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## Progressive phonagnosia in a telephone operator carrying a *C9orf72* expansion

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## Abstract

Selectivity is the rule, rather than the exception, in neurodegenerative disease. A retired telephone operator carrying a *C9orf72* expansion developed phonagnosia, a selective impairment of voice recognition, contrasting with intact person knowledge and recognition of faces, as a presenting sign of genetically confirmed fronto-temporal dementia. Since the dysfunction in this patient fell into his area of professional expertise, we discuss if overload in voice related neural networks might have caused failure propagating to connected nodes. The interaction with downstream molecular events, triggered by the *C9orf72* expansion, may have led to breakdown at the network level, leading to this specific phenotype.

Keywords: Phonagnosia; Frontotemporal lobar degeneration; C9orf72; Person knowledge; Selective vulnerability

## 1. Introduction

Selectivity is the rule, rather than the exception, in neurodegenerative disease and can result in isolated aphasia (Mesulam 2001) or amnesia (Didic et al., 1998). With increasing evidence for neural network selectivity in neurodegeneration (Seeley et al., 2009), the reason why one network is targeted rather than another remains unknown. While genetic factors are known to influence the phenotype, patients with autosomal dominant Fronto-Temporal Dementia (FTD) carrying the same mutation within the same family often display a wide variety of clinical signs suggesting degeneration of different neural systems.

Phonagnosia is a rare selective impairment of voice recognition, contrasting with relatively intact person specific knowledge and recognition of faces (Van Lancker & Canter 1982, Van Lancker et al., 1988). In the only report suggesting that this rare condition could occur in neurodegenerative disease, no genetic or neuropathological evidence was available to sustain this claim (Hailstone et al., 2010).

We here report on PM, a patient with a genetic form of FTD related to a *C9orf72* expansion, a former telephone operator, whose initial main complaint was a difficulty recognizing voices and who presented with progressive phonagnosia. We hypothesise that his professional activity, combined with genetic mechanisms, led to overload in voice related neural networks triggering network dysfunction.

## 2. Case description :

At the age of 72, PM, a married retired telephone operator with a family history of FTD presented to our department with the complaint of difficulty recognizing his interlocutors on the phone, while he had no difficulty recognizing the same people when he met them face to face. He had been working for a security agency for nearly ten years answering emergency phone-calls and subsequently relaying them to colleagues through the telephone. During his

full-time occupation, he spent entire days listening to both unknown voices (people who called because an emergency), as well as known voices (his colleagues). Given his particularly developed skill in recognizing speakers on the phone, his difficulty came as a surprise and became a matter of concern for his family. A pure tone audiogram and auditory potentials were within normal limits. He was socially and physically active and there was not the slightest sign of decline in everyday function. Personal past medical history included hypertension and dyslipidemia. His mother had been diagnosed with FTD after having developed behavioural change, as had four of his siblings who were all found to carry a *C9orf72* repeat expansion. Because of concern over his family history, he had been followed in our department since the age of 65. Informed consent for a study assessing genetic and clinical features in patients with cognitive decline, approved by the Ethics Committee Ile de France II (formerly CCPPRB Paris-Necker), Paris, was obtained. When first assessed at the age of 65, within the context of concern about his family history, mildly impaired executive function was found, which remained stable over the following seven years. There was not the slightest indication for behavioural dysfunction.

At the age of 72, when he complained of difficulty recognizing voices, there was no change in his behaviour. Neurological examination was unremarkable. Global cognitive function as assessed by the Mini Mental State Examination was intact (27/30). Sustained attention, language, object-naming, anterograde episodic and semantic memory, visuo-spatial and visuo-perceptive skills were within normal limits (see Table). Executive functions were mildly impaired, but there was no significant decline in comparison with previous assessments. By contrast, when asked to match voices of individuals that he knew personally with their photographs, he was only able to match two voices out of ten correctly. Surprisingly, he was unable to match the voice of his wife with her face.

In order to gain a better understanding of his complaint, a more detailed assessment of voice and face processing was conducted (for results, see Table and Fig 1). We report how we determined our sample size in the control group, all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study. We used the Famous People Test, a computerized test assessing naming, identification and familiarity of voices, faces and names of famous people (political figures, actors, singers, athletes, etc.) and compared the patient's results with normative data for 20 subjects (Joubert et al. 2006). As stimuli consist of faces, names and voices of famous people with several different copyright holders and right to image, public archiving of the stimuli used is not possible. E-prime scripts can be accessed via <https://osf.io/j6vha/>. Readers seeking access the test including the stimuli should contact the lead author Dr. Mira Didic. Access will be granted to named individuals in accordance with ethical procedures governing the use of sensitive data. Faces, names and voices are presented using E-Prime software (v1.1, PST Inc, PA, USA). Responses are not time-limited and error rates and reaction times measured. For the naming task, 20 faces and voices (10 seconds-long verbal extracts) are presented one by one and the subject has to retrieve the name. For the identification task, the same stimuli used in the naming task and 20 names of French celebrities are presented and the subject has to answer four semantic questions (*1. What is the profession of this person? 2. Is this person alive or deceased? 3. What information can you tell me that is specific about this person? 4. What other information can you tell me that is specific about this person?*). For the familiarity task, 48 faces/voices (10 seconds-long verbal extracts)/names, 24 belonging to French celebrities and 24 to unknown persons, are presented one by one and the subject is asked to determine whether it is familiar or unfamiliar. PM was only able to name two out of 20 French celebrities from their voice (Coluche, a famous French comedian and Patrick Bruel, a famous singer), his performance being significantly

worse as compared to matched controls, but he had no difficulty naming people from their face (Crawford, Garthwaite and Howell 2009, control data from Joubert et al. 2006). While he was severely impaired when asked to retrieve semantic information about celebrities from their voice (voice identification task), this contrasted with intact knowledge when presented with faces and names of the same person. He was able to judge whether voices and faces were familiar or unfamiliar, although familiarity for faces was superior to familiarity for voices. Naming objects and animals from their sounds was mildly impaired (15/18 correct), while object naming assessed through the visual modality was normal. Moreover, recognition of unfamiliar voices as well as environmental sounds (bells) was assessed using the Glasgow Voice Memory Test, a task that can be accessed online via <http://experiments.psy.gla.ac.uk/> (Aglieri et al. 2016). This brief test (5 minutes) targets perceptual and memory aspects of vocal processing by first getting participants to learn 8 voices (vowel /a/, 4 females) and 8 bell sounds before assessing recognition of these stimuli among 8 new ones. Normative data for 1120 adults above the age of 18 are available (Aglieri et al. 2016) and data from 10 age-matched subjects were taken from this sample and used for comparison. PM's accuracy for both voices and bells was significantly worse than controls, but he was significantly slower recognizing voices than bells (t-test comparing reaction time for bells and voices:  $p=0.0238$ ). However, in a sound discrimination test that requires listening to 32 pairs of two voices (vowels of the English alphabet pronounced by girls, boys, women and men) or two instruments (e.g. guitar, clarinet) and subsequently state if 1) two consecutive vowels were produced by the same person and 2) if two consecutive notes were produced by the same instrument (e.g. guitar), performance did not significantly differ from that of 18 controls matched for age. The task can be accessed via <https://amubox.univ-amu.fr/s/DJHYfNci8F6atYr>.

While there was no focal lesion on CT-scan, mild widening of the sylvian fissure and frontal atrophy was found.

The conditions of our ethics approval do not permit public archiving of the patient data supporting this study. Readers seeking access to this data should contact the lead author Dr. Mira Didic. Access will be granted to named individuals in accordance with ethical procedures governing the reuse of sensitive data. Specifically, to obtain the data, requestors must complete a formal data sharing agreement.

-----Table about here -----

-----Figure 1 about here -----

18 months later, his wife reported a change in his social behaviour with disinhibition and lack of initiative. There was a decline in executive function as assessed by the Trail Making Test part B (222 s; percentile 10 - 25<sup>th</sup>) and verbal fluency (23 animals). His performance on the mini-Social cognition and Emotional Assessment (Bertoux et al., 2012), a task assessing social cognition, was impaired (18,75; z-score - 3,912). Object naming, assessed with the French DO 80 naming task (Deloche and Hannequin, 1997), remained within normal limits (77/80 items correctly named). At the GRETOP, a French standardized task assessing famous face recognition, PM's ability to name and retrieve as well as semantic knowledge about celebrities was mildly impaired (score 51/60; 5<sup>th</sup> – 10<sup>th</sup> percentile), but he remained able to recognize celebrities in a forced-choice picture presentation (score 11/12; 25<sup>th</sup> – 50<sup>th</sup> percentile). MRI showed atrophy within fronto-temporal regions, with widening of the superior temporal sulcus on both sides (Fig 2). There was hypometabolism within the right fronto-temporal regions on FDG-PET. CSF biomarkers for Alzheimer's disease (AD) were negative (beta-amyloid 1-42 1063.00 pg/ml, total tau 1063.00 pg/ml, phospho-tau : 49.00



pg/ml, total tau : 325.00; Innotech). DNA was extracted from a blood sample after informed consent for genetic studies was obtained. Given the patient's family history, and phenotype at time of testing, as well as current recommendations, following a suggested flowchart for genetic testing, the *C9orf72* repeat expansion was specifically searched (Le Ber et al., 2013). Molecular testing revealed a pathogenic heterozygous GGGGCC repeat expansion (>30 hexanucleotides) in the first intron of the *C9orf72* gene (for family tree see Fig 3). No mutation has been identified in all other genes responsible for FTD/ALS by sequencing the whole exome in an affected sib of the patient.

-----Figure 2 about here -----

-----Figure 3 about here -----

### 3. Discussion

This report on PM, a patient with definite FTLN, demonstrates that selectively impaired speaker recognition, or phonagnosia, can occur in neurodegenerative disease. The present findings also provide further support that voices, as faces, can be considered “special” stimuli, leading some authors to label them “auditory faces” (Belin, Fecteau & Bédard 2004, Yovel & Belin 2012), although neural processes involved in face and voice processing differ (Schirmer 2018). Auditory potentials and a pure tone audiogram showed that there was no general auditory impairment and that ascending auditory pathways were intact. Also, the results of the present assessment suggest that the patient was able to analyse the structure of complex acoustic features, as indicated by the patient's ability to discriminate voices. This suggests that his difficulty in voice processing can be characterised as associative phonagnosia, i.e. an

inability to associate complex acoustic features with cross-modal knowledge, similar to the patient reported by Hailstone et al. (2010), but also one of the patients with developmental phonagnosia (Roswadowitz et al., 2014) and a recently reported patient who suffered from a vascular lesion to the right anterior temporal lobe (Luzzi et al., 2018). Moreover, the patient's selective incapacity to retrieve semantic information about individuals from voices only argues for a modality-specific person recognition deficit, and hence, for modality-specific person identity nodes (Gainotti et al., 2011).

Progressive phonagnosia differs from “progressive prosopagnosia” within the clinical spectrum of right temporal variant of FTD (Tyrrell et al., 1990, Joubert et al., 2004, Joubert et al. 2006). In the latter, person specific knowledge accessed through faces is impaired, while phonagnosia is a selective impairment of voice recognition. Also, unlike what is found in the left temporal variant of FTD, or “semantic dementia”, object and person related knowledge are initially intact (Snowden, Goulding & Neary 1989). Significant impairments in voice recognition have been reported in Alzheimer's disease and found to be particularly severe in the temporal variant of frontotemporal lobar degeneration, while being associated with other symptoms (Hailstone et al., 2011). However, the complaint of the patient in the present report was limited to voice recognition. Moreover, compared to the patient QR reported by Hailstone et al., (2010), who, when assessed, had a less “pure” deficit as he presented additional behavioural dysfunction and impaired face recognition, the deficit of the patient of the present report clearly predominated in the domain of voice recognition. Finally, as behavioural dysfunction subsequently appeared and a known pathogenic mutation was identified, the present case meets criteria for behavioral variant FTD with *definite* FTLD pathology (Raskovsky et al., 2011) thus confirming that this degenerative condition can cause isolated phonagnosia. Neuroanatomical specificity of particular frontotemporal lobar degeneration pathologies has been suggested to depend on an interaction of disease-specific

and network-specific factors (Rohrer et al., 2011). On a pathological level, *C9orf72* gene expansions are most often associated with FTLD-TDP type B, sometimes type A pathology, or a combination of both (Mackenzie & Neumann 2017). Following a clinico-anatomical series of 4 cases with a selective impairment of auditory word comprehension, all associated with FTLD-TDP type A, it has recently been suggested that FTLD-TDP may present with remarkably selective impairments of auditory semantics/oral language impairments (Mesulam et al., 2019). The present case might provide further evidence for this hypothesis.

An intriguing issue is that the presenting sign, impaired voice recognition, fell into the area of the patient's professional expertise. This raises the question of whether degeneration can selectively target "over-used" neural networks. Although previous reports relating occupation attributes to location of atrophy in FTD have provided some evidence that performance spanning decades may strengthen – rather than weaken - resistance to pathology through mechanisms of cognitive reserve (Spreng et al., 2010, Dodich et al., 2018), others have reported more rapid cognitive decline with higher lifetime cognitive experience (Massimo et al. 2019). Moreover, an association between progressive speech and language disorders and the occupation of teaching, a communication demanding occupation, has been reported. (Josephs et al., 2013). Also, motor neuron disease (MND), associated with *C9orf72* expansions (Chio et al., 2005, Lehman et al. 2012) in players of professional sports raised the question if vigorous physical activity could trigger degeneration of neural networks involved in motricity. Alternatively, a genetic profile or lifestyle promoting physical fitness may increase MND susceptibility (Huisman et al., 2013). Recent models suggest that excessive neuronal activity leads to degeneration as an explanation for hub vulnerability in Alzheimer's disease (De Haan et al., 2012), or within the context of "cascading network failure" (Jones et al., 2013). Local overload, through high connectivity, could therefore trigger downstream molecular events and cause a failure propagating to connected downstream nodes eventually

leading to more widespread system failure. In PM, although speculative, the question arises whether his professional activity as a telephone operator caused selective overload in voice related neural networks. Downstream interaction with molecular events, in his case the *C9orf72* expansion, an autosomal dominant genetic form of FTD (and/or ALS) that most certainly explained the patient's phenotype given his family history and its nearly complete cumulative penetrance (Murphy et al. 2017), in the absence of any other causative FTD/ALS mutation in this family, may have led to the involvement of other systems containing prominent connectivity hubs, leading to additional loss of person specific knowledge and behavioural dysfunction. While mechanisms of neurodegeneration are likely to be multifactorial and differ between individuals, the present case thus raises the question of an interaction of changes on both the network level – in this case overload - and molecular-level related to genetic factors, rather than one event driving the other, leading to a specific phenotype. Finally, it may also provide further insight into the understanding of how lifestyle factors influence the expression of disease, through interaction with genetic risk factors.

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Author contributions:

Mira Didic, Virginia Aglieri, Olivier Felician: Conceptualization; formal analysis; Methodology; Original draft; Writing; Editing; Eve Tramoni-Nègre, Lucas Ronat, Mathieu Ceccaldi: Investigation; Isabelle Le Ber, Pascal Belin: Review.

Potential Conflicts of Interest: Nothing to report.

Publicly archived anonymised public study data or digital study materials are not available for ethical reasons, but readers seeking access to the data can contact the lead author. No part of the study procedures or analysis plans was preregistered in an institutional registry prior to the research being conducted.

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Table:

Assessment	PM	Controls	Comparisons with controls (p)/Norms
Voice naming <sup>1,2</sup>	10 %	70.9 % ± 16.8 (n=20; mean age = 58,9 ± 9,1)	<sup>3</sup> p= .002*
Voice identification <sup>1,2</sup>	25 %	81.7 % ± 11.6 (n=20; mean age = 58.9 ± 9.1)	<sup>3</sup> p = .00013**
Voice familiarity <sup>1,2</sup>	54.2 %	70.7 % + 9 (n=20; mean age = 58,9 ± 9,1)	<sup>3</sup> p = .09
Voice discrimination <sup>2</sup>	46.9 %	63.2 % ± 7.8 (n=18; mean age = 70.7 ± 7.3)	<sup>3</sup> p = .058
Instrument discrimination <sup>2</sup>	81.3 %	61,11 % + 7,84 (n=18; mean age = 70.7 ± 7.3)	<sup>3</sup> p = .051
GVMT (voices) <sup>2</sup>	37.5 %	66,25 % ± 6,72 (n=10; mean age = 71.0 ± 6.7)	<sup>3</sup> p = .002*
GVMT (bells) <sup>2</sup>	43.8 %	84.37 % ± 13.58 (n=10; mean age = 71.0 ± 6,7)	<sup>3</sup> p= .02*
Face familiarity	75 %	86.1 % + 7.8 (n=20; mean age = 58.9 ± 9.1)	<sup>3</sup> p = .18
Face naming <sup>1,2</sup>	75 %	85 % ± 12.5 (n=20; mean age = 58.9 ± 9.1)	<sup>3</sup> p = .44
Face identification <sup>1,2</sup>	92.5 %	93,6 % ± 5,4 (n=20; mean age = 58.9 ± 9.1)	<sup>3</sup> p = .84
Name familiarity	93.8 %	92.8 % ± 4.1 (n=20; mean age = 58.9 ± 9,1)	<sup>3</sup> p = .82
Name identification <sup>1,2</sup>	92.5 %	97 % ± 4.4 (n=20; mean age = 58.9 ± 9.1)	<sup>3</sup> p = .33
Semantic knowledge about famous people (GRETOP)	59/60		50 <sup>th</sup> percentile
Verbal fluency (number of animals in 2 minutes)	30	26.8 % ± 7.4	50 <sup>th</sup> -75 <sup>th</sup> percentile
Visuo-spatial skills (score on Judgment of line orientation - test)	27		impaired if below 20
Picture Naming (items named correctly on naming test DO80)	80/80	75.7 ± 3.2 (n=36)	impaired if below 69
Sustained attention (number of seconds to complete Trail Making Test A)	70 s		25 <sup>th</sup> -50 <sup>th</sup> percentile
Divided attention (number of seconds to complete Trail Making Test B)	158 s		25 <sup>th</sup> -50 <sup>th</sup> percentile
Verbal memory (score on delayed total recall FCSR)	16		z-score:- 0.48

Neuropsychological assessment. <sup>1</sup> Famous People Test (control data Joubert et al. 2006) <sup>2</sup> Percent correct <sup>3</sup>Crawford test for single case and controls (Crawford, Garthwaite and Howell 2009). \* p < .05; \*\* p < .001. GVMT = Glasgow Voice Memory Test (control data Aglieri et al. 2016), FCSR = Free and Cued Selective Reminding Test

## Figure legends

Figure 1. Results obtained in the voice, face and name recognition assessments by the patient (PM) and matched controls. First line: results obtained at the voice familiarity, naming and identification task (Joubert et al. 2006<sup>14</sup>) (left) and in the assessment of discrimination of voices and instruments (right). Second line: results obtained in the test for faces and names (Joubert et al. 2006<sup>14</sup>). Error bars represent 95% confidence interval. \* = significant at  $p < 0.05$ ; \*\* = significant at  $p < 0.01$ .

Figure 2. Coronal slices of MRI (T1 sequences) showing atrophy within fronto-temporal regions, with widening of the superior temporal sulcus on both sides.

Figure 3. Family tree. Individuals are represented by diamonds for confidentiality. Black diamonds: individuals carrying the pathogenic heterozygous GGGGCC repeat expansion (>30 hexanucleotides) in the first intron of the C9orf72 gene. bvFTD = behavioral variant Fronto-temporal dementia.





