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Dysarthria in individuals with Parkinson's disease: a bi-national, cross-sectional, case-controlled study in French and European Portuguese (FraLusoPark)

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Dysarthria in individuals with Parkinson's disease: a bi-national, cross-sectional, case-controlled study in French and European Portuguese (FraLusoPark)

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ABSTRACT

Introduction: Individuals with Parkinson’s disease (PD) have to deal with several aspects that contribute to voice and speech decline and thus, alteration of communication ability during the course of the disease: (i) The orofacial motor dysfunction, so-called dysarthria, which depends on the neurodegenerative processes; (ii) The effects of the medical treatment, which vary according to the disease stage; and (iii) The particular speech modifications that can be language-specific, *i.e.* dependent on the language spoken by the patients. The main objective of the FralusoPark project is to evaluate changes in PD speech as a result of medical treatment and disease duration in two different languages (French vs. European Portuguese).

Methods and analysis: Individuals with PD will be enrolled in the study in France (N = 60) and Portugal (N = 60). Their global motor disability and orofacial motor functions will be assessed with specific clinical rating scales, without (OFF) and with (ON) medical treatment. Two groups of 60 healthy age-matched volunteers will provide the reference for between-group comparisons. Along with the clinical examinations, several speech tasks will be recorded to obtain acoustic and perceptual measures. Self-evaluation questionnaires will be used to assess the psychosocial impact of dysarthria on quality of life.

Ethics and dissemination: This study has been approved by the local responsible committees on human experimentation and it is conducted in accordance with the ethical standards. The project combines an interdisciplinary and cross-linguistic approach to study motor speech disorders and will allow for a better understanding of the progression of speech symptoms in PD and their response to medical treatment. It will provide recommendations on how to assess speech and voice disorders in individuals with PD in order to monitor symptom progression and management.

Registration details: ClinicalTrials.gov Identifier: NCT02753192. Registered on 26 April 2016.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- A multicentre (bi-national), cross-sectional, case-controlled study
- A cross-language, multiparametric and global study of speech in Parkinson's disease
- An interdisciplinary approach gathering together data analyses from both speech sciences and neurosciences
- A small, but clinically reasonable, number of individuals with PD
- Inability of precise targeting phonetic distortions
- Not a longitudinal study, unable to address patients' own speech deterioration with time

INTRODUCTION

Dysarthria in Parkinson’s disease

Dysarthria denotes a motor speech disorder resulting from a lesion of the peripheral or central nervous system [1, 2, 3]. Dysarthria is a particularly disabling symptom: between 70% and 79% of individuals with PD mention speech disorders [4, 5] during the progression of the disease, affecting communication [6], and contributing to social isolation [7] and degradation of social interactions [8]. These speech disorders also contribute to aggravation of other non-motor symptoms, such as depression [9] and cognitive impairment [10]. Dysarthria can appear at any stage of PD, and usually worsens with disease progression [11], which suggests that it is also linked to the progression of the pathological processes and non-dopaminergic brain circuits [12, 13, 14]. The main deficits of PD speech are: loss of intensity (hypophonia), monotony of pitch and loudness, reduced stress, inappropriate silences, short rushes of speech, variable rate, imprecise consonants and dysphonia (harsh and breathy voice) [1, 2, 15]. Treatments in PD have been shown to have variable effects on these voice and speech symptoms [16, 17].

Although behavioural treatments mainly focus on two key indices of PD speech (*i.e.*, pitch and intensity), dysprosody has been understudied so far. Nevertheless, prosody deficits represent an acoustic hallmark of dysarthria. First, perceptual and acoustic investigations of PD speech have reported alterations on fundamental frequency (F0), as part of their phonatory inability, and thus the reduction of the frequency range is clearly an indicator of dysarthria in PD [18]. In particular, individuals with PD show a loss of the upper part of the tonal range [19]. Therefore, degradation of prosody impacts speech intelligibility and communication (*e.g.* [20]). Secondly, the temporal organization of speech in PD has been addressed in reading tasks [21, 22, 23]: in French, for example, speech rate tends to be slower in PD which in turn seems to be correlated with longer pause times; average durations of pauses are found to be longer in individuals with PD than in healthy individuals,

while the average duration of sound sequences are similar [22, 23]. Studying dysprosody is thus important for differential diagnosis, designating severity and the need and focus of treatment [18].

Remaining challenges to assess dysarthria in PD: the rationale of the FraLusoPark study

Individuals with PD have to deal with several aspects that contribute to voice and speech decline, and thus alteration of communication ability during the course of the disease: (i) The orofacial motor dysfunction, so-called dysarthria, which depends on the neurodegenerative processes; (ii) The effects of the medical treatment, which vary according to the disease stage; and (iii) The particular speech modifications that can be language-specific, that is dependent on the language spoken by the patients. The main objective of the FraLusoPark project is to evaluate changes in dysarthric speech in PD as a result of medical treatment and disease duration using acoustic parameters (voice and prosody), perceptual markers (intelligibility), and the patient-based outcomes (psychosocial impact on quality of life) in two different languages (French vs. European Portuguese). Based upon a large-scale bi-national collaboration, the current interdisciplinary FraLusoPark project aims to address these issues by providing important insights to the domains of neurodegenerative disorders, speech sciences, neuropsychology, clinical research and patient rehabilitation.

Medication effects along disease progression

Early studies assessing the effect of the levodopa (L-dopa) on PD speech reached favorable results, arguing towards a beneficial effect, similar as for limb impairments [24, 25, 26, 27]. However, the long-term use of L-dopa is associated with unavoidable motor complications which occur in up to 80% of patients [28, 29]. This may be the reason why following studies reported no improvement [30, 31] and/or deleterious effects of L-dopa on speech [32, 33]. More recent studies face similar problems: beneficial effects of L-dopa can be observed in advanced PD patients [34, 35], whereas a lack of improvement is reported for speech parameters in early stage PD patients [36]. It is also

commonly accepted that in the later stages of PD, non-motor symptoms (dementia, psychosis, depression and apathy) are a major source of disability together with axial symptoms (*e.g.*, alteration of gait, balance, posture, speech) [37]. Thus, both clinicians and researchers have to dissociate among various intermingled effects. For example, when individuals with PD respond to L-dopa at an early stage of the disease, they are likely to experience speech decline with time that may result from the degeneration of non-dopaminergic structures and/or L-dopa adverse effects (*i.e.* dyskinesia). Despite the recent and important number of studies that have focused on the effect of L-dopa on speech in PD [34, 35, 36, 37, 38, 39, 40, 41, 42], the question of disease evaluation still remains a matter of debate.

Language specificities of prosody

Regarding language-specific properties, one missing component in the description of PD speech deficits is dysprosody. Prosodic information, including intonation, tempo, stress and rhythm, serves many functions for the listener and speaker: it helps to segment the continuous flow of spoken language into words, groups these words into phrases for interpretation, and indicates the relative importance and function of the interpreted meanings [43, 44, 45, 46]. Each language has its own prosodic structure. For example, although they are sister languages, French and European Portuguese (both Romance languages) differ prosodically in a number of important ways. European Portuguese has contrastive lexical stress: each content word (noun, adjective, verb, etc.) has one syllable that is particularly salient or stressed, and changing the position of the lexical stress can change the meaning of a word [45, 47, 48, 49]. Stressed syllables may be accompanied by a pitch accent, realized as a modulation in F0 (*e.g.*, a rise or a fall) and aligned in language-specific ways with the syllable. In contrary, French has a fixed stress, characterized by a systematic F0 rise on the last syllable in a word [50, 51]. Stress is not a property of the word, but of a larger unit called the accentual phrase that can include one or more content words and any preceding function words

(articles, prepositions, etc.), often realized with F0 rises at its right and left edges. French listeners use these F0 rises as cues to word segmentation, finding the beginning and ends of words in the speech stream, and to lexical access, retrieving words from the mental lexicon [46, 52].

Such differences across languages make the comparison of prosodic deficits in individuals with PD particularly interesting. Very few studies of PD dysprosody have looked beyond global measures to examine the extent to which linguistically important, language-specific patterns are affected [53, 54]. Therefore, studying speech in individuals with PD whose language implies different prosodic modulations is important to determine the role of prosody for patients' speech intelligibility and quality of life. Does a Portuguese patient experience different communication impairments when compared to a French patient? And if this is the case, is this difference related to the fact that European Portuguese stress is distinctive and varies in position? And finally, how do these differences relate to the patients' disease duration and pharmacological treatment? Our project presents a novel approach to these questions and is important for the gathering of cross-linguistic data in a single cohort.

METHODS AND ANALYSIS

FraLusoPark is a **bi-national** (data collection is performed in two countries: France and Portugal), **cross-sectional** (data is collected once for each participant) and **case-controlled** (both individuals with PD and control subjects are recruited) study, carried out in two different languages (French and European Portuguese).

Aims and hypotheses

The main objectives of our project are to evaluate modulations in acoustics parameters (voice and prosody), perceptual markers (intelligibility) and patient-based outcomes (psychosocial impact of dysarthria in PD) across two different languages (French vs. European Portuguese).

Our three a priori hypotheses are the following: (i) Global acoustic features are altered similarly in French and Portuguese individuals with PD; (ii) Language-specific prosodic patterns might be altered differently in French and Portuguese individuals with PD; and (iii) The impact of speech disorders on intelligibility and quality of life depends on the cultural and linguistic environment. In addition, the FraLusoPark project will allow for a better understanding of the progression of the speech symptoms and their response to medical treatment, which is important regarding pathophysiological aspects and clinical management.

Participants

Two groups of 60 healthy volunteers (one in France and one in Portugal) are age- and sex-matched with the individuals with PD to provide control references for the obtained performance measures. Individuals with PD are recruited in France (N = 60; Neurology Department, Centre Hospitalier du Pays d’Aix, Aix-en-Provence, France) and in Portugal (N = 60; Movement Disorders Unit, Hospital de Santa Maria, Lisbon, and CNS - Campus Neurológico Sénior, Torres Vedras, Portugal) and correspond to the UK Parkinson’s Disease Brain Bank Criteria [55] for the diagnosis of idiopathic PD. Individuals with PD and healthy controls are all French-native or European Portuguese-native speakers (French-European Portuguese bilinguals were excluded) and right-handed (Handedness Edinburgh test > 80 %; [56]). Exclusion and inclusion criteria of PD patients and healthy controls are summarized in **Table 1**. To assess L-dopa effects at various stages of the disease, patients’ recruitment considers three sub-groups (N = 20 patients each): Sub-group 1, *mild* impairment (modified Hoehn & Yahr stage: 1 or 2; [57]) with a disease duration between zero and 3 years and no motor fluctuations; Sub-group 2, *moderate* impairment (Hoehn & Yahr stage: 2 and 3) with a disease duration between 4 and 10 years, experiencing motor fluctuations; Sub-group 3, *marked* impairment (Hoehn & Yahr stage: 4 and 5) with a disease duration of over 10 years.

Table 1. Exclusion and inclusion criteria

<i>All participants</i>	<i>Control subjects</i>	<i>Parkinson's disease patients</i>
Inclusion Criteria		
Age between 35 and 85 years old		
Good cooperation		
Ability to understand the information sheet		
Given signed consent		
Affiliation to a medical-social insurance regimen		
Other stable medical problems not interfering with the proposed study		
Absence of any neurological, psychiatric or behavioural pathology		
Idiopathic Parkinson's disease		
Absence of medication-induced psychosis, severe depression or dementia		
Exclusion Criteria		
Illiteracy		
French/Portuguese not as native language, or bilingual participants		
Participant under tutorship or guardianship, or any other administrative or legal measure		
No cooperation or withdrawn consent		
Cognitive deficits, depression, psychosis or behavioural, neurological, medical, psychological disorders that may interfere with vital prognostic and evaluations		
Non-idiopathic Parkinson's disease		
(Too) severe motor impairment impeding to participate in the study		

Study design

Healthy control participants will undergo the same non-invasive assessments and examinations as the individuals with PD. The only constraint for the patients is to be evaluated twice, in the OFF and ON L-dopa states, that means: (i) at least twelve hours after withdrawal of all anti-parkinsonian drugs and (ii) following the administration of the usual medication. The full study design is illustrated in

Figure 1.

Speech recordings

In a quiet room, special speech recording equipment (EVA2© system, SQLab, Aix-en-Provence, France; <http://www.sqlab.fr/>; Marantz PMD661 MKII recorder, USA) is used for the speech/voice recordings. Participants are recorded while performing several tasks: (i) Steady vowel /a/ phonation, at a comfortable pitch and loudness, repeated three times; (ii) Maximum phonation time (vowel /a/ sustained as long as possible), twice; (iii) Oral diadochokinesia (repetition of the pseudoword ‘pataka’ at a fast rate during 30 seconds); (iv) Reading aloud of 10 words and 10 sentences created by adapting the intelligibility section of the Frenchay Dysarthria Assessment, version 2 (FDA2; [58]); (v) Reading aloud of short text (“The North wind and the Sun”, French and European Portuguese adaptations; [48, 59]); (vi) Oriented speech, storytelling with visual stimuli (images from Mercer Mayer’s word-less story ‘Frog, where are you ?’, [60]; for the rationale of using this procedure and this book, cf. [61]; (vii) Free conversation during 3 minutes; (viii) Reading aloud of a set of sentences with different and specific prosodic properties (31 sentences in French, 20 in European Portuguese).

Acoustic measures

The acoustic measures characterize dimensions of aero-phonatory control [62]. For the steady vowel /a/ phonation, two kinds of measures will be extracted: First, for a macro-analysis: fundamental frequency (F0, Hertz) and F0 variation (%); and second, for a micro-analysis: perturbation measures such as jitter factor (%), absolute shimmer (dB), and harmonics-to-noise ratio (HNR, %). For the maximal phonation time, the longest duration (in seconds) of the sustained vowel /a/ will be extracted. For the oral diadochokinesia task, the extracted measures will be the following: (i) the number of breath groups, *i.e.* each period during which the pseudoword was repeated in a single expiration, (ii) the ratio between the cumulated speech duration of the breath groups and the total duration of the session, *i.e.*, the speech proportion, (iii) the articulatory rate (syllables/second), (iv) the pause-to-sound ratio (%), and e) the speech proportion per number of breath groups. Global

prosodic aspects of PD speech compared to healthy controls are investigated by extracting the F0 curve of one sentence selected from the short text. This sentence has been selected to be comparable across French and European Portuguese in terms of semantics and syllable length. This will provide a global phrasal pattern of F0 and intensity for patients and controls within and across languages. A summary of the acoustic measures that will be analysed are listed in **Table 2**.

Table 2. Acoustic measures

Speech tasks	Function assessed	Acoustic measures
<i>Steady vowel /a/ phonation</i>	<i>Phonation</i>	Mean fundamental frequency (F0, in Hz) Fundamental frequency variation (F0 SD, in Hz) Shimmer (%) - <i>cycle-to cycle F0 variation</i> Jitter (%) – <i>cycle-to cycle intensity variation</i> Harmonics-to-noise ratio (HNR, in %)
<i>Maximal phonation time of the vowel /a/</i>	<i>Aero-phonatory control</i>	Longest duration (in seconds)
<i>Oral diadochokinesia</i>	<i>Supra-laryngeal articulatory control</i>	Number of breath groups Proportion of breath groups (%) Articulatory rate (in syllables/second) Pause-to-sound ratio (%) Speech proportion ratio (%)
<i>Reading aloud of text</i>	<i>Prosody</i>	Fundamental frequency range (F0 range, Hz) Intensity (in dB)

Clinical assessments

The neurological assessment is the Unified Parkinson's Disease Rating Scale [63], using the revised version provided by the *Movement Disorders Society* (MDS-UPDRS; [64]). The FDA2 is used to assess the functions of the speech organs [58], reflecting the state of the muscular effectors involved in speech production. The original FDA2, in English, includes an evaluation of intelligibility through 10 words and 10 short sentences. Using the same methodology, we developed cross-linguistic adapted lists of words and sentences in French and European Portuguese that will be used for the

intelligibility assessment in each language. During the OFF medication state, individuals with PD will be administered the FDA2 and the motor part (section 3) of the MDS-UPDRS. During the ON medication state, these two assessments will be performed together with the non-motor (section 1.A) and motor complication (section 4) sections of the MDS-UPDRS. During the ON medication state, the participants' cognitive abilities are evaluated using the Montreal Cognitive Assessment (MoCA; [65]) and the Clinical Global Impression (CGI) is also reported [66]. For healthy controls, the assessment is similar to that of the PD patients ON medication (except section 4 of the MDS-UPDRS). A summary of the clinical assessments that will be analysed are listed in **Table 3.A**.

Table 3. Clinical assessments and self-evaluation questionnaires

Description	Sub-sections	Min – Max scores (worse values in bold)
A. Clinical assessments		
Movement Disorders Society – Unified Parkinson’s Disease Rating Scale (MDS – UPDRS) <i>Assessment of motor and non-motor features of Parkinson’s disease</i> (Movement Disorder Society Task Force on Rating Scales for Parkinson's Disease, 2003)	Non-motor experience of daily living – Motor experience of daily living – Motor examination – Motor complications	0 – 260
Frenchay Dysarthria Assessment (FDA-2) - <i>Assessment of speech and voice organs</i> (Enderby & Palmer, 2007)	Reflexes – Respiration – Lips – Palate – Larynx – Tongue – Intelligibility	0 – 104
Montreal Cognitive Assessment (MoCA) - <i>Global assessment of cognitive functions</i> (Nasreddine et al., 2005)	Visuospatial – Naming – Memory – Attention – Verbal fluency – Abstraction – Orientation	0 – 30
Clinical Global Impression (CGI) - <i>Global impression of the clinician on the symptom</i> (Busner & Targum, 2007)	Speech	1 – 7
B. Self-administered questionnaires		
Parkinson’s Disease Questionnaire (PDQ-39) - <i>Quality of life in Parkinson’s disease</i> (Peto et al., 1995)	Mobility – Daily living Activities – Emotional well-being – Stigma – Social support – Cognition – Communication – Body discomfort	0 – 156
Voice Handicap Index (VHI) (Jacobson et al., 1995)	Physical – Functional – Emotional	0 – 120
Dysarthria Impact Profile (DIP) - <i>Psychosocial impact of speech deficits</i> (Walshe et al., 2009)	Effect of dysarthria on me – Accepting my dysarthria – How I feel others react to my speech – How dysarthria affects my communication – Dysarthria relative to other worries and concerns	48 – 240
Patient Global Impression (PGI) - <i>Global impression of the patient on the dysfunction</i> (Hurst & Bolton, 2004)	Speech	1 – 7
Beck Depression Inventory (BDI) - <i>Global assessment of the depression profile</i> (Beck et al., 1961)		0 – 84

Patient-reported outcome measures

Patient-reported outcome measures (PROMs), such as the Dysarthria Impact Profile (DIP; [67]), are used to obtain self-reported information about the functional impact of their speech/communication impairment [68]. Additional self-assessments focus on the patients’ perception of their quality of life (the 39-Item Parkinson's Disease Questionnaire [PDQ-39]; [69, 70]) and on how voice/speech impairment may induce a handicap (Voice Handicap Index, VHI; [71]). The French [72] and European Portuguese adapted DIP, VHI [73, 74] and PDQ-39 [75, 76, 77] will be used in our study. The Patient Global Impression (PGI) scoring [78] and the Beck Depression Inventory (BDI; [79]) are also administered. The MDS-UPDRS also includes a patient self-assessment (sections 1.B and 2), which are administered together with the other questionnaires under medication. For healthy controls, the assessment is the same to that of the individuals with PD. A summary of the patient-reported outcome measures that will be analysed are listed in **Table 3.B**.

Statistical analyses

The analyses of the data (acoustic, clinical measures, and self-questionnaire ratings) will be performed with linear mixed-effects models that account for the variability across individuals, using the latest version of the statistical software R [80] and the library for performing linear mixed-effects models (currently: [81]). For each performance measure, the between-group factors ‘group’ (patients vs. controls), ‘disease duration’ (early vs. medium vs. advanced), and ‘language’ (French vs. European Portuguese) will be investigated. In addition, we will explore the effects of the within-patient factor medication (OFF vs. ON) for all measures. Age and gender will be included as control variables in the analyses.

DISCUSSION

The present study will allow for a unique, exhaustive, and reliable assessment of PD voice, speech and prosody disorders and an evaluation of how this impacts on quality of life of individuals with PD.

Main and subsequent analyses of the FraLusoPark study

Acoustic and prosodic measurements (**Table 2**), clinical scores and patient's indices (**Table 3**) are the dependent variables to be analysed according to the statistical plan. These findings will be reported in a primary analysis as the main results of the project. However, the FraLusoPark investigation protocol allows conducting additional analyses that focus on specific sub-dimensions of speech and voice deficits. At least three extensions of the main study are considered.

First, the intelligibility section of the FDA2 [58] implies that the words and sentences produced by the patient will be rated perceptually by the clinician who is in charge of the assessment. Since these speech productions are recorded during the FraLusoPark protocol, an evaluation of speech intelligibility involving auditory juries will be run. This allows an additional and unbiased judgment of speech and voice disorders beyond that of the speech therapists and experts involved in the study. This approach further complements the global assessment of dysarthric speech in PD patients.

Second, further prosodic analysis will be conducted on the set of sentences, modulating prosodically general and language-specific details. One particular focus will be the analysis of tonal alignment in the F0 curve, that is the temporal coordination of high and low tones with specific syllables in the sentences [82, 83, 84]. Tonal alignment is likely to be a relevant factor in the study of PD dysprosody since it relies on precise coordination of glottal and articulatory gestures to achieve language-specific temporal patterns for pitch accents and boundary tones.

Finally, production and prosodic parameters from the three different speech tasks (*i.e.*, short text reading, orientated image description, and conversation) will be compared. This allows comparing speech and voicing disorders in increasingly more complex communication contexts. In fact,

communication abilities in PD are quite different in the presence of external cueing, such as during reading compared to spontaneous speech which involves more complex speech planning strategies.

Recommendations for speech and voice assessments in PD

Improving quality of healthcare and encouraging clinicians to adopt a more holistic approach to the assessment and treatment of patients is a significant recommendation of the International Classification of Functioning Disability and Health [85]. Research in the field of speech sciences needs to incorporate this viewpoint when studying pathological speech. Since this framework has been proposed, the consideration of patients’ personal feelings regarding physical, psychological and social domains has received increasing interest over the last decade. Individuals with PD are affected by voice and speech disorders, which contribute to an impairment of general communication abilities. Consequently, individuals with PD are less likely to participate in conversations or social interactions [8]. Several studies suggest that a growing discomfort in verbal communication during the progression of the disease leads to an important negative impact on social life [69, 86, 87]. Altogether, these arguments are in favour of experimental designs that include different types of speech assessments (clinical, perceptual and instrumental) as in the FraLusoPark project. We will be able to provide recommendations on how to assess speech and voice disorders in individuals with PD in different languages, in order to monitor the progression of symptoms and their management. In addition, we adopt a cross-language and cross-cultural perspective for an improved understanding of dysarthria in PD.

ETHICS AND DISSEMINATION

This study has been approved by the local responsible committees on human experimentation (France: Comité de Protection des Personnes, Sud Méditerranée 1, project reference n° 13-84, approval date 09/01/2014; Portugal: Ethics Committee of the Lisbon Academic Medical Centre,

project reference n° 239-14, approval date 12/06/2014). The study is conducted in accordance with the ethical standards of the Declaration of Helsinki [88]. The patients are included in the study after providing their written informed consent. The FraLusoPark trial has been registered under the reference NCT02753192 (26 April 2016) on <https://clinicaltrials.gov/>.

Due to inter-speaker variability, any generalization drawn from speech parameters in clinical population requires data from a large number of speakers [89]. Thus, the FraLusoPark project is in line with this idea by building a large-scale corpus of PD speech and by providing a large set of meta-data (clinical examinations, speech measurements, linguistic features, patient-based indices). This allows a more accurate description of PD dysarthria, with the evolution of the symptom and its response to medical treatment. In both medical (*e.g.*, <http://www.mrc.ac.uk/research/research-policy-ethics/data-sharing/data-sharing-population-and-patient-studies/>) and linguistic (<http://sldr.org/>) domains, it is important to consider data sharing to maximize the life-time value of human health data. It is our intention to contribute to this trend by archiving our data for long-term preservation and making them accessible after the completion of our analyses.

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AUTHORS' CONTRIBUTIONS

SP and JJF are the principal investigators of the FraLusoPark study. They designed the study and ensure the proper realization of the study. JJF and FV are the neurologists in charge of patients' recruitment and neurological assessments. RC, JS, HS, CM, JC, FV and SP perform data acquisition and other clinical examinations. RC, JS, PO and IG are in charge of the pre-processing and analyses of acoustic measurements. CA-C and AL are in charge of the analyses of the self-questionnaires and clinical assessments. PW, PO, MD, MC, SF and MV are the linguist experts in charge of the prosody evaluations. IP is the neurobehaviour, language and cognition expert. All co-authors commented the present study protocol article.

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COMPETING INTERESTS STATEMENT

The authors report that there is no competing interest.

FIGURE LEGEND

Figure 1. Overview of the FraLusoPark study design.

Patient OFF-medication assessments (*i.e.*, anamnesis, speech recordings and clinical evaluations, without medication) are shown in dark grey. ON-medication assessments (*i.e.*, speech recordings and clinical evaluations after medication is effective) are shown in light grey.

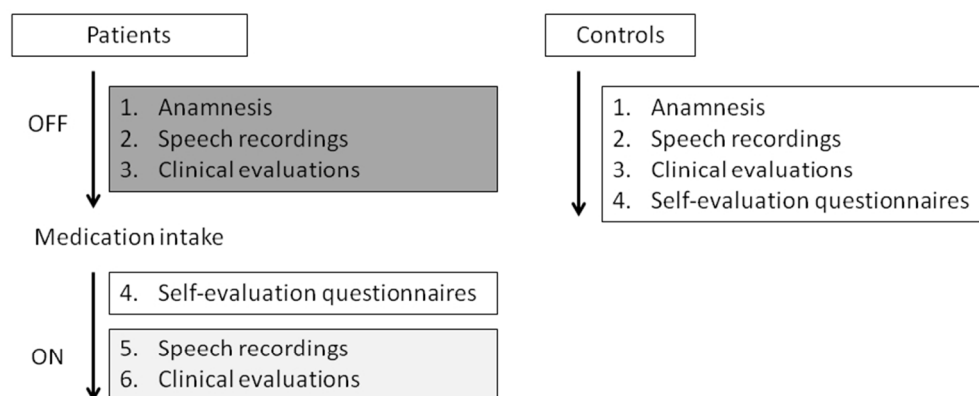


Figure 1. Overview of the FraLusoPark study design. Patient OFF-medication assessments (i.e., anamnesis, speech recordings and clinical evaluations, without medication) are shown in dark grey. ON-medication assessments (i.e., speech recordings and clinical evaluations after medication is effective) are shown in light grey.

Figure 1
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DEMANDE D'AVIS AU COMITÉ DE PROTECTION DES PERSONNES

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Titre ▶ La dysarthrie dans la maladie de Parkinson : comparaison luso-francophone

Titre abrégé ▶ FraLusoPark

1 - INFORMATIONS GÉNÉRALES

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2 - JUSTIFICATION SCIENTIFIQUE ET DESCRIPTION GENERALE DE LA RECHERCHE

2.1 - Synthèse de l'état des connaissances et hypothèses.

Contexte économique et social

Les maladies neurodégénératives constituent l'une des affections les plus fréquentes du système nerveux central. Elles partagent toutes l'existence d'une dégénérescence progressive de tout ou partie du système nerveux. Leur fréquence, la sévérité de leurs atteintes et les handicaps auxquels elles conduisent en font des maladies de la vie courante et un problème majeur de santé publique. Parmi ces pathologies, la maladie de Parkinson (MP) affecte entre 1% et 2% de la population mondiale âgée de 60 ans et plus. En Europe, sa prévalence est d'environ 150 patients parkinsoniens pour 100 000 personnes, de l'ordre de 140 000 malades en France. L'âge moyen auquel les symptômes apparaissent est d'environ 58 ans (Marsden, 1994), mais les patients peuvent développer des symptômes avant l'âge de 40 ans.

La MP est essentiellement associée à une triade symptomatique comportant tremblement, akinésie et rigidité. Si l'expression motrice de ces symptômes se traduit principalement au niveau des membres, la musculature impliquée dans la production de parole est également assujettie à des dysfonctionnements caractéristiques. Des troubles de la parole peuvent donc être développés par les patients parkinsoniens, souvent tardivement dans l'évolution des symptômes, et s'associant alors volontiers à l'apparition de fluctuations motrices induites par le traitement pharmacologique de référence, la lévodopa (L-dopa). Soixante-dix pour cent des patients atteints de MP indiquent que leur parole est altérée au cours de la progression de la maladie (Hartelius & Svensson, 1994; Ramig et al., 1994).

L'ensemble des troubles de la parole dans la MP est regroupé sous le terme générique de dysarthrie et à ce jour, les données concernant la physiopathologie de ce trouble demeurent incomplètes. Si la dysarthrie dans la MP a été largement documentée dans la littérature, à la fois en termes de description du symptôme et de sa réponse aux traitements, plusieurs divergences entre les études et entre les symptômes sont toujours débattues. La dysarthrie implique des mécanismes de compensation et des modifications physiopathologiques différents de ceux rencontrés dans la motricité des membre (Pinto et al., 2011) et de plus, contrairement au dysfonctionnement des membres, la dysarthrie répond de façon erratique aux traitements (Maillet et al., 2012). Un autre problème persistant dans l'évaluation de la dysarthrie dans la MP implique le petit nombre de patients inclus dans les études, les évaluations fragmentées n'utilisant souvent qu'un seul paramètre rendant les comparaisons entre études partielles.

La dysarthrie dans la maladie de Parkinson

La dysarthrie caractérise un déficit du contrôle moteur des organes de la parole, résultant d'une lésion du système nerveux périphérique ou central (Darley et al., 1969a; 1969b; 1975; Duffy, 2005). La dysarthrie hypokinétique de la MP présente une insuffisance prosodique, liée à une monotonie de hauteur et d'intensité, une réduction de l'accentuation, un débit variable et de possibles imprécisions de phonèmes. Dans la plupart des cas, la voix est rauque et soufflée. Certains auteurs préfèrent se référer à la parole dans la MP en tant que « dysarthrophonie », afin de souligner le dysfonctionnement au niveau du larynx parmi les différentes dysfonctions (Ackermann & Ziegler, 1989; Klostermann et al., 2008; Moreau et al., 2011). La dysarthrie dans la MP peut affecter la voix et la parole, mais impacte aussi la prosodie et l'intelligibilité.

Soixante-dix pour cent des patients parkinsoniens mentionnent un trouble de la parole au cours de la progression de la maladie, affectant leur communication dans leurs activités quotidiennes (Ramig et al., 1994). La dysarthrie peut apparaître à n'importe quel stade de la MP, et s'aggrave dans les derniers stades de la maladie (Klawans, 1986); par ailleurs, la dopathérapie, la neurochirurgie fonctionnelle et la rééducation orthophonique ont des effets variables sur la qualité de la voix et de la parole dans la MP (Pinto et al., 2004a). Dans ce contexte, les évaluations perceptives et instrumentales sont complémentaires et peuvent aider à mieux comprendre la physiopathologie spécifique de la dysarthrie.



Physiopathologie de la dysarthrie dans la MP

L'activation du réseau moteur au cours de la production de parole dans la MP a été étudiée en utilisant la tomographie par émission de positons (TEP) et l'imagerie par résonance magnétique fonctionnelle (IRMf). Ces études en neuroimagerie ont initialement (Liotti et al., 2003; Pinto et al., 2004b) rapporté que parole parkinsonienne semblait être liée à l'altération du recrutement des principales régions motrices cérébrales (cortex moteur primaire orofacial, cervelet) et une participation accrue du cortex frontal (cortex préfrontal dorso-latéral, aire motrice supplémentaire, cortex prémoteur latéral supérieur). Des activations supplémentaires, telles que le recrutement des régions temporales, ont également été observées dans des conditions sans médicaments (Sachin et al., 2008; Pinto et al., 2011), ce qui suggère qu'une réorganisation spécifique sous-tend le profil d'activation altéré et associé à la parole dans la MP. Dans la plupart des expériences en TEP, l'activation des noyaux gris centraux atteint à peine la significativité statistique. Une activation réduite de l'aire motrice supplémentaire (Rektorova et al., 2007; Narayana et al., 2009; Narayana et al., 2010; Rektorova et al., 2012) et une activation significativement plus importante dans le cortex sensori-moteur primaire (orofacial) droit, par rapport à des témoins sujets, ont également été observés dans des conditions avec administration de L-dopa. Ces modifications d'activations ont été interprétées comme un phénomène compensatoire permettant de préserver la parole dans la MP (Rektorova et al., 2007). Ces modifications peuvent refléter soit un phénomène compensatoire ou alors, le profil d'activation cérébrale sous-tendant les dysfonctionnements cérébraux inhérents à la parole dans la MP. Dans tous les cas, **ce profil d'activation n'est pas semblable à celui observé dans les tâches motrices impliquant la main**, ce qui peut expliquer les réponses différentes des mouvements des membres et de la parole face aux traitements. Comprendre la dysarthrie demeure un défi tant pour le clinicien et le chercheur, au cœur d'une recherche pluridisciplinaire, à la fois fondamentale et clinique.

Description perceptive de la dysarthrie dans la MP

Une description perceptive de la dysarthrie dans la MP a été réalisée avec précision dans la classification des dysarthries de Darley, Aronson et Brown (Darley et al., 1969a):

*"The 32 patients in the parkinsonism group presented phenomena constituting what may be called "hypokinetic dysarthria" (...). All four of the neurologic groups previously reviewed displayed **monopitch** and **monoloudness**, but the severity of these dimensions is decidedly greater in parkinsonism; together with **reduced stress** they comprise the most striking phenomena. Related prosodic changes distinctively present here are **inappropriate silences**, **short rushes of speech**, and **variable rate** (...) **Imprecise consonants** is prominent, apparently being the result of reduced excursion of the articulators rather than simply the rate of articulation. Both harsh voice and breathy voice are heard" (Darley et al., 1969a, page 258).*

Le regroupement de ces perturbations a conduit à mettre en avant l'**insuffisance prosodique** en tant que caractéristique principale de la dysarthrie hypokinétique dans la MP. Les perturbations vocales ont également conduit à considérer un regroupement secondaire, relevant de l'incompétence phonatoire : plusieurs études perceptives (Darley et al., 1975; Uziel et al., 1975; Holmes et al., 2000) ont effectivement montré des anomalies de la fonction laryngée dans la MP. L'articulation est clairement modifiée, en particulier en ce qui concerne les consonnes plosives (Darley et al., 1975), les consonnes sourdes ayant tendance à être voisées (Canter, 1963; Uziel et al., 1975). La dysarthrie hypokinétique présente une réduction des mouvements articulatoires et une diminution de la modulation de la voix à l'origine d'une monotonie. L'évaluation subjective clinique de l'état moteur du patient parkinsonien repose sur l'utilisation de l'échelle UPDRS (Unified Parkinson's Disease Rating Scale ; Fahn et al., 1987). Cette échelle contient deux items pour l'évaluation perceptive de la parole: l'item 5, présent dans la sous-échelle « Activités de la vie quotidienne » et l'item 18, faisant partie de la sous-échelle « Évaluation motrice ». Ces items permettent aux neurologues d'avoir une idée approximative du degré de dysarthrie, sur la base d'une notation sur 5 points (de 0 = parole normale à 4 = parole inintelligible).



Caractéristiques périphériques de la dysarthrie dans la MP

- Caractéristiques aérodynamiques

Au repos, la respiration des patients parkinsoniens a un rythme respiratoire plus rapide que la normale et une baisse relative des mouvements thoraciques, aucune différence n'ayant été observée sur la durée inspiratoire. Au cours de production de la parole, les patients montrent une diminution des volumes inspiratoires de la cage thoracique et l'abdomen, ce qui suggère une modification de la quantité d'air nécessaire pour la vibration des cordes vocales (Solomon & Hixon, 1993). La pression sous-glottique est significativement plus élevée que la normale dans la MP (Jiang et al., 1999), résultant d'un mauvais contrôle du flux d'air expiratoire. Ainsi, les patients parkinsoniens ont à développer un effort supplémentaire afin de maintenir une phonation acceptable, nécessaire pour être compréhensible.

- Paramètres phonatoires

L'analyse acoustique a confirmé une diminution de la dynamique de fréquence de la parole et une gamme vocale réduite sur la voyelle soutenue, en raison de la rigidité du larynx (Holmes et al., 2000). Cependant, il existe des biais expérimentaux liés à l'âge (élévation de la fréquence fondamentale, ou f_0), le sexe (plus d'effets pour les hommes), la durée de progression de la maladie (avec la participation de stratégies compensatoires), les effets de traitements antiparkinsoniens (avec L-Dopa ; les études sont moins nombreuses avec des patients en *off*), ou encore la variabilité des performances inter- et intra-individuelles. Il faut également mentionner l'hétérogénéité des méthodes d'évaluation ou de mesure. Il semble plus réaliste de considérer un large éventail d'anomalies de la f_0 moyenne qui peut être : **abaissée**, en raison de l'absence initiale de dopamine, conduisant à une diminution de la pression sous-glottique et à l'incompétence phonatoire par le biais d'une hypokinésie de la musculature laryngée ; **élevée**, par l'effet du traitement antiparkinsonien et à la suite de stratégies de compensation permettant d'optimiser la fermeture du larynx ; voire même **inchangée**, les facteurs d'élévation et de réduction étant compensés (Viallet et Teston, 2007). La monotonie de l'intensité est plus difficile à objectiver, mais la dominance va dans le sens d'une légère réduction de l'intensité moyenne (Ramig et al., 2001) et de la dynamique de l'intensité dans la parole, associée à une diminution des volumes expiratoires (Ho et al., 2001).

- Caractéristiques articulatoires supra-laryngés

Sur la base de mesures électromyographiques réalisées chez des patients atteints de la MP, la rigidité musculaire de la lèvre inférieure a été décrite (Leanderson et al., 1972). En termes d'imprécision des consonnes, les plosives (/t/, /d/, /p/, /b/) sont souvent réalisées comme des fricatives (/s/, /z/, /f/, /v/) (Logemann & Fisher, 1981). Le conduit vocal n'est pas complètement fermé, de l'air s'échappe en permanence avec un bruit de frottement (Robert & Spezza, 2005) : ainsi, sur le signal acoustique, un bruit se trouve à la place d'un silence, un phénomène défini comme une spirantisation (Kent & Rosenbek, 1982; Ackermann & Ziegler, 1991) et qui est en corrélation avec le degré de dysarthrie des patients. Ceci est probablement la conséquence de l'hypo- et la bradykinésie des organes articulatoires, ainsi que la rigidité musculaire. Des erreurs de voisement peuvent également être observées sur les consonnes sourdes, ainsi que des raccourcissements sur les fricatives (par exemple /s/, /f/) et la fermeture des occlusives ; de plus, la durée des voyelles semble variable au vu des spectrogrammes. Ce voisement et le défaut de fermeture vélo-pharyngé observé (Kent & Netsell, 1971) pourraient être issus d'un mécanisme compensatoire au défaut d'initiation et d'arrêt des mouvements articulatoires du patient parkinsonien, qui éviterait certains mouvements pour rendre sa parole plus aisée.

Aspects suprasegmentaux de la dysarthrie dans la MP

L'étude de la distribution de la f_0 chez les patients parkinsoniens a indiqué une perte de la partie supérieure de la gamme de tons (Viallet et al., 2000). En ce qui concerne le rythme, festination de la parole, palilalie, pseudo-bégaiement et dysfluences ont été décrits depuis longtemps dans la MP et soulignés encore récemment (Monfrais-Pfauwadel, 2005). L'organisation temporelle de la parole dans la MP a été abordée par une analyse détaillée des signaux acoustiques de la parole au cours d'une tâche de lecture (Duez, 2005) : le débit de parole tend à être plus lent et il semble être corrélé à un temps de pause plus



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important; la durée moyenne des pauses est significativement plus longue chez les patients parkinsoniens que chez les sujets témoins, tandis que la longueur moyenne des séquences sonores n'a montré aucune différence significative entre patients et contrôles. Ces résultats, en accord avec les données précédentes (Hammen & Yorkston, 1996), suggèrent que l'allongement anormal des pauses et les pauses à l'intérieur des mots et des phrases contribuent à la dégradation de l'intelligibilité de la parole (Duez, 2005). La plupart des patients ont tendance à maintenir le contraste de durée entre consonnes et voyelles, ce qui suggère que les processus de bas niveau sont préservés et opèrent de la même manière chez les patients et sujets contrôles (Duez, 2009). L'allongement final est préservé chez les patients: la fonction syntaxique de la prosodie est maintenue, au moins dans les stades précoces de la maladie (Duez et al., 2009; 2012).

Objectifs et hypothèses

L'objectif principal de notre projet est d'évaluer les paramètres physiologiques (acoustiques), les marqueurs de perception (intelligibilité) et l'impact psychosocial de la parole parkinsonienne dans un contexte de modulation de langue (français vs. portugais). Nos hypothèses sont les suivantes :

- 1) les paramètres acoustiques sont physiologiquement contraints, liés aux aspects moteurs de la parole dysarthrique : un même degré d'altération devrait être présent chez tous les patients, indépendamment de la langue ;
- 2) les marqueurs prosodiques diffèrent significativement selon la langue chez les témoins, mais pas chez les patients, compte-tenu des perturbations prosodiques associées à la dysarthrie dans la MP (i.e. monotonie);
- 3) l'intelligibilité et l'impact psychosocial sont fonctions de l'altération des marqueurs prosodiques et diffèrent significativement selon la langue.

Ces questions représentent le cœur de notre approche, qui aura pour objectif de comparer les données des deux langues **afin de déterminer si la dysarthrie dans la MP affecte tous les patients de la même manière en termes de qualité vocale, d'intelligibilité et de compétence communicationnelle**. Par ailleurs, l'effet du traitement pharmacologique de référence, c'est-à-dire dopaminergique, sera également étudié afin de comprendre au mieux les modulations de son effet en fonction du degré de sévérité de la maladie des patients et de la durée d'évolution.

Enjeux dans l'évaluation de la dysarthrie dans la MP

Nécessité de corpora de grande échelle

En raison de la forte variabilité inter-individuelle, toute généralisation interprétative des paramètres de parole calculés dans une population pathologique nécessite des données provenant d'un grand nombre de locuteurs (Ghio et al., 2012). Dans de telles bases de données, des informations sont souvent manquantes (origine et organisation des données non-détaillées, évaluations fragmentées...). Il est d'un grand intérêt de construire un corpus à grande échelle de parole dysarthrique de la MP, dans le but de fournir de solides analyses statistiques permettant de clarifier les inconnues persistantes. Il est important d'être en mesure de répondre aux attentes des patients quant à leur parole et de documenter les possibilités d'évolution de leur symptôme. **Ce point sera pris en compte dans le présent projet.**

Évaluation de la parole dans le cadre d'une évaluation globale de trouble de la communication

Il y a différentes façons d'étudier la dysarthrie: clinique, instrumentale, en réponse aux traitements... Cependant, une question importante et longtemps négligée est la propre expérience du patient au sujet de son déficit potentiel de communication. Seule une littérature sporadique rapporte l'évaluation auto-rapportée de l'impact psychosocial du trouble de la parole dans la MP. Afin de pallier ce manque d'outils d'évaluation, le *Dysarthria Impact Profile* (DIP) a été récemment développé (Walshe et al., 2009) et adapté en français (Letanneux et al., 2013). Il peut représenter un instrument qui réponde à ce besoin à la fois pour la pratique clinique et la recherche expérimentale. **Ce point sera pris en compte dans le présent projet.**



Modulations linguistiques

Les évaluations perceptives et acoustiques de la parole dans la MP ont rapporté des altérations de la fréquence fondamentale (f0), dans le cadre d'une incompétence phonatoire: la réduction de la gamme de fréquence et de la variabilité est clairement un indicateur de la dysarthrie dans la MP. La dégradation de la prosodie peut avoir des conséquences cruciales pour l'intelligibilité de la parole et de la communication. Par conséquent, l'étude de la parole chez des patients dont la langue implique des modulations prosodiques nécessaires est d'un fort intérêt pour quantifier le rôle de la prosodie dans l'intelligibilité de la parole des patients (Ma et al., 2010; Whitehill, 2010). **Ce point sera pris en compte dans le présent projet.**

Pour répondre aux questions que nous avons soulevées, il est important de tenir compte: 1) d'un plus grand nombre de patients parkinsoniens à étudier; 2) d'une évaluation globale et multidisciplinaire de la parole des patients; 3) de la langue des patients: de fait, chaque langue transmet des spécificités idiomatiques pouvant faciliter, ou bien rendre plus difficile, la parole des patients.

2.2 - Résumé des bénéfices, le cas échéant, et des risques prévisibles et connus pour les personnes se prêtant à la recherche.

Aucun bénéfice n'est attendu pour les personnes se prêtant à cette étude. Elle entre dans le cadre d'une recherche biomédicale dont la balance bénéfices/risques n'a pas d'impact direct sur l'état du patient. L'objectif est d'améliorer notre connaissance sur la dysarthrie dans la MP, et sa réponse au traitement médicamenteux. Aucun prélèvement sanguin ni aucune administration de produits médicamenteux autres que ceux que prennent habituellement les patients ne seront pratiquées. La méthodologie utilisée fait appel à des techniques d'exploration sans aucun risque connu : aucun risque n'est attendu. La principale contrainte pour l'ensemble des patients est l'inconfort transitoire que leur état sans médicament peut générer. En outre, les tâches expérimentales ne rentrent pas un cadre difficile de réalisation, à la portée de tous les participants.

2.3 - Description de la population à étudier

Les patients parkinsoniens seront recrutés par le médecin investigateur, chef du service de neurologie au Centre Hospitalier du Pays d'Aix. Le jour de leur inclusion à l'étude, ils recevront une notice d'information leur expliquant l'étude (cf. pièce jointe au dossier intitulée *notice_information_patient_fralusopark*), afin d'envisager de leur part un accord éclairé qu'ils devront confirmer par la signature d'un consentement de participation (cf. pièce jointe *consentement_patient_fralusopark*), et ce conformément à la réglementation en vigueur émanant de la déclaration de Helsinki (World Medical Association, 2004). Toutes les investigations sont non invasives et sûres : ainsi, aucun effet secondaire ou délétère n'est attendu, ni aucune interférence avec les activités et/ou traitements des sujets et patients.

Les patients parkinsoniens qui seront inclus dans l'étude, à Aix-en-Provence (N = 60; Service de Neurologie, Centre Hospitalier du Pays d'Aix) seront tous des locuteurs français natifs. Tous les patients seront évalués au moins douze heures après le retrait de tous médicaments anti-parkinsoniens (c'est-à-dire la non-prise de la première dose de médicament du matin), puis dans une deuxième condition avec traitement. Cette évaluation sans (*off*), puis avec (*on*) médicaments, est pratiquée de manière courante par le neurologue pour le suivi des patients : notre évaluation s'insérera dans ce contexte. **Il ne sera pas demandé de manière spécifique aux patients de venir sans médicament. Ces derniers seront étudiés dans le cadre de leur évaluation de routine à l'Hôpital de Jour par le Dr. François Viallet, investigateur principal de l'étude.** Trois sous-groupes de 20 patients seront constitués :

- Sous-groupe A : troubles légers (échelle Hoen & Yahr modifiée : 1 à 1,5), durée de maladie comprise entre 0 et 3 ans, pas de fluctuations motrices ;
- Sous-groupe B : troubles modérés (échelle Hoen & Yahr : 2 à 3), durée de maladie comprise entre 3 et 10 ans, avec fluctuations motrices ;



- Sous-groupe C : troubles importants (échelle Hoen & Yahr : 4 à 5), durée de maladie > à 10 ans.

Dans chacune des 2 conditions *off* et *on* médicaments, le handicap moteur global sera évalué par l'échelle UPDRS – Unified Parkinson's Disease Rating Scale (Fahn et al., 1987). L'état cognitif des patients sera évalué par le Mini-Mental State Examination (Folstein et al., 1975).

Par ailleurs, 1 groupe de 60 volontaires sains, appariés en âge et en genre avec les patients parkinsoniens, fourniront une référence pour l'état normal des tâches que nous considérerons ; ils seront également locuteurs français natifs. Ils seront principalement recrutés au sein de l'environnement proche des patients (conjoint, famille, amis), dans le service de Neurologie du Centre Hospitalier du Pays d'Aix par le Dr. Viallet (cf. pièce jointe *consentement_témoin_fralusopark*). Les critères d'exclusion incluent toute histoire de perturbation neurologique, psychiatrique ou comportementale. Avant la participation des sujets, un examen médical de routine sera réalisé par le médecin investigateur de l'étude et les résultats de cet examen seront communiqués au sujet, conformément à la réglementation et comme précisé dans la notice d'information (cf. pièce jointe *notice_information_témoin_fralusopark*). En outre, cet examen ne sera pas réalisé pour les patients, le suivi étant déjà effectué par les médecins investigateurs dans le cadre de la prise en charge habituelle des patients ayant accepté de participer à l'étude.

2.4 - Références à la littérature scientifique et aux données pertinentes servant de référence pour la recherche (les références émanant des investigateurs de la présente étude sont individualisées en gras, afin de montrer leur forte implication dans le domaine de recherche)

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3 - OBJECTIFS DE LA RECHERCHE

L'objectif principal de notre projet est d'évaluer les paramètres physiologiques (acoustiques), les marqueurs de perception (intelligibilité) et l'impact psychosocial de la parole parkinsonienne dans un contexte de modulation de langue (français vs. portugais). Ces questions représentent le cœur de notre approche, qui aura pour objectif de comparer les données des deux langues **afin de déterminer si la dysarthrie dans la MP affecte tous les patients de la même manière en termes de qualité vocale, d'intelligibilité et de compétence communicationnelle**. Par ailleurs, l'effet du traitement pharmacologique de référence, c'est-à-dire dopaminergique, sera également étudié afin de comprendre au mieux les modulations de son effet en fonction du degré de sévérité de la maladie des patients et de la durée d'évolution.

4 - CONCEPTION DE LA RECHERCHE

4.1 - Énoncé précis des critères d'évaluation principaux et, le cas échéant, des critères d'évaluation secondaires.

Les critères d'évaluation principaux seront :

- les variables acoustiques (cf. paramètres phonatoires et marqueurs prosodiques de la tâche 3) ;
- les scores d'intelligibilité (cf. tâche 4) ;
- les scores des auto-questionnaires (cf. tâche 5).

Les critères d'évaluation secondaires permettront de moduler, dans un second temps, les analyses statistiques concernant les critères principaux. Ce seront :



- la durée de la maladie ;
- la dose quotidienne de traitement dopaminergique ;
- la langue parlée par les patients.

4.2 - Description de la méthodologie de la recherche, accompagnée de sa présentation schématique précisant notamment les visites et les examens prévus.

Tâche	Objectif	Description de la tâche
1	Accord du Comité de Protection des Personnes (CPP)	<i>Soumission du dossier éthique</i>
2	Acquisition des données (= 1 visite / témoin ou patient)	<i>Recrutement des témoins et patients Examen clinique (motricité globale et de la parole) Enregistrement de la voix/parole Passation des auto-questionnaires</i>
3	Analyses acoustiques	<i>Paramètres phonatoires Marqueurs prosodiques</i>
4	Analyse de l'intelligibilité	<i>Segmentation du corpus Evaluation par jury d'écoute</i>
5	Analyse de la qualité de vie	<i>Traitement des auto-questionnaires</i>
6	Traitements statistiques	<i>Comparaisons inter-groupes (témoins vs. patients) Comparaisons inter-langues (français vs. portugais)</i>

4.3 - Description des mesures prises pour réduire et éviter les biais telles que notamment le tirage au sort.

Non applicable.

4.4 - Description précise du déroulement de la recherche comportant notamment une description des produits utilisés au cours de la recherche, des actes pratiqués et des méthodes utilisées, le cas échéant, une description de la posologie et des modalités d'administration du ou des produits expérimentaux. Description de la forme unitaire, du conditionnement et de l'étiquetage du ou de ces produits.

Tâche 1 – Avis du Comité de Protection des Personnes (CPP) et de l'autorité compétente (ANSM)

L'étude sera réalisée avec l'avis favorable émis par le Comité d'éthique local (Sud-Méditerranée 1, Marseille) et l'autorité compétente (Agence Nationale de Sécurité du Médicament et produits de santé - ANSM). Témoins et patients recevront la notice d'information détaillée de l'étude et seront invités à signer un formulaire de consentement éclairé, conformément à la Déclaration d'Helsinki (World Medical Association, 2008). Tous les aspects éthiques seront envisagés, incluant également la protection des données. Ces documents sont joints à la présente demande.



Tâche 2 - Acquisition des données

- Recrutement des témoins, patients et examen clinique

Les patients parkinsoniens seront recrutés par le médecin investigateur, chef du service de neurologie au Centre Hospitalier du Pays d'Aix, Aix-en-Provence. Il ne sera pas demandé de manière spécifique aux patients de venir sans médicament. Ces derniers seront étudiés dans le cadre de leur évaluation de routine à l'Hôpital de Jour par le Dr. François Viallet, investigateur principal de l'étude.

Les patients parkinsoniens qui seront inclus dans l'étude (N = 60; Service de Neurologie, Centre Hospitalier du Pays d'Aix) seront tous des locuteurs français natifs. Tous les patients seront évalués au moins douze heures après le retrait de tous médicaments anti-parkinsoniens (c'est-à-dire la non-prise de la première dose de médicament du matin), puis dans une deuxième condition avec traitement. **Cette évaluation sans (off), puis avec (on) médicaments, est pratiquée de manière courante par le neurologue pour le suivi des patients : notre évaluation s'insérera dans ce contexte.** Trois sous-groupes de 20 patients seront constitués :

- Sous-groupe A : troubles légers (échelle Hoen & Yahr modifiée : 1 à 1,5), durée de maladie comprise entre 0 et 3 ans, pas de fluctuations motrices ;
- Sous-groupe B : troubles modérés (échelle Hoen & Yahr : 2 à 3), durée de maladie comprise entre 3 et 10 ans, avec fluctuations motrices ;
- Sous-groupe C : troubles importants (échelle Hoen & Yahr : 4 à 5), durée de maladie > à 10 ans.

Dans chacune des 2 conditions *off* et *on* médicaments, le handicap moteur global sera évalué par l'échelle UPDRS – Unified Parkinson's Disease Rating Scale (Fahn et al., 1987). L'état cognitif des patients sera évalué par le Mini-Mental State Examination (Folstein et al., 1975). Par ailleurs, 1 groupe de 60 volontaires sains, appariés en âge et en genre avec les patients parkinsoniens, fourniront une référence pour l'état normal des tâches que nous considérerons ; ils ne présenteront aucune pathologie neurologique ou psychiatrique (vérification faite lors de l'examen médical réalisé par le médecin investigateur) et seront également des locuteurs français natifs.

- Enregistrements de la voix/parole

L'acquisition des données orales se fera à l'aide d'un enregistreur numérique et d'un microphone-casque de haute qualité. Les tâches de production de parole seront les suivantes:

- Tenue de la voyelle /a/, 3 fois ;
- Temps maximal de phonation (voyelle /a/ tenue aussi longtemps que possible), 1 fois;
- Tâche de diadococinésie (répétition du pseudomot *pataka*), à débit rapide, 30 secondes;
- Lecture de 10 mots (issus de l'adaptation française de la version 2 du Frenchay Dysarthria Assessment (FDA) ; Enderby, 1980; Enderby & Palmer, 2008) ;
- Lecture de 10 phrases (issues du FDA) et de 20 phrases prosodiquement contrôlées;
- Lecture d'un court paragraphe (environ 10 lignes) ;
- Parole spontanée orientée (description d'image).

Le temps total pour mener à bien tous ces enregistrements sera de 15 minutes, pour chacune des conditions médicamenteuses.

- Evaluation des organes de la parole

Cette évaluation (Batterie d'Evaluation Clinique de la Dysarthrie, BECD ; Auzou et Monnoury, 2006) se



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concentre sur les capacités des organes supralaryngés (lèvres, langue, joues, la mâchoire) en mesurant la force, la vitesse et l'intégrité des organes, ce qui représente une bonne appréciation qualitative des compétences motrices des effecteurs musculaires impliqués dans la production de parole.

Le temps total pour réaliser cette évaluation sera de 15 minutes, pour chacune des conditions médicamenteuses.

- Auto-questionnaires

Le développement d'un auto-questionnaire qui prend en compte le ressenti des patients quant à l'impact fonctionnel de sa parole, le *Dysarthria Impact Profile* (DIP; Walshe et al, 2009), représente à notre sens une approche novatrice et un outil intéressant (Walshe, 2011). D'autres auto-questionnaires se concentrent également sur la façon dont les troubles de la voix/parole peuvent induire un handicap (Voice Handicap Index [VHI]) (Jacobson et al., 1997) et altérer la qualité de vie des patients (qualité de vie dans la maladie de Parkinson [PDQ-39]) (Jenkinson et al., 1995). Ces deux échelles sont considérées comme les *gold-standard* de ces évaluations, et afin de corréliser nos résultats avec le DIP (Letanneux et al., 2013), ces questionnaires seront également utilisés dans notre étude. Les patients recevront les questionnaires au moment des évaluations cliniques et de la parole. Ils seront invités à remplir ceux-ci à la maison et les renvoyer aux investigateurs dans le mois suivant leur examen.

Tâche 3 – Analyses acoustiques

- Paramètres phonatoires

L'analyse acoustique sera obtenue automatiquement (Phonedit-Signaix ; <http://aune.lpl.univ-aix.fr/~lpldev/Phonedit/>).

Pour la voyelle /a/ tenue, les paramètres calculés seront les suivants : la fréquence fondamentale (f0, Hz), le coefficient de variation de f0 (%), le niveau sonore de parole (SPL, dB), l'écart-type de SPL (dB), le jitter (%) le schimmer (dB), le rapport signal/bruit (SNR, %).

Pour la voyelle /a/ tenue le plus longtemps possible, les paramètres mesurés seront : le temps maximal de phonation (MPT, s); la fréquence fondamentale (MPT_f0, Hz); le niveau sonore de parole (MPT_SPL, dB).

Pour la tâche de diadococinésie, l'analyse acoustique sera basée sur le calcul des paramètres dans la fenêtre de signal comprise entre les deux curseurs qui délimitent le début et la fin de la production au cours de tous les groupes de souffle qui ont été produits au cours de la réalisation de la tâche. Les paramètres calculés seront les suivants: durées des groupes de souffle (s), débit articulatoire (phonèmes/minute) et rapport pause/son (%).

- Marqueurs prosodiques

La structure prosodique est dans une large mesure spécifique à la langue, mais très peu d'études ont examiné la dysprosodie dans la MP. Dans notre projet, tous les sujets témoins et les patients parkinsoniens parlant la même langue auront produit le même texte, ce qui permettra une évaluation standardisée des aspects prosodiques. L'annotation prosodique se placera dans le cadre d'auto-segmentaire métrique (Pierrehumbert, 1980 ; voir aussi Ladd, 1996). Le cadre a été adapté en français par Jun & Fougeron (2002; voir aussi Welby, 2006), et en portugais par Frota (2000 ; 2002a ; 2002b ; sous presse). Une attention particulière sera accordée à l'analyse de l'alignement tonal (tons hauts et bas) dans la courbe de f0. L'alignement est susceptible d'être un facteur pertinent dans l'étude de la dysprosodie parkinsonienne car il repose sur une coordination précise des gestes glottiques et articulatoires.

Les mesures comprendront entre autres: le temps de parole (= temps de parole + pauses silencieuses; en s), le nombre de pauses et leur durée moyenne, le débit de parole (syllabes/temps de parole), la fréquence



fondamentale f_0 moyenne (Hz), l'intensité moyenne SPL (dB), la distribution des pauses, le pattern tonal et l'alignement tonal de repères sectoriels.

Tâche 4 – Analyse de l'intelligibilité

- Segmentation du corpus

Parmi les tâches incluses dans l'enregistrement de la parole des patients, la lecture de 10 mots et 10 phrases issus de l'adaptation française du Frenchay Dysarthria Assessment (Enderby, 1983), version 2 (Enderby & Palmer, 2008) permettra l'évaluation de l'intelligibilité de la parole. La traduction et l'adaptation préalables de l'échelle (version 2) ont déjà été réalisées. Par la suite, après l'acquisition des données orales, un travail long et crucial portera sur la segmentation des fichiers audio: chaque mot et phrase des fichiers devront être définis (en tant que fenêtres temporelles) et étiquetés avec le stimulus présenté.

- Evaluation par jurys d'écoute et analyse

Ces étiquettes seront alors automatiquement extraites pour générer des fichiers audio qui seront présentés aux jurys d'écoute, à qui il sera demandé d'entendre et de transcrire à l'aide d'un système informatisé « ce qui aura été compris ». Après l'expérience, un important travail *a posteriori* mettra l'accent sur deux paramètres: 1) le calcul des pourcentages de mots correctement compris, et 2) le temps de réponse, hypothétiquement corrélé avec le pourcentage précédent.

Tâche 5 – Analyse de la qualité de vie

Dans une étude pilote (Letanneux et al., 2013), nous avons administré une version préliminaire de l'échelle française à 10 patients parkinsoniens, présentant des degrés divers de dysarthrie, et 10 sujets témoins appariés en âge. Les propriétés psychométriques de DIP ont été examinées à travers la comparaison avec d'autres échelles, qui ont également été administrées (PDQ-39, VHI, UPDRS III). Principalement, le DIP a été en mesure de différencier de façon significative les deux populations étudiées: le score total du DIP pour les patients parkinsoniens était significativement plus faible que pour les témoins (test U de Mann-Whitney, $p < 0,025$). L'analyse en composante principale démontré la capacité du DIP à mesurer l'impact des troubles de la parole dans la population parkinsonienne. Le DIP a montré une bonne cohérence interne, en dépit d'une fidélité intra-évaluateur variable. Par ailleurs, les données des patients parkinsoniens ont révélé une forte corrélation avec le VHI (test Pearson, $p = -0,85$). L'échelle doit être encore affinée et ses propriétés psychométriques confirmées sur une population plus large: notre projet sera le contexte adéquat pour exécuter de tels travaux.

Tâche 6 – Traitements statistiques

Les données obtenues seront analysées à l'aide de modèles linéaires à effets mixtes (logiciel R; <http://www.r-project.org/>), qui fournissent un outil puissant pour l'analyse de données groupées. Principalement, les paramètres mentionnés ci-dessus représentent les variables dépendantes des modèles. L'objectif principal de notre projet est d'évaluer l'existence d'une modulation des paramètres physiologiques (acoustiques), des marqueurs de perception (intelligibilité) et de l'impact psychosocial de la parole dysarthrique dans la MP, dans un contexte de modulation de langue (français vs. portugais).



4.5 - Durée prévue de participation des personnes, et description de la chronologie et de la durée de toutes les périodes de la recherche, y compris le suivi, le cas échéant.

- La durée de participation des personnes sera d’une matinée.
- La durée totale de l’ensemble des évaluations sera de 30 minutes (2 x 30 minutes dans le cas des patients qui réaliseront l’expérience une première fois sans, puis une deuxième avec médicaments).
- Les sujets devront retourner aux investigateurs les auto-questionnaires remplis, dans un délai de 1 mois après le jour de l’évaluation.

4.6 - Durée totale de la recherche (temps nécessaire pour l’inclusion de tous les sujets)

36 mois.

4.7 - Description des règles d’arrêt définitif ou temporaire

4.7.1 - De la participation d’une personne à la recherche

- Retrait de consentement du participant

Conformément à la réglementation, chaque participant pourra à tout moment, s’il le désire, arrêter sa participation à l’étude. La participation à l’étude et l’arrêt de cette participation n’entraînent aucune responsabilité ou engagement spécifique de la part des participants. Le participant est libre de justifier ou non sa décision. Il sera remplacé pour garantir le nombre de sujets prévus.

- Arrêt par décision de l’investigateur

Dans les cas où les participants ne peuvent pas se soumettre aux évaluations (fatigue intense, incapacité à réaliser les tâches expérimentales), les investigateurs proposeront aux sujets de mettre fin à leur participation librement et sans aucune conséquence pour eux.

4.7.2 - D’une partie ou de la totalité de la recherche

En cas d’événement indésirable grave, pouvant mettre en jeu la santé des sujets, l’investigateur arrêtera l’étude en accord avec le promoteur. Un document sera transmis, daté et signé, par l’investigateur pour informer le promoteur de l’arrêt anticipé en indiquant les raisons.

4.7.3 - Arrêt de l’étude par le promoteur

Le promoteur peut arrêter l’étude à tout moment, pour les raisons suivantes :

- Absence de consentement signé ;
- Violations majeures au protocole sans justification et amendement.

4.8 - Identification de toutes les données à recueillir directement dans les cahiers d’observation, qui seront considérées comme des données source.

- Code du sujet, genre, année de naissance
- Anamnèse et scores des évaluations cliniques
- Code des fichiers des données orales

Le formulaire de consentement signé sera inséré dans le cahier d’observation : l’anonymisation sera respectée pour la partie expérimentale de ce cahier. Le patient/témoin conservera par ailleurs une copie de son consentement. Concrètement, le patient/témoin sera approché par l’investigateur principal (Dr.



François Viallet). Une notice d'information lui sera donnée et un premier accord de principe sera demandé. S'il y a acceptation de participation, un rendez-vous sera pris pour les examens.

5 - SELECTION ET EXCLUSION DES PERSONNES DE LA RECHERCHE

5.1 - Critères d'inclusion des personnes qui se prêtent à la recherche

L'inscription au fichier national des personnes participant à des protocoles de recherche biomédicale sera renseignée par nos soins. Les critères d'inclusion et d'exclusion spécifiant la participation à l'étude sont indiqués dans le tableau ci-après.

5.2 - Critères de non-inclusion

Cf. tableau ci-après.

5.3 - Procédure d'arrêt prématuré de la recherche ou d'exclusion pour une personne de la recherche et procédure de suivi de la personne.

L'arrêt prématuré de la recherche et/ou l'exclusion d'une personne sont sans conséquences pour les personnes participant aux expériences. Comme précisé précédemment, la méthodologie utilisée fait appel à des techniques d'exploration sûres : aucun risque n'est attendu. La principale contrainte pour les patients sera l'inconfort transitoire que leur état sans médicament pourra générer. Dans les cas où les participants ne pourront pas réaliser les tâches expérimentales du fait d'un état trop sévère (fatigue intense, inconfort trop important), les investigateurs proposeront aux sujets de mettre fin à leur participation librement.

Tous participants	
Spécifique patient parkinsonien	
Spécifique sujet contrôle	
Critères d'inclusion	Critères d'exclusion
<i>Agés entre 35 et 80 ans, De langue maternelle française</i>	
<i>Coopérant</i>	<i>Non coopérant ou retirant son consentement</i>
<i>De langue maternelle française</i>	<i>Participant sous tutelle, curatelle ou toute autre mesure administrative ou judiciaire de privation de droit et de liberté</i>
<i>Capable de comprendre le document d'information et donner un consentement signé</i>	<i>Troubles cognitifs, psychose ou autres troubles comportementaux ou neurologiques</i>
<i>Affilié à un régime de sécurité sociale</i>	<i>Dépression sévère, prolongée et idées suicidaires</i>
<i>Maladie de Parkinson idiopathique</i>	<i>Problèmes médicaux ou psychologiques pouvant interférer avec l'expérimentation</i>
<i>Absence de démence, de psychose</i>	<i>Maladie en relation avec une cause autre que celle acceptée dans la sélection des patients</i>
	<i>Score UPDRS III trop élevé</i>
<i>Absence de pathologie neurologique, psychiatrique ou comportementale</i>	



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6 - EVALUATION DE LA SECURITE

6.1 - Description des paramètres d'évaluation de la sécurité

L'environnement expérimental fourni par l'hôpital de jour du service de neurologie du Centre Hospitalier du pays d'Aix assurera la pleine sécurité des participants lors des expérimentations.

6.2 - Méthodes et calendrier prévus pour mesurer, recueillir et analyser les paramètres d'évaluation de la sécurité

Non applicable.

6.3 - Procédures mises en place en vue de l'enregistrement et de la notification des événements indésirables

Tout événement indésirable (par exemple, arrêt de l'expérimentation suite à un problème technique ou à la demande du participant) sera indiqué dans le cahier d'observation. En cas d'événement indésirable grave, cf. section 7.

6.4 - Modalités et durée du suivi des personnes suite à la survenue d'événements indésirables

cf. section 7.

7 - EFFETS INDESIRABLES

L'investigateur doit évaluer pour chaque évènement indésirable recueilli au cours de la recherche :

- Sa gravité,
- Le lien de causalité entre l'évènement indésirable et la recherche.

Comme précisé plus haut, dans les cas où les participants ne pourront pas réaliser les tâches expérimentales du fait d'un état trop sévère (fatigue intense, inconfort trop important), les investigateurs proposeront aux sujets de mettre fin à leur participation librement. L'arrêt prématuré de la recherche et/ou l'exclusion d'une personne sont sans conséquences pour les personnes participant aux expériences. Tout événement indésirable inattendu de ce type sera indiqué dans le cahier d'observation.

7.1 - Critères permettant de déterminer le caractère inattendu d'une suspicion d'effet indésirable grave sous la forme d'une liste d'effets indésirables prévisibles ou sous la forme de critères de fréquence ou de gravité ou de tout autre élément pertinent.

Selon l'article R.1123-39 du code de la santé publique, un évènement indésirable concerne toute manifestation nocive survenant chez une personne qui se prête à une recherche biomédicale, que cette manifestation soit liée ou non à la recherche ou au produit sur lequel porte cette recherche. Un événement indésirable est considéré comme grave dans les cas suivants :

- Il entraîne le décès du patient ou met en jeu le pronostic vital ;
- Il entraîne une hospitalisation ou une prolongation d'hospitalisation ;
- Il entraîne une invalidité ou incapacité sévère ou permanente.



7.2 - Gestion des événements indésirables

Tout événement indésirable (par exemple, arrêt de l'expérimentation suite à un problème technique ou à la demande du participant) sera indiqué dans le cahier d'observation (comme indiqué section 5, §5.3).

Concernant les événements indésirables graves, sans délai à compter du jour où il a connaissance d'un événement indésirable grave, l'investigateur doit :

- Informer dans les 24 heures ouvrables par téléphone ou fax le promoteur de l'étude de la survenue de l'événement indésirable grave ; lors de cette notification, l'investigateur transmet au promoteur son évaluation du lien de causalité de l'événement indésirable grave avec la recherche (c'est-à-dire avec la procédure, la méthode et/ou l'acte faisant l'objet de la recherche).
- Remplir et adresser dans les 48 heures ouvrables la fiche de déclaration d'événement indésirable grave, dûment complétée.

Le promoteur déclare sans délai les **événements indésirables graves**, inattendus et les faits nouveaux survenus au cours de la recherche au CPP compétent. Le comité s'assure, si nécessaire, que les sujets participant à la recherche ont été informés des effets indésirables et qu'ils confirment leur consentement.

7.3 - Recueil et notification d'un événement indésirable grave

Tous les événements indésirables spontanément rapportés par le sujet volontaire et/ou notés par l'investigateur ou son équipe au cours de l'étude, attendus ou inattendus, seront obligatoirement notés dans le cahier d'observation sur le formulaire « Effets indésirables » et feront l'objet d'un résumé détaillé comprenant les renseignements sur le patient, les antécédents et les affections en cours, les traitements associés, la description de l'effet indésirable, une évaluation de sa gravité, sa date de survenue, sa durée, son délai de survenue, les mesures prises, les traitements symptomatiques mis en œuvre, l'hospitalisation éventuelle ou la prolongation d'hospitalisation liée à cet effet indésirable, les examens complémentaires réalisés et l'évolution. Le formulaire comportera également le jugement de l'investigateur sur la relation avec le matériel ou la procédure de l'étude et la nécessité ou non d'une exclusion du volontaire du fait de l'événement. Les coordonnées de la personne à contacter en cas de survenue d'un événement indésirable (i.e. le représentant du promoteur) seront fournies aux volontaires.

Tout effet grave nécessitera, outre la notification sur le formulaire « Effets indésirables », selon la même procédure et comportant les mêmes renseignements que lors de la notification habituelle, la réalisation d'un résumé clinique.

8 - STATISTIQUES

8.1 - Description des méthodes statistiques prévues, y compris du calendrier des analyses intermédiaires prévues

Les données obtenues seront analysées à l'aide de modèles linéaires à effets mixtes (logiciel R ; <http://www.r-project.org/>), qui fournissent un outil puissant pour l'analyse de données groupées. Une valeur de $p < 0,05$ sera retenue comme seuil de significativité statistique.

Principalement, les paramètres mentionnés ci-dessus représentent les variables dépendantes des modèles. L'objectif principal de notre projet est d'évaluer l'existence d'une modulation des paramètres physiologiques (acoustiques), des marqueurs de perception (intelligibilité) et de l'impact psychosocial de la parole dysarthrique dans la MP, dans un contexte de modulation de langue (français vs. portugais).



8.2 - Nombre prévu de personnes à inclure dans la recherche, avec sa justification statistique

Le nombre de patients choisi ne provient pas de considérations statistiques, mais est basé sur des critères cliniques de faisabilité (recrutement de patients et possibilité d'analyse). Les évaluations seront réalisées lors d'une visite de suivi des patients, en hôpital de jour, en adéquation avec la réalité clinique de suivi des patients dans le service.

8.3 - Choix des personnes à inclure dans les analyses

Toutes celles répondant aux critères d'inclusion.

9 - DROIT D'ACCES AUX DONNEES ET DOCUMENTS SOURCE

En vue du respect de la confidentialité des participants à l'étude, chaque sujet recevra un code arbitraire au moment du questionnaire médical d'entrée dans le protocole. La liste qui donne accès au code sera conservée dans le laboratoire, sous la responsabilité de l'investigateur principal dans un meuble fermé à clef. Le nom des sujets ne sera répertorié que sous la forme d'un code alphanumérique pendant tout le protocole et le traitement des données. Le code consistera en :

- les 2 premières du pays d'enregistrement (= FR) ;
- les trois premières lettres du nom et les 2 premières lettres du prénom du sujet ;
- le numéro de passation.

En conséquence l'accès aux données cliniques et informatiques sources peut être direct en cas de monitoring, d'audits commandés par le promoteur et/ou d'inspections menées par les autorités administratives compétentes. D'autre part, tout participant à cette étude pourra à sa demande avoir accès à l'ensemble des données le concernant à n'importe quel moment et disposera d'un droit de rectification.

10 - CONTROLE ET ASSURANCE DE LA QUALITE

Toutes les données de l'étude seront transcrites dans le cahier d'observation. Le cahier d'observation sera rempli de manière indélébile ; les corrections nécessaires devront être motivées et authentifiées, et la première inscription devra rester lisible. Ces cahiers seront remplis sous la responsabilité de l'investigateur principal et des co-investigateurs qui devront veiller à la fiabilité des données saisies. Les informations correspondantes seront accessibles auprès de l'investigateur en cas de contrôle ou de monitoring externe par le promoteur. Le contrôle qualité sera effectué, tout au long de l'étude, par l'équipe investigatrice, sous la responsabilité de l'investigateur principal. Ce contrôle de qualité portera sur :

- Les données recueillies au cours de l'étude ;
- Les consentements de tous les sujets inclus ;
- L'archivage des données.

11 - CONSIDERATIONS ETHIQUES

La recherche sera menée dans le respect de la réglementation française en vigueur, en conformité avec la loi numéro 88-1138 du 20 Décembre 1988, dite loi Huriot, modifiée par la loi n° 2004-806 du 9 août 2004 relative à la politique de santé publique, notamment des dispositions relatives à la recherche biomédicale du Code de la Santé Publique, article L 1121-1 et suivants, des lois de Bioéthique, de la loi Informatique, Fichiers et Libertés (et notamment de la méthodologie de référence MR-001 relative aux recherches biomédicales), de la Déclaration d'Helsinki (Hong-Kong, septembre 1989 ; actualisé en 2008), ainsi que des Recommandations de Bonnes Pratiques Cliniques (ICH, mai 1997) et du présent protocole.



L'investigateur s'engage à mener la recherche conformément à ces dispositions éthiques et réglementaires. Il est conscient que tous les documents ainsi que toutes les données relatives à la recherche pourront faire l'objet d'audits et d'inspections réalisées dans le respect du secret professionnel et sans que puisse être opposé le secret médical. L'investigateur reconnaît que les résultats de la recherche sont la propriété du promoteur de la recherche.

Une demande de promotion a été faite au CNRS, parallèlement à la soumission du protocole au CPP. Le promoteur s'engage à respecter la législation en vigueur. Le promoteur a souscrit à une assurance garantissant relative aux recherches biomédicales (Gerling, contrat n° : 0100630314037). Le promoteur assumera, même sans faute, l'indemnisation des conséquences dommageables de la recherche pour la personne qui s'y prête et celle de ses ayants droit, sans que puisse être opposé le fait d'un tiers ou le retrait volontaire de la personne qui avait initialement consenti à se prêter à la recherche. (Code de la Santé Publique, Art L1121-10).

Le promoteur adressera une demande d'autorisation à l'autorité de tutelle compétente (Agence Nationale de Sécurité du Médicament et des Produits Santé - ANSM) afin de prévoir un début d'étude pour le mois de février 2014.

11.1 - Consentement

Les volontaires seront informés, par le biais d'une notice d'information, des objectifs et des contraintes de l'étude, de leur droit de refuser de participer à l'étude ou de la quitter à tout moment. Lorsque l'essentiel de l'information aura été donné au sujet et lorsque l'investigateur se sera assuré que la personne qui se prête à la recherche aura bien compris les implications de sa participation et aura eu le temps de prendre sa décision librement, son consentement écrit sera recueilli en deux exemplaires originaux. Un exemplaire original du formulaire d'information et de consentement signé sera remis au sujet.

11.2 - Modifications substantielles au protocole

Le protocole, la notice d'information et le consentement de participation à l'étude sont soumis pour analyse et avis au CPP Sud Méditerranée 1, Marseille. La notification de l'accord du CPP sera fournie au promoteur de l'étude et à chacun des investigateurs avant le début de l'étude.

L'étude sera conduite conformément aux directives du présent protocole. Si des modifications substantielles au protocole s'avèrent nécessaires, c'est-à-dire qui en modifient le sens ou les objectifs ou qui modifient les contraintes subies ou les risques encourus par les participants, ils seront d'abord soumis à l'avis du promoteur de l'étude. Après réception de l'accord du promoteur, ces modifications substantielles seront ensuite soumis à l'avis du CPP ayant examiné le protocole initial avant leur mise en application (le protocole amendé fera l'objet d'une version actualisée datée). Ils ne prendront effet qu'après l'avis favorable du CPP et notification à l'ANSM. Les formulaires d'information et de recueil du consentement du patient devront être modifiés si besoin.

Les modifications mineures, non substantielles, seront envoyées par l'investigateur principal au CPP et au promoteur à titre d'information. Toutes les modifications mineures et substantielles seront communiquées à tous les investigateurs de l'étude.

11.3 - Anonymat des données

Le nom des sujets ne sera répertorié que sous la forme d'un code alphanumérique pendant tout le protocole et le traitement des données. Le code est présenté ci-avant, en section 9. Il consistera en : les 2 premières lettres du pays d'enregistrement (= FR), les trois premières lettres du nom et les 2 premières lettres du prénom du sujet, ainsi que son numéro de passation. Exemple : FR-MAR-PI-01, pour le premier sujet appelé *Pierre Martel*. Ce code sera appliqué sur le cahier d'observation ainsi que sur tous supports de sauvegarde (CD, dossiers de disque dur).



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Les modalités d’anonymisation des données des participants seront les suivantes : 2 premières lettres du pays d’enregistrement, première lettre du nom, suivie de la première lettre du prénom, suivi du numéro de participation, suivi du groupe de participant (cont pour contrôle, park pour parkinsonien), suivi de la condition médicamenteuse le cas échéant (uniquement pour les patients, donc). Ce code sera utilisé pour identifier les fichiers informatiques porteurs de données expérimentales, ainsi que sur tous supports (CD de sauvegarde, documentation papier, ...).

Exemple : FR-MP_01_park_on, pour le premier patient parkinsonien participant à l’étude, dans la condition avec médicaments, s’appelant *Pierre Martel*.

L’investigateur s’assurera que l’anonymat de chaque volontaire participant à l’étude est garanti. Aucune information permettant l’identification des personnes ne sera communiquée à des tiers autres que ceux, représentants du promoteur et du Ministère de la Santé, réglementairement habilités à détenir cette information (et qui sont tous tenus au secret professionnel).

11.4 - Indemnités en compensation des contraintes subies

Afin de les remercier pour leur participation, une indemnité sera versée à tous les sujets contrôles (20€) et patients parkinsoniens (40€) participant à cette étude. Le montant de cette indemnité est précisé dans la notice d’information et dans le consentement éclairé.

11.5 - Lieu de Recherche

Service de Neurologie, Centre Hospitalier du Pays d’Aix
Avenue des tamaris
13100 Aix-en-Provence

N° autorisation 21031M (copie en annexe).

11.6 - CNIL

Les données de l’étude seront saisies sur un cahier d’observation, les mentions référant aux patients étant anonymisées de la manière décrite ci-avant. Les fichiers informatiques utilisés pour réaliser la présente recherche seront également anonymisés selon les modalités décrites ci-avant. Cette étude fait l’objet d’une déclaration à la CNIL par le promoteur dans le cadre de la procédure simplifiée de déclaration des essais cliniques. Le promoteur et l’unité de recherche dans laquelle se déroule la recherche se sont engagés à se conformer à la méthodologie de référence MR-001 pour les traitements de données personnelles opérés dans le cadre de recherches biomédicales.

Les données médicales de chaque patient ne seront transmises qu’au promoteur, et, le cas échéant aux autorités sanitaires habilitées, dans les conditions garantissant leur confidentialité. Le promoteur et les autorités de tutelle pourront demander un accès direct au dossier médical pour vérification des procédures et/ou des données de l’essai clinique, sans violer la confidentialité et dans les limites autorisées par les lois et réglementations.

11.7 - Fichier national d’enregistrement des volontaires

Selon la recommandation de la Direction Générale de la Santé (DGS), et compte tenu du fait que les participants à l’étude seront indemnisés, les patients et les sujets contrôles seront inscrits sur le fichier national d’enregistrement des volontaires participant à une recherche biomédicale. Chaque participant aura la possibilité de vérifier auprès du titulaire de l’autorisation du lieu de recherche ou du ministre chargé de la santé l’exactitude des données le concernant présentes dans le fichier et la destruction de ces données



au terme du délai prévu par la réglementation. La participation à d'autres protocoles de recherche ne sera pas contre-indiquée.

12 - TRAITEMENT DES DONNEES ET CONSERVATION DES DOCUMENTS ET DES DONNEES RELATIVES A LA RECHERCHE

Toutes les données, tous les documents et rapports pourront faire l'objet d'audits et d'inspections réglementaires sans que puisse être opposé le secret médical. Un cahier d'observation (dossier créé pour les besoins de l'étude) sera tenu pour chaque sujet participant à l'étude ; l'observation et le suivi médical concernant l'étude seront consignés dans le document source.

Toutes les données de l'étude seront transcrites dans le cahier d'observation par les investigateurs. Les cahiers d'observation seront remplis de manière lisible et indélébile au stylo à bille bleu ou noir. En cas d'erreur, les informations erronées seront barrées d'un simple trait, la donnée initiale devant rester visible, et l'information correcte sera inscrite à côté. Chaque correction sera motivée et authentifiée (datée et signée ou paraphée par l'investigateur). L'investigateur principal signera chaque cahier d'observation pour attester de son accord avec les données y figurant.

La clôture de l'étude sera effectuée en accord avec les Bonnes Pratiques Cliniques. Les dossiers médicaux, administratif, et cahiers d'observations seront conservés pendant toute la durée de l'étude dans le service, puis archivés pendant une durée minimum de 15 ans.

13 - SOURCES DE FINANCEMENT DU PROJET

Ce projet est financé par l'ANR dans le cadre d'une subvention de recherche obtenu dans le programme ANR BLANC 2013 – Accords Bilatéraux France/Portugal. Le projet **FraLusoPark** est identifié sous la référence ANR-13-ISH2-0001-01.



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Annexe – Autorisation de lieu de recherche



RÉPUBLIQUE FRANÇAISE

N° du lieu : 21031M

DECISION DU 24 JUIL. 2002

AUTORISANT UN LIEU

DE RECHERCHES BIOMEDICALES SANS BENEFICE INDIVIDUEL DIRECT

LE DIRECTEUR GENERAL DE L'AGENCE FRANCAISE
DE SECURITE SANITAIRE DES PRODUITS DE SANTE

Vu le code de la santé publique et notamment ses articles L.5311-1, L.1121-3, L.1124-6 et R.2021 à R.2027 ;
Vu la demande adressée au préfet de la région Provence-Alpes-Côte d'Azur le 15 mars 2002 ;
Vu le rapport d'enquête du pharmacien inspecteur de santé publique en date du 20 juin 2002;

DECIDE :

ARTICLE 1er - L'autorisation mentionnée à l'article L.1124-6 du code de la santé publique est accordée, pour effectuer des recherches biomédicales sans bénéfice individuel direct au :

SERVICE DE NEUROLOGIE
Bâtiment Cézanne, Aile Est 2ème et 3ème étages, Aile Nord 3ème étage
Centre Hospitalier du Pays d'Aix
Avenue des Tamaris
13090 AIX-EN-PROVENCE

placé sous la responsabilité de Monsieur François VIALLET, dans les conditions prévues à l'article 2.

ARTICLE 2 - Cette autorisation concerne les recherches biomédicales sans bénéfice individuel direct, ayant trait au MEDICAMENT, menées dans le domaine de la neurologie, chez le volontaire majeur, dans le cadre d'études de tolérance, de pharmacodynamie et de pharmacocinétique incluant, notamment, la biodisponibilité et la bioéquivalence, à l'exception de celles conduites chez le volontaire sain.

Le Directeur Général

BMJ Open

Dysarthria in individuals with Parkinson's disease: protocol for a bi-national, cross-sectional, case-controlled study in French and European Portuguese (FraLusoPark)

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2016-012885.R1
Article Type:	Protocol
Date Submitted by the Author:	22-Jul-2016
Complete List of Authors:	<p>Pinto, Serge; Laboratoire Parole et Langage, Aix-Marseille Université / CNRS; Brain and Language Research Institute</p> <p>Cardoso, Rita; Campus Neurológico Sénior; Universidade de Lisboa Instituto de Medicina Molecular</p> <p>Sadat, Jasmin; Laboratoire Parole et Langage, Aix-Marseille Université / CNRS; Brain and Language Research Institute</p> <p>Guimarães, Isabel; Universidade de Lisboa Instituto de Medicina Molecular; Escola Superior de Saude do Alcoitao</p> <p>Mercier, Céline; Laboratoire Parole et Langage, Aix-Marseille Université / CNRS; Centre Hospitalier du Pays d'Aix, Neurology Department</p> <p>Santos, Helena; Campus Neurológico Sénior</p> <p>Atkinson-Clement, Cyril; Laboratoire Parole et Langage, Aix-Marseille Université / CNRS; Brain and Language Research Institute</p> <p>Carvalho, Joana; Campus Neurológico Sénior</p> <p>Welby, Pauline; Laboratoire Parole et Langage, Aix-Marseille Université / CNRS; Brain and Language Research Institute</p> <p>Oliveira, Pedro; Universidade de Lisboa Instituto de Medicina Molecular; Universidade de Lisboa, Center of Linguistics, School of Arts and Humanities,</p> <p>D'imperio, Mariapaola; Laboratoire Parole et Langage, Aix-Marseille Université / CNRS; Brain and Language Research Institute</p> <p>Frota, Sonia; Universidade de Lisboa, Center of Linguistics, School of Arts and Humanities</p> <p>Letanneux, Alban; Laboratoire Parole et Langage, Aix-Marseille Université / CNRS</p> <p>Vigario, Marina; Universidade de Lisboa, Center of Linguistics, School of Arts and Humanities</p> <p>Cruz, Marisa; Universidade de Lisboa, Center of Linguistics, School of Arts and Humanities</p> <p>Martins, Isabel; Hosp. Santa Maria,</p> <p>Viallet, François; Centre Hospitalier du Pays d'Aix, Neurology Department; Laboratoire Parole et Langage, Aix-Marseille Université / CNRS</p> <p>Ferreira, Joaquim; Campus Neurológico Sénior; Universidade de Lisboa Instituto de Medicina Molecular</p>
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Communication, Ear, nose and throat/otolaryngology, Medical management, Patient-centred medicine, Pharmacology and therapeutics

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Keywords:	Parkinson’s disease, Dysarthria, Speech, Cross-language, Disease progression, Pharmacological treatment

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Dysarthria in individuals with Parkinson's disease: protocol for a bi-national, cross-sectional, case-controlled study in French and European Portuguese (FraLusoPark)

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Key-words: Parkinson's disease; Dysarthria; Speech; Voice; Cross-linguistic; Pharmacological treatment; Disease progression

Word count: 3,524 (excl. title page, abstract, strengths & limitations, references, figures & tables)

ABSTRACT (296 words)

Introduction: Individuals with Parkinson’s disease (PD) have to deal with several aspects that contribute to voice and speech decline and thus, alteration of communication ability during the course of the disease. Among these communication impairments, three major challenges are: (i) Dysarthria, consisting of orofacial motor dysfunction and dysprosody, which is tight to the neurodegenerative processes (ii) The effects of the pharmacological treatment, which vary according to the disease stage; and (iii) Particular speech modifications that may be language-specific, *i.e.* dependent on the language spoken by the patients. The main objective of the FraLusoPark project is to provide an exhaustive evaluation of changes in PD speech as a result of pharmacological treatment and disease duration in two different languages (French vs. European Portuguese).

Methods and analysis: Individuals with PD will be enrolled in the study in France (N = 60) and Portugal (N = 60). Their global motor disability and orofacial motor functions will be assessed with specific clinical rating scales, without (OFF) and with (ON) pharmacological treatment. Two groups of 60 healthy age-matched volunteers will provide the reference for between-group comparisons. Along with the clinical examinations, several speech tasks will be recorded to obtain acoustic and perceptual measures. Patient-reported outcome measures will be used to assess the psychosocial impact of dysarthria on quality of life.

Ethics and dissemination: The study has been approved by the local responsible committees on human experimentation and is conducted in accordance with the ethical standards. A valuable large-scale database of speech recordings and meta-data from PD patients in France and Portugal will be constructed. Results will be disseminated in several articles in peer reviewed journals, and presentations at conferences. Recommendations on how to assess speech and voice disorders in individuals with PD to monitor symptom progression and management will be provided.

Registration details: ClinicalTrials.gov Identifier: NCT02753192. Registered on 26 April 2016.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- A multicentre (bi-national), cross-sectional, case-controlled study
- A cross-linguistic, multiparametric and global study of speech in Parkinson's disease
- An interdisciplinary approach bringing together data analyses from the speech sciences and neurosciences
- A clinically reasonable number of individuals with PD
- No analysis of phonetic distortions
- So far not a longitudinal study, unable to address individuals' speech deterioration with time

INTRODUCTION

Dysarthria in Parkinson’s disease

Dysarthria denotes a motor speech disorder resulting from a lesion of the peripheral or central nervous system [1, 2, 3]. For individuals with PD, dysarthria together with the psychosocial aspects of communication impairments are particularly disabling. During the progression of the disease between 70% and 79% of individuals with PD mention that speech [4, 5] and functional communication are impaired [6, 7], contributing to social isolation [8] and degradation of social interactions [9]. These speech and communication disorders also interact with and contribute to aggravation of other non-motor symptoms, such as depression [10] and cognitive impairment [11, 12]. Dysarthria can appear at any stage of PD, and usually worsens with disease progression [13], which suggests that it is also linked to the progression of the pathological processes and non-dopaminergic brain circuits [14, 15, 16]. The main deficits of PD speech are: loss of intensity (hypophonia), monotony of pitch and loudness, reduced stress, inappropriate silences, short rushes of speech, variable rate, imprecise consonants and dysphonia (harsh and breathy voice) [1, 2, 17]. Treatments in PD have been shown to have variable effects on these voice and speech symptoms [18, 19].

Although behavioural treatments mainly focus on two key indices of PD speech (*i.e.*, pitch and intensity), dysprosody has been understudied so far. Nevertheless, prosody deficits represent an acoustic hallmark of dysarthria. First, perceptual and acoustic investigations of PD speech have reported alterations on fundamental frequency (F0), as part of their phonatory inability, and thus the reduction of the frequency range is clearly an indicator of dysarthria in PD [20]. In particular, individuals with PD show a loss of the upper part of the tonal range [21]. Therefore, degradation of prosody impacts speech intelligibility and communication (*e.g.* [22]). Secondly, the temporal organization of speech in PD has been addressed in reading tasks [23, 24, 25]: in French, for example, speech rate tends to be slower in PD which in turn seems to be correlated with longer pause times;

average durations of pauses are found to be longer in individuals with PD than in healthy individuals, while the average duration of sound sequences are similar [24, 25]. Studying dysprosody is thus important for differential diagnosis, designating severity and the need and focus of treatment [20].

Remaining challenges to assess dysarthria in PD: the rationale of the FraLusoPark study

Individuals with PD have to deal with several aspects that contribute to voice and speech decline, and thus alteration of communication ability during the course of the disease. Among these communication impairments, three major challenges are: (i) Dysarthria, consisting of orofacial motor dysfunction and dysprosody, which is tight to the neurodegenerative processes; (ii) The effects of the pharmacological treatment, which vary according to the disease stage; and (iii) The particular speech modifications that may be language-specific, that is dependent on the language spoken by the patients. The main objective of the FralusoPark project is to provide an extensive evaluation of dysarthric speech in PD as a result of pharmacological treatment and disease duration, using acoustic parameters (voice and prosody), perceptual markers (intelligibility), and patient-based outcome measures (PROMs; psychosocial impact on quality of life) in two different languages (French vs. European Portuguese). Based upon a large-scale bi-national collaboration, the current interdisciplinary FralusoPark project aims to address these issues by providing important insights to the domains of neurodegenerative disorders, speech sciences, neuropsychology, clinical research and patient rehabilitation.

Medication effects along disease progression

Early studies assessing the effect of the levodopa (L-dopa) on PD speech reached favorable results, arguing towards a beneficial effect, similar as for limb impairments [26, 27, 28, 29]. However, the long-term use of L-dopa is associated with unavoidable motor complications which occur in up to 80% of patients [30, 31]. This may be the reason why following studies reported no improvement

[32, 33] and/or deleterious effects of L-dopa on speech [34, 35]. More recent studies face similar problems: beneficial effects of L-dopa can be observed in advanced PD patients [36, 37], whereas a lack of improvement is reported for speech parameters in early stage PD patients [38]. It is also commonly accepted that in the later stages of PD, non-motor symptoms (dementia, psychosis, depression and apathy) are a major source of disability together with axial symptoms (*e.g.*, alteration of gait, balance, posture, speech) [39]. Thus, both clinicians and researchers have to dissociate among various intermingled effects. For example, when individuals with PD respond to L-dopa at an early stage of the disease, they are likely to experience speech decline with time that may result from the degeneration of non-dopaminergic structures and/or L-dopa adverse effects (*i.e.* dyskinesia). Despite the recent and important number of studies that have focused on the effect of L-dopa on speech in PD [36, 37, 38, 39, 40, 41, 42, 43, 44], the question of disease evaluation still remains a matter of debate.

Language specificities of prosody

Regarding language-specific properties, one missing component in the description of PD speech deficits is dysprosody. Prosodic information, including intonation, tempo, stress and rhythm, serves many functions for the listener and speaker: it helps to segment the continuous flow of spoken language into words, groups these words into phrases for interpretation, and indicates the relative importance and function of the interpreted meanings [45, 46, 47, 48]. Each language has its own prosodic structure. For example, although they are sister languages, French and European Portuguese (both Romance languages) differ prosodically in a number of important ways. European Portuguese has contrastive lexical stress: each content word (noun, adjective, verb, etc.) has one syllable that is particularly salient or stressed, and changing the position of the lexical stress can change the meaning of a word [47, 49, 50, 51]. Stressed syllables may be accompanied by a pitch accent, realized as a modulation in F0 (*e.g.*, a rise or a fall) and aligned in language-specific ways with

the syllable. In contrary, French has a fixed stress, characterized by a systematic F0 rise on the last syllable in a word [52, 53]. Stress is not a property of the word, but of a larger unit called the accentual phrase that can include one or more content words and any preceding function words (articles, prepositions, etc.), often realized with F0 rises at its right and left edges. French listeners use these F0 rises as cues to word segmentation, finding the beginning and ends of words in the speech stream, and to lexical access, retrieving words from the mental lexicon [48, 54].

Such differences across languages make the comparison of prosodic deficits in individuals with PD particularly interesting. Very few studies of PD dysprosody have looked beyond global measures to examine the extent to which linguistically important, language-specific patterns are affected [55, 56]. Therefore, studying speech in individuals with PD whose language implies different prosodic modulations is important to determine the role of prosody for patients' speech intelligibility and quality of life. Does a Portuguese patient experience different communication impairments when compared to a French patient? And if this is the case, is this difference related to the fact that European Portuguese stress is distinctive and varies in position? And finally, how do these differences relate to the patients' disease duration and pharmacological treatment? Our project presents a novel approach to these questions and is important for the gathering of cross-linguistic data in a single cohort.

METHODS AND ANALYSIS

FraLusoPark is a **bi-national** (data collection is performed in two countries: France and Portugal), **cross-sectional** (data is collected once for each participant) and **case-controlled** (both individuals with PD and control subjects are recruited) study, carried out in two different languages (French and European Portuguese).

Aims and hypotheses

The main objectives of our project are to evaluate modulations in acoustics parameters (voice and prosody), perceptual markers (intelligibility), and PROMs (psychosocial impact of dysarthria in PD) across two different languages (French vs. European Portuguese).

Our three a priori hypotheses are the following: (i) Global acoustic features are altered similarly in French and Portuguese individuals with PD; (ii) Language-specific prosodic patterns might be altered differently in French and Portuguese individuals with PD; and (iii) The impact of speech disorders on intelligibility and quality of life depends on the cultural and linguistic environment. In addition, the FraLusoPark project will allow for a better understanding of the progression of the speech symptoms and their response to pharmacological treatment, which is important regarding pathophysiological aspects and clinical management.

Participants

Two groups of 60 healthy volunteers (one in France and one in Portugal) are age- and sex-matched with the individuals with PD to provide control references for the obtained performance measures. Individuals with PD are recruited in France (N = 60; Neurology Department, Centre Hospitalier du Pays d'Aix, Aix-en-Provence, France) and in Portugal (N = 60; Movement Disorders Unit, Hospital de Santa Maria, Lisbon, and CNS - Campus Neurológico Sénior, Torres Vedras, Portugal) and correspond to the UK Parkinson's Disease Brain Bank Criteria [57] for the diagnosis of idiopathic PD. Individuals with PD and healthy controls are all French-native or European Portuguese-native speakers (French-European Portuguese bilinguals were excluded) and right-handed (Handedness Edinburgh test > 80 %; [58]). Inclusion and exclusion criteria of PD patients and healthy controls are summarized in **Table 1**. To assess L-dopa effects at various stages of the disease, patients' recruitment considers three sub-groups (N = 20 patients each): Sub-group 1, *mild* impairment with a disease duration between zero and 3 years and no motor fluctuations; Sub-group 2, *moderate* impairment with a disease

duration between 4 and 10 years, experiencing motor fluctuations; Sub-group 3, *marked* impairment with a disease duration of over 10 years.

Table 1. Inclusion and exclusion criteria

<i>All participants</i>	<i>Control subjects</i>	<i>Parkinson's disease patients</i>
Inclusion Criteria		
Age between 35 and 85 years old		
Good cooperation		
Ability to understand the information sheet		
Given signed consent		
Affiliation to a medical-social insurance regimen		
Other stable medical problems not interfering with the proposed study		
Absence of any neurological, psychiatric or behavioural pathology		
Idiopathic Parkinson's disease		
Absence of medication-induced psychosis, severe depression or dementia		
Exclusion Criteria		
Illiteracy		
French/Portuguese not as native language, or bilingual participants		
Participant under tutorship or guardianship, or any other administrative or legal measure		
No cooperation or withdrawn consent		
Cognitive deficits, depression, psychosis or behavioural, neurological, medical, psychological disorders that may interfere with vital prognostic and evaluations		
Non-idiopathic Parkinson's disease		
Deep brain stimulation		
(Too) severe motor impairment impeding to participate in the study		

Study design

Healthy control participants will undergo the same non-invasive assessments and examinations as the individuals with PD. The only constraint for the patients is to be evaluated twice, in the OFF and ON L-dopa states, that means: (i) at least twelve hours after withdrawal of all anti-parkinsonian drugs

and (ii) following at least one hour after the administration of the usual medication. The full study design is illustrated in **Figure 1**.

Speech recordings

In a quiet room, special speech recording equipment (EVA2© system, SQLab, Aix-en-Provence, France; <http://www.sqlab.fr/>; Marantz PMD661 MKII recorder, USA) is used for the speech/voice recordings. Participants are recorded while performing several speech production tasks with increasing complexity in a fixed order: (i) Steady vowel /a/ phonation (at a comfortable pitch and loudness) repeated three times; (ii) Maximum phonation time (vowel /a/ sustained as long as possible on one deep breath at a comfortable pitch and loudness), repeated twice; (iii) Oral diadochokinesia (repetition of the pseudoword ‘pataka’ at a fast rate during 30 seconds); (iv) Reading aloud of 10 words and 10 sentences created by adapting the intelligibility section of the Frenchay Dysarthria Assessment, version 2 (FDA-2; [59]); (v) Reading aloud of short text (‘The North Wind and the Sun’, French and European Portuguese adaptations; [50, 60]); (vi) Oriented speech through storytelling with visual stimuli (images from Mercer Mayer’s word-less story ‘Frog, where are you ?’, [61]; for the rationale of using this procedure and this book, cf. [62]; (vii) Reading aloud of a set of sentences with specific prosodic properties (31 sentences in French, 20 in European Portuguese); (viii) Free conversation during three minutes.

Acoustic measures

The acoustic measures characterize dimensions of aero-phonatory control [63]. For the steady vowel /a/ phonation, two kinds of measures will be extracted: First, for a macro-analysis, fundamental frequency (F0, Hertz) and F0 variation (%); and second, for a micro-analysis, perturbation measures such as jitter factor (%), absolute shimmer (dB), and harmonics-to-noise ratio (HNR, %). For the maximal phonation time, the longest duration (in seconds) of the sustained vowel /a/ will be

extracted. For the oral diadochokinesia task, the extracted measures will be the following: (i) the number of breath groups, *i.e.* each period during which the pseudoword was repeated in a single expiration, (ii) the ratio between the cumulated speech duration of the breath groups and the total duration of the session, *i.e.*, the speech proportion, (iii) the articulatory rate (syllables/second), (iv) the pause-to-sound ratio (%), and (v) the speech proportion per number of breath groups. As an initial step to investigate global prosodic aspects of PD speech compared to healthy controls, we will extract the F0 curve of one sentence selected from the short text ('The North Wind and the Sun'). This sentence is selected to be comparable across French and European Portuguese in terms of semantics and syllable length. This will provide a global phrasal pattern of F0 and intensity for patients and controls within and across languages (see below for subsequent studies with a more detailed focus on prosody). A summary of the acoustic measures that will be analysed are listed in

Table 2.

Table 2. Acoustic measures

Speech tasks	Function assessed	Acoustic measures
<i>Steady vowel /a/ phonation</i>	<i>Phonation</i>	Mean fundamental frequency (F0, in Hz) Fundamental frequency variation (F0 SD, in Hz) Shimmer (%) - <i>cycle-to cycle F0 variation</i> Jitter (%) – <i>cycle-to cycle intensity variation</i> Harmonics-to-noise ratio (HNR, in %)
<i>Maximal phonation time of the vowel /a/</i>	<i>Aero-phonatory control</i>	Longest duration (in seconds)
<i>Oral diadochokinesia</i>	<i>Supra-laryngeal articulatory control</i>	Number of breath groups Proportion of breath groups (%) Articulatory rate (in syllables/second) Pause-to-sound ratio (%) Speech proportion ratio (%)
<i>Reading aloud of text</i>	<i>Prosody</i>	Fundamental frequency range (F0 range, Hz) Intensity (in dB)

Clinical assessments

The neurological assessment is the Unified Parkinson’s Disease Rating Scale [64], using the revised version provided by the *Movement Disorders Society* (MDS-UPDRS; [65]). The FDA-2 is used to assess the functions of the speech organs [59], reflecting the state of the muscular effectors involved in speech production. The original FDA-2, in English, includes an evaluation of intelligibility through 10 words and 10 short sentences. Using the same methodology, we developed a set of cross-linguistically adapted words and sentences in French and European Portuguese that will be used for the intelligibility assessment in each language. During the OFF medication state, individuals with PD will be administered the FDA-2 and the motor part (section 3) of the MDS-UPDRS. During the ON medication state, these two assessments will be performed together with the non-motor (section 1.A) and motor complication (section 4) sections of the MDS-UPDRS. During the ON medication state, the participants’ cognitive abilities are evaluated using the Montreal Cognitive Assessment (MoCA; [66]) and the Clinical Global Impression (CGI) is also reported [67]. For healthy controls, the assessment is similar to that of the PD patients during ON medication (except section 4 of the MDS-UPDRS). A summary of the clinical assessments are listed in **Table 3.A**.

Table 3. Clinical assessments and patient-reported outcome measures

Description	Sub-sections	Min – Max scores (worse values in bold)
A. Clinical assessments		
Movement Disorders Society – Unified Parkinson’s Disease Rating Scale (MDS – UPDRS) <i>Assessment of motor and non-motor features of Parkinson’s disease</i> (Movement Disorder Society Task Force on Rating Scales for Parkinson's Disease, 2003)	Non-motor experience of daily living – Motor experience of daily living – Motor examination – Motor complications	0 – 260
Frenchay Dysarthria Assessment (FDA-2) - <i>Assessment of speech and voice organs</i> (Enderby & Palmer, 2007)	Reflexes – Respiration – Lips – Palate – Larynx – Tongue – Intelligibility	0 – 104
Montreal Cognitive Assessment (MoCA) - <i>Global assessment of cognitive functions</i> (Nasreddine et al., 2005)	Visuospatial – Naming – Memory – Attention – Verbal fluency – Abstraction – Orientation	0 – 30
Clinical Global Impression (CGI) - <i>Global impression of the clinician on the symptom</i> (Busner & Targum, 2007)	Speech	1 – 7
B. Patient-reported outcome measures (PROMs)		
Parkinson’s Disease Questionnaire (PDQ-39) - <i>Quality of life in Parkinson’s disease</i> (Peto et al., 1995)	Mobility – Daily living Activities – Emotional well-being – Stigma – Social support – Cognition – Communication – Body discomfort	0 – 156
Voice Handicap Index (VHI) (Jacobson et al., 1995)	Physical – Functional – Emotional	0 – 120
Dysarthria Impact Profile (DIP) - <i>Psychosocial impact of speech deficits</i> (Walshe et al., 2009)	Effect of dysarthria on me – Accepting my dysarthria – How I feel others react to my speech – How dysarthria affects my communication – Dysarthria relative to other worries and concerns	48 – 240
Patient Global Impression (PGI) - <i>Global impression of the patient on the dysfunction</i> (Hurst & Bolton, 2004)	Speech	1 – 7
Beck Depression Inventory (BDI) - <i>Global assessment of the depression profile</i> (Beck et al., 1961)		0 – 84

Patient-reported outcome measures

PROMs, such as the Dysarthria Impact Profile (DIP; [68]), are used to obtain self-reported information about the functional impact of an individual’s speech/communication impairment [69]. Additional self-assessments focus on the patients’ perception of their quality of life (the 39-Item Parkinson's Disease Questionnaire [PDQ-39]; [70, 71]) and on how voice/speech impairment may induce a handicap (Voice Handicap Index, VHI; [72]). The French [73] and European Portuguese adapted DIP, VHI [74, 75] and PDQ-39 [76, 77, 78] will be used in our study. The Patient Global Impression (PGI) scoring [79] and the Beck Depression Inventory (BDI; [80]) are also administered. The MDS-UPDRS also includes a patient self-assessment (sections 1.B and 2), which are administered together with the other questionnaires under medication. For healthy controls, the assessment is the same as for individuals with PD. A summary of the PROMs from the self-administered questionnaires are listed in **Table 3.B.**

Statistical analyses

The analyses of the data (acoustic, clinical measures, and PROMs) will be performed with linear mixed-effects models that account for the variability across individuals, using the latest version of the statistical software R [81]. For each performance measure, the between-group factors ‘group’ (patients vs. controls), ‘disease duration’ (early vs. medium vs. advanced), and ‘language’ (French vs. European Portuguese) will be investigated. In addition, we will explore the effects of the within-patient factor ‘medication’ (OFF vs. ON) for all measures. Further relevant participant-related measures such as age, gender, or education level will also be taken into account for the analyses.

DISCUSSION

The present study will provide a unique, exhaustive, and reliable assessment of PD voice, speech and prosody disorders and an evaluation of how this impacts on quality of life of individuals with PD.

Main and subsequent analyses of the FraLusoPark study

Acoustic and prosodic measurements (**Table 2**), clinical assessment, and PROMs (**Table 3**) are the dependent variables to be analysed according to the statistical plan. These findings will be reported in a primary analysis as the main results of the project. However, the FraLusoPark investigation protocol allows conducting additional analyses that focus on specific sub-dimensions of speech and voice deficits. At least four subsequent analyses derive from the main study, further exploring important aspects of PD speech and communication in more detail.

First, the intelligibility section of the FDA-2 [59] implies that the words and sentences produced by the patient will be rated perceptually by the clinician who is in charge of the assessment. Since these speech productions are recorded during the FraLusoPark protocol, an evaluation of speech intelligibility involving auditory juries in France and Portugal will be run. This allows an additional and unbiased judgment of speech and voice disorders beyond that of the speech therapists and experts involved in the study. This approach further complements the global assessment of dysarthric speech in PD patients.

Second, further prosodic analysis will be conducted on the defined set of sentences, modulating prosodically general and language-specific details. One particular focus will be the analysis of tonal alignment in the F0 curve, that is the temporal coordination of high and low tones with specific syllables in the sentences [82, 83, 84]. Tonal alignment is likely to be a relevant factor in the study of PD dysprosody since it relies on precise coordination of glottal and articulatory gestures to achieve language-specific temporal patterns for pitch accents and boundary tones.

Third, the consideration of patients’ personal feelings regarding physical, psychological and social domains has received increasing interest over the last decade. Individuals with PD are affected by voice and speech disorders, which contribute to an impairment of general communication abilities. Consequently, individuals with PD are less likely to participate in conversations or social interactions [6, 9]. Several studies suggest that a growing discomfort in verbal communication during the progression of the disease leads to an important negative impact on social life [70, 85, 86]. Altogether, this argument is in favour of experimental designs that include different types of speech assessments (clinical, perceptual, instrumental, and psychosocial) as in the current protocol and to explore the relationships between these different measures. Thus, further analyses will focus on linking the different dimensions of voice and speech description (e.g., acoustic measures, FDA-2) with the contributions of various participant-related measures such as intelligibility, cognition and functional communication.

Finally, production and prosodic parameters from the three different speech tasks (*i.e.*, short text reading, orientated image description, and conversation) will be compared. This allows comparing speech and voicing disorders in increasingly more complex communication contexts. In fact, communication abilities in PD are quite different in the presence of external cueing, such as during reading compared to spontaneous speech which involves more complex speech planning strategies.

Moreover, the FraLusoPark study provides the opportunity to address speech deterioration of individuals with PD over time. This longitudinal perspective can be realized in an additional follow-up study by recruiting a sub-group of the patients from Group 1 (up to 4 years of disease duration) and 2 (disease duration between 4 and 10 years) who will be evaluated again at a later time point (about five years later). This will allow describing the precise progression of speech deficits associated with PD within the same individual for French and Portuguese speakers.

ETHICS AND DISSEMINATION

This study has been approved by the local responsible committees on human experimentation (France: Comité de Protection des Personnes, Sud Méditerranée 1, project reference n° 13-84, approval date 09/01/2014; Portugal: Ethics Committee of the Lisbon Academic Medical Centre, project reference n° 239-14, approval date 12/06/2014). The study is conducted in accordance with the ethical standards of the Declaration of Helsinki [87]. The patients are included in the study after providing their written informed consent. The FraLusoPark trial has been registered under the reference NCT02753192 (26 April 2016) on <https://clinicaltrials.gov/>.

Results of the FraLusoPark project will be disseminated at several research conferences at the national and international level and published as articles in peer-reviewed journals. The publication strategy is based on one principal article reporting the main results of the project and several subsequent articles deriving from it, including more detailed analyses of specific sub-dimensions of speech and voice deficits.

Due to inter-speaker variability, any generalization drawn from speech parameters in clinical population requires data from a large number of speakers [88]. The FraLusoPark project is in line with this idea by building a large-scale corpus of PD speech recordings and providing a large set of meta-data (clinical examinations, speech measurements, linguistic features, patient-based indices). This allows a more accurate description of PD dysarthria, documenting the evolution of the symptom and its response to pharmacological treatment. In both medical (e.g., <http://www.mrc.ac.uk/research/research-policy-ethics/data-sharing/data-sharing-population-and-patient-studies/>) and linguistic (<http://sldr.org/>) domains, data sharing is important to maximize the life-time value of human health data. It is our intention to contribute to this trend by archiving our data for long-term preservation and making them accessible after the completion of our analyses.

Furthermore, a significant recommendation from the International Classification of Functioning Disability and Health [89] is to improve quality of healthcare and encouraging clinicians to adopt a

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more holistic approach to the assessment and treatment of patients. Research in the field of speech sciences needs to incorporate this viewpoint when studying pathological speech. The current FraLusoPark project is in line with this perspective and will provide further important recommendations for speech and voice assessments in PD patients. This will not only be helpful to health practitioners and clinicians when monitoring the progression of symptoms and their management, but also advance our understanding of dysarthria in PD within a cross-language and cross-cultural context.

For peer review only

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AUTHORS' CONTRIBUTIONS

SP and JJF are the principal investigators of the FraLusoPark study. They designed the study and ensure the proper realization of the study. JJF and FV are the neurologists in charge of patients' recruitment and neurological assessments. RC, JS, HS, CM, JC, FV and SP perform data acquisition and other clinical examinations. RC, JS, PO and IG are in charge of the pre-processing and analyses of acoustic measurements. CA-C and AL are in charge of the analyses of the PROMs and clinical assessments. PW, PO, MD, MC, SF and MV are the linguist experts in charge of the prosody evaluations. IP is the neurobehaviour, language and cognition expert. All co-authors commented on the present study protocol article.

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COMPETING INTERESTS STATEMENT

The authors report that there is no competing interest.

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FIGURE LEGEND

Figure 1. Overview of the FraLusoPark study design.

Patient OFF-medication assessments (*i.e.*, clinical history, speech recordings and clinical assessments, without medication) are shown in dark grey. ON-medication assessments (*i.e.*, speech recordings and clinical assessments after medication is effective) are shown in light grey.

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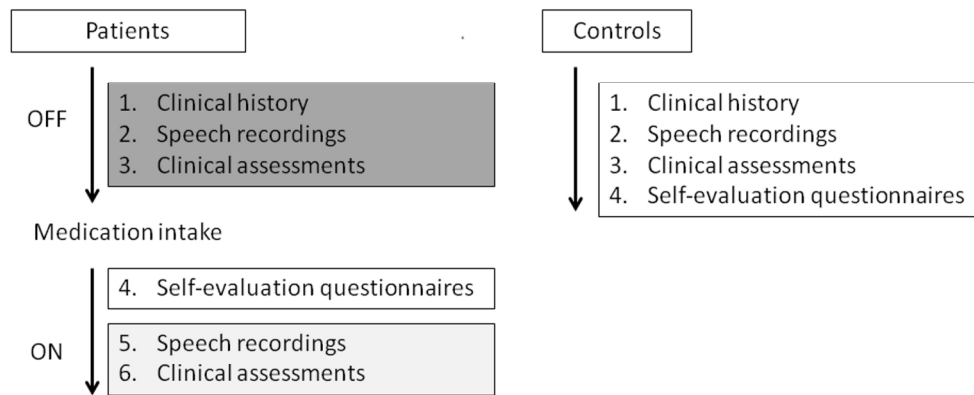


Figure 1. Overview of the FraLusoPark study design. Patient OFF-medication assessments (i.e., clinical history, speech recordings and clinical assessments, without medication) are shown in dark grey. ON-medication assessments (i.e., speech recordings and clinical assessments after medication is effective) are shown in light grey.

Figure 1
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Keywords:	Parkinson’s disease, Dysarthria, Speech, Cross-language, Disease progression, Pharmacological treatment

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Dysarthria in individuals with Parkinson's disease: a protocol for a binational, cross-sectional, case-controlled study in French and European Portuguese (FraLusoPark)

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ABSTRACT (300 words)

Introduction: Individuals with Parkinson’s disease (PD) have to deal with several aspects of voice and speech decline and thus alteration of communication ability during the course of the disease. Among these communication impairments, three major challenges include: (i) Dysarthria, consisting of orofacial motor dysfunction and dysprosody, which is linked to the neurodegenerative processes (ii) The effects of the pharmacological treatment, which vary according to the disease stage; and (iii) Particular speech modifications that may be language-specific, *i.e.* dependent on the language spoken by the patients. The main objective of the FraLusoPark project is to provide a thorough evaluation of changes in PD speech as a result of pharmacological treatment and disease duration in two different languages (French vs. European Portuguese).

Methods and analysis: Individuals with PD are enrolled in the study in France (N = 60) and Portugal (N = 60). Their global motor disability and orofacial motor functions is assessed with specific clinical rating scales, without (OFF) and with (ON) pharmacological treatment. Two groups of 60 healthy age-matched volunteers provide the reference for between-group comparisons. Along with the clinical examinations, several speech tasks are recorded to obtain acoustic and perceptual measures. Patient-reported outcome measures are used to assess the psychosocial impact of dysarthria on quality of life.

Ethics and dissemination: The study has been approved by the local responsible committees on human experimentation and is conducted in accordance with the ethical standards. A valuable large-scale database of speech recordings and metadata from PD patients in France and Portugal will be constructed. Results will be disseminated in several articles in peer-reviewed journals and in conference presentations. Recommendations on how to assess speech and voice disorders in individuals with PD to monitor the progression and management of symptoms will be provided.

Registration details: ClinicalTrials.gov Identifier: NCT02753192. Registered on 26 April 2016.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- A multicentre (bi-national), cross-sectional, case-controlled study
- A cross-linguistic, multiparametric and holistic study of speech in Parkinson's disease
- An interdisciplinary approach bringing together data analyses from the speech sciences and neurosciences
- A clinically reasonable, number of individuals with PD
- No analysis of phonetic alterations
- So far, not a longitudinal study: unable to address individuals' speech deterioration with time

INTRODUCTION

Dysarthria in Parkinson’s disease

Dysarthria denotes a motor speech disorder resulting from a lesion of the peripheral or central nervous system [1, 2, 3]. Dysarthria and the psychosocial aspects of communication impairments are particularly disabling for individuals with PD. During the progression of the disease between 70% and 79% of individuals with PD mention that speech [4, 5] and functional communication are impaired [6, 7], contributing to social isolation [8] and degradation of social interactions [9]. These speech and communication disorders worsen along with the aggravation of other non-motor symptoms such as self-perception, depression, [10] and cognitive impairment [11]. In addition to the alteration of speech intelligibility, signally a motor-driven speech deficit, it is also important to consider the importance of cognitive impairment on everyday communication in individuals with PD [12]. Dysarthria can appear at any stage of PD, and usually worsens as the disease progresses [13], which suggests that it is also linked to the evolution of the pathological processes and non-dopaminergic brain circuits [14, 15, 16]. The main deficits of PD speech are: loss of intensity (hypophonia), monotony of pitch and loudness, reduced stress, inappropriate silences, short rushes of speech, variable rate, imprecise consonant articulation, and dysphonia (harsh and breathy voice) [1, 2, 17]. Previous studies have shown that treatments in PD have variable effects on these voice and speech symptoms [18, 19].

Although behavioural treatments mainly focus on two key indices of PD speech, pitch and intensity, dysprosody has been understudied. Yet, prosody deficits represent an acoustic hallmark of dysarthria. First, perceptual and acoustic investigations of PD speech have reported alterations on fundamental frequency (F0), as part of speakers' reduced phonatory capacity, and thus the reduction of the frequency range is an indicator of dysarthria in PD [20]. In particular, individuals with PD show a loss of the upper part of the frequency range [21]. Degradation of prosody has been found to impact speech intelligibility and communication (*e.g.* [22]). Secondly, the temporal organization of

speech in PD has been addressed in reading tasks [23, 24, 25]. In French, for example, speech rate tends to be slower in PD, which in turn seems to be correlated with longer pause times. Average durations of pauses are found to be longer in individuals with PD than in healthy individuals, while the average duration of sound sequences are similar [24, 25]. Studying dysprosody is thus important for differential diagnosis, identifying severity and the need and focus of treatment [20].

Remaining challenges to assess dysarthria in PD: the rationale of the FraLusoPark study

Individuals with PD have to cope with several issues that contribute to voice and speech decline and thus to the alteration of communication ability during the course of the disease. Among these communication impairments, three major challenges include: (i) Dysarthria, consisting of orofacial motor dysfunction and dysprosody, which is linked to the neurodegenerative processes; (ii) The effects of the pharmacological treatment, which vary according to the disease stage; and (iii) The particular speech modifications that may be language-specific, *i.e.* dependent on the language spoken by the patients. The main objective of the FralusoPark project is to provide an extensive evaluation of dysarthric speech in PD as a result of pharmacological treatment and disease duration, using acoustic parameters (voice and prosody), perceptual markers (intelligibility), and patient-reported outcome measures (PROMs; psychosocial impact on quality of life) in speakers of two different languages (French and European Portuguese). Based upon a large-scale binational collaboration, the interdisciplinary FralusoPark project aims to address these issues by providing important insights in the domains of neurodegenerative disorders, speech sciences, neuropsychology, clinical research, and patient rehabilitation.

Medication effects along disease progression

Early studies assessing the effect of the levodopa (L-dopa) on PD speech found favourable results, arguing for a beneficial effect, as for limb impairments [26, 27, 28, 29]. However, the long-term use

of L-dopa is associated with motor complications which occur in up to 80% of patients [30, 31]. This may be the reason why following studies reported no improvement [32, 33] and/or detrimental effects of L-dopa on speech [34, 35]. More recent studies face similar problems: beneficial effects of L-dopa can be observed in advanced PD patients [36, 37], whereas a lack of improvement is reported for speech parameters in early stage PD patients [38]. It is also commonly accepted that in the later stages of PD, non-motor symptoms (dementia, psychosis, depression and apathy) are a major source of disability together with axial symptoms (*e.g.* alteration of gait, balance, posture, speech) [39]. Thus, both clinicians and researchers have to dissociate various intermingled effects. For example, when individuals with PD respond to L-dopa at an early stage of the disease, in time they are likely to experience speech decline that may be the result of the degeneration of non-dopaminergic structures and/or adverse effects of L-dopa (*i.e.* dyskinesia). Despite the large number of recent studies that have focused on the effect of L-dopa on speech in PD [36, 37, 38, 39, 40, 41, 42, 43, 44], the question of disease evaluation still remains a matter of debate.

Language specificities of prosody

One missing component in the description of PD speech deficits is language-specific aspects, in particular of dysprosody. Prosodic information, including intonation, tempo, stress, and rhythm, serves many functions for the listener and speaker: it helps to segment the continuous flow of spoken language into words, groups these words into phrases for interpretation, and indicates the relative importance and function of the interpreted meanings [45, 46, 47, 48]. Each language has its own prosodic structure. For example, although they are sister languages, French and European Portuguese (both Romance languages) differ prosodically in a number of important ways. European Portuguese has contrastive lexical stress: each content word (noun, adjective, verb, etc.) has one syllable that is particularly salient or stressed, and changing the position of the lexical stress can change the meaning of a word [47, 49, 50, 51]. Stressed syllables may be accompanied by a pitch

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3 accent, realized as a modulation in F0 (e.g. a rise or a fall) and aligned in language-specific ways with
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5 the syllable. In contrary, French has a fixed stress, characterized by a systematic F0 rise on the last
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7 syllable in a word [52, 53]. In French, stress is not a property of the word, but of a larger unit called
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9 the accentual phrase that can include one or more content words and any preceding function words
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11 (articles, prepositions, etc.), often realized with F0 rises at its right and left edges. French listeners
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13 use these F0 rises as cues to word segmentation, finding the beginning and ends of words in the
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15 speech stream, and to lexical access, retrieving words from the mental lexicon [48, 54].
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18 Such differences across languages make the comparison of prosodic deficits in individuals with PD
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20 particularly interesting. Very few studies of PD dysprosody have looked beyond global measures to
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22 examine the extent to which linguistically important, language-specific patterns are affected [55, 56].
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24 Therefore, studying speech in individuals with PD whose languages include different prosodic
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26 modulations is essential in determining the role of prosody in patients' speech intelligibility and
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28 quality of life. Does a Portuguese patient experience different communication impairments
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30 compared to a French patient? If this is the case, could this difference be related, for example, to the
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32 fact that in Portuguese stress is distinctive and varies in position? Finally, how do these differences
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34 relate to disease duration and pharmacological treatment? Our project presents a novel approach to
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36 these questions and is characterized by the collection of cross-linguistic data in a single cohort.
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43 METHODS AND ANALYSIS

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45 FraLusoPark is a **binational** (data collection is performed in two countries: France and Portugal),
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47 **cross-sectional** (data is collected once for each participant) and **case-controlled** (both individuals
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49 with PD and control subjects are recruited) study, carried out in two different languages (French and
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Aims and hypotheses

The main objectives of our project are to evaluate modulations in voice/speech acoustics parameters (acoustics and prosody), perceptual markers (intelligibility), and PROMs (psychosocial impact of dysarthria in PD) across two different languages (French and European Portuguese).

Our three a priori hypotheses are the following: (i) Global acoustic features are altered similarly in French and Portuguese individuals with PD; (ii) Language-specific prosodic patterns are altered differently in French and Portuguese individuals with PD; and (iii) The impact of speech disorders on intelligibility and quality of life depends on the cultural and linguistic environment. In addition, the FraLusoPark project will allow for a better understanding of the progression of speech symptoms and their response to pharmacological treatment, which is important for pathophysiological aspects and clinical management.

Participants

Two groups of 60 healthy volunteers (one in France and one in Portugal) are age- and sex-matched with the individuals with PD to provide control references for the obtained performance measures. Individuals with PD are recruited in France (N = 60; Neurology Department, Centre Hospitalier du Pays d'Aix, Aix-en-Provence, France) and in Portugal (N = 60; Movement Disorders Unit, Hospital de Santa Maria, Lisbon, and CNS - Campus Neurológico Sénior, Torres Vedras, Portugal) and correspond to the UK Parkinson's Disease Brain Bank Criteria [57] for the diagnosis of idiopathic PD. Individuals with PD and healthy controls are all native speakers of French or of European Portuguese speakers (French-European Portuguese bilinguals were excluded) and right-handed (Handedness Edinburgh test > 80 %; [58]). Inclusion and exclusion criteria of PD patients and healthy controls are summarized in **Table 1**. To assess the effects of L-dopa at various stages of the disease, we consider three subgroups of patients (N = 20 patients each): Subgroup 1, *early*, with a disease duration between zero and three years and no motor fluctuations; Sub-group 2, *medium*, with a disease duration

between four and ten years, experiencing motor fluctuations; Sub-group 3, *advanced*, with a disease duration of over ten years.

Table 1. Inclusion and exclusion criteria

<i>All participants</i>	<i>Parkinson's disease patients</i>	<i>Control subjects</i>
Inclusion Criteria		
Age between 35 and 85 years old		
Good cooperation		
Ability to understand the information sheet		
Given signed consent		
Enrolled in a medical-social insurance plan		
Other stable medical problems not interfering with the proposed study		
Idiopathic Parkinson's disease		
Absence of any neurological, psychiatric or behavioural pathology		
Exclusion Criteria		
Illiteracy		
French/Portuguese not native language, or bilingual		
Participant under tutorship or guardianship, or any other administrative or legal dependence		
No cooperation or consent withdrawn		
Cognitive deficits, severe depression, dementia, psychosis (including medication-induced) or behavioural, neurological, medical, psychological disorders that may interfere with vital prognostic and evaluations		
Non-idiopathic Parkinson's disease		
Deep brain stimulation		
Severe motor impairment impeding participation in the study		

Study design

Healthy control participants undergo the same non-invasive assessments and examinations as individuals with PD. The only difference for patients is that they are evaluated twice, in the OFF and ON L-dopa states. This entails: (i) at least twelve hours after withdrawal of all anti-Parkinsonian drugs

and (ii) following at least one hour after the administration of the usual medication. The full study design is illustrated in **Figure 1**.

Speech recordings

In a quiet room, specialized speech recording equipment (EVA2© system, SQLab, Aix-en-Provence, France; <http://www.sqlab.fr/>; Marantz PMD661 MKII recorder, USA) is used for the speech/voice recordings. Participants are recorded while performing several speech production tasks with increasing complexity in a fixed order: (i) Steady vowel /a/ phonation (at a comfortable pitch and loudness) repeated three times; (ii) Maximum phonation time (vowel /a/ sustained as long as possible on one deep breath at a comfortable pitch and loudness), repeated twice; (iii) Oral diadochokinesia (repetition of the pseudoword *pataka* at a fast rate for 30 seconds); (iv) Reading aloud of 10 words and 10 sentences created by adapting the intelligibility section of version 2 of the Frenchay Dysarthria Assessment (FDA-2; [59]); (v) Reading aloud of a short text ("The North Wind and the Sun", French and European Portuguese adaptations; [50, 60]); (vi) Storytelling speech guided by visual stimuli (pictures from the wordless story "Frog, Where are you?", [61]; for the rationale of using this procedure and this book, see [62]; (vii) Reading aloud of a set of sentences with specific language-specific prosodic properties (31 sentences in French, 20 in European Portuguese); (viii) Free conversation for three minutes.

Acoustic measures

The acoustic measures characterize dimensions of aero-phonatory control [63]. For the steady vowel /a/ phonation, two kinds of measures will be extracted: First, for a macro-analysis, fundamental frequency (F0 in Hertz (Hz)) and F0 variation (%); and second, for a micro-analysis, perturbation measures such as jitter factor (%), absolute shimmer (dB), and harmonics-to-noise ratio (HNR, %). For the maximal phonation time, the longest duration (in seconds) of the sustained vowel /a/ will be

extracted. For the oral diadochokinesia task, the extracted measures will be the following: (i) the number of breath groups, *i.e.* the period during which the pseudoword was repeated in a single expiration, (ii) the ratio between the cumulated speech duration of the breath groups and the total duration of the session, *i.e.* the proportion of speech, (iii) the articulatory rate (syllables/second), (iv) the pause-to-sound ratio (%), and (v) the speech proportion per number of breath groups. As an initial step to investigate global prosodic aspects of PD speech compared to the speech of healthy controls, we will extract the F0 curve of one sentence selected from the short text ("The North Wind and the Sun"). This sentence is selected to be comparable across French and European Portuguese in terms of semantics and syllable length. This will provide a global phrasal pattern of F0 and intensity for patients and controls within and across languages (see below for subsequent studies with a more detailed focus on prosody). A summary of the acoustic measures that will be analysed are listed in

Table 2.

Table 2. Acoustic measures

Speech tasks	Function assessed	Acoustic measures
<i>Steady vowel /a/ phonation</i>	<i>Phonation</i>	Mean fundamental frequency (F0, in Hz) Fundamental frequency variation (F0 SD, in Hz) Shimmer (%) - <i>cycle-to cycle F0 variation</i> Jitter (%) – <i>cycle-to cycle intensity variation</i> Harmonics-to-noise ratio (HNR, in %)
<i>Maximal phonation time of the vowel /a/</i>	<i>Aero-phonatory control</i>	Longest duration (in seconds)
<i>Oral diadochokinesia</i>	<i>Supra-laryngeal articulatory control</i>	Number of breath groups Proportion of breath groups (%) Articulatory rate (in syllables/second) Pause-to-sound ratio (%) Speech proportion ratio (%)
<i>Reading aloud of text</i>	<i>Prosody</i>	Fundamental frequency range (F0 range, Hz) Intensity (in dB)

Clinical assessments

The neurological assessment is the Unified Parkinson’s Disease Rating Scale [64], using the revised version provided by the *Movement Disorders Society* (MDS-UPDRS; [65]). The FDA-2 is used to assess the functions of the speech organs [59], reflecting the state of the muscular effectors involved in speech production. The original FDA-2, in English, includes an evaluation of intelligibility through ten words and ten short sentences. Using the same methodology, we developed a set of cross-linguistically adapted words and sentences in French and European Portuguese that will be used for the intelligibility assessment in each language. During the OFF medication state, individuals with PD will be administered the FDA-2 and the motor part (section 3) of the MDS-UPDRS. During the ON medication state, these two assessments are performed together with the non-motor (section 1.A) and motor complication (section 4) sections of the MDS-UPDRS. During the ON medication state, the participants’ cognitive abilities are evaluated using the Montreal Cognitive Assessment (MoCA; [66]), and the Clinical Global Impression (CGI) is also reported [67]. For healthy controls, the assessment is similar to that of the PD patients during ON medication (except section 4 of the MDS-UPDRS). A summary of the clinical assessments is given in **Table 3.A**.

Table 3. Clinical assessments and patient-reported outcome measures

Description	Sub-sections	Min – Max scores (worst values in bold)
A. Clinical assessments		
Movement Disorders Society – Unified Parkinson’s Disease Rating Scale (MDS – UPDRS) <i>Assessment of motor and non-motor features of Parkinson’s disease</i> (Movement Disorder Society Task Force on Rating Scales for Parkinson’s Disease, 2003)	Non-motor experience of daily living – Motor experience of daily living – Motor examination – Motor complications	0 – 260
Frenchay Dysarthria Assessment (FDA-2) - <i>Assessment of speech and voice organs</i> (Enderby & Palmer, 2007)	Reflexes – Respiration – Lips – Palate – Larynx – Tongue – Intelligibility	0 – 104
Montreal Cognitive Assessment (MoCA) - <i>Global assessment of cognitive functions</i> (Nasreddine et al., 2005)	Visuospatial – Naming – Memory – Attention – Verbal fluency – Abstraction – Orientation	0 – 30
Clinical Global Impression (CGI) - <i>Global impression of the clinician for the symptom</i> (Busner & Targum, 2007)	Speech	1 – 7
B. Patient-reported outcome measures (PROMs)		
Parkinson’s Disease Questionnaire (PDQ-39) - <i>Quality of life in Parkinson’s disease</i> (Peto et al., 1995)	Mobility – Daily living activities – Emotional well-being – Stigma – Social support – Cognition – Communication – Body discomfort	0 – 156
Voice Handicap Index (VHI) (Jacobson et al., 1995)	Physical – Functional – Emotional	0 – 120
Dysarthria Impact Profile (DIP) - <i>Psychosocial impact of speech deficits</i> (Walshe et al., 2009)	Effect of dysarthria on me – Accepting my dysarthria – How I feel others react to my speech – How dysarthria affects my communication – Dysarthria relative to other worries and concerns	48 – 240
Patient Global Impression (PGI) - <i>Global impression of the patient on the dysfunction</i> (Hurst & Bolton, 2004)	Speech	1 – 7
Beck Depression Inventory (BDI) - <i>Global assessment of the depression profile</i> (Beck et al., 1961)		0 – 84

Patient-reported outcome measures

PROMs, such as the Dysarthria Impact Profile (DIP; [68]), are used to obtain self-reported information about the functional impact of an individual’s speech/communication impairment [69]. Additional self-assessments focus on the patients’ perception of their quality of life (the 39-Item Parkinson's Disease Questionnaire [PDQ-39]; [70, 71]) and on how voice/speech impairment may induce a handicap (Voice Handicap Index, VHI; [72]). The French [73] and European Portuguese adapted DIP, VHI [74, 75] and PDQ-39 [76, 77, 78] are used in our study. The Patient Global Impression (PGI) scoring [79] and the Beck Depression Inventory (BDI; [80]) are also administered. The MDS-UPDRS also includes a patient self-assessment (sections 1.B and 2), which are administered together with the other questionnaires in the ON condition. For healthy controls, the assessment is the same as for individuals with PD. A summary of the PROMs from the self-administered questionnaires are listed in

Table 3.B.

Statistical analyses

The analyses of the data (acoustic, clinical measures, and PROMs) will be performed with linear mixed-effects models that account for the variability across individuals, using the latest version of the statistical software R [81]. For each performance measure, the between-group factors *group* (patients vs. controls), *disease duration* (early vs. medium vs. advanced), and *language* (French vs. European Portuguese) will be investigated. In addition, we will explore the effects of the within-patient factor *medication* (OFF vs. ON) for all measures. Further relevant participant-related measures such as age, gender, and education level will also be taken into account in the analyses.

DISCUSSION

The present study will provide a unique, thorough, and reliable assessment of PD voice, speech and prosody disorders and an evaluation of the impact of these aspects on the quality of life of individuals with PD.

Main and subsequent analyses of the FraLusoPark study

Acoustic and prosodic measurements (**Table 2**), clinical assessment, and PROMs (**Table 3**) are the dependent variables to be analysed according to the statistical plan. These findings will be reported in the primary analysis as the main results of the project. However, the FraLusoPark investigation protocol will allow us to conduct additional analyses focusing on specific sub-dimensions of speech and voice deficits. There are at least four such subsequent analyses, exploring important aspects of PD speech and communication in more detail.

First, the intelligibility section of the FDA-2 [59] requires the words and sentences produced by the patient to be perceptually rated by the clinician in charge of the assessment. Since these speech productions are recorded during the FraLusoPark protocol, an evaluation of speech intelligibility by panels of auditory judges in France and Portugal will be run. This will allow an additional and unbiased judgment of speech and voice disorders beyond that of the speech therapists and experts involved in the study. This approach further complements the global assessment of dysarthric speech in PD patients.

Second, further prosodic analysis will be conducted on the defined sets of sentences, which manipulate both language-general and language-specific details of prosody. One particular focus will be the analysis of tonal alignment in the F0 curve, that is the temporal coordination of high and low tones with specific syllables in the sentences [82, 83, 84]. Tonal alignment is likely to be a relevant factor in the study of PD dysprosody since it relies on the precise coordination of glottal and

supraglottal articulatory gestures required to achieve language-specific temporal patterns for pitch accents and boundary tones.

Third, taking into consideration patients’ personal feelings with respect to the physical, psychological, and social domains has received increasing interest over the last decade. Individuals with PD are affected by voice and speech disorders, which contribute to an impairment of general communication abilities. Individuals with PD are therefore less likely to participate in conversations or social interactions [6, 9]. Several studies suggest that a growing discomfort in verbal communication during the progression of the disease leads to an important negative impact on social life [70, 85, 86]. Taken together, these studies argue for experimental designs that include different types of speech assessments (clinical, perceptual, instrumental, and psychosocial), as in the current protocol, and that explore the relationships between these different measures. Further analyses will therefore focus on linking the different dimensions of voice and speech description (e.g., acoustic measures, FDA-2) with the contributions of various participant-related measures such as intelligibility, cognition, and functional communication.

Fourth, production and prosodic parameters from the three different speech tasks (*i.e.* short text reading, orientated picture description, and conversation) will be compared. This will allow us to compare speech and voicing disorders in increasingly more complex communication contexts. These comparisons are of interest since communication abilities in PD are quite different in the presence of external cueing, such as during reading compared to spontaneous speech, which involves more complex speech planning strategies.

Finally, the FraLusoPark study might provide us the opportunity to address the deterioration of the speech of individuals with PD over time. In a longitudinal follow-up study, we would recruit a subgroup of patients from Group 1 (disease duration up to four year) and Group 2 (disease duration between four and ten years). These patients would be evaluated again at a later point in time (about

five years after the original recordings). This would allow us to describe the precise progression of speech deficits associated with PD within the same individual for French and Portuguese speakers.

ETHICS AND DISSEMINATION

This study has been approved by the local responsible committees on human experimentation (France: Comité de Protection des Personnes, Sud Méditerranée 1, project reference n° 13-84, approval date 9 January 2014; Portugal: Ethics Committee of the Lisbon Academic Medical Centre, project reference n° 239-14, approval date 1 June 2014). The study is conducted in accordance with the ethical standards of the Declaration of Helsinki [87]. The patients are included in the study after providing their written informed consent. The FraLusoPark trial is registered under the reference NCT02753192 (26 April 2016) on <https://clinicaltrials.gov/>.

Results of the FraLusoPark project will be disseminated at several research conferences at the national and international levels and published as articles in peer-reviewed journals and clinical magazines. The publication strategy is based on one principal article reporting the main results of the project and several subsequent articles deriving from it, including more detailed analyses of specific sub-dimensions of the speech and voice deficits.

Due to inter-speaker variability, any generalization drawn from speech parameters in clinical population requires data from a large number of speakers [88]. The FraLusoPark project is in line with this idea in that it builds a large-scale corpus of PD speech recordings and includes a large set of metadata (clinical examinations, speech measurements, linguistic features, patient-based indices). This allows a more accurate description of PD dysarthria, documenting the evolution of the symptoms and their response to pharmacological treatment. In both medical (*e.g.*, <http://www.mrc.ac.uk/research/research-policy-ethics/data-sharing/data-sharing-population-and-patient-studies/>) and linguistic (<http://sldr.org/>) domains, data sharing is important to maximize the

lifetime value of human health data. It is our intention to contribute to this practice by archiving our data for long-term preservation and making them accessible after the completion of our analyses.

Furthermore, an important recommendation from the International Classification of Functioning Disability and Health [89] is to improve quality of healthcare and to encourage clinicians to adopt a more holistic approach to the assessment and treatment of patients. Research in the field of speech sciences needs to incorporate this vantage point when studying pathological speech. The FraLusoPark project is in line with this perspective and will provide important recommendations for speech and voice assessments in PD patients. This will not only be helpful to health practitioners and clinicians when monitoring the progression of symptoms and their management, but will also advance our understanding of dysarthria in PD within a cross-linguistic and cross-cultural context.

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AUTHORS' CONTRIBUTIONS

SP and JJF are the principal investigators of the FraLusoPark study. They designed the study and ensure the proper realization of the study. JJF and FV are the neurologists in charge of patient recruitment and neurological assessments. RC, JS, HS, CM, JC, FV and SP perform data acquisition and other clinical examinations. RC, JS, PO and IG are in charge of the pre-processing and analyses of acoustic measurements. CA-C and AL are in charge of the analyses of the PROMs and clinical assessments. PW, PO, MD, MC, SF and MV are the linguist experts in charge of the prosody evaluations. IP is the neurobehaviour, language, and cognition expert. SP wrote the draft of the present article. All co-authors commented and revised it critically for important intellectual content, and approved the final version to be published.

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COMPETING INTERESTS STATEMENT

The authors report that there are no competing interests.

FIGURE LEGEND

Figure 1. Overview of the FraLusoPark study design.

Patient OFF-medication assessments (clinical history, speech recordings, and clinical assessments, without medication) are shown in dark grey. ON-medication assessments (speech recordings and clinical assessments after medication is effective) are shown in light grey.

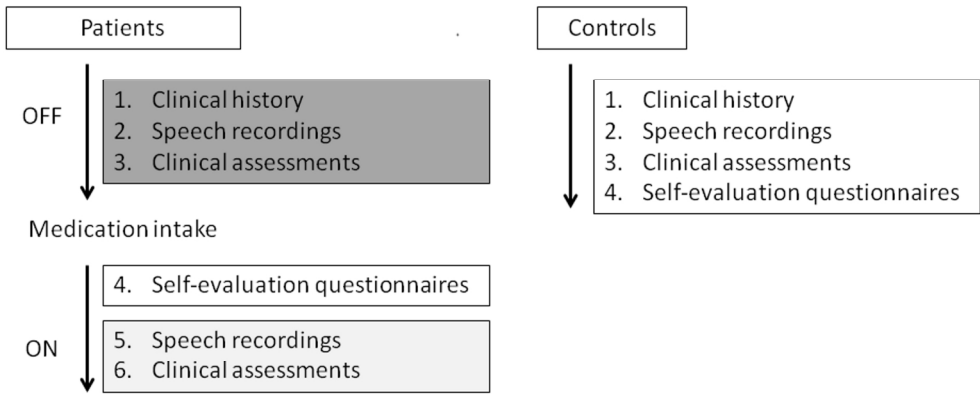


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Figure 1
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