Journal of Neurology (2019) 266:1274–1279
https://doi.org/10.1007/s00415-019-09298-w

SHORT COMMENTARY

Crossed aphasia confirmed by fMRI in a case with nonfluent variant of primary progressive aphasia carrying a GRN mutation

Elisa Canu[1] · Valentina Bessi[3] · Michela Leocadi[1] · Sonia Padiglioni[3] · Benedetta Nacmias[3] · Sandro Sorbi[3,4] · Massimo Filippi[1,2] · Federica Agosta[1]

Received: 13 March 2019 / Revised: 22 March 2019 / Accepted: 23 March 2019 / Published online: 29 March 2019
© Springer-Verlag GmbH Germany, part of Springer Nature 2019

Abstract

Objectives To characterize patterns of language lateralization in a right-handed woman with nonfluent/agrammatic primary progressive aphasia (nfvPPA) clinical picture despite showing a prevalent right-sided brain damage.

Methods We report a case of a 58-year-old woman with nfvPPA diagnosis (age at onset = 55) previously described as a crossed aphasia case with progranulin mutation. At 2 years from the first visit, patient underwent 3DT1-weighted and a task-based functional MRI (fMRI). During the fMRI task, she was asked to perform a letter fluency test as the task of interest and to count forward as the control condition. Image processing and data analysis were performed using SPM12 and the effect of each task was tested at $p < 0.05$ FWE corrected.

Results The structural MRI confirmed a widespread right fronto-temporal atrophy mainly involving the right inferior frontal gyrus. During the letter fluency task, we observed an increased activation centered at the right inferior orbitofrontal gyrus and right middle frontal gyrus. By reducing the threshold, the pattern of functional activation was still dramatically prevalent at the right side.

Conclusions We provided evidence of the right language lateralization in a previously suspected crossed nfvPPA. Despite the long disease duration and the large amount of atrophy at the right side, there was no fMRI evidence of a left-hemisphere contribution to language function. We might speculate that compensatory effects do not appear when the premorbid language lateralization is purely right. The investigation of the underlying functional brain substrates in crossed nfvPPA cases may help understanding disease vulnerability in these neurodegenerative conditions.

Keywords Crossed aphasia · Nonfluent/agrammatic primary progressive aphasia · Functional MRI (fMRI) · Progranulin (GRN) mutation

Elisa Canu and Valentina Bessi contributed equally to this work.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00415-019-09298-w) contains supplementary material, which is available to authorized users.

✉ Federica Agosta
agosta.federica@hsr.it

[1] Neuroimaging Research Unit, Institute of Experimental Neurology, Division of Neuroscience, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Via Olgettina, 60, 20132 Milan, Italy

[2] Department of Neurology, Institute of Experimental Neurology, Division of Neuroscience, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy

[3] Department of Neuroscience, Psychology, Drug Research and Child Health (NEUROFARBA), University of Florence, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy

[4] IRCCS Fondazione Don Carlo Gnocchi, Florence, Italy

Dear Sirs,

The nonfluent/agrammatic primary progressive aphasia (nfvPPA) is characterized by agrammatism, apraxia of speech and, usually, by a left fronto-insular brain involvement [1]. The term 'crossed aphasia' in dextrals denotes any aphasic syndrome resulting from brain damage ipsilateral to the dominant right hand [2]. So far, few crossed nfvPPA cases have been reported [3–6], but only one has been studied with advanced neuroimaging [6]. Using a task-based functional MRI (fMRI) paradigm, we aimed to characterize patterns of language network lateralization in a 58-year-old, right-handed woman with a nfvPPA clinical picture despite a prevalent right-sided brain damage. We hypothesized that the patient is right-hemisphere dominant for language. Her case has been previously described clinically as a crossed aphasia with progranulin (GRN) mutation [3].

At 2 years from the first visit and at three from the symptoms' onset, patient underwent neurological and neuropsychological visits (Table 1), and 3D T1-weighted and task-based fMRI sequences on a 3.0 Tesla scanner (Ingenia CX, Philips). During the fMRI task, she was asked to perform a silent letter fluency test as task of interest and to count forward as control condition. A block design with 4 counting and 6 fluency alternating periods was used, for a total of 100 dynamic periods. Image processing and data analysis were performed using SPM12, and single-subject results of the effect of the fluency task (vs the control task) were tested at $p < 0.05$ FWE corrected for multiple comparisons.

Neurological examination was normal except for the appearance of a Myerson's sign. Patient's dexterity was confirmed by the Edinburgh handedness inventory [7]. Furthermore, the patient and her husband reported that she was dextral since her first limb activities in the childhood. Compared with the first visit [3], her insight and independence in self-care and housekeeping were still intact, but she showed a slight emotionally detached behavior and apathy. On detailed language examination, speech was characterized by several phonological errors, moderate apraxia of speech, and decreased prosody. Agrammatism was evident in speech (patient was able to produce correct but short and simple phrases) and sentence production. Despite speech progressive disturbances, the semantic domain was still spared as well as repetition, reading, and writing. On the other hand, general neuropsychological evaluation showed deficits in attention, visuospatial and executive functions, while verbal memory and praxis were spared. The patient's cognitive performances are shown in Table 1 and a detailed description of the administered neuropsychological assessment is provided in the supplementary material.

Structural MRI confirmed a right fronto-temporal atrophy with a further involvement of the right and medial dorsolateral frontal cortex, basal ganglia and medial parietal regions, as typically described in GRN-mutated cases [8]. During the letter fluency fMRI task, we observed activations centered at the right middle frontal and inferior orbitofrontal gyri (Fig. 1). By reducing the statistical threshold ($p < 001$ uncorrected), the pattern of functional activation was still dramatically prevalent at the right side.

This study provided evidence of the right language network lateralization in a previously suspected crossed nfvPPA [3]. In cases with stroke, the locus of the infarct provides indisputable evidence that the aphasia is indeed crossed. Because conventional imaging abnormalities associated with PPA are not as definitive as in cases with stroke, the evidence provided by fMRI is a valuable additional source of certainty. Specifically, fMRI offers a non-invasive tool for assessing language function lateralization, which complements a pure localization of the damage provided by structural MRI. The silent word generation task paradigms are known to show high concordance with the invasive Wada testing in pre-surgical patients [9] and to be the most robust paradigm for determining language lateralization [10–12]. Despite the long disease duration and the large amount of atrophy at the right side, there was no fMRI evidence of a left-hemisphere contribution to language function. This is surprising since an additional recruitment of right-hemispheric regions is usually observed during aging and in aphasic patients after stroke [13, 14]. In a previous fMRI-supported crossed aphasia case [6], a premorbid bilateral pattern of language lateralization was hypothesized in combination with compensatory mechanisms at the left side. In this context, we might speculate that comparable compensatory effects do not appear when the premorbid language lateralization is purely right. The investigation of the underlying functional brain substrates in crossed nfvPPA cases may help understanding disease vulnerability and brain functional reorganization after neuronal loss in these neurodegenerative conditions.

Table 1 Demographic and clinical features of our patient

Age, years	58			
Age at onset, years	55			
Sex	F			
Education, years	13			
Edinburgh handedness inventory	100%			
Global cognition	Raw score	Adjusted score	Cut-off	Presence of deficits
MMSE	25	23.00	< 23.8	[a]
FAB	11	10.30	< 13.5	[a]
Verbal memory				
Digit span, forward	6	5.83	5	
RAVLT, immediate recall	43	41.00	28.53	
RAVLT, delayed recall	10	9.50	4.69	
RAVLT, recognition accuracy	99%	–	< 88%	
Non-verbal memory				
Spatial span, forward	4	3.81	5	[a]
Rey's figure, recall	4	5.25	11.22	[a]
Executive functions				
Stroop test, time interference	44	43.25	> 31.66	[a]
Digit span, backward	2	1.79	< 3	[a]
Spatial span, backward	2	1.79	< 3	[a]
MCST, categories	1	–	> 3	[a]
MCST, perseverations	7	6.75	> 6.40	[a]
Raven's coloured progressive matrices	18	18.5	< 18	[b]
Attention				
TMT-A, seconds	65	59.00	> 94	
Attentive matrices	18	14.40	< 31	[a]
Barrage (double) test, accuracy	84%	–	< 90	[a]
Visuospatial abilities				
Rey's figure, copy	14	13.70	< 30.06	[a]
Drawing copy	7	6.96	< 7.18	[a]
Drawing copy with planning elements	60	59.50	< 61.85	[a]
Clock Drawing test	2	–	> 2	[b]
Praxia				
Orofacial apraxia	20	–	< 18	
Ideomotor apraxia	19	–	< 18	
Social cognition				
SET, global score	8	8.03	< 8.30	[a]
SET, intention attribution	2	2.02	< 2.35	[a]
SET, causal inference	3	3.03	< 2.42	[b]
SET, emotion attribution	3	3.03	< 2.21	[b]
Language				
Fluency				
Letter fluency	24	21.00	< 17	
Semantic fluency	33	31.00	< 25	
Syntactic comprehension				
Token test	30.5	28.75	< 26.5	[b]
ENPA, comprehension of auditory sentences	13	12.90	< 11.6	
ENPA, comprehension of visual sentences	12	11.60	< 11.3	
Syntactic production				
NAT-I	29	–	< 35.75	[a]
Single-word comprehension				
ENPA, auditory comprehension of words	20	–	< 18.4	
CaGi, comprehension of visual stimuli	48	47.76	41.48	
Object knowledge				
Pyramids and palm tree test	50	48.51	< 40.15	
Confrontation naming				
ENPA, oral naming, nouns	10	–	< 8.2	

Table 1 (continued)

ENPA, oral naming, actions	8	7.50	< 6.1	[b]
ENPA, oral naming, colours	5	–	< 4.0	
ENPA, written naming, nouns	5	–	< 2.7	
ENPA, written naming, actions	5	–	< 3.0	
Repetition				
ENPA, repetition of words	10	–	< 8.8	
ENPA, repetition of non-words	3	3.00	< 2	
ENPA, repetition of sentences	3	–	< 3	
Reading				
ENPA, reading of words	10	–	< 6.4	
ENPA, reading of non-words	5	–	< 4.0	
ENPA, reading of sentences	2	–	< 1.3	
Writing				
ENPA, writing of words	10	–	< 6.3	
ENPA, writing of non-words	3	2.30	< 1.4	
ENPA, writing of sentences	2	–	< 0.6	
Speech sample (picture description)				
Total *N* of words	153	147.07	≤ 42.428	
N of nouns/total *N* of words	0.17	–	≤ 0.198	[a]
N of verbs/total *N* of words	0.16	0.16	≤ 0.115	
N of sentences	16	18.10	≤ 3.553	
N of subordinates/*N* of sentences	0.25	–	= 0	
N of repaired sequences/*N* of words	0.12	–	≥ 0.121	[a]
N of phonological errors/*N* of words	0.08	–	≥ 0.0186	[a]
N of lexico-semantic errors/N of words	0.007	0.01	≥ 0.035	
Numbers				
ENPA, number repetition	10	–	< 8.8	
ENPA, number reading	9	8.30	< 7.6	
ENPA, number writing	8	–	< 6.3	
ENPA, word-number transformation	7	–	< 4.2	
Calculations				
ENPA, additions	3	–	< 2.2	
ENPA, subtractions	2	1.80	< 1.0	
ENPA, multiplications	3	2.40	< 1.4	
Mood and behavior				
Neuropsychiatric inventory	4	–	–	
Frontal behavioral battery, A	5	–	–	
Frontal behavioral battery, B	0	–	–	
Frontal behavioral battery, total	5	–	–	
Severity and independency				
Clinical dementia rating	0	–	–	
Clinical dementia rating, sum of boxes	0.5	–	–	
Clinical dementia rating, FTD	1.5	–	–	
BADL	6/6	–	–	
IADL	8/8	–	–	

Values denote means ± standard deviations (or frequencies). Cognitive scores are expressed as raw and adjusted scores (for age, education and—when available—gender) according to the normative data (when available)

BADL basic activities of daily living, *ENPA* esame neuropsicologico per l'afasia ('neuropsychological examination for aphasia'), *F* female, *FAB* frontal assessment battery, *FTD* frontotemporal degeneration, *IADL* instrumental activities of daily living, *MCST* modified card sorting test, *MMSE* mini mental state examination, *N* number, *NAT-I* northwestern anagram test-Italian, *RAVLT* Rey auditory verbal learning test, *SET* story-based empathy task, *TMT* trail making test

[a]Pathological and [b]bordeline performances according to the normative data (see supplementary material for details)

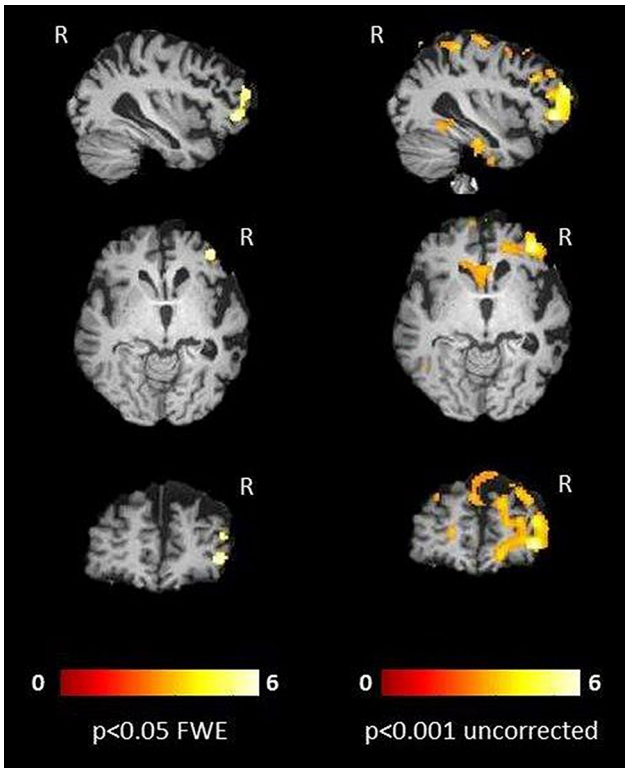

Fig. 1 Functional MRI during the letter fluency task compared with the control (counting) task. Results are overlaid on the 3D T1-weighted patient's sequence in neurological convention (right is right), and displayed at $p < 0.05$ family wise correction (FWE) and at $p < 0.001$ uncorrected within 100 contiguous voxels. Colored bars denote *T* values

Acknowledgements This study has been supported by the Italian Ministry of Health (GR-2011-02351217).

Compliance with ethical standards

Conflicts of interest E. Canu has received research supports from the Italian Ministry of Health. M. Leocadi, V. Bessi, S. Padiglioni, B. Nacmias, S. Sorbi report no disclosures. M. Filippi is Editor-in-Chief of the *Journal of Neurology*; has received compensation for consulting services and/or speaking activities from Biogen Idec, Merck Serono, Novartis, and Teva Pharmaceutical Industries; and receives research support from Biogen Idec, Teva Pharmaceutical Industries, Novartis, Merck Serono, Roche, Italian Ministry of Health, Fondazione Italiana Sclerosi Multipla, and ARiSLA (Fondazione Italiana di Ricerca per la SLA). F. Agosta is Section Editor of *NeuroImage: Clinical*; has received speaker honoraria from Biogen Idec and Novartis; and receives or has received research supports from the Italian Ministry of Health, AriSLA (Fondazione Italiana di Ricerca per la SLA), and the European Research Council.

Ethical standards This study has been approved by the local ethics committee and has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The patient gave her informed consent prior to their inclusion in the study.

References

1. Gorno-Tempini ML, Hillis AE, Weintraub S, Kertesz A, Mendez M, Cappa SF, Ogar JM, Rohrer JD, Black S, Boeve BF, Manes F, Dronkers NF, Vandenberghe R, Rascovsky K, Patterson K, Miller BL, Knopman DS, Hodges JR, Mesulam MM, Grossman M (2011) Classification of primary progressive aphasia and its variants. Neurology 76(11):1006–1014. https://doi.org/10.1212/WNL.0b013e31821103e6
2. Bramwell B (1899) On "crossed" aphasia and the factors which go to determine whether the "leading" or "driving" speech-centers shall be located in the left or in the right hemisphere of the brain: with notes of a case of "crossed" aphasia (aphasia with right-sided hemiplegia) in a left-handed man. Lancet 153:1473–1479
3. Bessi V, Piaceri I, Padiglioni S, Bagnoli S, Berti V, Sorbi S, Nacmias B (2018) Crossed aphasia in nonfluent variant of primary progressive aphasia carrying a GRN mutation. J Neurol Sci 392:34–37. https://doi.org/10.1016/j.jns.2018.06.026
4. Jeong EH, Lee YJ, Kwon M, Kim JS, Na DL, Lee JH (2014) Agrammatic primary progressive aphasia in two dextral patients with right hemispheric involvement. Neurocase 20(1):46–52. https://doi.org/10.1080/13554794.2012.732084
5. Repetto C, Manenti R, Cotelli M, Calabria M, Zanetti O, Borroni B, Padovani A, Miniussi C (2007) Right hemisphere involvement in non-fluent primary progressive aphasia. Behav Neurol 18(4):239–243. https://doi.org/10.1155/2007/423631
6. Spinelli EG, Caso F, Agosta F, Gambina G, Magnani G, Canu E, Blasi V, Perani D, Comi G, Falini A, Gorno-Tempini ML, Filippi M (2015) A multimodal neuroimaging study of a case of crossed nonfluent/agrammatic primary progressive aphasia. J Neurol 262(10):2336–2345. https://doi.org/10.1007/s00415-015-7845-x
7. Oldfield RC (1971) The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9(1):97–113. http://www.ncbi.nlm.nih.gov/pubmed/5146491. Accessed 20 Mar 2019
8. Cash DM, Bocchetta M, Thomas DL, Dick KM, van Swieten JC, Borroni B, Galimberti D, Masellis M, Tartaglia MC, Rowe JB, Graff C, Tagliavini F, Frisoni GB, Laforce R Jr, Finger E, de Mendonca A, Sorbi S, Rossor MN, Ourselin S, Rohrer JD, Genetic FTD Initiative, GENFI (2018) Patterns of gray matter atrophy in genetic frontotemporal dementia: results from the GENFI study. Neurobiol Aging 62:191–196. https://doi.org/10.1016/j.neurobiolaging.2017.10.008
9. Black DF, Vachha B, Mian A, Faro SH, Maheshwari M, Sair HI, Petrella JR, Pillai JJ, Welker K (2017) American Society of Functional Neuroradiology-Recommended fMRI Paradigm algorithms for presurgical language assessment. AJNR Am J Neuroradiol 38(10):E65–E73. https://doi.org/10.3174/ajnr.A5345
10. Brannen JH, Badie B, Moritz CH, Quigley M, Meyerand ME, Haughton VM (2001) Reliability of functional MR imaging with word-generation tasks for mapping Broca's area. AJNR Am J Neuroradiol 22(9):1711–1718. http://www.ncbi.nlm.nih.gov/pubmed/11673166. Accessed 10 Mar 2019
11. Friedman L, Kenny JT, Wise AL, Wu D, Stuve TA, Miller DA, Jesberger JA, Lewin JS (1998) Brain activation during silent word generation evaluated with functional MRI. Brain Lang 64(2):231–256. https://doi.org/10.1006/brln.1998.1953
12. Sabbah P, Chassoux F, Leveque C, Landre E, Baudoin-Chial S, Devaux B, Mann M, Godon-Hardy S, Nioche C, Ait-Ameur A, Sarrazin JL, Chodkiewicz JP, Cordoliani YS (2003) Functional MR imaging in assessment of language dominance in epileptic patients. Neuroimage 18(2):460–467. https://doi.org/10.1016/S1053-8119(03)00025-9
13. Meinzer M, Flaisch T, Wilser L, Eulitz C, Rockstroh B, Conway T, Gonzalez-Rothi L, Crosson B (2009) Neural signatures of semantic and phonemic fluency in young and old adults. J

Cogn Neurosci 21(10):2007–2018. https://doi.org/10.1162/jocn.2009.21219
14. Saur D, Lange R, Baumgaertner A, Schraknepper V, Willmes K, Rijntjes M, Weiller C (2006) Dynamics of language reorganization after stroke. Brain 129(Pt 6):1371–1384. https://doi.org/10.1093/brain/awl090