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Altered speech-related cortical network in frontotemporal dementia

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ABSTRACT

Background: In healthy subjects (HS), transcranial magnetic stimulation (TMS) demonstrated an increase in motor-evoked potential (MEP) amplitudes during specific linguistic tasks. This finding indicates functional connections between speech-related cortical areas and the dominant primary motor cortex (M1).

Objective: To investigate M1 function with TMS and the speech-related cortical network with neuroimaging measures in frontotemporal dementia (FTD), including the non-fluent variant of primary progressive aphasia (nfv-PPA) and the behavioral variant of FTD (bv-FTD).

Methods: M1 excitability changes during specific linguistc tasks were examined using TMS in 24 patients (15 with nfv-PPA and 9 with bv-FTD) and in 18 age-matched HS. In the same patients neuroimaging was used to assess changes in specific white matter (WM) bundles and grey matter (GM) regions involved in language processing, with diffusion tensor imaging (DTI) and voxel-based morphometry (VBM).

Results: During the linguistic task, M1 excitability increased in HS, whereas in FTD patients it did not. M1 excitability changes were comparable in nfv-PPA and bv-FTD. DTI revealed decreased fractional anisotropy in the superior and inferior longitudinal and uncinate fasciculi. Moreover, VBM disclosed GM volume loss in the left frontal operculum though not in the parietal operculum or precentral gyrus. Furthermore, WM and GM changes were comparable in nfv-PPA and bv-FTD. There was no correlation between neurophysiological and neuroimaging changes in FTD. Atrophy in the left frontal operculum correlated with linguistic dysfunction, assessed by semantic and phonemic fluency tests.

Conclusion: We provide converging neurophysiological and neuroimaging evidence of abnormal speech-related cortical network activation in FTD.

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Introduction

Frontotemporal dementia (FTD) is a heterogeneous degenerative disorder including a behavioral variant (bv-FTD), characterized by prominent behavioral and executive symptoms, and variants manifesting with progressive language deterioration, as the non-fluent variant of primary progressive aphasia (nfv-PPA) [1,2]. Several neuroimaging studies have shown structural grey matter (GM) and white matter (WM) degeneration, and altered resting-state functional connectivity in specific frontotemporal brain regions in FTD. In particular, structural and functional changes involved fronto-insular, temporal, and limbic regions in bv-FTD patients, whereas nfv-PPA was characterized by abnormalities in frontotemporal networks associated with language function [3–10].

Language requires a complex interaction between functionally-integrated brain regions, including the primary motor cortex (M1), that mainly subserve expressive functions [11,12]. Transcranial magnetic stimulation (TMS) studies performed in healthy subjects (HS) demonstrated a functional connection between speech-related cortical areas and the dominant M1. During specific linguistic tasks M1 excitability increases, reflecting the speech-related cortical network activation [13–19].

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Abbreviations

bv-FTD	behavioural variant of frontotemporal dementia
CDR-FTD	Clinical Dementia Rating Scale & Frontotemporal Dementia
DTI	diffusion tensor imaging; FA, fractional anisotropy
FAB	frontal assessment battery
FDT	FMRIB's Diffusion Toolbox
FSL	FMRIB's Software Library
FTD	frontotemporal dementia
GM	grey matter
ILF	inferior longitudinal fasciculus
MDS-UPDRS-III	Movement Disorder Society-Unified Parkinson's Disease Rating Scale part III
MMSE	Mini-Mental State Examination
MNI	Montreal Neurological Institute
MPRAGE	magnetization-prepared rapid acquisition gradient echo sequence
nfv-PPA	non-fluent variant of primary progressive aphasia
PPA	primary progressive aphasia
SLF-t	superior longitudinal fasciculus temporal tract
TBSS	Tract-Based Spatial Statistic
TMT	trail making test
VSP	verbal semantic fluency
UnF	uncinate fasciculus
VPF	verbal phonemic fluency
WM	white matter

No studies have used TMS to investigate speech-related cortical network activation in FTD or compared possible neurophysiological changes in nfv-PPA and bv-FTD. Moreover, none have clarified whether possible TMS abnormalities during a linguistic task reflect structural changes in WM bundles and GM regions involved in language processing in the same patient subgroups.

In this study, we investigated the speech-related network activation in FTD patients and HS using a modified version of the TMS protocol described by Tokimura et al. (1996) [13]. This protocol entails assessing motor-evoked potentials (MEPs) induced by single TMS pulses over the dominant and non-dominant M1 during non-linguistic and linguistic tasks, including reading single words aloud [13]. We then compared the neurophysiological results in nfv-PPA patients with those in bv-FTD. As approximately 20% of FTD patients may also manifest clinical signs of Parkinsonism [20], which is known to affect intrinsic M1 activity [21,22], we also compared responses in patients with and without Parkinsonism. Another relevant issue is the possible pathophysiological link between alterations in speech-related cortical network activation and the structural changes in associative WM bundles and GM regions involved in language processing. Hence, we examined possible WM changes, by using diffusion tensor imaging (DTI), in specific language-related tracts (temporal part of the superior longitudinal fasciculus, inferior longitudinal fasciculus and uncinate fasciculus), and possible GM structural changes, by using voxel based morphometry (VBM), in specific speech-related cortical areas of the dominant hemisphere (left frontal operculum, left precentral gyrus and left parietal operculum). Finally, to clarify the pathophysiological link between neurophysiological and neuroimaging changes in FTD, we assessed the correlations between language-related M1 excitability changes and structural WM and GM neuroimaging measures.

Our main hypothesis is that FTD patients are characterized by abnormal language-related M1 excitability as well as WM and GM degeneration in language-related structures, with significant correlation between neurophysiological and neuroimaging measures. We also expect that the aforementioned abnormalities will be prominent in nfv-PPA compared to bv-FTD. Clarifying these points would shed light on the pathophysiology of language dysfunction in FTD.

Material and methods

Participants

The participants, who were recruited from the Department of Human Neurosciences, Sapienza University of Rome, Italy, consisted of 24 patients (13 M, mean age±SD: 69 ± 7.7) with a clinically probable diagnosis of FTD, classified as manifesting nfv-PPA (n = 15; 8 M, mean age±SD: 69 ± 8.2) and bv-FTD (n = 9; 5 M, mean age±SD: 69 ± 7.3), and 18 age-matched healthy subjects (HS) (10 M, mean age±SD: 66 ± 8.5). All the participants were right-handed and native Italian speakers. The diagnosis of probable bv-FTD and of imaging-supported nfv-PPA was based on recent international consensus criteria [1,23]. MRI and FDG-PET revealed patterns of atrophy and hypometabolism that were consistent with a diagnosis of FTD and the respective clinical variants in all the patients [1,23,24]. The neurological examination excluded signs of upper or lower motor neuron involvement, while EMG excluded lower motor neuron involvement. At the time of the experiment, 6 patients were being treated with memantine at 10 mg/day while the remaining patients were not taking any drugs that act on the central nervous system [25]. Patients gave their written informed consent to the study, which was approved by the Institutional Review Board in accordance with the Declaration of Helsinki.

Clinical and neuropsychological assessment

All the participants underwent a complete neuropsychological evaluation performed by an experienced neuropsychologist. All patients were examined using the Mini-Mental State Examination (MMSE) [26], the Frontal Assessment Battery (FAB) [27], and the Trail Making Test (TMT) (subtype A e B) [28]. Language function was assessed in all patients using Verbal Semantic Fluency (VSF) [29,30] and Verbal Phonemic Fluency (VPF) tests [29]. Dementia severity was also assessed using the Clinical Dementia Rating Scale & Frontotemporal Dementia (CDR-FTD) [31]. Parkinsonism was evaluated using the Movement Disorder Society-Unified Parkinson's Disease Rating Scale part III (MDS-UPDRS-III) [32].

Stimulation techniques and recordings

Single TMS pulses over M1 of both the left (dominant hemisphere) or right (non-dominant hemisphere) were delivered using a Magstim 200 stimulator (Magstim Co., Whitland, UK) connected to a figure-of-eight shaped coil placed over the optimal position to elicit MEP in the contralateral first dorsal interosseous (FDI) muscle. A neuronavigation stereotaxic system (SofTaxic Navigator System, EMS Italy) was used to continuously target the FDI hotspot during the experiment. The resting motor threshold (RMT) was measured in either FDI muscle in accordance with standardized procedures [33]. TMS intensity was adjusted to elicit a baseline MEP of about 0.8–1 mV in amplitude (MT_{1mV}). EMG was recorded using surface electrodes, amplified by a Digitimer D360 (Digitimer Ltd, Welwyn

Garden City, UK), filtered and digitized by a 1404 unit (Cambridge Electronic Design, Cambridge, UK). Trials with background peri-stimulus EMG activity greater than 100 μV in a time window of 500 ms preceding MEPs were rejected. Mean peak-to-peak MEP amplitudes were calculated and averaged across trials by using Signal 5 software (Cambridge Electronic Design, Cambridge, UK).

Experimental procedures

All the subjects participated in a single experimental session in which they were seated in front of a computer screen (15-inch, distance 70 cm) and were instructed to relax, keep their hands still and look at a fixation point (black cross) displayed at the centre of the monitor. Visual cues generated through dedicated software (E-Prime 2 Professional, Inc. Pittsburgh, PA, USA) consisted in four different linguistic and non-linguistic tasks: 1) in the "reading aloud" task, subjects were instructed to read single words aloud (high-frequency, two-syllable Italian nouns, e.g. "casa") as soon as they appeared at the centre of the computer screen; 2) in the "silent reading" task, they were required to read a similar set of words in silence; 3) in the "syllabic phonation" task, subjects had to overtly articulate the sequence "ba/ba/ba" as soon as a black circle appeared on the screen; 4) the only non-linguistic task consisted in passively viewing a set of abstract meaningless figures consisting of non-letter strings that matched the letters of the words in font size but did not resemble them in shape ("non-letter string" task) (Fig. 1). During the linguistic tasks, subjects were instructed to produce a constant voice intensity (80–90 dB) that was tested by means of a sound meter. M1 excitability was assessed during both linguistic and non-linguistic tasks by delivering single TMS pulses to the dominant and non-dominant M1 600 ms after the onset of a visual stimulus (word, non-letter string figure or black circle) [15,17–19]. Twelve MEPs were recorded at baseline from each FDI muscle and then during each task. The order in which the tasks were evaluated and of the dominant and non-dominant M1 stimulation was randomized and counterbalanced across subjects. A subgroup of 10 FTD patients (6 with nfv-PPA and 4 with Bv-FTD) also underwent a control experiment in which 12 MEPs were recorded both at rest and during 20% maximum contraction of the FDI muscle.

MRI acquisition and analysis

Participants underwent MRI scan with a 3 T magnet (Verio, Siemens AG, Germany), equipped with a 12-channel head coil designed for parallel imaging. The MRI protocol included DTI and a T1weighted (w)-3D sequence according to standardized procedures (for methodological details see Supplementary Material 2). On the basis of the JHU White-Matter Tractography Atlas [34,35] we extracted mean FA values within specific language-related tracts: temporal part of the superior longitudinal fasciculus (SLF-t), inferior longitudinal fasciculus (ILF) and uncinate fasciculus (UnF), on the left and right side. Concerning GM analysis, we selected, as regions of interest, two specific speech-related cortical areas, i.e. the left frontal and parietal opercula, and a control area, i.e. the left precentral gyrus from the Harvard-Oxford Cortical Atlas in MNI brain space. GM masks were thresholded to minimize overlap with nearby cortical areas and mean local GM densities were estimated (for methodological details see Supplementary Material 1).

Statistical analysis

Possible differences in age and gender between HS and FTD patients, as well as between nfv-PPA and bv-FTD patients, were evaluated by using the Mann-Whitney *U* test and the Fisher-exact test, respectively. The Mann-Whitney *U* test was also used to compare clinical and neuropsychological measures (i.e. disease duration, MMSE, FAB, CDR-FTD, VPF and VSF scores, TMT subtypes A and B) in nfv-PPA and bv-FTD patients.

The statistical analysis of the neurophysiological data was performed by using the unpaired Student t-test to compare RMTs, MT_{1mV} and the baseline MEP amplitude for each hemisphere in

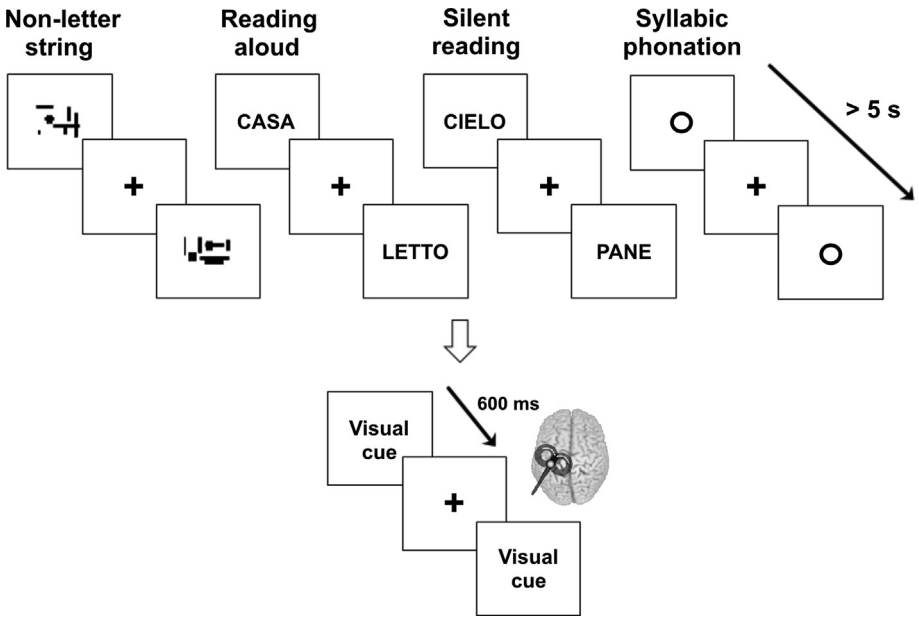

Fig. 1. Neurophysiological TMS paradigm.
Experimental design: four different 'linguistic' ('reading aloud', 'silent reading', 'syllabic phonation') and 'non-linguistic' ('non-letter strings') tasks randomly presented with an inter-trial interval of at least 5 s. During the inter-trial interval, subjects were instructed to look at a fixation point (small cross) placed exactly at the centre of the computer screen. Single TMS pulses were applied to the primary motor cortex over the dominant and non-dominant hemisphere 600 ms after visual cue onset. Twelve motor evoked potentials were recorded for each condition during the 'linguistic' and 'non-linguistic' tasks.

patients with FTD and HS. A repeated measures ANOVA (rmANOVA), with 'task' (5 levels: baseline, reading aloud, silent reading, non-letter strings, syllabic phonation) and 'hemisphere' (2 levels: dominant and non-dominant hemisphere) as within-subject factors, was used to test differences in MEP amplitude in the HS group. To evaluate neurophysiological differences between HS and FTD patients, we normalized the MEP amplitudes to their corresponding baseline value. We then conducted a rmANOVA with the between-subject factor 'group' (2 levels: HS and FTD) and the within-subject factors 'task' (4 levels: reading aloud, silent reading, non-letter strings, syllabic phonation) and 'hemisphere'. We used an unpaired *t*-test to determine whether changes in the MEPs observed during the reading aloud task differed in the two clinical variants of FTD (i.e. nfv-PPA and bv-FTD). The same test was used to evaluate neurophysiological differences in the reading aloud task between FTD patients with and without Parkinsonism, and in patients who were being chronically treated or were not being treated with memantine. A rmANOVA with 'experiment' (2 levels: main experiment and control experiment) and 'condition' (2 levels: baseline and task) as factors was used to detect any differences between MEP amplitude changes during the FDI 20% maximum contraction task and during the reading aloud task. Greenhouse-Geisser corrections were applied when a violation of sphericity in Mauchly's tests was detected. Post-hoc comparisons were performed by means of paired t-tests when significant interactions in the rmANOVAs occurred. The level of significance was initially set at $p < 0.05$, with Bonferroni's correction subsequently being applied to multiple comparisons.

In order to detect possible differences in mean FA values between HS and FTD patients as well as between nfv-PPA and bv-FTD, neuroimaging data were analysed by using the tool "Randomise" of FSL and a general linear model (GLM). Voxel-wise non-parametric (permutation-based) two-group comparison test was applied. Another GLM tool was used to examine possible correlations between FA values and neurophysiological measures and constrained analysis within the abovementioned regions of interest. We used the threshold-free cluster enhancement method for clustering [36], both with and without correction for multiple comparisons through Family-wise Error (FWE) at $p < 0.05$. Mean FA values from the left and right-sided SLF-t, ILF and UnF were compared using an unpaired FTD-HS group *t*-test. Multiple comparisons were used for this purpose ($p < 0.05$, False Discovery Rate).

We used Spearman's rank-correlation to examine the possible pathophysiological link between clinical, neurophysiological, and neuroimaging measures.

Unless otherwise stated, all the values are presented as mean ± SD. Statistical analyses were all performed using SPSS Statistics for Windows (version 20.0.0; IBM).

Results

Three patients with nfv-PPA were excluded from the study because they were unable to complete the linguistic task owing to severe aphasia. A total of 21 patients (12 M, mean age±SD: 70 ± 6.8), 12 with nfv-PPA (7 M, mean age±SD: 71 ± 6.9) and 9 with bv-FTD (5 M, mean age±SD: 69 ± 7.3) completed the study successfully. There were no differences in either age ($p = 0.2$) or gender distribution ($p = 0.59$) between FTD patients and HS or between nfv-PPA and bv-FTD patients (age: $p = 0.55$; gender: $p = 0.62$). Patients with nfv-PPA and bv-FTD also had comparable disease duration, MMSE, FAB, CDR-FTD, and TMT subtypes A and B (all p values < 0.05), whereas the two variants differed in terms of VPF and VSF scores, being lower in nfv-PPA than bv-FTD ($p = 0.002$ and $p < 0.001$). Seven FTD patients (6 nfv-PPA; 7 M, mean age±SD: 68 ± 8.3) manifested Parkinsonism (MDS-UPDRS≥1) whereas the remaining 14 (6 nfv-PPA; 6 M, mean age±SD: 70 ± 8.0) did not (MDS-UPDRS = 0). Clinical-neuropsychological characteristics of FTD patients are summarized in Table 1.

Neurophysiological measures in FTD

RMTs, MT_{1mV} and baseline MEP amplitudes in both hemispheres were comparable in FTD patients and HS (all p values > 0.05), as well as in FTD patients who were being chronically treated and those not being treated with memantine (all p values > 0.05).

When we compared HS and the whole group of FTD patients, the rmANOVA revealed a significant 'Group'x'Hemisphere'x'Task' interaction ($F_{3,111} = 2.80$; $p = 0.04$). Follow-up rmANOVAs demonstrated a significant 'Group'x'Task' interaction for the dominant hemisphere ($F_{3,111} = 4.34$, $p = 0.006$), while no interaction was detected for the non-dominant hemisphere ($F_{3,111} = 0.69$, $p = 0.55$). In particular, the reading aloud task produced MEP facilitation in the dominant hemisphere in HS but not in FTD patients ($p = 0.013$). Conversely, MEPs were similar in HS and FTD patients in the silent reading ($p = 0.71$), non-letter strings ($p = 0.25$) and syllabic phonation ($p = 0.99$) tasks (Fig. 2A, Fig. 2B). No significant effect of the main factor 'Group' emerged ($F_{1,37} = 0.83$, $p = 0.37$).

The unpaired *t*-test did not disclose any significant differences in MEP amplitudes during the reading aloud task between nfv-PPA and bv-FTD patients ($p = 0.2$) (Fig. 2C). Changes in MEPs induced by this specific task were also comparable in patients with and those without Parkinsonism ($p = 0.81$) (Fig. 2C) as well as in patients who were being chronically treated and those not being treated with memantine ($p = 0.44$).

The rmANOVA conducted on data acquired in our control experiment, in which we tested possible differences between MEP amplitude changes during the FDI 20% maximum contraction task and during the reading aloud task, demonstrated a significant 'Experiment'x'Condition' interaction ($F_{1,9} = 16.07$, $p < 0.001$). The post-hoc analysis yielded comparable baseline MEPs in these two experiments ($p = 0.99$) and a similar MEP amplitude between the baseline recording and the reading aloud task in the main experiment ($p = 0.99$). By contrast, MEPs increased during FDI contraction if compared both with the baseline recorded in the control experiment ($p = 0.001$) and with the reading aloud task ($p = 0.003$).

Neuroimaging measures in FTD

DTI analysis showed decreased FA values in FTD patients with respect to HS in most WM tracts (Fig. 3A). Concerning the WM tracts under examination, significant FA differences between HS and FTD patients are shown in Fig. 3A and Table 2. By contrast, when comparing the two FTD clinical variants (bv-FTD and nfv-PPA), the FA values were comparable in all the WM tracts considered in the dominant and in the non-dominant hemisphere (Table 2).

The volumetric analysis showed significant lower GM density in the left frontal operculum ($p = 0.01$) in patients than HS (Fig. 3B), whereas the left parietal operculum ($p = 0.24$) and the left precentral gyrus ($p = 0.07$) GM density was within normal ranges (Table 3). Finally, the degree of GM changes in the left frontal operculum was similar between nfv-PPA and bv-FTD ($p = 0.28$) (Table 3).

Spearman's rank-correlation test disclosed a significant correlation between the degree of GM loss in the left frontal operculum and scores in the VPF ($R = 0.65$; $p = 0.01$) and VSF ($R = 0.47$; $p = 0.05$) tests (Fig. 4). Voxel-wise analysis confirmed two clusters of significant correlation between the VPF test scores and GM density in the frontal operculum ($p < 0.05$) (Fig. 3B). Conversely, no

Table 1
Demographic and clinical features of patients with FTD.

N°	Gender	Age	Disease duration (years)	FTD subtype	CDR-FTD	MMSE	FAB	TMT A (sec)	TMT B (sec)	VPF	VSF	MDS-UPDRS-III
1	F	68	3	nfv-PPA	6.5	25	13.2	96	166	0	14	0
2	M	81	10	nfv-PPA	5	26	11.5	132	221	15	23	35
3	M	65	4	bv-FTD	8	21	11.5	125	230	19	25	0
4	F	72	2	bv-FTD	6.5	21	10.2	122	209	22	36	0
5	F	74	7	nfv-PPA	11	20	11	99	140	4	11	14
6	M	81	2	bv-FTD	11	13	9.5	141	300	14	29	0
7	M	69	8	nfv-PPA	6.5	25	13	44	79	11	5	0
8	M	76	3	nfv-PPA	7	27	10.9	131	189	13	13	20
9	M	73	9	nfv-PPA	8.5	22	11.4	151	176	9	3	0
10	F	68	8	bv-FTD	5.5	28	16.5	111	130	31	31	0
11	M	57	3	nfv-PPA	5	21	13.2	30	64	2	7	0
12	M	69	2	nfv-PPA	4	29	11.5	122	–	16	31	0
13	M	79	6	nfv-PPA	7	17	11.7	144	–	0	16	7
14	F	72	1	nfv-PPA	6.5	17	8.2	204	300	0	20	0
15	F	75	2	nfv-PPA	7.5	20	7	–	–	8	7	21
16	M	74	2	bv-FTD	9	15	9.5	–	–	14	23	0
17	M	71	2	bv-FTD	9	17	16.7	121	300	19	25	0
18	F	61	2	nfv-PPA	11	13	9	320	–	5	8	8
19	F	65	2	bv-FTD	5.5	20	11	250	–	6	19	0
20	M	56	2	bv-FTD	6.5	20	12.2	44	122	23	36	0
21	F	76	2	bv-FTD	7	25	7.2	–	300	8	23	8
Avg.		70.5	3.95		7.3	21.5	10.7	132.6	195.0	11.84	19.94	5.38
SD		6.96	2.78		2.0	5.06	2.38	70.34	80.34	8.77	10.33	9.57

Demographic and clinical features of our cohort of 21 patients with FTD (bv-FTD and nfv-PPA). CDR-FTD: Clinical Dementia Rating scale & Frontotemporal dementia; MMSE: Mini-Mental State Examination; FAB: Frontal Assessment Battery; VPF: Verbal Phonemic Fluency test; VSF: Verbal Semantic Fluency test; MDS-UPDRS-III: Movement Disorder Society Unified Parkinson's Disease Rating Scale, part III; "-": the patient was not able to complete the test.

correlations emerged between DTI data and clinical neuropsychological scores (all p values > 0.05). Moreover we found no correlation between neuroimaging measures and MEP amplitudes during the reading aloud task (all p values > 0.05). Furthermore, there were no significant correlations between MEP amplitudes during the reading aloud task and VPF ($R = -0.01$; $p = 0.96$), VSF ($R = -0.05$; $p = 0.83$), FAB ($R = 0.18$; $p = 0.45$), TMT-A ($R = -0.14$; $p = 0.58$) and TMT-B scores ($R = -0.07$; $p = 0.77$). Lastly, changes in MEP amplitudes during the reading aloud task did not correlate with either the disease duration ($R = 0.04$; $p = 0.86$) or with the CDR-FTD score ($R = -0.06$; $p = 0.8$).

Discussion

In this study, the reading aloud task increased MEPs in HS but failed to do so in FTD patients. Abnormalities in the linguistic task were comparable in patients with nfv-PPA and bv-FTD. Moreover, abnormal responses were similar in patients with and without Parkinsonism. DTI revealed lower mean FA values in FTD than in HS in the superior longitudinal fasciculus, inferior longitudinal fasciculus and uncinate fasciculus. Moreover, VBM analysis disclosed lower GM volumes in the left frontal operculum, though not in the precentral gyrus and in the parietal operculum in patients than in HS. The extent of both WM and GM changes was comparable in patients with nfv-PPA and bv-FTD. Lastly, a correlation was detected only between the extent of GM loss in the left frontal operculum and the severity of language dysfunction in FTD.

Accuracy in the clinical diagnosis of FTD and its variants was achieved by means of the most recent standardized clinical criteria [1,23]. Furthermore, brain MRI and FDG-PET supported the clinical diagnosis in our patients by revealing the fronto-temporal pattern of atrophy and hypometabolism that is typical of nfv-PPA and bv-

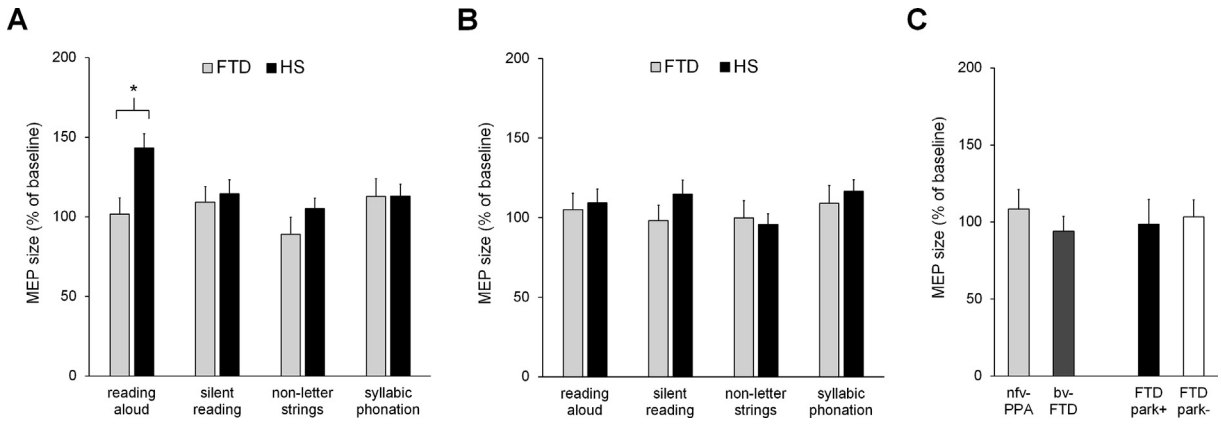

Fig. 2. Primary motor cortex excitability changes during linguistic and non-linguistic tasks.
Motor evoked potential (MEP) amplitude changes after single-pulse TMS delivered over the dominant (**A**) and non-dominant (**B**) hemisphere during linguistic ('reading aloud', 'silent reading', 'syllabic phonation') and non-linguistic ('non-letter strings') tasks in our cohort of frontotemporal dementia (FTD) patients and healthy subjects (HS); **C.** MEP amplitude changes after single-pulse TMS delivered over the dominant hemisphere during the reading aloud task in the non-fluent variant of Primary Progressive Aphasia (nfv-PPA) and the behavioral variant of FTD (bv-FTD), and in patients with (park+) and without (park-) Parkinsonism. Values are expressed as a percentage of the baseline condition. Each column corresponds to the mean MEP amplitude. Vertical bars denote standard error of means. Asterisks indicate significant P values.

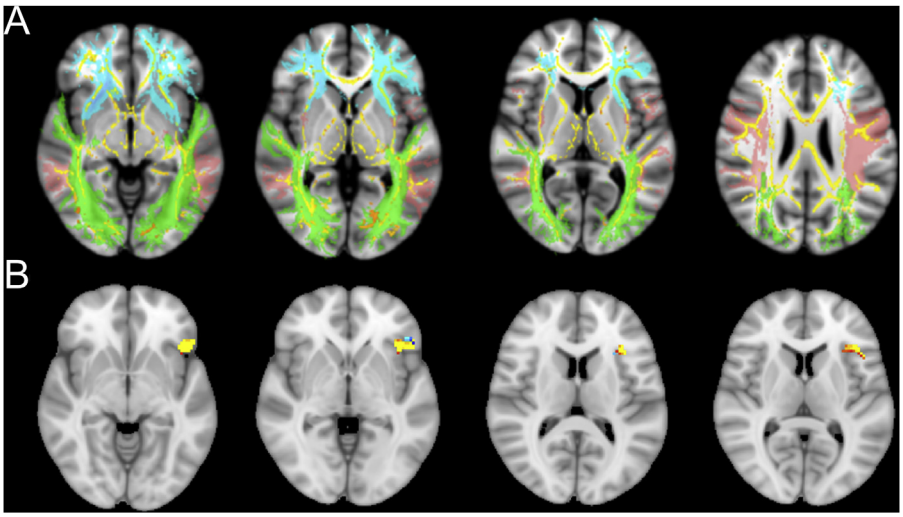

Fig. 3. DTI and VBM analysis. A.
Tract-Based Spatial Statistics (TBSS) results. Reduced FA values (red-yellow dots) in patients with FTD compared to healthy subjects, overlapped with standard MNI T1 brain images ($p < 0.05$, threshold-free cluster enhancement corrected). In the same figure the three WM tracts of interest are represented in different colours: temporal part of the superior longitudinal fasciculus (SLF-t) in pink, inferior longitudinal fasciculus (ILF) in green, and uncinate fasciculus (UnF) in light blue, both on the left and right side. Images are shown according to radiological convention. **B.** FSL-VBM results. Reduced GM density (red-yellow dots) in patients with FTD compared to healthy subjects, overlapped with standard MNI T1 brain images. Voxelwise analysis confirmed two clusters of significant correlation between the VPF and GM density ($p < 0.05$) (represented in blue colour). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

FTD [1,23,24]. As no age or gender differences were observed either between HS and patients or between the nfv-PPA and bv-FTD subgroups, and all the participants were right-handed, any effects of age, gender or manual dominance-related hemispheric asymmetry on the TMS and imaging findings can be ruled out [13]. The two variants differed in terms of VPF and VSF scores, with both lower in nfv-PPA than bv-FTD, indicating prominent language impairment in nfv-PPA. All the patients included in the study were able to complete the linguistic task successfully, hence our findings cannot be ascribed to incorrect or incomplete word production related to the specific experimental design. Moreover, the linguistic and non-linguistic tasks were randomly presented and the voice intensity was kept constant during the experiments. The words used for the linguistic task were not represented by action verbs or manipulable objects, thus excluding a possible modulation of M1 excitability by the processing of language material expressing a motor content [37–39]. Lastly, the similar RMTs, MT_{1mV}, baseline MEP amplitudes and MEP changes during the reading aloud task in patients treated or not treated with the N-methyl-D-aspartate antagonist memantine allowed us to exclude any effect of this drug on our results.

Neurophysiological abnormalities in FTD

The main finding of the study is that when TMS was delivered over the dominant hemisphere, the reading aloud task did not facilitate MEPs in patients with FTD but did in HS. One possible explanation is that this abnormality merely reflects intrinsic changes in M1. This hypothesis is, however, unlikely for several reasons: first, none of the patients studied exhibited clinical or electrophysiological signs of corticospinal damage; second, patients and controls had comparable RMTs, MT_{1mV} and baseline MEPs, which suggests that the baseline neurophysiological measures in our FTD patients were normal; third, the volumetric analysis revealed that the GM volumes in the left precentral gyrus were comparable in both patients and HS, which points to the structural integrity of M1. Another possible explanation besides the structural damage of M1 is that the lack of MEP facilitation during the reading aloud task in FTD reflects a global and unspecific impairment in the physiological mechanisms responsible for MEP facilitation. However, we found that MEP facilitation during a simple motor task (mild muscle contraction) [40] was normal in FTD. In a previous study conducted on FTD patients, we

Table 2
Fractional anisotropy values from DTI analysis in FTD patients and HS.

	HS vs FTD					nfv-PPA vs bv-FTD				
	HS		FTD			nfv-PPA		bv-FTD		
	mean	SD	mean	SD	*p*	mean	SD	mean	SD	*p*
Dominant hemisphere										
ILF	0.0849	0.0039	0.0756	0.0074	0.001	0.0755	0.0087	0.0758	0.0062	0.47
SLF-t	0.0889	0.0039	0.0783	0.0078	<0.001	0.0783	0.0090	0.0783	0.0070	0.50
UnF	0.0938	0.0054	0.0820	0.0108	0.002	0.0828	0.0112	0.0811	0.0113	0.40
Non-dominant hemisphere										
ILF	0.0943	0.0043	0.0844	0.0070	<0.001	0.0847	0.0086	0.0839	0.0053	0.42
SLF-t	0.0889	0.0035	0.0785	0.0062	<0.001	0.0799	0.0072	0.0769	0.0050	0.20
UnF	0.1020	0.0059	0.0894	0.0088	<0.001	0.0910	0.0095	0.0876	0.0085	0.25

Fractional Anisotropy (FA) values in selected regions of interest (ROIs) - SLF-temporal part (SLF-t), Inferior Longitudinal fasciculus (ILF) and Uncinate Fasciculus (UnF), both left- and right-sided – in our cohort of FTD patients and HS. Values are expressed as mean FA values and standard deviation.

Table 3
Gray matter volumetric analysis in FTD patients and HS.

	HS vs FTD					nfv-PPA vs bv-FTD				
	HS		FTD			nfv-PPA		bv-FTD		
	mean	SD	mean	SD	*p*	mean	SD	mean	SD	*p*
Left frontal operculum	0.5097	0.0559	0.4329	0.0972	0.01	0.4174	0.0918	0.4509	0.1088	0.28
Left parietal operculum	0.4941	0.1019	0.4633	0.1123	0.24	0.4911	0.1199	0.4309	0.1032	0.18
Left precentral gyrus	0.3783	0.0470	0.3475	0.0517	0.07	0.3298	0.0605	0.3681	0.0328	0.10

Grey matter (GM) mean densities in selected regions (left frontal operculum, left parietal operculum and left precentral gyrus) in our cohort of FTD patients and HS. Values are expressed as mean and standard deviation.

demonstrated that Parkinsonism may lead to changes in a number of TMS parameters that probe M1 facilitation [21,22]. However, the similarities in the neurophysiological abnormalities between patients with and those without Parkinsonism allowed us to exclude that this clinical syndrome affects responses to the linguistic task. Hence, we conclude that in FTD, the lack of MEP facilitation during the reading aloud task could reflect abnormal activation of expressive language areas, including M1, in the speech-related cortical network.

Another novel finding that emerges from this study is that responses to TMS during the linguistic task were comparable in patients with bv-FTD and nfv-PPA. The observation that the linguistic task failed to induce MEP facilitation in patients with bv-FTD and nfv-PPA points to abnormal speech-related cortical network activation in FTD, independently from the specific clinical variant. We also found a lack of correlation between neurophysiological abnormalities and the severity of language dysfunction, as assessed by the verbal phonemic and semantic fluency tests, in FTD.

Neuroimaging abnormalities in FTD

DTI analysis demonstrated structural damage in language-related WM bundles, highlighted by the reduced FA values in the SLF-t, ILF and UnF, in both hemispheres. No correlation resulted between DTI measures, the clinical evaluation of language dysfunction severity, and M1 excitability changes in FTD. DTI also revealed that the extent of damage in all the WM bundles involved in the speech-related network was similar in bv-FTD and nfv-PPA patients. Our findings are fully in line with previous neuroimaging studies which reported severe WM damage in FTD, regardless of the specific clinical variant [4–9]. Interestingly, WM abnormalities have been also described in the pre-symptomatic stage of FTD, as shown in microtubule-associated protein tau, C9ORF72 and progranulin gene mutation carriers [41–43] a finding which strongly supports the early pathophysiological involvement of WM changes in FTD.

In addition to the DTI findings, VBM analysis demonstrated significant GM loss localized in the left frontal operculum [44–46] but not in the left parietal operculum and precentral gyrus, in patients with FTD. Furthermore, VBM demonstrated similar abnormalities (comparable GM loss in the left frontal operculum) in bv-FTD and nfv-PPA patients. Previous studies have demonstrated prominent GM loss in paralimbic areas and insula in bv-FTD [24,47], whereas nfv-PPA is characterized by GM atrophy in the left fronto-insular cortex [24,44,45]. However, our results are in line with studies directly comparing GM in bv-FTD and nfv-PPA and demonstrating similar amount of GM atrophy in frontal operculum in the two clinical variants [4,6]. Our findings therefore suggest that GM atrophy in the left frontal operculum combined with widespread changes in language-related WM bundles are shared pathophysiological features in bv-FTD and nfv-PPA patients.

Overall our neuroimaging findings may raise the hypothesis that WM changes and GM loss in the frontal operculum do not play a role in the pathophysiology of language dysfunction in patients with FTD. However, in the whole group of patients with FTD, we found that the degree of GM atrophy in the left frontal operculum correlated significantly with verbal phonemic and semantic fluency tests. Indeed, some of our bv-FTD patients showed reduced scores

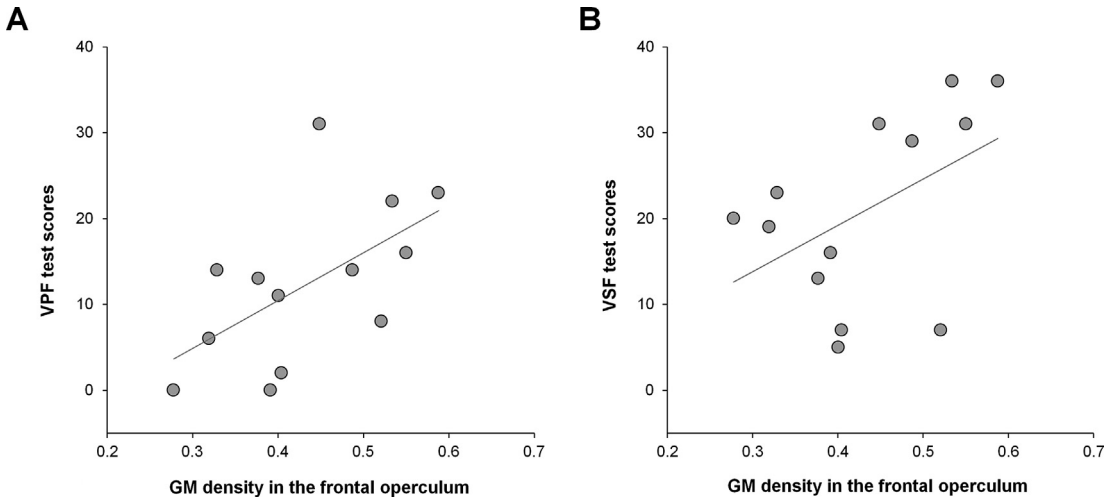

Fig. 4. Clinico-neuroradiological correlations.
Correlation between verbal phonemic fluency (VPF – left panel) and verbal semantic fluency (VSF – right panel) test scores, and the degree of GM loss in the left frontal operculum in FTD patients.

in the verbal phonemic and semantic fluency tests, which is consistent with the progressive language deterioration often observed in bv-FTD during the course of the disease [47–50]. We therefore speculate that the degree of GM atrophy in the frontal operculum likely contributes to the pathophysiology of language dysfunction in our cohort of patients.

In this study in FTD, we found no significant correlation among structural neuroimaging data and neurophysiological measures, possibly due to different factors. WM and GM changes in cortical regions other than those here examined would have possibly contributed to the neurophysiological abnormalities we observed in the present study. Also, our neurophysiological and neuroimaging measures would differ in terms of sensitivity in discriminating functional connectivity changes in frontal regions in FTD.

Our study has certain limitations that should be considered. The sample size we tested was relatively small, in part owing to the low prevalence of this rare disease. In addition, although we applied the most recent clinical radiological criteria for the diagnosis of FTD and its variants [1,23], our study did not include a diagnostic confirmation of the specific neurodegenerative FTD pathology by means of bio-humoral markers or a post-mortem examination. Regarding the neuropsychological evaluation, we did not use specific tests to evaluate agrammatism nor behavioural tasks to differentiate patients with nfv-PPA and bv-FTD. Concerning the experimental paradigm, our linguistic task implying a non-invasive TMS approach only allowed an indirect assessment of functional connectivity among frontal regions responsible for expressive language functions. Since we focused the neuroimaging analysis on specific WM bundles and cortical areas, we cannot exclude the possibility that other WM tracts or cortical regions also contributed to the language dysfunction in our cohort of patients with FTD.

Conclusion

The results of the present study provide converging neurophysiological and neuroimaging evidence of abnormal speech-related cortical network activation in patients with FTD. The functional alterations in the linguistic task, as documented by TMS point to a disconnection in the speech-related cortical network in FTD patients, regardless of the clinical variant. Our structural neuroimaging study also disclosed WM and GM alterations in brain regions included in the speech-related cortical network which are shared by the two clinical variants of FTD. Hence, differently from what we expected, the two clinical variants did not differ in terms of neurophysiological or neuroimaging measures. However, although there was no correlation between these measures, VBM analysis disclosed a significant correlation between GM loss in the frontal operculum and language impairment severity in the whole group of FTD. We suggest that the functional and structural disconnection in the speech-related cortical network we demonstrated with neurophysiological and neuroimaging techniques reflects an abnormal neurobiological substrate of FTD. On the other hand, cortical atrophy in the frontal operculum plays the major role in the pathophysiology of language dysfunction in FTD. Future studies on patients with different stages of the disease and on mutation carriers may clarify whether functional and structural abnormalities occur with different timing during the course of the disease, and whether combined TMS, VBM, and DTI measures represent useful biomarkers in FTD.

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Author contribution section

Antonio Suppa: Conceptualization, Methodology, Writing-Original draft **Andrea Fabbrini:** Conceptualization, Methodology, Writing-Original draft **Andrea Guerra:** Methodology, Investigation, Formal analysis **Nikolaos Petsas:** Methodology, Investigation, Formal analysis **Francesco Asci:** Methodology, Investigation **Flavio Di Stasio:** Methodology, Investigation **Alessandro Trebbastoni:** Formal analysis, Investigation **Federica Vasselli:** Formal analysis, Investigation **Carlo De Lena:** Writing – Review & Editing, Supervision **Patrizia Pantano:** Writing – Review & Editing, Supervision **Alfredo Berardelli:** Writing – Review & Editing, Supervision.

Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2020.02.029.

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