.773$ $p=0.158$	n.s.
Praxis (/12)	**11.0(1.4)**	11.9(0.4)	11.8(0.6)	11.7(1.0)	**$F=6.237$ $p=0.001$**	nfvPPA < svPPA, lvPPA, unPPA
Copy of Cube (/3)	**1.9(1.1)**	2.2(0.8)	2.6(0.7)	2.1(0.9)	**$F=2.743$ $p=0.046$**	nfvPPA < lvPPA
Clock Drawing Test (/3)	**1.5(0.9)**	2.2(0.8)	1.9(0.8)	2.3(0.8)	**$F=4.781$ $p=0.003$**	nfvPPA < svPPA, unPPA
Calculation (/14)	**7.5(5.2)**	9.7(4.5)	9.1(4.1)	10.9(3.7)	**$F=4.145$ $p=0.008$**	nfvPPA < unPPA
CPM (Ab series; /12)	6.1(3.1)	7.5(2.8)	6.7(2.6)	7.0(2.5)	$F=1.438$ $p=0.235$	n.s.
Right-left orientation (/6)	**4.9(1.9)**	5.6(1.0)	5.5(1.0)	5.7(0.8)	**$F=2.860$ $p=0.040$**	nfvPPA < unPPA
BDRS						
Total (/28)	3.2(1.6)	2.9(1.9)	2.4(1.7)	2.9(2.0)	$F=1.088$ $p=0.357$	n.s.
ADLs (/8)	0.8(0.7)	1.0(0.8)	0.9(0.8)	0.8(0.6)	$F=0.460$ $p=0.711$	n.s.

The figures in the table are raw mean values, the figures in parentheses are raw standard deviations; bolded values represent statistically significant differences

ADLs: activities of daily living; BDRS: Blessed Dementia Rating Scale; CPM: Coloured Progressive Matrices; F: one-way ANOVA parametric test; lvPPA: logopenic variant primary progressive aphasia; nfvPPA: non-fluent variant primary progressive aphasia; N: no; n.s.: non-significant; *p*: *p*-value; SVNT: Snodgrass & Vanderwart Naming Test; svPPA: semantic variant primary progressive aphasia; TMT: Trail Making Test; unPPA: unclassifiable primary progressive aphasia; WMS – III: Wechsler Memory Scale Third Edition; Y: yes; χ^2: chi-square test.

separate group. Instead, they emerged within groups containing svPPA, lvPPA or nfvPPA cases. Since the main goal of this analysis was to infer whether the automated procedure was able to separate the patients according to their predefined variant, we decided to discard the unclassifiable cases for the

subsequent analyses, thus removing noise from the dataset.

Overall, considering only the classifiable or model patients, clustering with K-Means and EM also produced clusters composed of a mixture of PPA subtypes. This means that the gold standard (clinical judgment) was not concordant with the clusters generated. Table IV (left hand side panels) shows clustering results when k was set to 3, based on the hypothesis that three groups would emerge, each representing the three major PPA phenotypes. Clustering the classifiable patients with the total set of variables (Table IV, first panel) produced a group with a mixture of six lvPPA, 12 nfvPPA and six svPPA cases (Cluster $\mathbf{C0_{k3}}$), a group with 13 lvPPA, 12 nfvPPA and eight svPPA cases (Cluster $\mathbf{C1_{k3}}$), and finally a group of 19 lvPPA, seven nfvPPA and 21 svPPA cases (Cluster $\mathbf{C2_{k3}}$). With regard to the model patients (with the same set of variables) the results were slightly better given the emergence of a small but isolated nfvPPA group (Table IV, second panel, cluster $\mathbf{C0_{k3}}$). However, the majority of lvPPA and svPPA cases were still grouped together within the same cluster (Table IV, second panel, cluster $\mathbf{C1_{k3}}$). Beyond that, the remaining majority of nfvPPA cases were also grouped with some lvPPA and svPPA cases (Table IV, second panel, cluster $\mathbf{C2_{k3}}$). Results were similar after grouping the classifiable patients with a more specific language set of variables (Table IV, third panel). After applying K-Means to model patients with the dataset of model variables, a single cluster composed only of nfvPPA cases was again evident, containing now the majority of nfvPPA cases (Table IV, fourth panel, Cluster $\mathbf{C2_{k3}}$), while the other subtypes scattered among the remaining clusters. Thus, this reduced set of variables allowed for a clearer isolation of nfvPPA cases. It is worth noting that none of the other two clusters showed a preponderance of lvPPA over the other PPA subtypes. The outcome produced by the application of EM, when k was increased to 4 to the dataset of language variables and all classifiable patients, included a small cluster of mainly svPPA cases (Table IV, fifth panel, cluster $\mathbf{C3_{k4}}$) and another group of 12 nfvPPA cases (Table IV, fifth panel, cluster $\mathbf{C2_{k4}}$). The other two clusters were primarily constituted of mixtures of svPPA plus lvPPA (Table IV, fifth panel, cluster $\mathbf{C0_{k4}}$) and nfvPPA/lvPPA patients (Table IV, fifth panel, cluster $\mathbf{C1_{k4}}$), i.e. even for large values of k, no group comprising almost exclusively lvPPA cases was found, since these cases were spread over the remaining groups. Notwithstanding this, the identification of a really isolated semantic cluster was only achieved with model patients and using the operational criteria variables (Table IV, sixth panel, cluster $\mathbf{C3_{k4}}$). Within this analysis, a single cluster composed only of nfvPPA cases was again observed (Table IV, sixth panel, cluster $\mathbf{C1_{k4}}$). The remaining clusters (Table IV, sixth panel, clusters $\mathbf{C0_{k4}}$ and

Table IV. Clustering results when k = 3 (left hand side): dataset with the total set of variables for all classifiable patients (first panel), model patients (second panel) and language variables for all classifiable patients (third panel), using EM, and model variables for model patients, using K-Means (fourth panel); Clustering results when k = 4 (right hand side): dataset with language variables for all classifiable patients using EM (fifth panel); data set with operational criteria variables for model patients, using K-Means (sixth panel).

	EM (k = 3)						K-Means (k = 3)						EM (k = 4)						K-Means (k = 4)					
	Total set of variables						Language variables			Model variables			Language variables			Operational criteria variables								
	1st panel			2nd panel			3rd panel			4th panel			5th panel			6th panel								
	All Classifiable patients			Model patients			All Classifiable patients			Model patients			All classifiable patients			Model patients								
Clinical classification	$\mathbf{C0_{k3}}$	$\mathbf{C1_{k3}}$	$\mathbf{C2_{k3}}$	$\mathbf{C0_{k3}}$	$\mathbf{C1_{k3}}$	$\mathbf{C2_{k3}}$	$\mathbf{C0_{k3}}$	$\mathbf{C1_{k3}}$	$\mathbf{C2_{k3}}$	$\mathbf{C0_{k3}}$	$\mathbf{C1_{k3}}$	$\mathbf{C2_{k3}}$	$\mathbf{C0_{k4}}$	$\mathbf{C1_{k4}}$	$\mathbf{C2_{k4}}$	$\mathbf{C3_{k4}}$	$\mathbf{C0_{k4}}$	$\mathbf{C1_{k4}}$	$\mathbf{C2_{k4}}$	$\mathbf{C3_{k4}}$
lvPPA	6	13	19	0	6	4	17	18	3	5	5	0	13	20	2	3	6	0	4	0
nfvPPA	12	12	7	4	1	9	15	5	11	1	3	10	5	13	12	1	6	6	2	0
svPPA	6	8	21	0	10	2	9	20	6	6	6	0	20	5	0	10	0	0	3	9

Note: Figures in each cell represent number of cases; C: cluster; EM: Expectation Maximization; k: clustering parameter; lvPPA: logopenic variant primary progressive

$\mathbf{C2_{k4}}$) constituted, once again, mixtures of lvPPA with nfvPPA and svPPA patients, respectively.

Due to the aforementioned inconsistency between automated clustering and gold standard with k = 3 (expected number of clusters) and 4, we decided to perform a detailed evaluation of the emergent clusters in order to discover a distribution pattern of PPA cases and/or to find the real number of clusters detected by this study.

It is well known that finding the ideal number of clusters is a difficult task in unsupervised learning. If k is too small the cluster may aggregate many cases, which are very different from each other. Nevertheless, if k is too large similar cases tend to be split in different groups. In this context, we used, in several datasets (different sets of variables), a variant of the K-Means algorithm (X-Means) that is able to estimate the number of clusters without pre-assigning any number of clusters. This algorithm produced successively two clusters in all the datasets, which suggests that the ideal number of clusters found for the datasets in this study was two. Setting k = 2 generated two clusters whose composition was very consistent along the analyses, independently of the algorithms, set of features or set of patients used (Table V). In model patients, EM (k = 2) revealed the emergence of a nfvPPA cluster when applied to the dataset of model variables (Table V, first panel, cluster $\mathbf{C0_{k2}}$) or a majority of nfvPPA with some lvPPA cases, when applied to the datasets of language (Table V, second panel, $\mathbf{C0_{k2}}$), total (Table V, third panel, $\mathbf{C0_{k2}}$) or operational criteria variables (Table V, fourth panel, $\mathbf{C0_{k2}}$). The second cluster obtained with the same datasets of variables was, in turn, mostly composed of svPPA and lvPPA cases (Table V, first, second, third and fourth panels, cluster $\mathbf{C1_{k2}}$). Basically, nfvPPA and svPPA cases were easily separated into two different groups while lvPPA cases could be found in both groups, although most of them were frequently clustered with svPPA rather than with nfvPPA patients. A similar pattern of results was observed with all classifiable patients either using model (Table V, fifth panel) or language variables (Table V, sixth panel).

Hierarchical Clustering

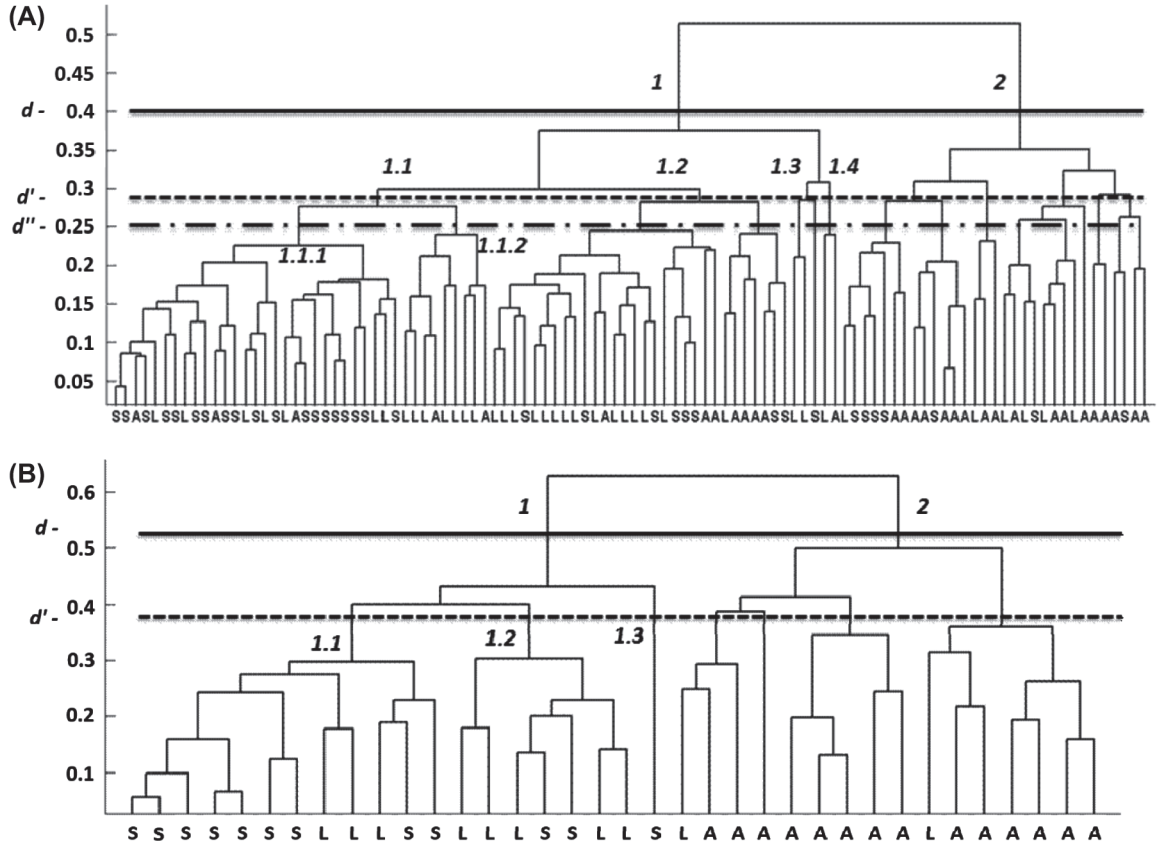
The results obtained with Hierarchical Clustering showed the formation of two main groups, both in the dataset of classifiable patients with the total set of variables (Figure 2A) and in the dataset of model patients with model variables (Figure 2B). By inspection of the dendrogram for all the classifiable patients with the total set of variables (Figure 2A), with a cut at a distance close to around d = 0.4, cluster 1 aggregated most of the svPPA and lvPPA patients (32 lvPPA, 13 nfvPPA and 28 svPPA cases) whereas cluster 2 included the majority of the nfvPPA cases (18 nfvPP plus seven svPPA and six lvPPA cases). The procedure of cutting the dendrogram at a lower level (d' = 0.28) to inspect sub-clusters within the main clusters was again performed. Sub-cluster 1.1 comprised 14 lvPPA, five nfvPPA and 19 svPPA patients while sub-cluster 1.2 included 15 lvPPA, seven nfvPPA and eight svPPA cases. The remaining sub-clusters comprised three lvPPA, one nfvPPA (sub-cluster 1.3) and one svPPA (sub-cluster 1.4) cases. It was only at a deeper level of the dendrogram (d" = 0.25) that it was possible to isolate a majority of svPPA patients (seven lvPPA, four nfvPPA and 19 svPPA).

In a similar fashion, the dendrogram for model patients with model variables (Figure 2B) revealed the emergence of two main clusters (with a cut at a distance close to d = 0.5): one with a mixture of eight lvPPA and 12 svPPA cases (Figure 2B, cluster 1) and another with 14 nfvPPA and two lvPPA cases (Figure 2B, cluster 2). Since cluster 1 included the majority of svPPA and lvPPA, we decided to explore its corresponding sub-clusters

Table V. Clustering results when k = 2: dataset with model patients and the set of model (first panel), language variables (second panel), total set (third panel) or operational criteria variables (fourth panel), dataset with classifiable patients and the set of model (fifth panel) or language variables (sixth panel), using EM.

		EM (k = 2)											
		Model patients								All Classifiable patients			
		1st Panel		2nd Panel		3rd Panel		4th Panel		5th Panel		6th Panel	
		Model variables		Language variables		Total set of variables		Operational criteria variables		Model variables		Language variables	
		$\mathbf{C0_{k2}}$	$\mathbf{C1_{k2}}$	$\mathbf{C0_{k2}}$	$\mathbf{C1_{k2}}$	$\mathbf{C0_{k2}}$	$\mathbf{C1_{k2}}$	$\mathbf{C0_{k2}}$	$\mathbf{C1_{k2}}$	$\mathbf{C0_{k2}}$	$\mathbf{C1_{k2}}$	$\mathbf{C0_{k2}}$	$\mathbf{C1_{k2}}$
Clinical classification	lvPPA	0	10	3	7	3	7	6	4	30	8	3	35
	nfvPPA	11	3	12	1	10	4	12	2	13	18	17	14
	svPPA	0	12	0	12	1	11	2	10	28	7	4	31

Note:Figures in each cell represent number of cases; C: cluster; EM: Expectation Maximization; k: clustering parameter; lvPPA: logopenic variant primary progressive aphasia; nfvPPA: non-fluent variant primary progressive aphasia; svPPA: semantic variant primary progressive aphasia.



Note: The continuous black line indicates one potential cut to obtain two clusters; the fragmented black lines indicate potential cuts to obtain sub-clusters; the y-axis represents distances; the x-axis represents patients' PPA classification: A = nfvPPA; S = svPPA; L = lvPPA.

Figure 2. Dendrograms obtained by applying hierarchical clustering to: (A) all classified patients with the total variables, and (B) model patients with the model variables.

(at a lower level of the dendrogram; d' = 0.35). Results showed that sub-cluster 1.1 aggregated nine svPPA patients and only three lvPPA cases. The sub-cluster 1.2 included five lvPPA and three svPPA cases. Therefore, at a lower level of the dendrogram, it was still not possible to separate svPPA from lvPPA patients.

Consensus Clustering

The results obtained through Consensus Clustering showed that, when k (global) = 3, the emergent clusters did not allow a clear separation of the PPA variants according to their predefined classification. Despite this, usually one of these clusters was composed mainly of patients from a unique PPA variant (typically nfvPPA). When k (global) = 2, the composition of the two emergent clusters was similar to the ones obtained with the algorithms K-Means and EM in isolation, i.e. a group yielded lvPPA and svPPA cases while another comprised mainly nfvPPA and some lvPPA cases. Increasing k (global) did not improve the results as lvPPA and svPPA cases continued inseparable and the remaining clusters were represented by intersections from various sub-types, thus confirming the results found with both Partitional and Hierarchical Clustering.

Discussion

The aim of the present study was to test whether data mining techniques, through an unsupervised learning approach, supported the three-group diagnostic model of PPA (according to recent published criteria) versus the existence of two main/classic groups. Running the algorithms (with k set as 3) revealed that the composition of the groups obtained and the gold standard did not match, meaning that clustering algorithms were unable to detect the three PPA variants proposed in the literature. We also intended to evaluate how many distinct groups of patients were present in the clinical series. Results with clustering techniques consistently revealed the emergence of two main groups (even with cases with high confidence in diagnosis) that stayed largely unchangeable independently of the algorithms used and of the set of quantitative or qualitative variables analysed. Although those groups tended to include a mixture of all PPA variants (in particular with all classifiable patients), it is worth noting that one group comprised mainly svPPA and lvPPA cases whereas the other included the majority of nfvPPA and some lvPPA cases. Unclassifiable patients did not form an individual group. Instead, they belonged in the main to the cluster comprising mainly svPPA and lvPPA cases. When data were clustered in two

groups, there was a clear separation of most of the svPPA and nfvPPA cases. Nevertheless, lvPPA remained undoubtedly the most difficult class to individualize, being frequently grouped together with svPPA cases and with some nfvPPA cases as well. The variant that was most easily separated was the nfvPPA. The detachment of most of the svPPA and lvPPA cases was only feasible for large values of predefined number of clusters (k) or in deep levels of the dendrogram (Hierarchical Clustering).

Based on the analysis of connected speech samples, Sajjadi et al. (26) have previously used a factor analysis to examine if the three recent defined subtypes would emerge in a group of 46 consecutive PPA patients. They found a four-factor solution, where the two first factors accounted together for 42% of the total variance. The first factor clustered semantic measures (single-word comprehension, nonverbal associative knowledge, picture naming and irregular word reading), whereas the second one clustered grammatical features, namely, sentence repetition, apraxia of speech and mean length of utterance. None of the remaining factors resembled a canonical logopenic profile. The authors suggest that lvPPA can hardly be considered an independent entity, since many patients who do not present semantic or agrammatic/non-fluent features may not necessarily display linguistic/neuropsychological characteristics of lvPPA (26). This clearly reveals the non-trivial separation of the three PPA variants and the difficulty to reproduce the criteria of Gorno-Tempini et al. (18). Our results, by using a more sophisticated and extensive data-driven analysis in a larger sample, confirm these findings and clarify the current debate around the classification of PPA syndromes.

For many years clinicians and researchers have considered PPA solely in the context of FTLD as PNFA and SD, whose criteria were defined by Neary et al. (7). A third lvPPA variant represents a relatively recent construct, although its description was already implicit in Mesulam's seminal report (56). Logopenic PPA was only formally described in 2004 (4), based on imaging findings (later correlated with clinical data), which contrasted with the mainly clinical-based description underlying the definition of PNFA and SD. Furthermore, lvPPA variant represents a heterogeneous entity whose diagnosis is based predominantly on the absence of core features of the other variants (absence of semantic impairment and of apraxia of speech/agrammatism) which leads to the inclusion in a same group of patients with probable distinct clinical features.

In our study, lvPPA patients were difficult to dissociate from the other cases and some of them were closer to svPPA patients, whereas others were closer to nfvPPA patients. This highlights the substantial variability of the lvPPA syndrome and its mixed nature: many lvPPA patients may display a relatively effortful speech which resembles that of patients with nfvPPA. On the other hand, their naming difficulties may make them look similar to svPPA patients (57), particularly at very early stages. Furthermore, these cases may vary in the extent of damage to the ventral language pathway that can manifest as variable semantic impairment, apart from the anomia, which further complicates classification (58).

One could argue that language/neuropsychological attributes used to assess patients in this study might not have been significant to discriminate logopenic patients from the other two variants. However, the recent consensus guidelines highlight the language areas that should be subjected to a thorough assessment but do not give information on specific tests or the cut-off points to use. Furthermore, one of the problems associated with retrospective studies is that tests tend to change over time as new instruments are introduced to assessment batteries. As a consequence, quantitative scores on those measures are lacking for many cases, which will influence analysis based solely upon quantitative performance. Nonetheless, other studies have failed to classify a significant proportion of PPA patients even though they used different batteries (26,28,32). The use of qualitative measures of impairment on main language areas affected in each PPA subtype did not seem to improve this situation as a full discrimination was still not feasible.

About one-third of our cases could not be classified into one of the subtypes, showing once again the limitation associated with the current criteria. Although the study of the unclassifiable cases was not the primary objective of this study, this finding is consistent with previous reports (28). Some of these 'difficult' cases have even been reported to remain like that after a certain time-period (25). This situation becomes worse when disease evolution is taken into account, as patient's linguistic profiles tend to lose their specificity, making it hard even for clinical experts to classify a patient into one of the variants. The majority of our unclassifiable cases present word retrieval and naming deficits, without definite semantic or agrammatic features. Since they do not display repetition deficits as well, they cannot be strictly classified as logopenic according to 2011 criteria, being left without a classification. Mesulam and Weintraub (59) addressed recently this issue, suggesting that the 'impairment of repetition' should be considered an ancillary rather than a core feature in order to include more patients into this group. Only then they should be subdivided as having or not having deficits in repetition. Mixed phenotypes tend also to be considered unclassifiable. Once again, the same authors highlight the need to consider a fourth 'mixed' variant, leading to a decrement of the number of the unclassifiable cases (59).

It is interesting to note that that nfvPPA cases had longer evolution times compared to svPPA, lvPPA

and unclassifiable cases. This can be due to the nature of language deficits presented by these patients: in cases where agrammatism is the most salient feature, this aspect can stay undetectable by patients and relatives and may only be identified through a thorough assessment. In most cases, patients seek medical help when their speech becomes profoundly disturbed, marked by several dysfluencies and at a time when apraxic symptoms are often quite evident. In addition, the differences observed in evolution times may be accounted for by differences in the speed of the underlying neurodegenerative processes known to be associated with each variant.

As strengths of the present work, we highlight the use of a robust clinical sample, larger than those reported to date in the literature, the exhaustive nature of the analyses in terms of type of algorithms, sets of variables and subgroups of patients used. Nonetheless, some limitations should be recognized as well. First, this is a retrospective study and, for that reason, data considered today essential for diagnosis might not have been obtained. This might represent a cause for misclassification in some cases and the impossibility of reaching a diagnosis into subtypes in others. Secondly, imaging and pathological data were not considered in the analyses. The inclusion of biomarkers beyond language and neuropsychological tests might improve clustering analysis. Furthermore, from a computational standpoint, the number of patients under study may be considered small for an unsupervised learning study (disproportion between the number of patients and variables). In data mining studies a larger cardinality of examples may lead to a more accurate outcome. This caveat could be attenuated through multicentric studies, in which several series of PPA patients from centres of expertise would be included. Furthermore, future work should focus on supervised machine learning, in order to help reaching a more accurate classification of patients and the identification of different profiles.

Conclusions

The main conclusion of this study is that unsupervised learning techniques do not support a clear distinction of a series of PPA cases into three PPA variants as defined by the current working research criteria (18). Results pointed to the existence of two main clinical phenotypes (even in prototypical patients), svPPA and nfvPPA, the lvPPA cases being spread over those groups. Unsupervised learning does not support a clear distinction of lvPPA as a separate variant of PPA.

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Original Research Article

Speech Therapy in Primary Progressive Aphasia: A Pilot Study

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Key Words
Primary progressive aphasia · Dementia · Cognitive rehabilitation · Speech and language therapy

Abstract
Background: Primary progressive aphasia (PPA) is a neurodegenerative disorder with no effective pharmacological treatment. Cognition-based interventions are adequate alternatives, but their benefit has not been thoroughly explored. Our aim was to study the effect of speech and language therapy (SLT) on naming ability in PPA. ***Methods:*** An open parallel prospective longitudinal study involving two centers was designed to compare patients with PPA submitted to SLT (1 h/week for 11 months) with patients receiving no therapy. Twenty patients were enrolled and undertook baseline language and neuropsychological assessments; among them, 10 received SLT and 10 constituted an age- and education-matched historical control group. The primary outcome measure was the change in group mean performance on the Snodgrass and Vanderwart naming test between baseline and follow-up assessments. ***Results:*** Intervention and control groups did not significantly differ on demographic and clinical variables at baseline. A mixed repeated measures ANOVA revealed a significant main effect of therapy ($F(1,18) = 10.763$; $p = 0.005$) on the performance on the Snodgrass and Vanderwart naming test. ***Conclusion:*** Although limited by a non-randomized open study design with a historical control group, the present study suggests that SLT may have a benefit in PPA, and it should prompt a randomized, controlled, rater-blind clinical trial.

L.F. and C.M. contributed equally to the present work.

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Introduction

Progressive cognitive syndromes with circumscribed deficits in the language domain and preserved intellect, associated with atrophy of the left-dominant hemisphere, have been recognized for more than a century [1]. However, interest in these clinical conditions only flourished in the 1980s following Mesulam's [2] publication of a series of 6 patients who in late middle age developed a 'slowly progressive aphasia', subsequently renamed 'primary progressive aphasia' (PPA) [3].

PPA is a clinical syndrome with an insidious onset, characterized by a progressive and isolated deterioration of word finding, object naming, fluency, syntax, and word comprehension, during at least a 2-year period and without an identifiable cause other than atrophy (ruling out non-neurodegenerative etiologies, such as stroke or malignancy). Memory, visuospatial skills, executive and social abilities should remain relatively preserved during the first years of the disease and, as other areas of cognition become eventually impaired, language still remains the domain that deteriorates faster [4].

Word-finding difficulties and anomia are amongst the earliest symptoms of PPA, though they evolve to different linguistic profiles [5]. Attempts to use the traditional taxonomy of aphasias (Broca's and Wernicke's aphasia) have not been entirely successful, possibly because degeneration tends to induce more widespread, less severe, and slowly evolving patterns of brain dysfunction. The non-fluent form of PPA has been referred to as progressive non-fluent aphasia [6], whereas the fluent form is known as semantic dementia [7, 8] due to the presence of a progressive disorder of the semantic memory [9]. Cases of PPA can be classified into variants based on linguistic/neuropsychological features [10–13], each variant being associated with distinct patterns of atrophy [12] and different likelihoods of underlying pathologies [14–16]. Recently, a new classification of PPA into subtypes has reached consensus, and three variants are now formally recognized (agrammatic, semantic, and logopenic) [17].

PPA is a very disabling disorder for which there is, at present, no available treatment. A few pharmacological trials (using bromocriptine, galantamine, and memantine) conducted so far have enrolled small numbers of patients and produced inconclusive results [18–21], and there have been no trials with other therapies. Taking into account this discouraging perspective, the implementation of non-pharmacological procedures, specifically designed to compensate for progressive language deficits, may seem a feasible alternative.

There is evidence from other neurodegenerative conditions that cognition-based interventions may be effective in maintaining or improving cognitive function and perhaps delay progression to dementia. A Cochrane collaboration study recently reviewed 36 trials on the effect of cognitive stimulation on mild cognitive impairment, revealing some beneficial effect of this type of intervention on measures of immediate and delayed recall, when comparing groups subjected to intervention and groups with no stimulation [22]. Similar results have also been reported in patients with mild dementia [23].

Speech and language therapy (SLT) has been extensively used in patients with aphasia of different etiologies and has been shown to be effective [24–28]. It aims to maximize the subject's communicative abilities. A recent meta-analysis [29] identified 30 controlled trials with speech therapy, performed between 1969 and 2009, showing beneficial effects in a variety of language measures (spontaneous speech, gestural use, aphasia severity, expressive written language, and comprehension). Functional neuroimaging studies have confirmed these results by showing neural reorganization following SLT [30, 31].

Because PPA affects mostly language, it is reasonable to presume that SLT might be effective in this condition given the fact that other behavioral interventions have proved to be useful in degenerative diseases. To date, case reports and single-subject experimental research have been presented [32–34]; however, the scarce number of participants and the ab-

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sence of a control intervention in the majority of the studies limit the significance of the results. Attempts to introduce other approaches based on training with a text-to-speech alternative communication device or sign language were also reported [35], but again the generalization of these preliminary encouraging results appears difficult.

The aim of our study was to find out whether a SLT program can mitigate language decline in PPA, by comparing a group exposed to this intervention with a historical control group of PPA patients who did not undergo any stimulation. Specifically, we tested the hypothesis that patients subjected to speech therapy would show significantly less decline over time on expressive language measures, namely naming ability, as compared to the control group. If positive results were found, they would encourage carrying out a formal randomized controlled trial to establish the efficacy of SLT in PPA. This intervention would hopefully assist in the maintenance or even transitory amelioration of patients' linguistic skills, promoting their ability to communicate and their quality of life.

Materials and Methods

Participants

Participants were patients referred to language/neuropsychological assessments at the two participating clinical institutions in Lisbon and who fulfilled the diagnostic criteria for PPA [17]. The intervention group comprised 10 patients who underwent speech therapy sessions at the institution (Memory Clinic) that offered the patients the possibility of being enrolled in a SLT program. The controls were 10 age- (±2 years) and education- (±3 years) matched PPA patients consecutively selected from the clinical institutions databases (Memory Clinic and Laboratory of Language Research) if they had at least two language/neuropsychological assessments and were not subjected to SLT. The study was approved by the local ethics committee.

Inclusion Criteria

All patients fulfilled the following criteria:

- The presence of PPA, according to the criteria recently proposed by Gorno-Tempini et al. [17]:
  - Insidious onset and gradual progressive impairment of language production, object naming, syntax, or word comprehension, apparent during conversation or through speech and language assessments;
  - Activities of daily living are maintained except those related to language (e.g. using the telephone);
  - Prominent, isolated language deficit at symptom onset, during the initial phase of the disease and at time of examination;
  - Absence of prominent episodic and nonverbal memory loss and visuospatial impairment during the initial stages of the illness;
  - Other cognitive functions may be affected later on, but language remains the most impaired domain throughout the course of the illness;
  - Absence of prominent behavioral disturbances at the time of diagnosis;
  - The pattern of deficits is not better accounted for by other non-degenerative diseases of the nervous system (e.g. stroke or tumor), as ascertained by neuroimaging, or medical disorders;
  - Cognitive disturbance is not better accounted for by a psychiatric diagnosis;
- Right-handedness;
- Native Portuguese speakers;
- Complete language/neuropsychological assessments.

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Exclusion Criteria

- Presence of dementia, according to DSM-IV-TR criteria [36];
- Other neurological or psychiatric disorders that might induce language or other cognitive deficits (e.g. stroke, brain tumor, traumatic brain injury, epilepsy, severe and uncontrolled medical illness, namely, hypertension, metabolic, endocrine, toxic or infectious disease).

Procedures

In all cases, clinical history was evaluated, and they underwent neurological examination and a detailed cognitive assessment which comprised language and neuropsychological evaluations.

An experienced neuropsychologist (M.G.) performed the neuropsychological assessment. The test battery consisted of the nonverbal subtests of the Battery of Lisbon for the Assessment of Dementia (BLAD [37]). Since results in many neuropsychological tests are somewhat difficult to interpret in patients with PPA, due to test reliance on verbal directions, verbal stimuli, and/or verbal responses, nonverbal tests were preferred to evaluate different cognitive domains (sustained attention, motor and graphomotor initiative, visuoconstructive abilities, visual memory, and matrix reasoning). Activities of daily living and behavioral changes were also assessed during the interview with the caregivers.

Language Assessment

At the baseline evaluation, patients were assessed by a speech therapist (L.F.) using a comprehensive language test battery (Lisbon Aphasia Examination Battery, BAAL [38–40]) that included the following instruments: (a) picture description (Goodglass and Kaplan's cookie theft [41]) for analysis of spontaneous speech; (b) visual object naming (BAAL); (c) Snodgrass and Vanderwart naming test [42]; (d) a short 22-item version of the token test [43]; (e) object identification and comprehension of oral commands (BAAL); (f) word and sentence repetition (BAAL); (g) text reading and comprehension (BAAL); (h) writing sentences to dictation (BAAL), and (h) spontaneous writing of a text. A global language measure, the Aphasia Quotient (AQ), was calculated for all patients by adding the scores (as percentages) of 4 BAAL subtests (fluency, object naming, repetition, and comprehension of oral commands) and dividing the sum by 4 [44]. Classification into PPA subtypes (agrammatic, semantic, and logopenic) followed specific criteria outlined by Gorno-Tempini et al. [17].

Speech Therapy Intervention

SLT comprised 60-min weekly sessions conducted by a trained speech therapist with experience in PPA (L.F.). The main goal of this intervention was the improvement of the patient's ability to communicate by verbal means with others in everyday life through a stimulation approach [45]. This method is considered an individualized multimodality stimulation approach [46]. Improvement in comprehension and expression of both spoken and written language was targeted through different exercises such as picture naming, description of picture actions, complex auditory-verbal comprehension, reading and writing, facilitation of expression of feelings and opinions, and enhancement of conversational skills. The patient's attention is directed to the content he/she wants to express [47]. These exercises were completed during sessions with the speech therapist. Depending on the patient's education level, motivation, and aphasia severity, about 5–10 of these exercises were given as homework. Conversational success, with the focus on functional outcome [48, 49], was also explored and stimulated by the use of all sorts of communication strategies (speaking, writing, drawing or gesturing). Thus, authentic opportunities are provided to patients to

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develop effective strategies for overcoming potential obstacles to communication. The main goal was always the exchange of ideas in a naturalistic and interactive manner in a supported conversation [50]. The main conversational topics usually included everyday life stories, recent news, episodes of soap operas and sports, restaurants, shops, family/friends, social life, and emotions. This was accomplished through picture description about personal safety, nonsense/unreal and decision-making situations. Tasks also included description and organization of sequences.

Primary Outcome Measure

The primary outcome measure was the mean change in the Snodgrass and Vanderwart naming test scores before and after the intervention. This test assesses the ability to visually name 128 black and white picture drawings [42]. Picture naming has been reported as the measure most positively affected by speech therapy in stroke aphasic patients [51, 52], and impairment of word finding (leading to anomia during visual confrontation naming) is the single most prominent deficit in PPA [4].

The remaining language measures (token test, object naming, word repetition, comprehension of oral commands, and object identification) were considered as secondary outcome measures.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics (version 19.0, SPSS, Chicago, Ill., USA). A significance level of 0.05 was used in the analyses. Since the variables displayed normal distribution and homogeneity of variances ($p > 0.05$), demographic and clinical numerical variables were compared in both groups using the parametric independent samples Student's t test. The Pearson χ^2 test was used for categorical variables. A mixed repeated measures analysis of variance (ANOVA) was performed to evaluate the effect of speech therapy on primary as well as secondary outcome measures, using the initial and the follow-up evaluations as the within-subjects condition, and the presence or absence of intervention as the between-subjects condition. Since both the severity of aphasic changes at baseline and the time elapsed could decisively influence the outcome, the initial AQ and the evolution time between baseline and follow-up were entered as covariates in the analysis.

Results

Table 1 shows the demographic and clinical data of both the intervention and the control group. Overall, more men participated in the study (70%). There were no statistically significant differences in the demographic and clinical data of the two groups. The SLT group and the control group did not significantly differ concerning aphasia severity as assessed by the AQ ($p = 0.720$; table 1). No significant differences were found in the mean scores of the Snodgrass and Vanderwart naming test at the baseline assessment between patients who underwent SLT (110.8 ± 18.2) and controls (87.7 ± 23.2; $t(18) = 1.402$; $p = 0.178$).

Effect of Speech Therapy

The intervention group received on average 37.1 speech therapy sessions during 11.1 months (table 1).

As shown in table 2, a mixed repeated measures ANOVA was conducted to assess whether there were statistical differences in the primary outcome measure with regard to evolution (baseline vs. follow-up) and therapy (with vs. without speech therapy). After controlling for evolution times and the initial AQ, a significant main effect of therapy ($p = 0.005$) was found

Table 1. Demographic and clinical results in SLT and control groups

	SLT group (n = 10)	Control group (n = 10)	Statistics*	p
PPA variant, A:S:L	2:2:6	0:6:4	–	–
Gender, f:m	4:6	2:8	$\chi^2 = 0.952$	0.329
Education, years	11.4 ± 3.8	8.1 ± 3.8	t = 1.991	0.062
Age, years				
At symptom onset	65.6 ± 7.9	64.6 ± 7.5	t = 0.292	0.774
At baseline	68.0 ± 7.8	66.2 ± 7.7	t = 0.518	0.611
Evolution times from baseline to follow-up, months	11.1 ± 9.3	14.9 ± 11.4	t = –0.817	0.424
AQ, %	85.9 ± 7.8	87.1 ± 7.2	t = 0.364	0.720
Sessions, n	37.1 ± 20.2	–	–	–

Values are means ± SD unless otherwise indicated. A = Agrammatic; S = semantic; L = logopenic; t = Student's independent samples t test; $\chi^2 = \chi^2$ test. * Statistical tests for the comparison of the two samples.

Table 2. Effect of SLT on primary and secondary outcome variables

	SLT group (n = 10)		Control group (n = 10)		Repeated measures ANOVA									
					evolution*		therapy**		evolution × therapy		evolution × evolution times		evolution × initial AQ	
	baseline	follow-up	baseline	follow-up	F	p	F	p	F	p	F	p	F	p
SVNT	100.8 ± 18.2	90.7 ± 31.6	87.7 ± 23.2	61.7 ± 26.0	1.037	0.324	**10.763**	**0.005**	2.772	0.115	**6.583**	**0.021**	0.857	0.368
Object naming	12.9 ± 3.6	11.8 ± 5.0	13.7 ± 2.6	11.5 ± 4.4	0.934	0.352	0.090	0.769	0.009	0.927	**10.458**	**0.007**	0.759	0.400
Comprehension of oral commands	7.8 ± 0.4	7.0 ± 1.3	7.8 ± 0.6	7.2 ± 0.9	0.563	0.467	0.208	0.656	0.117	0.739	2.417	0.146	0.550	0.473
Token test	15.4 ± 3.7	12.8 ± 4.6	15.4 ± 4.2	15.5 ± 3.7	3.008	0.105	0.157	0.698	3.910	0.068	**9.418**	**0.008**	3.761	0.073
Object identification	16 ± 0	15.3 ± 1.9	16.0 ± 0	15.8 ± 0.4	0.184	0.680	0.208	0.660	0.208	0.660	0.245	0.634	0.173	0.689
Word repetition	29.9 ± 0.3	29.6 ± 1.0	30.0 ± 0	30.0 ± 0	0.293	0.596	2.230	0.156	1.241	0.283	1.166	0.297	0.338	0.570

Values are means ± SD. Bold values indicate the statistically significat results at $p < 0.05$. SVNT = Snodgrass and Vanderwart naming test. * Within-subjects condition; ** between-subjects condition.

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on the primary variable, the performance on the Snodgrass and Vanderwart naming test (table 2), meaning that patients subjected to SLT declined less than controls. The interaction between evolution and therapy was not significant ($p = 0.083$); however, significant interactions were found between evolution and evolution times for the primary ($p = 0.021$) and secondary outcome measures (token test, $p = 0.008$; table 2), reflecting a more pronounced decline for longer follow-ups.

Discussion

The present study suggests that there is a tendency for a less severe decline of language, namely concerning naming abilities, in PPA patients subjected to SLT when compared with a control group that did not undergo SLT. We found that patients subjected to SLT declined significantly less in the primary variable, the Snodgrass and Vanderwart naming test.

An effect of language rehabilitation on picture naming has been previously reported, but only based on case reports and single-subject experimental research. Louis et al. [32] addressed the impact of intensive training on phonological skills in 3 PPA patients over a 42-day training period. The authors found that, in spite of global worsening of language abilities over intervention, some language functions (fluency, written comprehension, repetition, reading, and reduction of phonemic paraphasias) either remained stable or improved. Another study [33] followed 2 individuals with progressive language impairment and a stroke aphasia patient in a daily 90-min semantically based intensive treatment to improve lexical retrieval, during 16 days. Results indicated that all patients showed improved lexical retrieval on a generative naming task for specific categories trained during intervention. However, only 1 of the PPA patients and the stroke aphasia patient maintained improved performance on follow-up at 3 weeks and 4 months after treatment. The same research group reported similar results with the therapy of a logopenic PPA patient who performed follow-up assessment at 3 weeks, 4 and 6 months after intervention. This patient also presented an improvement in naming on the training task, which generalized towards an improvement in standardized measures of confrontation naming [34].

It must be emphasized that it would be particularly important to find effective non-pharmacological approaches to treat PPA, since no pharmacological treatments are currently available. A few clinical trials testing different drugs can be found in the literature, but they reported inconsistent results. The study of the effect of bromocriptine on the performance of various language tasks revealed that it did not produce significant effects on language measures during a 15-week double-blind cross-over study, when comparing PPA and placebo groups [18]. Another open-label study, this time with galantamine, in a sample of 36 behavioral frontotemporal dementia and PPA patients showed a non-significant trend for efficacy in the aphasic subgroup, suggesting that aphasia scores were more stable in the treatment than in the placebo group [19]. A similar open-label study with memantine [20] reported a relative stability on the ADAS-Cog over the 52 weeks of the study in progressive nonfluent aphasia patients, whereas patients with semantic dementia declined. Finally, a more recent double-blind, placebo-controlled trial showed a slight positive effect of this same drug, consisting of a smaller decline on the Western Aphasia Battery (WAB) aphasia quotient in the groups administered the drug than in the placebo group [21].

Considering cognitive therapy for neurodegenerative disorders in a broader context, it has certainly been difficult to find unequivocal benefits of this sort of interventions, for example, in mild cognitive impairment and mild dementia [22, 23]. However, the study of a specific form of cognitive intervention (speech therapy) in a homogenous group presenting a limited cognitive dysfunction (language impairment) may be particularly advantageous to

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reveal beneficial effects on cognitive performance. If we consider that the majority of techniques used in cognitive rehabilitation are designed to stimulate a broader range of impaired and/or preserved cognitive functions, the use of SLT in PPA patients can be representative of the possible impact of rehabilitation in neurodegenerative diseases.

As strengths of our study we underline the use of a sample followed longitudinally, the inclusion of a matched control group, and the fact that language intervention was always conducted by the same speech therapist, allowing the use of a consistent treatment structure (though adapted to each case).

We also acknowledge several limitations of the present work in the context of a pilot study undertaken to prompt future prospective trials. First of all, allocation to the treatment or the control group was not randomized, even though patients in both groups were age- and education-matched. This constitutes an important limitation, since the groups might differ in other variables relevant for the primary outcome measure that were not controlled for. However, we feel there was no clear allocation bias in the sense that patients more likely to benefit would have be directed to SLT. In fact, patients were offered the possibility of entering a SLT program at one institution, and this program was not available at the other institution. Thus, the allocation was essentially dependent on the clinical center and not on patients' characteristics, although it can be argued that socioeconomical status might have driven the choice of the center. Another limitation of the present study was a considerable variability of follow-up times in the intervention and control groups. This is partially due to the retrospective nature of the analysis that did not adhere to a formal assessment protocol at predetermined follow-up intervals, and to the historical nature of the control sample. A final limitation is that, due to the lack of a control intervention, the benefit of the language therapy might, at least partially, reflect nonspecific effects of contact with the speech therapist.

Future interesting directions in this area might be to consider the use of functional magnetic resonance imaging to observe possible changes in brain activation patterns over time as a result of speech therapy, as previously reported in stroke patients [31, 53]. On the other hand, a particular intervention might not equally impact on each syndrome, so that future prospective trials should take into account the specific PPA subtypes. Finally, future studies should not be confined to specific language measures, but address the possible impact of speech therapy on broader functional communication abilities, which are extensively stimulated during training sessions and might have important functional benefits. Language deficits can be extremely disabling as they disrupt the ability to express even basic thoughts and needs. The majority of aphasic patients are unable to maintain their previous job and suffer from a reduction of their social contacts, causing great problems at individual, social, and socio-economic levels [54]. In the therapy context, the patient learns new strategies to use in everyday life that improve his/her capacity to communicate with others and interact with the environment, allowing engagement in many language-based activities (e.g. making appointments, schedules, and using the telephone). As a consequence, the linguistic processes which are failing are further stimulated [55]. In fact, some studies suggest that therapy can have an impact on patients' views of their communicative activities and life participation by increasing their activity ratings, especially those that require active communication [52]. The use of functional communication scales such as the ASHA Functional Assessment of Communication Skills for Adults (ASHA FACS [56]) in future trials would provide more ecologically valid measures for everyday communication.

In conclusion, the present study suggests that the implementation of a non-pharmacological, language-based intervention in PPA might attenuate the progression of some language deficits, and should prompt further studies using randomized, controlled, rater-blind procedures to ascertain the effective role of speech therapy in PPA.

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