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A multimodal neuroimaging study of a case of crossed nonfluent/agrammatic primary progressive aphasia

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Abstract

Crossed aphasia has been reported mainly as post-stroke aphasia resulting from brain damage ipsilateral to the dominant right hand. Here, we described a case of a crossed nonfluent/agrammatic primary progressive aphasia (nfvPPA), who developed a corticobasal syndrome

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Compliance with the ethical standards

Ethical standard statement: Approval was obtained from the local ethical standards committee on human experimentation and written informed consent from all subjects before enrolment. The study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Conflicts of interest EG. Spinelli, F. Caso, G. Gambina, G. Magnani, E. Canu, V. Blasi, D. Perani, A. Falini, and M.L. Gorno-Tempini report no disclosures.
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(CBS). We collected clinical, cognitive, and neuroimaging data for four consecutive years from a 55-year-old right-handed lady (JV) presenting with speech disturbances. 18-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) and DaT-scan with ^{123}I-Ioflupane were obtained. Functional MRI (fMRI) during a verb naming task was acquired to characterize patterns of language lateralization. Diffusion tensor MRI was used to evaluate white matter damage within the language network. At onset, JV presented with prominent speech output impairment and right frontal atrophy. After 3 years, language deficits worsened, with the occurrence of a mild agrammatism. The patient also developed a left-sided mild extrapyramidal bradykinetic-rigid syndrome. The clinical picture was suggestive of nfvPPA with mild left-sided extrapyramidal syndrome. At this time, voxel-wise SPM analyses of ^{18}F-FDG PET and structural MRI showed right greater than left frontal hypometabolism and damage, which included the Broca's area. DaT-scan showed a reduced uptake in the right striatum. FMRI during naming task demonstrated bilateral language activations, and tractography showed right superior longitudinal fasciculus (SLF) involvement. Over the following year, JV became mute and developed frank left-sided motor signs and symptoms, evolving into a CBS clinical picture. Brain atrophy worsened in frontal areas bilaterally, and extended to temporo-parietal regions, still with a right-sided asymmetry. Tractography showed an extension of damage to the left SLF and right inferior longitudinal fasciculus. We report a case of crossed nfvPPA followed longitudinally and studied with advanced neuroimaging techniques. The results highlight a complex interaction between individual premorbid developmental differences and the clinical phenotype.

Keywords

Crossed aphasia; Nonfluent/agrammatic primary progressive aphasia (nfvPPA); Functional MRI; 18-Fluorodeoxyglucose positron emissi on tomography (^{18}F-FDG PET); Diffusion tensor tractography; Corticobasal syndrome (CBS)

Introduction

The nonfluent/agrammatic variant of primary progressive aphasia (nfvPPA) is characterized by motor speech difficulties and/or agrammatism, classically associated with predominantly left-sided fronto-insular involvement [1]. Overtime, many nfvPPA patients develop a progressive supranuclear palsy (PSP) or a corticobasal (CBS) syndrome [2, 3].

The term "crossed aphasia in dextral" denotes any aphasic syndrome resulting from brain damage ipsilateral to the dominant right hand [4]. This syndrome has been described mainly in post-stroke aphasia [5]. Few crossed neurodegenerative aphasia cases have been reported, mainly presenting as nfvPPA [4, 6–8], but none has been studied with advanced functional and structural neuroimaging techniques.

This report describes a case of a right-handed nfvPPA patient (JV) with a predominant right-sided frontal involvement. We followed JV over 4 years and performed extensive clinical, cognitive, and multimodal neuroimaging assessment, comprising conventional structural MRI and 18-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) at 1-year follow-up and conventional structural MRI, ^{18}F-FDG PET, DaT-scan with ^{123}I-Ioflupane,

diffusion tensor (DT) tractography, and task-related functional MRI (fMRI) at 2-year follow-up.

Case description

We collected ssyearly clinical, cognitive and neuroimaging data from a right-handed, native Italian speaker, 55-year-old woman (JV) for four consecutive years. JV had 5 years of education and worked as saleswoman until she was 30 years old, when she became a homemaker. She first came to medical attention at the Alzheimer Center, Azienda Ospedaliera Integrata in Verona, Italy in June 2011 (baseline) with a 1-year history of speaking difficulties. She reported a progressive lowering of her voice, effortful and slow speech with frequent sound errors and sporadic word-finding troubles. She developed depression and anxiety because of her communication problems. Medical history was not contributory. No birth stress was reported. No premorbid cognitive difficulties were referred. Her mother had late-onset Alzheimer's disease, and her father was affected by an unspecified parkinsonian syndrome. The Edinburgh handedness inventory showed strong right-handedness with a laterality index of 100 [9]. No early forced-handedness laterality was reported neither anomalous development of manual skills. There was no left-handedness in her family. Her general neurological examination was within normal limits, and no extrapyramidal signs were detected. The neuropsychological evaluation confirmed mild speech hesitancy, occasional word-finding pauses, effortful, and imprecise articulation with no clear errors but simplified grammar in production (see Supplementary Materials for details regarding the cognitive assessment). Single-word comprehension was preserved but she showed mild comprehension disturbances for complex sentences. Repetition, naming, reading and writing abilities, and other cognitive domains were preserved (Table 1).

At 1-year follow-up in Verona (2012), her language production was decreased, more effortful, and characterized by production of simple and short sentences. Syntax comprehension was stable with only mild difficulties with complex sentences. At this time, JV started showing some writing difficulties with substitutions and omissions of graphemes. Mild abstractive reasoning difficulties were also detected. General neurological examination was still normal. Conventional MRI (1.5 Tesla) showed a mild frontal atrophy, more evident on the right side (Fig. 1a). ^{18}F-FDG PET showed selective hypometabolism of the right middle (MFG) and inferior frontal gyri (IFG), including the Broca's area, and homolateral lenticular nucleus (Fig. 1b). At this point, considering the clinical and neuroimaging features, and the patient's strong right-handedness, a diagnosis of crossed nfvPPA was made.

At the 2-year follow-up (2013), the patient was evaluated at the San Raffaele Scientific Institute. She was still autonomous in self-care and housekeeping, but she reported a further decline in her speech output. On detailed language examination, speech was markedly reduced and characterized by a severe mixed dysarthria with mainly hypokinetic features (hypophonia, reduced stress, monoloudness, and inappropriate silence), and contributing apraxia of speech (AOS) with sound distortions and sequencing errors. Word-finding pauses, decreased prosody, and speech festination were also observed. JV was still able to produce correct simple phrases orally, but agrammatism was evident in written production and sentence comprehension. Confrontation naming was relatively spared, and errors were

characterized by deletions and substitutions of phonemes (Table 1). Single-word comprehension and semantic association abilities were within the normal range. General neuropsychological evaluation showed an impairment of executive functions, comprising working memory, abstract reasoning, and visuoconstructive abilities. Although tests of buccofacial and limb apraxia were within normal limits, mild deficits were detectable. Her insight was still intact. Neurological examination revealed a mild left-sided extrapyramidal bradykinetic-rigid syndrome, more evident at the upper limbs, particularly considering finger and hand dexterity movements. At this time point (2013), 3.0 Tesla MRI (Fig. 2a) and ^{18}F-FDG PET showed worsening of right frontal damage with an initial involvement of the contralateral homologous regions. The patient underwent also a DaT-scan with ^{123}I-Ioflupane showing a reduced uptake in the right striatum (putamen and, to a lesser extent, caudate nucleus). At this time point, experimental investigation of language activations and quantitative analyses of structural and metabolic patterns of brain damage were conducted as described below.

At three-year follow up, the clinical picture changed dramatically (2014), when JV became functionally mute. Her speech was markedly hypophonic and limited to a production of single words. She could no longer write. Object knowledge and single-word comprehension were only mildly affected, while grammatical comprehension was severely impaired. Furthermore, performance in all cognitive domains was decreased, likely in relation to a severe executive dysfunction (Table 1). Buccofacial apraxia became severe to the point that she was unable to perform even simple mouth movements or cough on command or imitation. Bilateral ideomotor apraxia (left greater than right) was also detected. At this time, she manifested a left-sided bradykinetic-rigid syndrome, left upper alien limb phenomenon, and dystonic posturing to left limbs (upper>lower limbs). She was still able to walk but slowly with supervision. The caregiver also referred initial swallowing problems with occasional choking/coughing to fluids. The clinical diagnosis at this point (2014) was corticobasal syndrome (CBS). MRI scan in 2014 revealed a worsened bilateral frontal atrophy extending to the anterior temporal lobes, lateral temporo-parietal regions, and hippocampi bilaterally, but still with a right-sided prevalence.

Quantification of functional and structural neuroimaging changes in 2013

MRI study

In 2013 and 2014, JV performed two MRI scans on average 1 year apart, on a 3T MRI scanner (Intera, Philips). Voxel-based morphometry (VBM) and fMRI analysis were performed on 2013 MRI scan. DT tractography was performed on 2013 and 2014 MRI scans. The following sequences were obtained: T2-weighted spin echo (SE); fluid-attenuated inversion recovery (FLAIR); 3D T1-weighted fast field echo; T2*-weighted blood-oxygen-level dependent echo-planar gradient-echo sequence; and pulsed-gradient SE echo planar with sensitivity encoding and diffusion gradients applied in 32 non-collinear directions. MRI sequences details are provided in the Supplementary material. Using the same protocol, a single MRI scan was obtained from 13 healthy controls. All HC were females and age-matched with JV.

Voxel-based morphometry (2013 MRI)—Grey matter (GM) volume differences between the patient and healthy controls were assessed using VBM [10] and the Diffeomorphic Anatomical Registration using Exponentiated Lie algebra registration method [11] in SPM8. VBM has been validated for single-subject's analysis, as long as a sufficient smoothing kernel is applied [12]. VBM results were tested at $p < 0.001$ uncorrected for multiple comparisons, to avoid false negatives that are likely to occur in single-subject VBM analyses. The analysis was adjusted for total intracranial volume. JV showed prominent right-sided cortical atrophy involving IFG-pars opercularis and pars-triangularis, MFG, precentral gyrus, and insula. In left hemisphere, JV showed GM atrophy of the insula (Fig. 2b).

Activation fMRI study (2013 MRI)—JV is right-handed and presented with nfvPPA clinical picture despite showing a prevalent right-sided brain damage. In order to characterize patterns of language lateralization, she underwent an fMRI activation study on the same scanner as described above. She was asked to perform a covert naming in response to visual cues as the task of interest and to observe visual patterns obtained from scrambled parts of the visual cues as the control condition. JV's naming abilities were tested during cognitive assessment (Table 1), before and after the scanning session. Her naming accuracy on cognitive testing was 90 % and errors were characterized as speech articulation and not lexical retrieval or semantic in nature. Image processing and data analysis were performed using SPM8, and single-subject results were tested at p value <0.001 uncorrected for multiple comparisons. For further details see Supplementary Material.

Results showed increased activation in bilateral (left more than right) precentral gyrus, supplementary motor area, superior temporal gyrus (STG), and in left inferior frontal gyrus, insula, and supramarginal gyrus ($p < 0.01$, Fig. 2c).

^{18}F-FDG PET (2013)

^{18}F-FDG-PET imaging scan was performed using a 3D PET/CT multi-ring General Electric Discovery STE PET/CT. Single-subject analysis was carried out with SPM5 software (www.fil.ion.ucl.ac.uk/spm) on MATLAB 8 (MathWorks Inc, Sherborn, Mass) as previously described [13, 14]. The significance threshold was set at $p < 0.05$, FWE-corrected for multiple comparisons at the voxel level. Minimum cluster size was set to $k = 100$. For further details see Supplementary Material.

Results showed a prevalent right hemispheric hypometabolism involving the dorsolateral frontal cortex, including the frontal operculum and Broca's area, and extending to the frontal medial cortex and inferior parietal cortex (Fig. 3). The right insula and putamen were also hypometabolic. A less extended but significant hypometabolism was detected in the left hemisphere in the dorsolateral frontal cortex and frontal operculum.

DT MRI tractography (2013 and 2014)

A DT MRI tractography analysis was performed on 2 follow-up scans in order to evaluate microstructural damage to the main WM tracts of the language network in the patient compared to 10 age-matched healthy female subjects. Fiber tracking was performed using a

probabilistic tractography algorithm implemented in FSL (probtrackx) [15]. Superior longitudinal (SLF) and inferior longitudinal (ILF) fasciculi, and frontal aslant were obtained. Tract average fractional anisotropy (FA) and mean diffusivity (MD) values were reported as estimated means along with their standard errors, and compared between the patient and controls, using a test for comparing an individual case with a small control sample [16]. A p value <0.05 was considered significant.

At 2-year follow-up (2013), tractography showed a trend toward a decreased FA and increased MD in the right SLF compared to healthy controls (Table 2; Fig. 4). The following year (2014, 3-year follow-up), DT MRI abnormalities became statistically significant in the right SLF and, to a lesser degree, in the left SLF and right ILF (Table 2; Fig. 4). At this time point, the right aslant tract also showed a trend for DT MRI alterations (Table 2).

Discussion

We report detailed clinical and neuroimaging description of JV, a case of “crossed” nfvPPA in a right-handed woman with prevalent GM and WM damage to the right hemisphere and, likely, a bilateral language representation.

JV presented initially with progressive motor speech impairment, characterized by severe dysarthria and signs of apraxia of speech. The clinical picture evolved into a typical nfvPPA with grammatical difficulties and eventually to a full-blown CBS, as suggested also by the occurrence of an extrapyramidal bradykinetic-rigid syndrome and the DaT-scan findings. This clinical evolution has been previously described [2, 17, 18] and is highly predictive of a tauopathy as the underlying pathology, more likely corticobasal degeneration [18–20]. DaT-scan findings are in line with previous studies reporting a high variability in terms of overall striatal binding, hemispheric asymmetry, and caudate-to-putamen ratio in CBS patients relative to patients with idiopathic Parkinson’s disease [21].

Surprisingly, JV’s neuroimaging studies showed greater damage of the right hemisphere language network, despite her right-handedness, indicating a diagnosis of crossed nfvPPA with anomalous premorbid language lateralization. A few cases of crossed nfvPPA [6, 8] and one case of crossed progressive apraxia of speech [7] have been reported in the literature. In these cases, neuroimaging data were mainly based on qualitative descriptions, and anomalous premorbid cortical representation of language was only hypothesized as no activation fMRI study was performed. We performed a multimodal neuroimaging study on JV in 2013, 3 years after symptom onset, when she showed a clinical picture of nfvPPA with motor speech impairment, agrammatism, and spared single-word comprehension. Voxel-wise analyses of GM volumes and ^{18}F-FDG-PET hypometabolism showed a clear pattern of a greater involvement of the right frontal regions, comprising Broca’s area and the insula with milder involvement of the left hemisphere. ^{18}F-FDG-PET results on JV were consistent with the only other reported quantified analysis of ^{18}F-FDG-PET data in a crossed nfvPPA patient [8]. The milder involvement of the left regions is ascribable to the progression of neurodegenerative process to the contralateral hemisphere over time. To our knowledge, no previous study has reported DT MRI tractography data in a patient with neurodegenerative crossed aphasia. As expected in nfvPPA [22–24], in JV the dorsal fronto-parietal and

intrafrontal language tracts were more involved than the ventral language comprehension pathway. Consistently with the location of atrophy, JV showed a right-sided pattern of WM abnormalities. In summary, objective metabolic and GM and WM structural neuroimaging abnormalities in JV confirmed greater right hemisphere involvement of the dorsal speech and language systems.

The pattern of early and greater right hemisphere damage in a right-handed aphasic patient suggests an anomalous premorbid language lateralization [25]. In order to investigate JV's pattern of language lateralization, an fMRI activation study was performed using a picture naming task. This paradigm is associated with left-lateralized activations of frontal, parietal, and temporal regions in right-handed healthy controls [26–28]. Based on her clinical and anatomical results suggesting crossed aphasia, we hypothesized that JV would show right-sided or bilateral language lateralization, at least in regions where atrophy is not prominent. We observed a complex pattern of fMRI responses with bilateral superior temporal and left more than right frontal activations. The bilateral temporal activations are more likely related to the premorbid language lateralization, since this region did not show significant atrophy or hypometabolism in JV. The prominent left versus right frontal activation might instead be a consequence of the occurrence of compensatory mechanisms in the less damaged frontal lobe. Previous studies have indeed showed increased activation in the early stages of atrophy and decreased activations when damage is severe [29]. Therefore, based on this data, we speculate that, despite her right-handedness, JV's premorbid pattern of language lateralization was likely bilateral. Bilateral, widespread premorbid language representations could also contribute to explain why, despite the extensive metabolic and anatomical abnormalities already evident at presentation, JV was still able to speak at baseline and first follow-up assessment.

The investigation of the underlying anatomical and functional substrates of this case of crossed nfvPPA might help to shed light on the challenging question of language lateralization and disease vulnerability in patients with neurodegenerative conditions. The integration of auditory and motor information necessary for articulation of speech in right-handers is thought to be sustained by the left dorsal fronto-parietal language pathway [30]. Furthermore, grammatical comprehension and production is also supported by a left-lateralized frontotemporal network in right-handers [31]. On the other hand, the right hemisphere usually sustains other aspects of language production, such as prosody and pragmatic processing [32]. This dichotomy has, however, been challenged by the fact that even in right-handers, language representation can be right-sided or bilaterally distributed [26, 33–35]. In addition, recent literature suggests that premorbid neurodevelopmental factors, such as language learning disabilities or hand lateralization, might contribute to brain vulnerability to PPA and phenotypic presentation [36–38]. These reports indicated an over-representation of language learning disability in patients with PPA [36], possibly more frequently in the logopenic variant [37]. Miller et al. also observed that non-right-handedness was more frequent in cases of semantic PPA, while right-handedness was more common in the nfvPPA than in healthy controls [37, 38].

We report a case of crossed nfvPPA in whom the prominent right fronto-parietal brain damage detected by VBM, DT MRI, and ^{18}F-FDG-PET was associated with a premorbid

bilateral language lateralization as revealed by fMRI. A distributed language representation and compensatory left frontal activation likely influenced the clinical presentation and progression. This case provides further evidence for recent models that emphasize a complex interaction between individual premorbid developmental differences and clinical phenotype in neurodegenerative diseases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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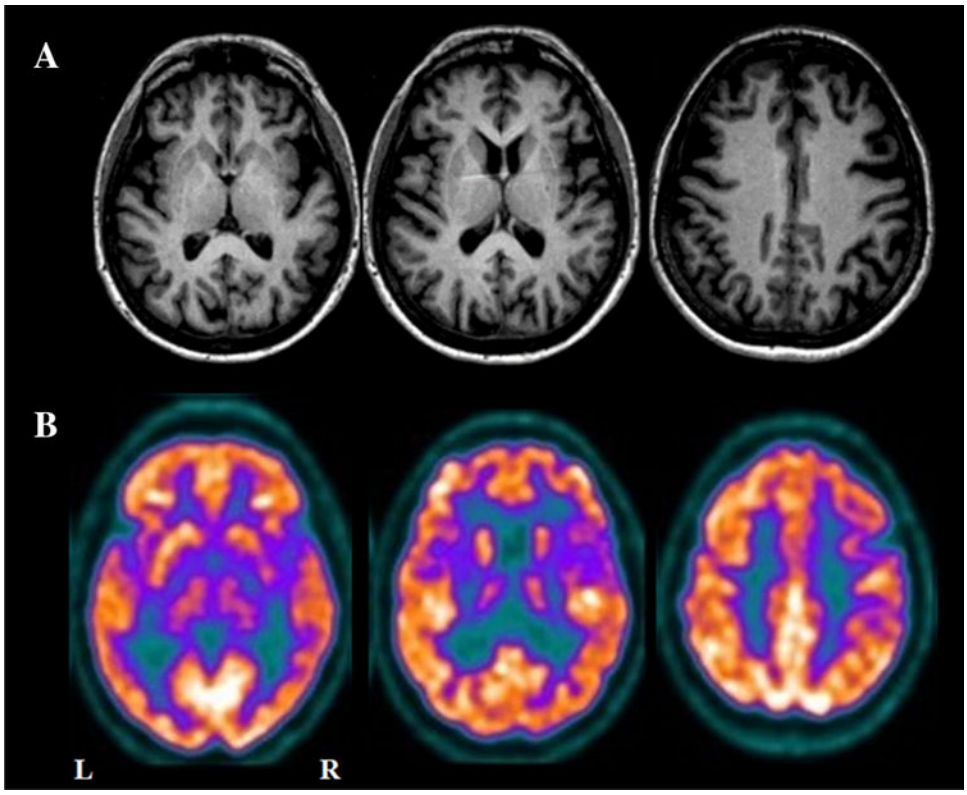

Fig. 1.

a 1.5 Tesla structural MRI and **b** ^{18}F-FDG-PET scan of JV obtained at 1-year follow-up (2012). *L* left, *R* right

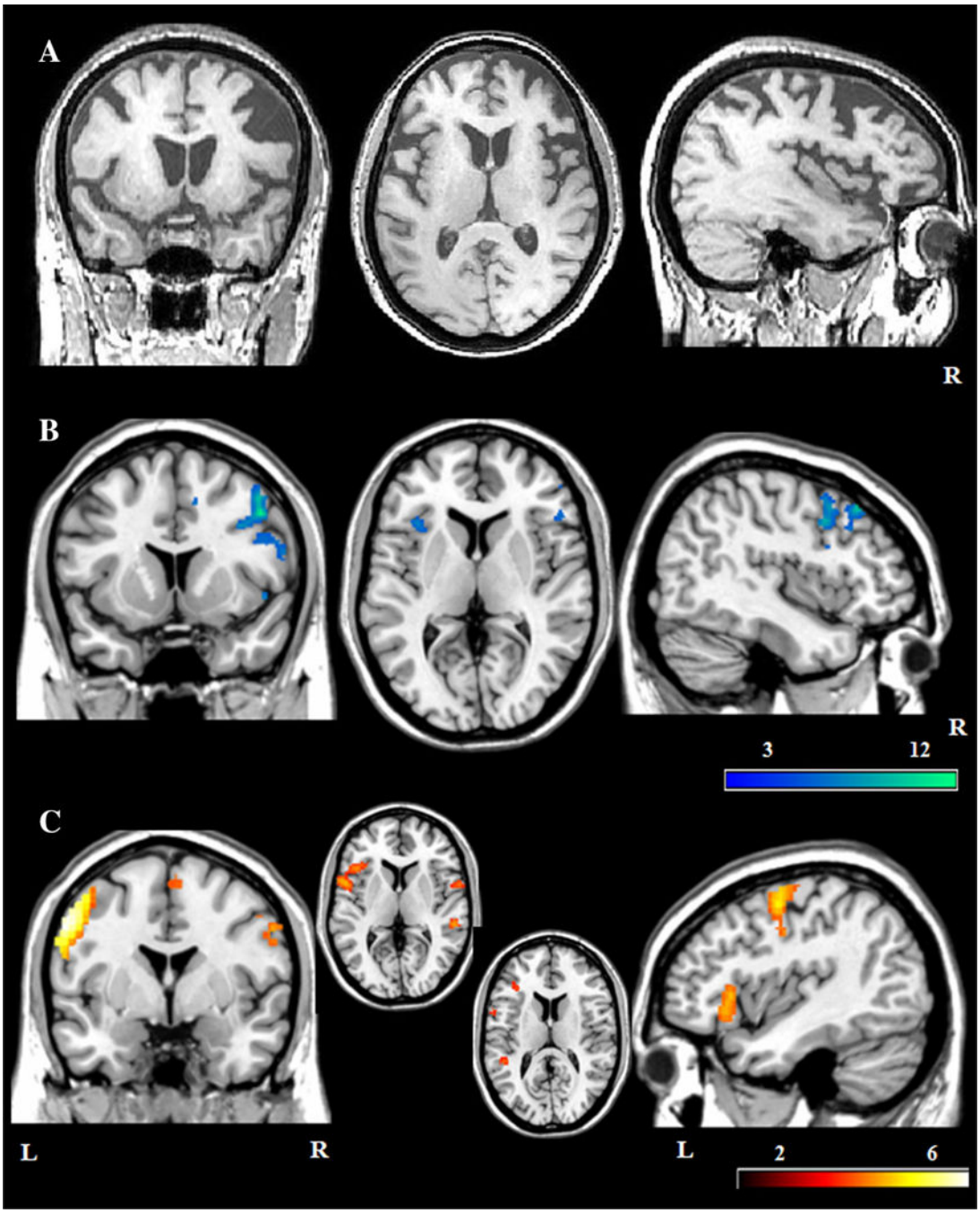

Fig. 2.

a 3.0 Tesla structural MRI obtained at 2-year follow-up (2013); **b** VBM results of GM atrophy in JV versus healthy controls obtained at 2-year follow-up (2013). *Color bar* (*blue* to *cyan*) represents *t* values ($p < 0.001$, uncorrected for multiple comparisons); and **c** fMRI results showing areas with increased *BOLD* signal during the covert naming task obtained at 2-year follow-up (2013). *Color bar* (*red* to *yellow*) represents *t* values ($p < 0.01$, uncorrected for multiple comparisons)

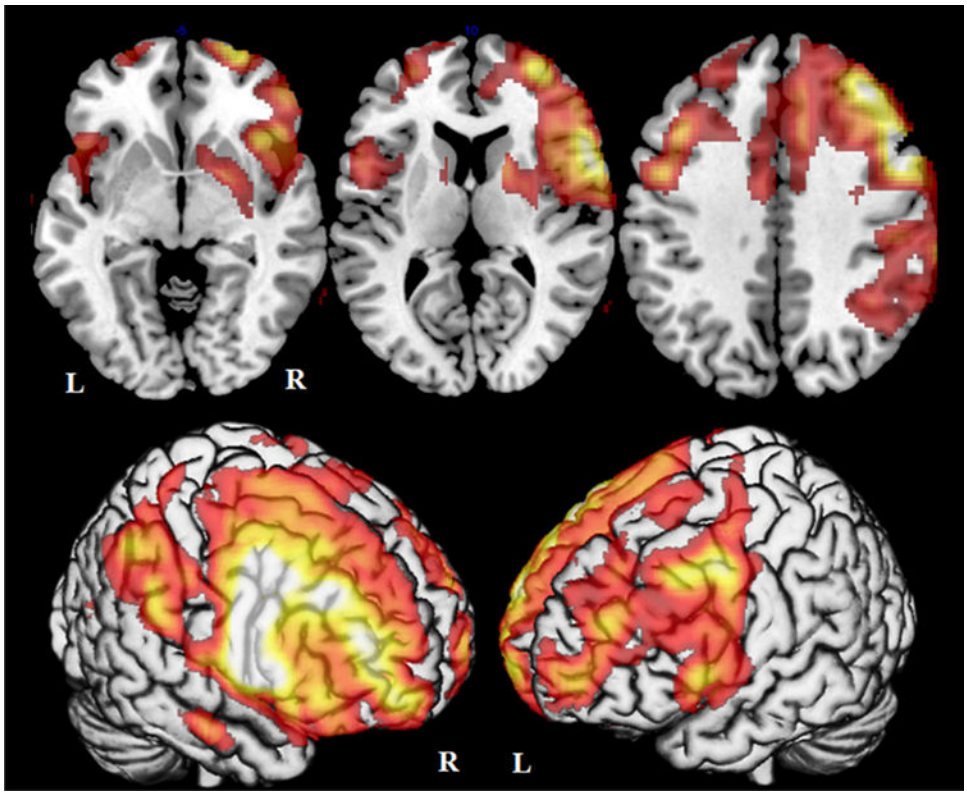

Fig. 3.

Voxel-wise results of ^{18}F-FDG-PET scan obtained at 2-year follow-up (2013), showing regions of significant (*red* to *yellow*) hypometabolism in JV versus healthy controls ($p < 0.05$, Family-wise error-corrected for multiple comparisons at the voxel level)

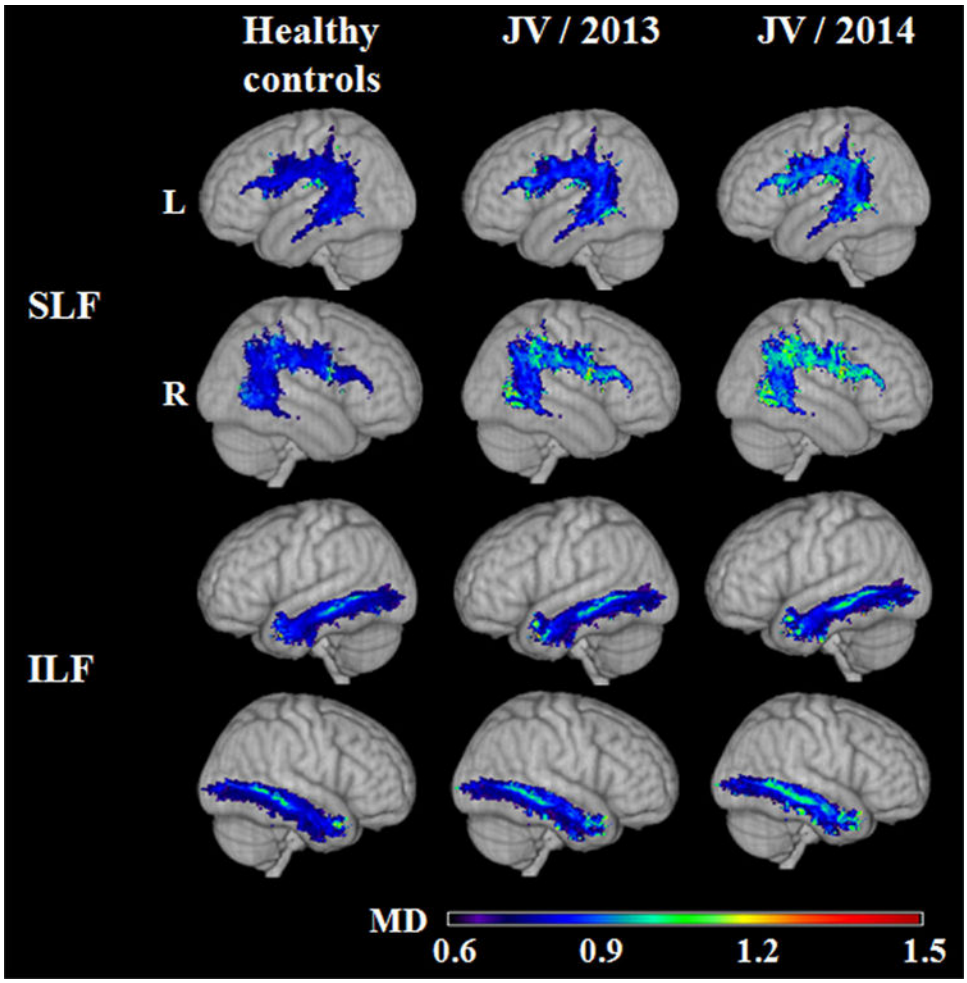

Fig. 4.

Diffusion tensor tractography results at 2-year (2013) and 3-year (2104) follow-up visits. The white matter tracts [superior longitudinal fasciculus (SLF), inferior longitudinal fasciculus (ILF)], showing significant differences between the patient and healthy controls are rendered as maps of mean diffusivity (MD). For healthy controls, probability maps are shown including only voxels that were detected in at least 20 % of subjects. The color scale represents the MD values ranging from lower (*violet–blue*) to higher values (*yellow–red*). MD values are $\times 10^{-3}$ mm^2 s^{-1}

Table 1

Longitudinal neuropsychological data collected from our patient

	2011	2012	2013	2014
MMSE (co 24)	29/30	29/30	25/30	15/30*
Language				
Token test (co 26.5)	36	36	29.25	10.5*
Phonemic fluency (co 17)	28	–	31	10*
Semantic fluency (co 25)	39	–	42	13*
Aachener Aphasia Test				
Spontaneous speech				
Communicative behavior	5	4	3	2
Articulation and prosody	4	3	3	2
Automatic language	5	5	4	4
Semantics	4	4	4	4
Phonology	5	4	3	2
Syntax	5	5	4	1
Repetition (co 142)	149	144	134*	61*
Written language (co 83)	87	84	–	–
Reading (L1) (co 28)	–	–	25*	15*
Writing (L3) (co 27)	–	–	20*	0*
Object naming (co 104)	120	120	115	
Comprehension (co 108)	111	112	–	
B.A.D.A. (errors)				
Oral objects comprehension (co 58)	–		10/60*	18/60*
Visual objects comprehension (co 43)	–		7 45*	–
Pyramid and palm tree test (co 40.15)	–		50	40.06*
CAGI				
Confrontation naming (co 41.49)			43/48	2/48*
Single-word comprehension (co 47.09)			48/48	46/48*
Verbal and spatial memory				
Digit span forward (co 3.75)	6.5	6.5	6.1	4.5
Digit span backward (co 3)	3*	3*	3*	<2*
Memory prose (co 8)	–	–	9	–
Rey's 15 item test				
Immediate recall (co 28.53)	38.8	40.8	26.3*	–
Delayed recall (co 4.69)	7.7	8.7	3.7*	–
Figure Rey Recall (co 9.47)	–	–	8.5*	3.25*
Visuospatial abilities				
Figure Rey copy (co 28.88)	–	–	26.5*	1.25*

	2011	2012	2013	2014
Attention and executive functions				
Attentive matrices (co 31)	41.25	50.25	29*	6.25*
Raven's matrices (co 18)	20.8	17.8*	26.5	–
TMT-A (co 93)	–	–	41	–
TMT-B (co 282)	–	–	Interrupted	–
Praxis				
Buccofacial apraxia (co 13)	–	–	16/20	4/20*
Ideomotor apraxia (co 14)				
Left arm	–	–		0/20*
Right arm	–	–		6/20*

BADA Batteria per l'Analisi dei Deficit Afasici, *co* cut-off, *MMSE* Mini Mental State Examination, *TMT* Trail Making Test

*Pathologic scores relative to normative data (see Supplemental Material)

Table 2

Diffusion tensor MRI metrics of white matter tracts in the patient and healthy controls in 2013 (2-year follow up) and 2104 (3-year follow up)

	MD ($\times 10^{-3}$ mm^2 s^{-1})					FA				
	Healthy controls	**JV (2013)**	p°	**JV (2014)**	$p^{\#}$	**Healthy controls**	**JV (2013)**	p°	**JV (2014)**	$p^{\#}$
SLF										
L	0.77 (0.05)	0.81	0.48	0.86	0.11	0.47 (0.02)	0.43	0.13	0.39	0.003
R	0.78 (0.04)	0.86	0.09	0.94	0.003	0.45 (0.03)	0.39	0.06	0.35	0.004
ILF										
L	0.83 (0.04)	0.85	0.64	0.90	0.07	0.46 (0.03)	0.46	0.96	0.42	0.22
R	0.82 (0.03)	0.88	0.10	0.91	0.01	0.46 (0.03)	0.45	0.71	0.38	0.02
Aslant										
L	0.82 (0.05)	0.83	0.92	0.87	0.43	0.40 (0.03)	0.39	0.72	0.37	0.46
R	0.85 (0.08)	0.90	0.61	1.01	0.08	0.38 (0.03)	0.39	0.85	0.34	0.24

Numbers are estimated means ± standard errors

FA fractional anisotropy, *ILF* inferior longitudinal fasciculus, *L* left, *MD* mean diffusivity, *R* right, *SLF* superior longitudinal fasciculus

p° Comparison between JV and healthy controls in 2013

$^{\#}$Comparison between JV and healthy controls in 2014 (see text for further details)