Nature versus Nurture in Frontotemporal Lobar Degeneration: the Interaction of Genetic Background and Education on Brain Damage

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Key Words

Frontotemporal dementia • Cognitive reserve • Genetic loading • SPECT • Statistical parametric mapping

Abstract

Background: Frontotemporal lobar degeneration (FTLD) is a progressive neurodegenerative disorder with a strong genetic background. It has been reported that modifiable factors, i.e. education (E), might act as proxies for reserve capacity. **Objective:** To evaluate the impact of genetic background (positive family history, FH) on reserve mechanisms, by measuring regional cerebral blood flow (rCBF) correlates in FTLD patients. **Methods:** 145 FTLD patients were recruited and underwent clinical, neuropsychological, behavioral assessment, and SPECT study. The main effect of E and FH on rCBF was evaluated. To test the potential interaction between the E and rCBF in FTLD patients with or without positive FH, a difference of slope analysis in the two groups was calculated. All the analyses were controlled for disease severity (Clinical Dementia Rating Scale, FTD-CDR). **Results:** A main effect of education (E+<E-) in frontal regions was reported, and high genetic loading (FH+<FH-) was associ-

ated with a greater bilateral temporoparietal hypoperfusion. Evaluating the relationship between E and rCBF, a greater hypoperfusion of cingulate region in FH+ as compared to FH- was observed. **Discussion:** Reserve mechanisms are available also in presence of an unfavorable genetic status. However, these compensatory mechanisms are modulated by the interaction with genetic factors.

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Introduction

Frontotemporal lobar degeneration (FTLD) is a progressive neurodegenerative disorder characteristically defined by behavioural changes, executive dysfunction and language deficits [1, 2]. FTLD has a strong genetic background, as supported by positive family history in up to 40% of cases, higher than what reported in other neurodegenerative disorders and by the identification of causative genes related to the disease [3]. It has been suggested that genetic background might affect disease outcomes and rate of survival [4–8], modulating the onset

and the progression of the pathological process when disease is overt.

Given the consolidated role of genetic loading in FTLT, the likely effect of environment has almost been neglected. Only recently, it has been reported that modifiable factors, i.e. education and occupation, might act as proxies for reserve capacity in FTLT. Patients with a high level of education and occupation can recruit an alternative neural network to cope better with cognitive functions [9–11].

This evidence suggests that both nonmodifiable and modifiable factors work and might interact in affecting disease aggressiveness and brain damage. Assessing their role is mandatory for a devastating condition still orphan of any evidence-based therapeutical intervention.

With these caveats in mind, in the present study we tested the influence of FTLT modifiable factors, i.e. educational attainment, and how these might be counteracted by the underneath unmodifiable genetic background, as measured by positive family history. Regional blood flow (rCBF) was used as in vivo proxy of FTLT pathological process, and the effect of each factor, separately, as well as their interaction, were evaluated.

Methods

Subjects

Patients fulfilling current clinical criteria for FTLT (bvFTD, PNFA, SD) [1, 12, 13] were evaluated at the Centre for Aging Brain and Neurodegenerative Disorders, University of Brescia, Italy. To be eligible for the present study, FTLT patients had to undergo single-photon emission computed tomography (SPECT) imaging (all the SPECT done on the same scanner).

Each patient underwent clinical evaluation, a routine laboratory examination (including genetic screening for *Microtubule Associated Protein Tau* and *Granulin* mutations), and a brain structural imaging study. An extensive cognitive assessment according to a standardized battery was accomplished, as already reported [14]. The disease status was considered according to the Frontotemporal Dementia-modified Clinical Dementia Rating scale (FTD-modified CDR) [15].

Demographic characteristics, including years of schooling and medical family history, were carefully recorded. Years of schooling were defined as the number of completed years of formal education, including university; apprenticeship was considered only when associated to formal education. Patients with a positive family history as index of a genetic loading were those who had at least a first-degree relative with a documented diagnosis of dementia, parkinsonism, or motor neuron disease.

Stringent exclusion criteria were applied as follows: (a) cerebrovascular disorders, previous stroke, hydrocephalus, and intracranial mass documented by MRI; (b) a history of trau-

matic brain injury or another neurological disease; (c) significant medical problems; (d) major depressive disorder, bipolar disorder, schizophrenia, substance abuse disorder, or mental retardation according to criteria of the DSM-IV; (e) lacking of demographic information.

The work was conformed to the Helsinki Declaration and was approved by the local Ethic Committee of Brescia Hospital, Italy.

^{99m}Tc-ECD SPECT Acquisition Image Pre-Processing and Analysis

FTLT patients were administered an intravenous injection of 1,110 MBq ^{99m}Tc-ECD (ethylcysteinate dimer, Neurolite, Bristol-Myers Squibb Pharma) with closed eyes in a rest condition, lying supine in a quiet, dimlylit room. All individuals were imaged using a dual-head rotating gamma camera (VG MILLENIUM GE) fitted with a low energy, high-resolution collimator, 30 min after intravenous injection of ^{99m}Tc-ECD. A 128 × 128 pixel matrix was used for image acquisition with 120 views over a 360° orbit (in 3° step) with a pixel size and slice thickness of 1 mm, in 27 min or more if total counts were lower than 5 × 10⁶. Image reconstruction was performed by a ramp filtered-back projection and three-dimensionally smoothed with a Metz filter (order 3, enhancement 1.24, FWHM 6.7 mm, cut-off 0.61 cycles cm⁻¹). The reconstructed images were corrected for gamma ray attenuation using the Chang method (attenuation coefficient: 0.11 cm⁻¹).

Statistical Parametric Mapping (SPM8, Wellcome Department of Cognitive Neurology, University College, London, UK), and Matlab 7.6 (Mathworks Inc., Sherborn, Mass., USA) were used for image pre-processing. Images were spatially normalized to a reference stereotactic template (Montreal Neurological Institute, MNI), and smoothed by a Gaussian kernel of 8 × 8 × 8 mm FWHM. In all the analyses, dementia severity (as measured by FTD-modified CDR) was included as covariate.

Statistical Analysis

Patients were grouped according to years of schooling (E), considering a cut-off of 5 years [16] (high education, E+; low education, E-), and family history (FH) (negative family history, FH-; positive family history, FH+). The main effect of E and FH was evaluated ($p < 0.005$, extension threshold set at 30 contiguous voxels).

Brain areas related to cognitive reserve (namely medial frontal gyri, left superior and inferior frontal gyrus, left cingulate gyrus) were used to build up an a priori mask (Talairach Demon Database (WFU PickAtlas 3.0) [17, 18]) to test the interaction of genetic loading on cognitive reserve. The residual main effect of E on rCBF after adjusting for FH was tested. Furthermore, analysis of covariance to test a possible additive effect of E and F was performed.

In order to test specifically for the relationship between E and rCBF in patients with and without FH, we included all subjects' scans in the same design matrix, and tested for difference in the correlation coefficient value (slope) in the two groups [19]. For this latter analysis, in order to increase the sensitivity, findings meeting a threshold of $p < 0.05$, uncorrected for mul-

Table 1. Results of the main effect of education and family history on rCBF in FTLT patients

	x	-y	-z	T	p	Cluster size
<i>Education</i>						
R medial frontal gyrus	26	38	20	3.72	<0.001	505
L superior frontal gyrus	-22	54	6	3.36	0.001	159
L inferior frontal gyrus	-32	32	14	3.22	0.001	134
L medial frontal gyrus	-2	40	40	3.06	0.001	132
L cingulate gyrus	0	6	38	2.82	0.003	38
<i>Family history</i>						
L cingulate gyrus	-18	-54	26	4.34	<0.001	422
L parahippocampal gyrus	-16	-30	-14	4.26	<0.001	250
R precuneus	18	-58	30	3.44	<0.001	238
L inferior parietal lobule	-48	-26	26	3.17	0.001	115
R cingulate gyrus	16	-10	42	3.04	0.001	73

Talairach coordinates of significant voxels, at $p < 0.005$ uncorrected. Threshold value = 30 voxels. R = Right hemisphere; L = left hemisphere.

multiple comparisons, was considered significant. The extension threshold was set at 30 contiguous voxels.

Results

One hundred and forty-five FTLT patients (103 bvFTD, 31 PNFA, 11 SD) were considered in the present study. The mean age of the FTLT group was 65.2 years, 50.3% of the patients were female, the mean years of schooling was 7.6 years, and 44.1% of patients had a positive FH, herein considered as a marker of genetic loading. Thirteen patients carrying *Granulin* mutations were identified (5 bvFTD and 8 PNFA); all these cases had positive FH, and they were significantly younger compared to the rest of the patients (58.9 ± 5.3 vs. 65.8 ± 7.6 , $p < 0.001$).

The mean educational level was 7.4 ± 3.5 (range 3–21 years) in the FH– group and 7.9 ± 3.7 (range 4–19 years) in FH+ group ($p = 0.40$). In E-group, 36.5% of patients had a positive FH, whereas in the E+ group 42.3% of patients had a positive family history ($p = 0.50$).

The cerebral perfusion assessment in the whole FTLT group revealed a significant frontotemporal reduction as compared to a group of age-matched controls (data not shown).

The main effect of E was represented by greater hypoperfusion in frontal regions in E+ versus E– group

(table 1; fig. 1a). The inverse relationship did not show any voxel above the pre-established threshold.

Moreover, we tested the effect of E on rCBF in Primary Progressive Aphasia group (PNFA and SD), as this has never been reported. As depicted in figure 1b, the same hypoperfusion pattern was evident, with a major involvement of the dominant hemisphere.

The main effect of FH was represented by a greater bilateral temporo-parietal hypoperfusion in FH+ as compared to FH– (table 1; fig. 1c). The inverse relationship did not show any voxel in frontal-temporal regions at the pre-established threshold.

The main effect of E on rCBF after correction for FH presents only a slight reduction of the dimension of the clusters defined above (data not shown).

The analysis of covariance showed an additive effect of E and FH in right frontal lobe ($x, y, z = +30, +40, +12$, $T = 3.11$, $p < 0.001$) (fig. 2).

Linear regression analysis between rCBF and E between FH– and FH+ subgroups showed a different pattern of hypoperfusion in cognitive reserve regions on the basis of genetic loading, but always involving frontal regions (table 2; fig. 3a). The difference of slope analysis, showed a greater correlation between higher E and lower perfusion in the cingulate region in FH+ as compared to FH– (table 2; fig. 3b). The inverse relationship did not show any voxels in frontal regions at the pre-established threshold.

Discussion

The high incidence of positive family history in FTLT, the relatively young disease onset in most of the cases, and the identification of a number of genes associated with inherited autosomal-dominant disorder have underlined the crucial role played by genetic background in the disease pathogenesis, although a relationship between family history and genetic background cannot be considered as unique. As a consequence, the effect of modifiable disease factors has been largely neglected. In a still orphan disease, identifying possible compensatory mechanisms and establishing whether these are modulated by genetic loading might open new avenues in defining treatment approaches.

It has been widely demonstrated that in other neurodegenerative diseases, including Alzheimer disease (AD), the educational level and the occupation status contribute to cognitive reserve; the higher the environmental attainments the greater the compensative mechanisms to cope

Fig. 1. The main effect of education ($E+<E-$) in all FTL patients (a) and in PPA patients (b), and the main effect of family history ($FH+<FH-$) (c) on rCBF in FTL patients, superimposed on a 3D brain template. $p < 0.005$ uncorrected, threshold = 30 voxels.

Fig. 2. Residual main effect of education ($E+<E-$) in FTL patients after covariation for family history, superimposed on a 3D brain template. $p < 0.005$ uncorrected, threshold = 30 voxels.

Table 2. Results of linear regression analysis between rCBF and education in FH– and FH+ groups, respectively, and the difference of slope between the FH+ and FH– groups

	x	y	z	T	p	Cluster size
<i>FH– group</i>						
L inferior frontal gyrus	–28	2	24	2.77	0.003	225
L inferior frontal gyrus	–32	30	14	3.02	0.002	139
L medial frontal gyrus	28	40	12	1.97	0.025	54
L superior frontal gyrus	–22	50	6	1.96	0.026	55
<i>FH+ group</i>						
L medial frontal gyrus	–22	50	10	2.84	0.003	225
L medial frontal gyrus	–4	36	44	2.55	0.006	223
L cingulate gyrus	–2	2	40	2.53	0.006	277
<i>Difference of slope</i>						
L cingulate gyrus	–2	0	44	2.21	0.014	144

Talairach coordinates of significant voxels, at $p < 0.05$ uncorrected. Threshold value = 30 voxels. R = Right hemisphere; L = left hemisphere.

with disease onset and progression [19–21]. At the same disease stage, AD patients with higher education levels had greater damage in those brain areas typically affected by the disease pathology [22, 23]. A recent study has also shown that the reserve phenomenon might compensate the unfavorable apolipoprotein epsilon 4 allele in AD, the most recognized genetic risk factor [24].

Previous reports showed that the cognitive reserve hypothesis is confirmed in FTLN as well [9, 11]. Accordingly, the present work further confirmed in a larger sample of patients that a greater hypoperfusion in frontal regions is consistently found in high-educated patients, as an index of the compensative mechanisms that work against the pathological process (fig. 1a). Interestingly, a similar pattern of cognitive reserve, but with a left predominance, was evident considering the subgroup of patients with primary progressive aphasia, claiming for the presence of cognitive reserve mechanisms in the whole of the FTLN spectrum (fig. 1b).

If in AD the reserve hypothesis has been almost studied on its own, in FTLN the assessment of the crucial weight determined by genetic background is mandatory

to elucidate the interaction between nature versus nurture in the modulation of disease onset and progression.

In this view, beyond cognitive reserve effect exerted by education, our study revealed a main effect of high genetic loading (represented by positive family history) on temporal and parietal regions (fig. 1c). This is in accordance with literature data that showed a more widespread involvement of grey and white matter structures [25–27] and an extension of damage in parietal and posterior temporal regions in patients with familial disease due to pathogenic mutations, i.e. *Granulin* mutations [28, 29].

More interestingly, the present work evaluated how education and genetic background interact in affecting disease. The presence of a residual cognitive reserve in frontal regions after correction for family history was observed, suggesting that high education can counteract an unfavorable genetic background. Moreover, an additive effect between the two factors in the right frontal lobe was demonstrated, arguing that this region is likely the most vulnerable when this disorder is overt (fig. 2). However, as demonstrated by the analysis of the difference of slope, the presence of genetic background might modulate the distribution of the cognitive reserve, with a greater involvement of the mesial frontal regions, i.e. anterior cingulate cortex, in those patients with higher genetic loading (fig. 3). The anterior cingulate cortex is affected in FTLN [30], and this type of damage has been demonstrated in monogenic forms as well [31, 32]. Indeed, the specific involvement of this high-connected brain structure may argue for a role of genetic background in maintaining cognitive reserve by activating different functional networks and in modulating the efficiency of the recruited neuronal networks [33–35] to obtain the resultant neural compensation.

In conclusion, our findings support the idea that reserve mechanisms may overcome genetic status, representing a potential therapeutic approach for modifying natural disease course.

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Fig. 3. Results of linear regression analysis between rCBF and education in the FH- and FH+ groups, respectively (a); test of the difference of slope between FH+ and FH- groups (left), explicative panel of difference of slope analysis (right) (b), superimposed on a 3D brain template. $p < 0.05$ uncorrected, threshold = 30 voxels.

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