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Note

Social and cognitive control skills in long-life occupation activities modulate the brain reserve in the behavioural variant of frontotemporal dementia

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ABSTRACT

Background: Cognitive reserve may delay disease onset and mitigate symptoms presentation in neurodegenerative dementias. Although high occupation levels can be associated with higher cognitive reserve in the behavioural variant of frontotemporal dementia (bvFTD), it was never addressed how specific occupation profiles involving social interaction, executive and attention abilities can modulate neural reserve in bvFTD.

Materials and methods: We retrospectively included thirty-seven bvFTD patients with clinical-neuropsychological and FDG-PET brain metabolic data. We considered occupation levels according to 1) a 5-point scale and 2) the specific cognitive dimensions from the O*Net network database. We used the Principal Component Analysis (PCA) with the O*Net variables most representative of "worker" and "occupation" socio-cognitive skills to merge the best components describing such occupation profiles. We then performed regression analyses with brain metabolism using either 5-level occupation scale or the PCA specific profiles as independent variables, controlling for education and disease severity.

Results: According to the brain reserve hypothesis, higher occupation levels were associated with a more severe hypometabolism in the dorsolateral prefrontal cortex. In addition, among the identified PCA profiles, social skills were associated with severe hypometabolism in medial and dorsolateral prefrontal regions, and cognitive control in the left fronto-insular cortex.

Discussion: This study contributes to define the role of specific occupation profiles as proxy of cognitive reserve in bvFTD, providing the first evidence for social interaction and

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cognitive control skills in life-occupation activities as influencing factors of neural reserve against neurodegeneration in bvFTD. Jobs placing high demand on such abilities seem to act as protective factors in bvFTD.

1. Introduction

The behavioural variant of frontotemporal dementia (bvFTD) is a progressive neurodegenerative disease characterized by behavioural changes and impairments in the socio-emotional and executive domains (Rascovsky, Hodges, et al., 2011). Social cognition disorders and subtle behavioral changes characterize the clinical presentation from the very early disease phases, and progressively affect professional and familial dimensions leading to a dramatic modification of patient's social networks (Cerami & Cappa, 2013).

Besides, executive dysfunction is emphasized as a core diagnostic criterion for bvFTD compared to relatively spare episodic memory and visuospatial functions (Rascovsky et al., 2011). Recent studies suggested that patients with severer executive dysfunctions might have worse functional disabilities (Moheb, Mendez, et al., 2017) and faster disease progression (Hornberger, Piguet, et al., 2008).

The clinical presentation of bvFTD is highly heterogeneous and depends on fix (e.g., genotype) and flexible (e.g., education or occupation) variables (Devenney, Bartley, et al., 2015). Lifelong experiences (i.e., education, occupation and leisure activities) may modulate disease onset and clinical presentation acting as proxies of cognitive reserve (CR). This concept has been introduced to account for the mismatch between the degree of brain dysfunctions and the clinical manifestations, suggesting that people with higher CR better cope with neuronal dysfunctions than others (Stern, 2002).

According to a recent hypothesis (Steffener & Stern, 2012), this is due to the role of CR that actively induces functional compensatory mechanisms to cope with neurodegeneration, improving the neural efficiency against the advance of the disease. Thus, patients with higher CR levels usually present with cognitive symptoms and behavioural manifestations once the neurodegenerative process is already severe (Barulli & Stern, 2013). PET functional imaging provided strong evidence of the role of CR in modulating neuronal functions in the course of neurodegenerative dementias [see (Borroni, Premi, et al., 2009; Garibotto, Borroni, et al., 2008; 2012; Kemppainen, Aalto, et al., 2008; Morbelli, Perneczky, et al., 2013; Perneczky, Diehl-Schmid, et al., 2007; Perneczky, Wagenpfeil, et al., 2010; Placek, Massimo, et al., 2016)]. The FDG-PET studies mainly reported a significant association between high proxies of CR, like education and occupation levels, and a more severe reduction of glucose metabolism. For instance, patients with Alzheimer's dementia with higher CR have more severe temporo-parietal glucose hypometabolism than patients with lower CR (Garibotto et al., 2008; 2012; Kemppainen et al., 2008; Morbelli et al., 2013; Perneczky et al., 2010). Notably, the former also have a more preserved brain cholinergic neurotransmission in the hippocampus and posterior cingulate gyrus (Garibotto, Tettamanti, et al., 2013).

Although patients with high CR better cope with neurodegeneration for a long time (Valenzuela & Sachdev, 2006), once the disease makes its first clinical appearance, it goes faster causing severe decline in cognition, functionality and increased mortality (Helzner, Scarmeas, et al., 2007; Scarmeas, Albert, et al., 2006).

Although the majority of reports provide strong support for the role of CR in AD and vascular dementias (Meng & D'Arcy, 2012), only few recent researches tested the CR hypothesis in bvFTD (Borroni et al., 2009; Massimo, Zee, et al., 2015; Placek et al., 2016; Premi, Garibotto, et al., 2013; Spreng, Rosen, et al., 2010). According to this literature, bvFTD patients with higher education and occupation show greater neuronal dysfunctions in frontal lobe, particularly in the dorsolateral prefrontal cortex compared to the patients with lower levels (Borroni et al., 2009; Perneczky et al., 2007; Placek et al., 2016).

Besides, previous authors suggested that CR might be extended as compensatory mechanisms not only for cognitive deficits but also for behavioural disturbances in bvFTD, reporting a significant interaction between behavioural phenotypes and CR expressed as educational achievements. For example, within the four possible behavioural phenotypes (i.e., disinhibited, apathetic, language, and aggressive), the "disinhibited" patients were the only in which higher education was associated to greater hypofunction in the right frontal cortex (Premi et al., 2013).

Notably, there is preliminary evidence suggesting that, beside the occupation levels, also specific skills involved in different jobs can influence the pattern of brain glucose hypometabolism in bvFTD (Spreng, Drzezga, et al., 2011). In particular, this previous study explored how macro-domains of cognitive functions (i.e., verbal, and visuo-spatial factors) and physical factors can modulate brain metabolism in bvFTD. The authors found that glucose metabolism in the left prefrontal cortex and right supplementary motor area was negatively associated to verbal or physical occupation characteristics of their premorbid jobs. In the present study we addressed the role of specific occupation features, as identified by the O*Net database involving social cognition, attentive and executive functions. Impairment in these cognitive skills represent the hallmarks of early bvFTD, thus the practice of these abilities during life-long job activities might significantly modulate the related neural reserve in these patients.

Thus, in this study we aimed at investigating the effect of specific occupation profiles on the brain functional reserve in bvFTD, as measured by FDG-PET cerebral metabolism. In particular, the underlying hypothesis is that specific occupation features (i.e., jobs with highly demanding social, attention and executive abilities), which represent the cognitive areas of early clinical impairment in bvFTD, may act as proxy of cognitive reserve, modulating brain metabolic changes in these patients. We thus explored the relationship between FDG-PET hypometabolism and a) occupation levels classified with a 5-point scale (Borroni et al., 2009) and b) social, executive and attention occupation profiles, investigated according to different dimensions (i.e., "worker" and "occupational" features) extracted from the O*Net network database.

2. Materials and Methods

2.1. *Participants*

Thirty-seven patients (26 males; 68.94 ± 8.15 years of age; 11.86 ± 4.56 years of education; Mini-Mental State Examination (MMSE) raw score 21.05 ± 6.81; CDR-FTD sum of boxes 6.97 ± 3.39) fulfilling diagnostic criteria for probable bvFTD (Rascovsky et al., 2011) were included in the study (Table 1). All patients were consecutively recruited from the memory clinics of the San Raffaele Scientific Institute (Milan, Italy) and evaluated by a team of experienced behavioural neurologists and neuropsychologists. Both patients and caregivers underwent a structured clinical interview. All subjects underwent a full neurological examination, neurobehavioral and neuropsychological assessments and MRI and FDG-PET scans.

All subjects, or their informants/caregivers, gave informed consent to the experimental procedure that had been approved by the local Ethical Committee.

2.2. *Occupation levels and profiles*

The occupation level was classified by means of a categorical 5-point scale (Borroni et al., 2009): (0) no occupation; (1) unskilled labourer; (2) skilled labourer, tradesman, lower-level civil servant, employee, self-employed small business, office or sales person; (3) mid-level civil servant or management, head of a small business, academician or specialist in a subordinate position; (4) senior civil servant or management, senior academic position, self-employed.

Occupation profiles were defined according to the O*Net database (i.e., United States Department of Labor Standard Occupational Classification Network, 1998), which codes over a thousand different jobs according to the specific occupation skills. Specifically, O*Net database provides a framework which contains detailed domains and features useful to describe job skills. These domains include worker characteristics, worker requirement, experience requirements, occupational requirements and occupation specific information. Despite the updated O*Net versions (latest version 21.3; https://www.onetcenter.org/), we decided to consider the classification published in 1998, as the one better representing the job features of the included patients in their period of job-life-activity. According to the study hypothesis, we selected a priori all the O*Net variables mostly related to the cognitive and social skills early impaired in bvFTD (i.e., social cognition, attention and executive skills).

First, we focused on "worker" descriptors, and variables were thus selected among "*worker-characteristics*" (i.e., idea generation & reasoning abilities; attentiveness) and "*worker-requirements*" (i.e., social skills) (see Table 2). Then, we explored "occupation" descriptors related to cognitive and social skills

Table 1 – Demographic, clinical and neuropsychological features of the bvFTD sample. Scores at the neuropsychological assessment are adjusted according to demographic variables. CDR: Clinical Dementia Rating Scale; RAVLT: Rey Auditory Verbal Learning Test.

	Mean ± SD
Age in years	68.94 ± 8.15
Years of education	11.86 ± 4.56
Disease duration in months	30.9 ± 21.25
Gender (M/F)	26/11
CDR-FTD sum of boxes	6.97 ± 3.39
CDR sum of boxes	5.47 ± 3.12
Neuropsychiatric inventory	31.05 ± 17.06
Mini mental state examination	21.05 ± 6.81
Verbal fluency on phonemic cue	12.13 ± 10.42
Verbal fluency on semantic cue	24.13 ± 13.73
Attention matrices	33.45 ± 9.15
Digit span forward	4.72 ± 1.14
RAVLT immediate recall	23.27 ± 12.02
RAVLT delayed recall	3.6 ± 3.47
Rey-Osterrieth complex figure copy	25.08 ± 8.40
Rey-Osterrieth complex figure recall	8.89 ± 6.16
Raven's progressive matrices	22.38 ± 6.95
Token test	24.51 ± 7.75

Table 2 – Results of the PCA on the O*Net worker descriptors.

O*Net worker descriptors	PCA components		
	First "Social networking and job context adaptation"	Second "Planning and creative thinking"	Third "Cognitive control"
Social perceptiveness	**.917**	.158	.142
Coordination	**.683**	.464	.298
Persuasion	**.897**	.301	.108
Negotiation	**.848**	.388	.086
Instructing	**.833**	.202	.212
Service orientation	**.726**	.041	.133
Fluency of ideas	.601	**.675**	.196
Originality	.501	**.733**	.224
Problem sensitivity	.578	**.688**	.142
Deductive reasoning	.443	**.839**	.167
Inductive reasoning	.479	**.778**	.150
Information ordering	−.146	**.861**	.264
Category flexibility	.125	**.725**	.537
Selective attention	.118	.289	**.895**
Time sharing	.504	.268	**.758**

The significant loading for each PCA component is in bold. Of note, these components define three precise domains ("Social networking and job context adaptation", "Planning and creative thinking", "Cognitive control").

extracted from "occupational requirements" (i.e., mental process and interacting with others) (Table 3).

In a subsequent phase we performed two principle component analyses-PCA (i.e., one for "worker" variables and one for "occupation" variables) to collapse the selected O*Net descriptors to composite PCA scores. According to the first PCA analysis, three components captured the 84% of the variance and they were interpreted as the best dimensional representation of the full dataset. Namely, the resulting components were 1) social networking and job context adaptation 2) planning and creative thinking and 3) cognitive control (See Table 2 for O*Net descriptors included in each component). In the PCA focused on occupation descriptors, three components emerged (86% of the variance explained) representing reasoning and information processing (i.e., PCA component #1) and social skills (i.e., PCA components #2 and #3) (See Table 3). Component names were derived according to the nature of the grouped O*Net variables in the different factors. PCA factors were then added as variables of interest in the regression analyses with FDG-PET metabolism.

2.3. FDG-PET imaging

2.3.1. FDG-PET scan acquisition

FDG-PET acquisitions were performed at the Nuclear Medicine Unit, San Raffaele Hospital (Milan, Italy). Before radiopharmaceutical injection of FDG (185–250 Mbq: usually, 5–8 mCi via a venous cannula), subjects were fasted for at least 6 h and their blood glucose level was <120 mg/dL. All images were acquired with a Discovery STE (GE Medical Systems, Milwaukee, WI) multi-ring PET tomography (PET-CT) system (time interval between injection and scan start = 45 min; scan duration = 15 min). Images were reconstructed using an ordered subset expectation maximization (OSEM) algorithm. Each PET phase was corrected for attenuation with CT data of the corresponding phase. For each PET scan, 47 transaxial tomographic slices of 4.25 mm, re-oriented into the coronal and the sagittal planes were acquired. The emission images were then reconstructed using a filtered back-projection algorithm, implemented in the software provided by the manufacturers.

2.3.2. FDG-PET data pre-processing and statistical analyses

Image processing and statistical analysis were performed according to validated procedures (Della Rosa, Cerami, et al., 2014; Perani, Della Rosa, et al., 2014). In particular, normalization procedure was performed at the individual level to a dementia-specific Statistical Parametrical Mapping (SPM) FDG-PET template (Della Rosa et al., 2014). SPM5 (http://www.fil.ion.ucl.ac.uk/spm/software/spm5) and MATLAB (Mathworks Inc., Sherborn, Mass., USA) software were used. Each patient scan was then tested for relative "hypometabolism" based on a validated procedure that includes comparison with a large image database of FDG-PET scans from normal controls on a voxel-by-voxel basis (Perani et al., 2014). Age was included as a covariate. Proportional scaling was used to remove inter-subject global variation in PET intensities. The threshold was set at $p = .05$, FWE-corrected for multiple

Table 3 – Results of the PCA on the O*Net occupation descriptors.

O*Net occupation descriptors	PCA components		
	First "Reasoning and information processing"	Second "Social skills"	Third "Social skills"
Interpreting meaning of info. to others	**.677**	.272	.585
Provide consultation & advice to others	**.710**	.512	.398
Judging qualities of things, srvc., people	**.622**	.580	.347
Processing information	**.704**	.474	.319
Evaluating info. against standards	**.841**	.270	.097
Analyzing data or information	**.901**	.272	.214
Making decisions and solving problems	**.852**	.395	.242
Thinking creatively	**.734**	.364	.037
Updating & using job-relevant knowledge	**.884**	.140	.306
Developing objectives and strategies	**.669**	.567	.356
Communicating with other workers	.598	**.629**	.315
Coordinating work & activities of others	.450	**.835**	.184
Developing and building teams	.410	**.843**	.249
Resolving Conflict, Negotiating with Others	.377	**.664**	.488
Guiding, directing & motivating subord	.358	**.861**	.156
Coaching and developing others	.325	**.788**	.340
Scheduling work and activities	.168	**.904**	.260
Organizing, planning, and prioritizing	.617	**.669**	.294
Performing for/working with public	.214	.147	**.889**
Teaching others	.291	.559	**.611**
Communicating with persons outside org.	.532	.380	**.646**
Establishing & maintaining relationships	.214	.545	**.689**
Assisting and caring for others	.090	.172	**.893**
Selling or influencing others	.473	.463	**.547**

The significant loading for each PCA component is in bold. These PCA components are related to cognitive (i.e., "reasoning and information processing") and social skills (i.e., second and third component).

comparisons at the voxel level. Only clusters containing more than 100 voxels were deemed to be significant.

With the aim to identify possible association between FDG-PET hypometabolism and occupation, we performed linear regression analyses using 5-point scale or PCA scores as independent variable, whereas disease severity (i.e., CDR-FTD sum of boxes) and education levels as nuisance variables. The p-value was set at $p < .005$ uncorrected.

3. Results

Regression analyses between the FDG-PET data and the categorical index of occupation levels revealed a positive association between the occupation levels and glucose hypometabolism in the dorsolateral prefrontal cortex bilaterally (DLPFC) (Fig. 1). This means the higher the occupation levels, the lower the brain metabolism in those regions.

As for the occupation profiles, taking into account disease severity and education, patients with jobs requiring higher social networking and job context adaptation showed a more severe hypometabolism in the left medial prefrontal cortex, the middle cingulate cortex and superior frontal gyrus, and in the right DLPFC (Fig. 2, in green); whereas patients with jobs requiring higher cognitive control showed a more severe hypometabolism in the left fronto-insular cortex (Fig. 2, in blue). No significant association was found between brain metabolism and planning and creative thinking.

Finally, the analysis on PCA scores based on occupation descriptors revealed that patients with jobs characterized by increased social skills (i.e., component #2 of PCA on occupation descriptors) showed a more severe hypometabolism in the left medial prefrontal cortex, and in the superior and middle frontal gyrus (see Fig. 3). No significant results were found with other PCA components related to occupation.

In order to evaluate the relationship between the specific occupation features, disease duration and global cognitive status (i.e., MMSE score), we performed partial correlation analyses between these variables using CDR-FTD as control variable. We found a significant positive association between MMSE score and components of social networking and job context adaptation ($r = .29$, $p < .05$) and social skills (i.e., component #2 of PCA on occupation descriptors, $r = .28$, $P < .05$).

In addition, the correlation analysis performed between overall education and occupation levels revealed a significant association ($r = .38$, $p < .05$). The correlation analysis between education levels and each PCA scores revealed a significant association only with occupation factors “social networking and job context adaptation” ($r = .5$, $p < .01$), “reasoning and information processing” ($r = .57$, $p < .01$) and social skills (i.e., component #3 of PCA on occupation descriptors, $r = .44$, $P < .01$).

No other significant correlations emerged.

4. Discussion

Premorbid life experiences can exert a significant effect on the clinical expression of neurodegenerative diseases. In this study, we assessed whether levels of occupancy and different profiles in premorbid occupation may modulate brain functional reserve in bvFTD as measured with FDG-PET brain metabolism. Differently from previous studies based on regions on interests (Perneczky et al., 2007), or focused only on education as proxy of CR (Perneczky et al., 2007), we adopted a whole-brain approach and more representative variables of life-long job experiences, that included social interaction and executive functions. Moreover, while previous evidence reported in this neurodegenerative condition an effect on brain metabolism of some cognitive and other general occupation features such as verbal, visuo-spatial cognitive functions and physical status (Spreng et al., 2011), in this study, we evaluated for the first time the protective role of specific job-related

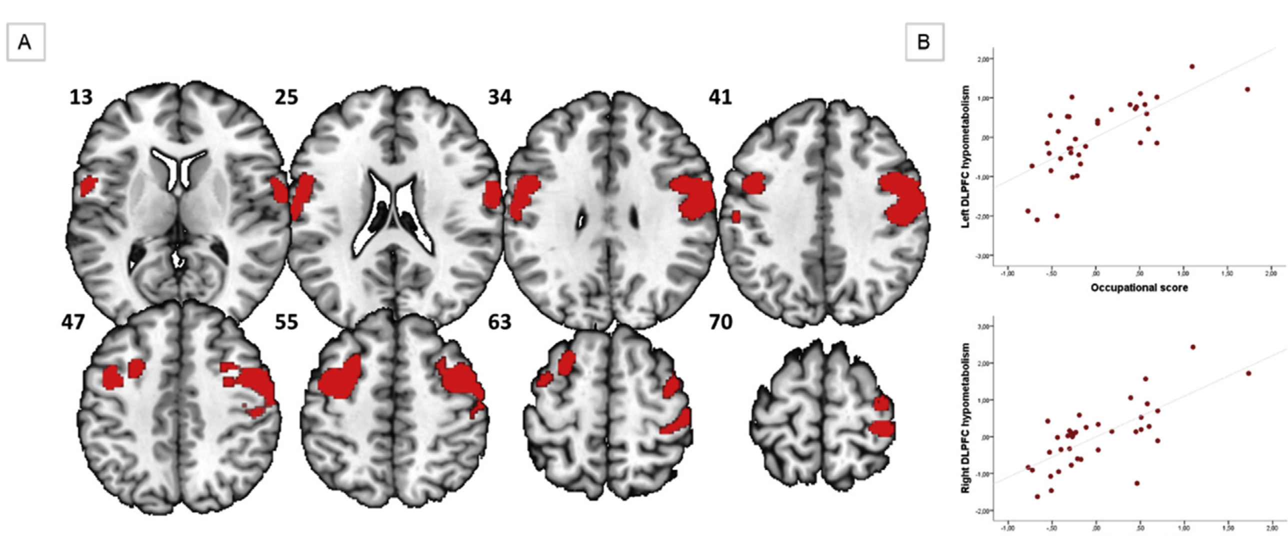

Fig. 1 – A) Significant regression between high occupation levels, according to a 5-point Likert scale, and more severe brain hypometabolism, $p < .005$ uncorrected, FWE corrected at cluster. B) Scatterplots showing the relationship between occupation categorical index and hypometabolism in left and right DLPFC.

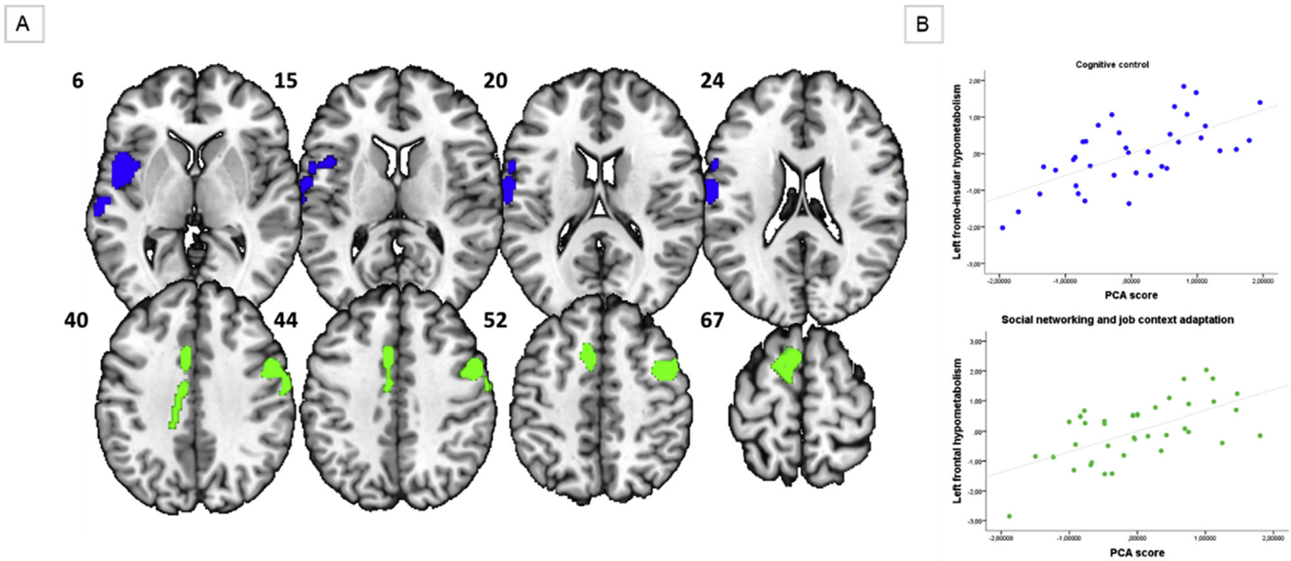

Fig. 2 – A) Significant regression between O*Net worker profiles (social networking and job context adaptation (in green) and cognitive control (in blue)) and brain hypometabolism; $p < .005$ uncorrected. B) Scatterplots showing the relationship between PCA scores and hypometabolism in left fronto-insular regions (i.e., in blue) and left medial frontal regions (i.e., in green).

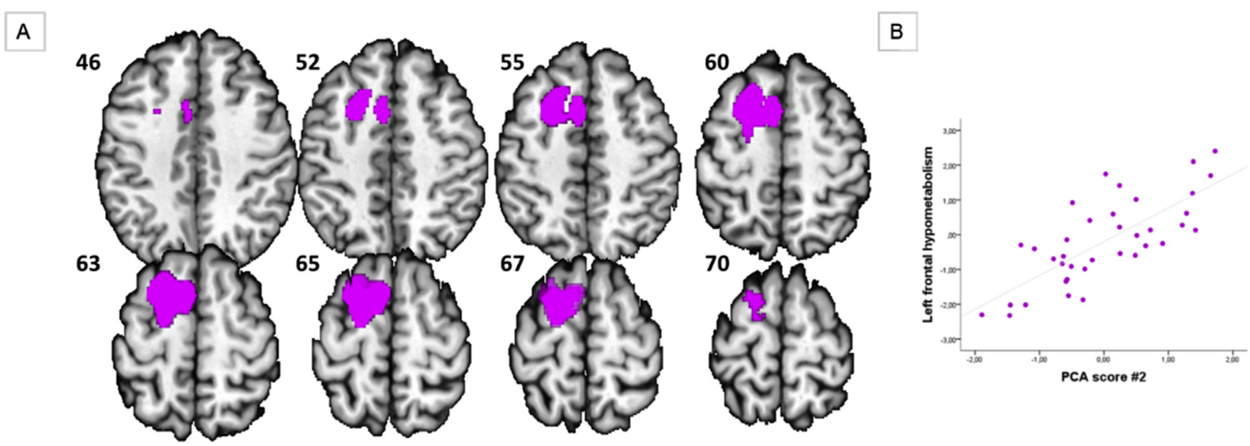

Fig. 3 – A) Significant regression between occupation PCA score #2 of social skills and brain hypometabolism; $p < .005$ uncorrected, FWE-corrected at cluster level. B) Scatterplots showing the relationship between PCA scores and hypometabolism in the significant cluster.

worker and occupation features covering the cognitive dysfunctional profile typical of the bvFTD since the early disease phases. In this matter, we provided further evidence that patients with specific high occupation levels, thus provided with a high CR, can better cope with neuronal degeneration. In particular, bvFTD patients with jobs characterized by higher social interaction and attentive control skills show more severe hypometabolism in prefrontal cortex and insular regions. Consistently with previous evidence (Borroni et al., 2009; Perneczky et al., 2007; Placek et al., 2016), we confirmed that occupation is a premorbid feature of CR influencing reserve in bvFTD in brain regions engaged for planning abilities (Massimo, Powers, et al., 2015), episodic memory (Wong, Flanagan, et al., 2014) and executive functions (Gansler, Huey, et al., 2017), and crucially involved in frontotemporal neurodegeneration.

More importantly, together with the above effect of occupation levels, we also observed a modulation of brain metabolism due to specific occupation profiles, as obtained by O*Net database. The analysis on "worker" features showed that patients with higher competences on social networking and job context adaptation showed more severe hypometabolism in medial frontal regions, i.e., the medial prefrontal cortex and the middle cingulate cortex. These areas are well-known regions involved in social cognition abilities, as they play a pivotal role in internal monitoring of action (Amodio & Frith, 2006), perspective-taking (Ruby & Decety, 2004), theory of mind (Schlaffke, Lissek, et al., 2015), and empathy for others' pain (Lamm, Decety, et al., 2011). These findings were further confirmed by the regression analysis on the occupation-related PCA score concerning social skills (i.e., component #2), as the results showed a pattern of hypometabolism including the medial and superior frontal gyrus and extending to the middle frontal gyrus, which have been previously associated to theory of mind abilities (Schlaffke et al., 2015).

These results add new evidence to recent literature (Bickart, Wright, et al., 2011; Von Der Heide, Vyas, et al., 2014) that suggests how real-world social networks might contribute to brain structural and functional re-organization of brain regions classically damaged in bvFTD patients (Cerami, Dodich, et al., 2015; Le Bouc, Lenfant, et al., 2012). Thus, jobs requiring high social interactions, attention and executive skills might help in promoting the inception of alternative or redundant neural networks to support cognitive functions in presence of neurodegenerative processes.

Notably, the analysis of specific worker skills also revealed an association between jobs requiring high cognitive control and the glucose metabolism in the left fronto-insular cortex. This brain region, together with the anterior cingulate cortex, is crucially involved in the "salience network", which is at the basis of top-down cognitive control (Seeley, Menon, et al., 2007). Together with the "executive control network", involving lateral prefrontal and parietal regions, the "salience network" contributes to the flexible and highly stable human behaviour, as it is optimized for rapid adaptive control and stable set-maintenance (Dosenbach, Fair, et al., 2008). Recent evidence suggests that the salience network might influence moment-to-moment information processing by identifying the most subjectively relevant stimuli (Seeley et al., 2007). A significant disruption of salience network hubs has been specifically indicated at the basis of bvFTD syndrome (Seeley, Allman, et al., 2007; Zhou, Greicius, et al., 2010). Overall, these results suggest the hypothesis that bvFTD patients with life-long occupation activities requiring high social functioning and attentive control can better cope with the neurodegenerative processes that mostly affect the social brain (Frith, 2007) and the neural networks at the base of top-down cognitive control. Notably, these results are further corroborated by the significant positive correlation we found between global cognitive status and the complexity of the occupation social skills, suggesting that higher social interaction in life can exert a protective role on patient global cognitive status. Moreover, we found a significant correlation between education and occupation levels, indicating that these variables might have reciprocal influence. However, not all PCA scores were significantly associated to education level. Even though it is probable that to a higher education corresponds a broader spectrum of high-level jobs, it is also possible that job experiences shape skills and abilities independently from the academic qualification. This might be the reason why not all PCA scores were correlated with education levels. As a proof of that, in whole-brain analyses we found significant results controlling for education level as nuisance variable. These findings seem to suggest that education and occupation represent partially independent sources of functional reserve.

Our findings contribute to enrich current literature on CR in bvFTD (Perneczky et al., 2007; Placek et al., 2016; Spreng et al., 2010; 2011) showing that specific occupation profiles may differently modulate the neural functional reserve in bvFTD. The potential beneficial effects of life-long experiences on neuroprotection are important factors in bvFTD for treatment trials and prognostic considerations.

Finally, these results underline the importance of investigating occupation levels and profiles as proxies of CR, in order to consider a more comprehensive picture of premorbid long-term life experiences that might enrich the cognitive resilience, despite the presence of brain damage.

Some limits of the study refer to the choice of O*Net variables in job characterization, as we included only few subsets of all the O*Net variables available. In addition, due to the retrospective nature of this study, information about the patient occupations was obtained from medical history, lacking important information such as the possible role of multiple occupations or career advancement during life.

Disclosure statement

All authors have no financial conflict of interests.

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