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Relationship between occupation attributes and brain metabolism in frontotemporal dementia

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ABSTRACT

Occupation has been associated with cognitive reserve in healthy aging and Alzheimer's disease. Here we assess the relationship between cerebral metabolic deficits in behavioral variant frontotemporal dementia (bvFTD) and occupation characteristics. Using factor analysis, we derived verbal, physical and visuospatial occupation scores from the US Department of Labor, Occupational Information Network and related these scores to regional cerebral metabolic rate of glucose utilization in 31 patients diagnosed with behavioral variant bvFTD, controlling for cognitive status (CERAD neuropsychological assessment battery), gender and education. Regression analyses showed a marked inverse association between glucose metabolism and (a) verbal occupation scores in left prefrontal cortex and, (b) physical occupation characteristics in right supplementary motor area. We concluded that, consistent with the cognitive reserve hypothesis, lifelong occupation characteristics are related to focal cerebral metabolic deficits in bvFTD. Specific occupation demands spanning decades may strengthen cognitive resistance to pathology.

1. Introduction

The cognitive reserve hypothesis predicts that increased intellectual abilities and life experiences alleviate the negative consequences of aging and dementia symptoms. Higher levels of premorbid intelligence have been associated with greater brain damage in Alzheimer's disease (AD) among patients with similar clinical severity levels (Alexander et al., 1997). This suggests that individuals of higher intelligence can somehow better compensate for pathology. Education and other life experiences, however, seem to impart reserve over and above innate intelligence (Stern, 2002). Individuals with more years of education have fewer to no symptoms of AD (Stern et al., 1994), despite having significant cerebral pathology at autopsy (Roe, Xiong, Miller, & Morris, 2007). Extending past a brief period of time spent in school, occupational attainment has been associated with cognitive reserve in both maintaining higher levels of cognitive functioning in healthy adults (Staff, Murray, Deary, & Whalley, 2004), and the attenuation of AD symptoms (Stern et al., 1994).

Frontotemporal lobar degeneration is the second most common pre-senile cause for neurodegenerative dementia (Harvey, Skelton-Robinson, & Rossor, 2003). In keeping with the cognitive reserve hypothesis, life experiences are hypothesized to extend protective effects in frontotemporal lobar degeneration, forestalling the symptoms of dementia despite a progressive neuropathology. In support of this relationship, an inverse association between years of education and frontal pathology, as measured by regional cerebral metabolic rate of glucose utilization (rCMRglc) has been observed in patients with behavioral variant frontotemporal dementia (bvFTD) (Perneczky, Diehl-Schmid, Drzezga, & Kurz, 2007), a subgroup of frontotemporal lobar degeneration with early behavioral symptoms (Neary et al., 1998). This association has been replicated and extended in a larger sample of bvFTD patients. In addition to years of education, occupation skill level was inversely associated with regional cerebral blood flow using SPECT in medial and lateral prefrontal regions typically affected by FTD disease pathology (Borroni et al., 2009). Occupation skill level, like years

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of education, provides a non-specific measure of cognitive ability. Broad measures of occupation skill neglect the diversity of work related activities individuals engage in over the course of many years. In AD, an association for specific occupational factors, interpersonal skills, physical demands, and AD-related reductions in parietal regional cerebral blood flow has been observed (Stern et al., 1995). In a large sample of frontotemporal lobar degeneration patients, occupation attributes have also been found to relate to lateralized functional impairment: Patients whose professions placed high demands on verbal skills had relatively preserved left temporal relative to right temporal lobe volumes (Spreng et al., 2010). In the present study, we examined the association between specific occupational attributes in patients with bvFTD and functional pathological load, measured by rCMRglc. Occupations can be divided according to certain characteristics, such as verbal, physical and visuospatial demands. By relating these dimensions to rCMRglc, we sought to assess the relationship between specific occupation attributes and reserve. After controlling for cognitive status, education and gender, we predicted an inverse relationship between rCMRglc and occupation characteristics. We expected associations in brain regions typically involved in verbal, motor, and visual processing.

2. Methods

2.1. Participants

Thirty-one patients with mild to moderate bvFTD were recruited at the Center for Cognitive Disorders at the Department of Psychiatry and Psychotherapy of the Technische Universität München. All clinical evaluations were performed by the same psychiatrist (JD-S) between 2003 and 2005. All consecutive patients that fulfilled inclusion criteria were selected for the present study. The diagnosis was established according to revised Lund-Manchester criteria (Neary et al., 1998) by consensus of two psychiatrist with profound experience in the field of frontotemporal lobar degeneration (JD-S and AK). The diagnosis was based on information gathered from a thorough neurological and psychiatric examination, informant interview, routine blood sampling, structural magnetic resonance imaging, and functional positron-emission-tomography with ^{18}F-fluoro-2-deoxy-glucose (^{18}F-FDG PET). All patients underwent a neuropsychological evaluation performed by an experienced psychometrician based on the German version of the Consortium to Establish a Registry for AD Neuropsychological Assessment Battery (CERAD-NAB) (Thalmann & Monsch, 1997), which incorporates the Mini-Mental-State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975). A total score of the CERAD-NAB was calculated for each patient according to recently published criteria (subtest addition method) (Chandler et al., 2005) to control for individual differences in cognitive status in the regression analysis of PET data. Briefly, total scores were obtained by summing scores from the individual subtests (excluding the MMSE score) into a total composite score (maximum for verbal fluency set at 24 points, maximum total score 100 points). This score was preferred to the MMSE score and scores of other neuropsychological tests because it covers a wider spectrum of cognitive functions. The use of the total score of the CERAD-NAB subtests to assess cognitive function in patients with bvFTD is a limitation as it was originally designed for patients with AD and therefore may not cover every aspect of cognitive decline in bvFTD. The CERAD-NAB covers a wide spectrum of cognitive impairment effected by bvFTD, however, and has been found to be significantly correlated with rCMRglc in the frontal cortex (Teipel et al., 2006), and has been used to control for differences in cognitive status in patients with bvFTD previously (Perneczky et al., 2007). No other comprehensive score for cognitive dysfunction in bvFTD was available at the time of the study.

Several tests for executive and frontal lobe functions were also administered, including the Frontal Assessment Battery (FAB) (Dubois, Slachevsky, Litvan, & Pillon, 2000), and the Trail Making Test (TMT) (Reitan, 1985). Behavioral symptoms were rated on the Frontal Behavioral Inventory (FBI) (Kertesz, Davidson, & Fox, 1997). Neuropsychiatric symptoms were rated on the Neuropsychiatric Inventory (NPI) (Cummings et al., 1994), and impaired everyday functioning was assessed using the Bayer Activities of Daily Living scale (B-ADL) (Hindmarch, Lehfeld, de Jongh, & Erzigkeit, 1998). Severity of dementia was rated using the Clinical Dementia Rating scale (CDR) (Morris, 1993), which allows a classification for questionable (CDR 0.5), mild (CDR 1), moderate (CDR 2) and severe dementia (CDR 3). The documentation also contained information on the patient's age, gender, age at the onset of symptoms, and years of formal education, defined as the years attending school plus the years of apprenticeship, technical school, college and university. Informed consent according to the Declaration of Helsinki was available for every patient. The study protocol was approved by the ethics committee of Klinikum rechts der Isar, Technische Universität München and the Rotman Research Institute at Baycrest.

2.2. Occupation characteristics

Patients' occupations were coded according to the US Department of Labor Standard Occupational Classification by O*Net (US Department of Labor National O*NET Consortium. Occupational information network: National Center for O*NET Development [http://online.onetcenter.org/]). For patients that engaged in numerous occupations, the career with the longest duration was included. O*Net provides a comprehensive database for worker attributes, job characteristics, work content and work context. It offers a common language for communication across the diversity of occupations with definitions and concepts for describing worker attributes and job characteristics that are broadly understood, easily accepted, and applied in many industrialized countries. Although the occupational categorization for the patients was derived from an American database, the international standard occupation classification system (ISCO-88) was ill-suited for comparing occupation characteristics across occupations. There is, however, a risk of cultural bias in occupation attributes; yet they are unlikely to substantively vary between Germany and the United States. The online database contains descriptor variables comparable across all occupations about abilities, knowledge, skills, and general work activities collected through surveys where the importance of these attributes were completed by people working in the various occupations or job analysts. O*Net 10.0 contains 161 descriptor variables for 796 occupations categorized under: (a) Abilities, defined as enduring attributes that influence job performance; (b) Knowledge, organized sets of principles and facts applying in general domains; (c) Skills, developed capacities that facilitate learning or rapid acquisition of knowledge and facilitate performance of activities that occur across jobs; and (d) Work activities, general types of job behaviors occurring on multiple jobs.

We used factor analysis to reduce the 161 variables to composite scores describing broad characteristics of occupations that were in turn related to ^{18}F-FDG PET findings. An iterated principal-axis factor analysis, with squared multiple correlations of each item with all other items as the initial communality estimates, was conducted on the occupation ratings variables with all 796 O*Net occupations treated as "participants". A Scree test (Cattell, 1966) revealed that the forth factor was nearly indistinguishable in slope from the subsequent factors, supporting an interpretation of a three factor solution. As such, three factors were retained and a varimax (orthogonal) rotation was then performed to maximize the variance of the squared loadings within the factors. These three factors accounted for 34%, 14%, and 9% of the variance across O*Net occupations. Factor one includes 97 items related to verbal attributes of an occupation, in addition to social demands, general intellectual and problem-solving attributes, loading from .90 to .39. Factor two includes 31 items related to the physical demands, with loadings ranging from .76 to .38. Factor three contained 30 items indicative of visuospatial job attributes, in addition to mechanical and mathematical demands, and had factor loadings ranging from .77 to .34. Two variables did not load above .30 on any of the three factors. Four of the top loading occupation variables for each factor are displayed in Table 1. These three factors are largely consistent with a factor analysis of worker functions and worker characteristics from The Revised Handbook for Analyzing Jobs, based upon the Dictionary of Occupational Titles which has been replaced by O*Net, where factors included general intellectual demands, human interactions and communication, physical exertion and visual attention (Potter, Plassman, Helms, Foster, & Edwards, 2006). Using a similar method to characterize occupation attributes in frontotemporal lobar degeneration, we previously reported a five factor solution in which mechanical and mathematical skills were separate factors (Spreng et al., 2010). For the present dataset, however, a three factor solution provided a better fit to the data. While a three factor solution is a parsimonious factor structure, we recognize that occupations are multifactorial, encompassing demands within and outside those characterized by O*Net and represent a complex combination of attributes. Verbal, physical and visuospatial factor scores were calculated by standardizing the sum of the occupation variables multiplied by the corresponding factor loading. Scaling of the computed scores was such that higher values indicated greater levels of engagement in the parameter.

2.3. Image acquisition and pre-processing

All patients were administered with an IV bolus of 185 MBq ^{18}F-FDG at rest 30 min prior to PET scanning. Scans were performed under standard resting conditions with the patient's eyes closed in dimmed ambient light. Exactly the same scanning protocol was applied to every patient. Imaging was performed on a Siemens ECAT/EXACT HR+PET scanner (CTI, Knoxville, TN, USA). A sequence of three frames (10 min; 5 min; 5 min) was started (three-dimensional mode, total axial field of view of 15.52 cm) and later combined into a single frame. Transmission scans were obtained for attenuation correction purposes using a rotating ^{68}Ge/^{68}Ga-source. Data were corrected for random, dead time and scatter, and images were reconstructed by filtered back-projection with a Hamm filter (cut-off frequency 0.5 cycles/projection element) resulting in 63 slices in a 128 × 128 pixel matrix (pixel size 2.06 mm) and interplane separation of 2.425 mm. Images were realigned and transformed into standard stereotactic space in the statistical parametric mapping software package SPM5 (Wellcome Functional Imaging Laboratory, London, UK), based on Matlab, v7.4 (The Mathworks Inc., Natick, MA, USA) running on a standard personal computer. Smoothing was performed with an isotropic Gaussian kernel with 12 mm full-width at half-maximum to compensate for inter-subject variability

Table 1
Top four O*Net occupation variables and their loadings for verbal, physical and visuospatial factors.

O*Net occupation variable	Factor loadings		
	Verbal	Physical	Visuospatial
Social Perceptiveness	**.90**	−.10	−.22
Establishing and Maintaining Interpersonal Relations	**.90**	−.17	−.13
Active Listening	**.89**	−.14	−.04
Speaking	**.88**	−.15	−.09
Multilimb Coordination	−.22	**.86**	.16
Static Strength	−.30	**.84**	.03
Gross Body Coordination	−.11	**.84**	−.07
Stamina	−.11	**.83**	−.12
Engineering and Technology	−.09	.05	**.77**
Quality Control Analysis	−.04	.02	**.77**
Troubleshooting	.16	.27	**.76**
Technology Design	.27	−.01	**.73**

in gyral anatomy, to minimize effects due to slight errors in image registration, and to improve signal-to-noise ratios. Individual global counts were normalized by proportional scaling to a mean value of 50 mg/100 ml/min.

2.4. Statistical analysis

Patient characteristics were analyzed in the Statistical Package for the Social Sciences (SPSS), v15.0 (SPSS Inc., Chicago, IL, USA). The sample consisted of 21 male and 10 female patients. Their diagnosis of mild to moderate dementia was supported by the MMSE score range (Perneczky et al., 2006). All patients had significant neuropsychiatric and behavioural symptoms as assessed with the FBI and NPI scales. The patients were rather well educated; their pre-senile age at onset of symptoms was typical for bvFTD (Table 2).

All imaging data analyses were carried out in SPM5. In order to identify brain regions with significant associations between the occupational scores and the rCMRglc, independent voxel-based linear regression analyses were carried out with the rCMRglc as the dependent and each occupational score (verbal, physical, visuospatial) as the independent variables. To control for differences in cognitive status, education and gender, the CERAD-NAB total score, years of education and gender were included as a co-variates of no interest in the linear predictor of regression analyses. The voxel-based analysis included the entire brain, but significant findings were only expected in brain regions with pre-described rCMRglc reductions in bvFTD, i.e. prefrontal cortex, temporal cortex and anterior cingulate (Diehl-Schmid et al., 2007). Findings were considered significant above a significance level of $p < .001$, uncorrected for multiple comparisons, in these predefined brain regions. This less stringent statistical threshold is usually accepted if an *a priori* hypothesis of involved brain regions is available (Drzezga et al., 2001). Only clusters with >50 contiguous voxels were considered significant in order to minimize the chance of false positive findings. The anatomical localization of the significant coordinates was determined in the SPM5 Anatomy toolbox (http://www.fz-juelich.de/inb/inb-3//spm_anatomy_toolbox) and stereotaxic coordinates are reported in MNI space.

Table 2
Patient characteristics.

Characteristic	Value
N	31
Age	62.87 (8.72)
Men:women	21:10
Handedness, Left:right:unknown	2:24:5
Age at onset	60.21 (8.82)
Years of education	12.65 (3.25)
Occupational scores	
Verbal	.58 (1.31)
Physical	.35 (2.18)
Visuospatial	−.32 (1.62)
MMSE	23.55 (5.30)
CERAD-NAB sum score	55.97 (17.57)
NPI total score	16.64 (8.86)
FBI total score	24.73 (15.56)
B-ADL total score	4.64 (2.23)
FAB	11.29 (4.73)
TMT A, in seconds	95.09 (62.06)

Mean (standard deviation) if appropriate.
MMSE: Mini-Mental-State Examination (0–30, higher values indicating better cognitive performance); CERAD-NAB: Consortium to Establish a Registry for Alzheimer's Disease neuropsychological assessment battery (0–100, higher values indicating better performance); NPI: Neuropsychiatric Inventory (0–120, higher scores indicating more severe neuropsychiatric symptoms); FBI: Frontal Behavioral Inventory (0–72, higher values indicating more severe symptoms); B-ADL: Bayer Activities of Daily Living scale (0–10, higher scores indicating worse everyday performance); FAB: Frontal Assessment Battery (0–18, higher values indicating better performance); TMT A: Trail Making Test A (0–240 s, higher values indicating worse performance).

3. Results

3.1. Statistical association between the rCMRglc and the occupational scores

3.1.1. Verbal

The voxel-based regression analysis revealed a significant inverse linear association ($p < .001$, uncorrected for multiple comparisons) between the verbal score and the adjusted rCMRglc (corrected for CERAD-NAB sum score, gender and education) in a cluster located at the left-hemispheric pars triangularis of the inferior frontal gyrus (Brodmann area, BA, 45; cluster of 551 contiguous voxels, maximum in −36, 38, 8; $z = 3.57$; Fig. 1). There was no positive association between the verbal score and the rCMRglc in any brain region.

3.1.2. Physical

There was a significant inverse association between the adjusted rCMRglc (corrected for CERAD-NAB sum score, gender and education) and the physical score in the right-sided supplementary motor area (SMA) of BA 6 (cluster of 327 contiguous voxels, maximum in 10, 14, 64; $z = 3.72$; Fig. 2). Again, there were no significant positive associations in any brain area.

3.1.3. Visuospatial

There were no significant associations between the adjusted rCMRglc and visuospatial occupation score in any brain region.

4. Discussion

The present findings indicate that occupation attributes are systematically associated with the functional integrity of associated brain regions in bvFTD. Consistent with the concept of cognitive reserve, we found an inverse association between two occupation characteristics and rCMRglc in regions of prefrontal cortex affected by the FTD disease pathology. The verbal occupation scores were inversely associated with pathological load in left inferior frontal gyrus; physical occupation scores, in the right SMA. Matched for clinical severity, patients with higher occupation scores had greater deficits in rCMRglc, suggesting a more advanced disease state. As such, verbal and physical professions may provide reserve against the clinical expression of FTD pathology. On the basis of our data, however, we cannot differentiate the effect of training based

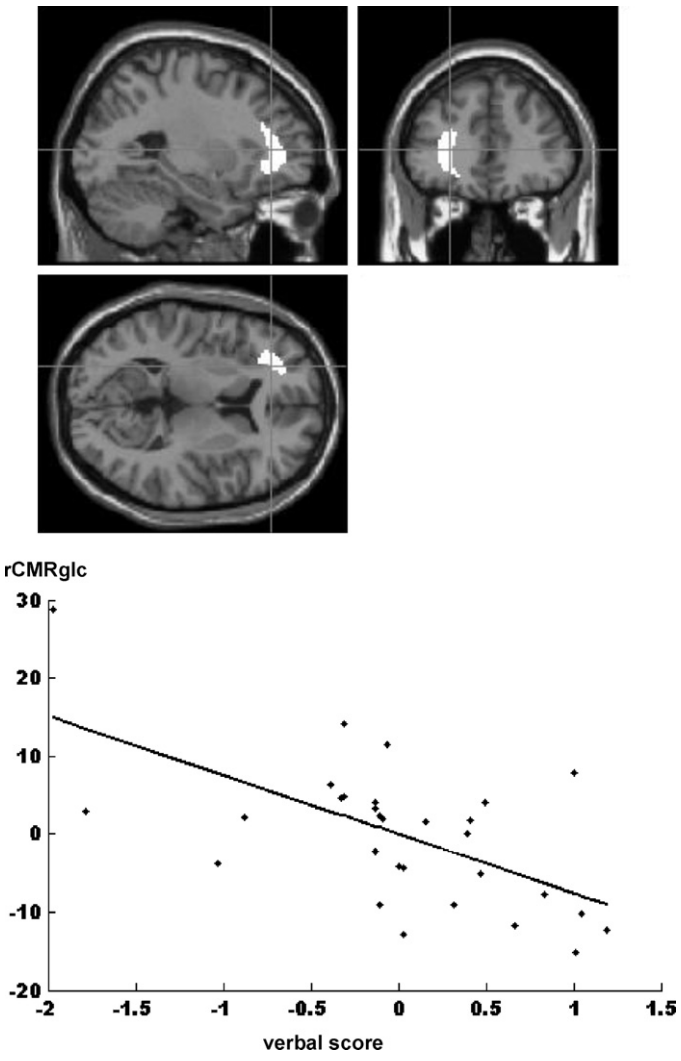

Fig. 1. Significant negative associations between the rCMRglc and the verbal occupational scores. Anatomical localizations as projected on sagittal, coronal, and axial sections of a normal MRI, spatially normalized to the MNI template ($p < .001$ uncorrected for multiple comparisons, maximum in MNI space at $x/y/z$ −36/38/8, left BA 45); and scatterplot between the rCMRglc (arbitrary units) at the global maximum and the verbal occupation score.

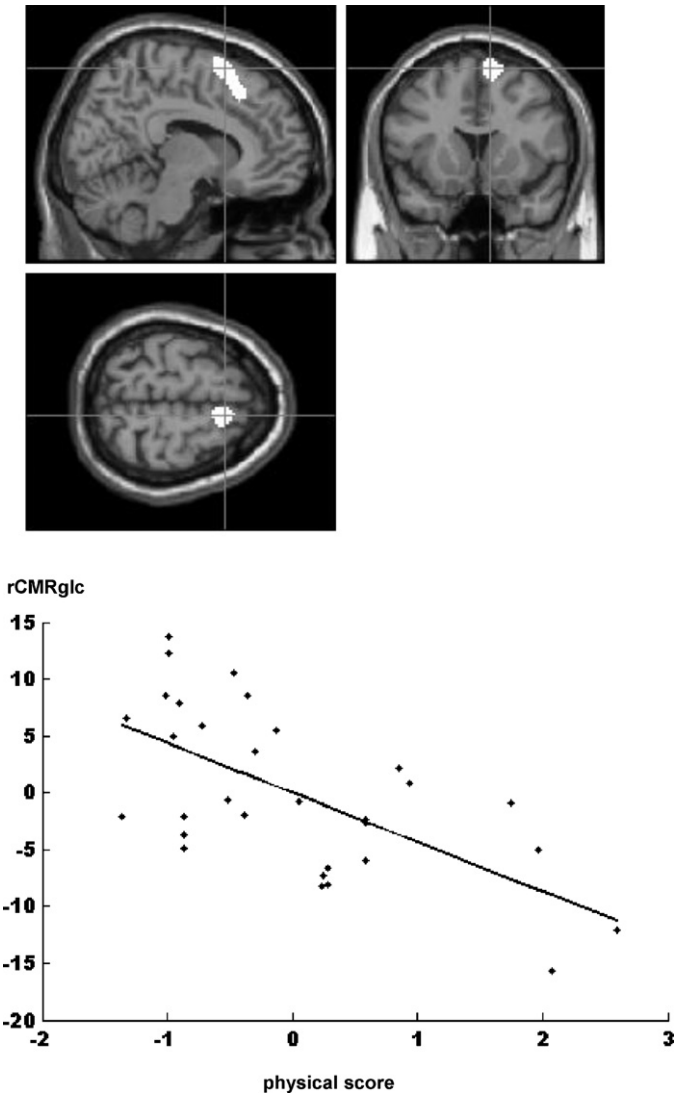

Fig. 2. Significant negative associations between the rCMRglc and the physical occupational scores. Anatomical localizations as projected on sagittal, coronal, and axial sections of a normal MRI, spatially normalized to the MNI template ($p < .001$ uncorrected for multiple comparisons, maximum at $x/y/z$ 10/14/64, right BA 6); and scatterplot between the rCMRglc (arbitrary units) at the global maximum and the verbal physical score.

on life-long occupation, a congenital higher level of skills/talents leading to more pronounced employment of specific cognitive capabilities throughout life, or their interaction. Patients were recruited in a specialized memory clinic and were rather well educated, which restricts the generalization of our findings to the population with bvFTD as such.

Previous work in bvFTD has shown education and occupational skill level to contribute to reserve status (Perneczky et al., 2007). This is the first study to examine how specific occupation attributes relate to brain metabolism and contribute to cognitive reserve in bvFTD. In both regression analyses, verbal and physical occupation scores provided significant predictive value over education and accounted for unique proportion of the variance in frontal rCMRglc. The verbal association is proximal to the peak cluster related to education and rCMRglc in bvFTD (Perneczky et al., 2007). The education effect was bifrontal, yet the verbal occupation score related only to the left-hemisphere. This may be due to the language specific processing (e.g. verbal working memory, semantic decision-making), rather than the generalized effects of education. The physical occupation score was uniquely associated with a cluster in the SMA, related to the planning and execution of volitional movements (Tanji, 1994). Further research into the occupations of patients with motor-neuron variants of frontotemporal lobar degeneration, such as motor neuron disease, corticobasal degeneration or progressive supranuclear palsy, may provide unique insight into a relationship between motor intention, function and reserve. There was no association for the visuospatial score in any brain region, potentially because visual processing is relatively spared in the early stages of bvFTD.

In AD and bvFTD, an inverse association between education and regional cerebral blood flow and rCMRglc have been observed, but only in regions affected by the disease process and not in healthy controls (Perneczky et al., 2007; Stern et al., 1994). Stern and colleagues found an association with specific occupation attributes similar to those observed here (interpersonal skills, physical demands) in posterior parietal regions affected by AD pathology (Stern et al., 1994). Here, measures of metabolism demonstrate advanced neuropathology inversely related to specific occupation attributes in regions of networks supporting the underlying processes. This finding may reflect a neuroplastic shift towards a more distributed process as a result of long-term occupational practice,

enabling function in spite of frontal lobe pathology. This putative distributed shift may be less effective in patients with pathology in the temporal lobe, where linguistic/semantic capacities have a stronger functional localization. Accordingly, in our previous study of frontotemporal lobar degeneration patients, there was a negative association between left temporal lobe integrity and verbal occupation attributes, while the opposite pattern held for frontal regions (Spreng et al., 2010). In other words, reserve conferred by verbal occupation practice can compensate for damage in the frontal lobes, where function is distributed, but not temporal areas, where function is more localized.

Previous work has related levels of occupational skill to cognitive reserve in medial prefrontal cortex, anterior cingulate and dorsolateral prefrontal cortex (Borroni et al., 2009), consistent with associations with years of education (Borroni et al., 2009; Perneczky et al., 2007). Unlike years of education and occupation skill level, however, occupation attributes provide a more specific measure of premorbid activities. The lifelong engagement of a career represents approximately 70,000 h of regular work activities. Practice effects have been observed to influence both the function and structure of the brain over much shorter intervals (Draganski et al., 2004; Pantev et al., 2003). The characteristics of a lifelong occupation are thus likely to influence, and be influenced by, cognitive function and the supporting neuroanatomy. Very long-term work effects for verbal and physical behavior may offer resilience of function in the face of frontal lobe damage, resilience that is derived through distributed, experience-dependent, neuroplastic changes.

To conclude, our study extends the growing literature on cognitive reserve, which so far mainly concentrated on global measures such as years of education or intellectual content of occupation. Our findings support studies, mainly in AD, which showed that higher indices of cognitive reserve were associated with more advanced neurodegeneration accounting for dementia severity. Importantly, the interaction between reserve and pathology was found in brain regions typically affected by the disease in these studies, which supports the mediating impact of cognitive reserve on the association between cerebral damage and the symptoms caused by it. Adopting a similar approach, our study takes this general idea one step further by showing that specific occupational demands show distinct associations with functional neurodegenerative pathology.

Disclosure statement

The authors do not report any conflicts of interest. Appropriate approval and procedures were used concerning human subjects.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuropsychologia.2011.09.025.

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