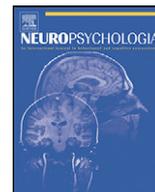




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## Occupation attributes relate to location of atrophy in frontotemporal lobar degeneration

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## ABSTRACT

Frontotemporal lobar degeneration (FTLD) often presents with asymmetric atrophy. We assessed whether premorbid occupations in FTLD patients were associated with these hemispheric asymmetries. In a multi-center chart review of 588 patients, occupation information was related to location of tissue loss or dysfunction. Patients with atrophy lateralized to the right had professions more dependent on verbal abilities than patients with left-lateralized or symmetrical atrophy. In a subgroup of 96 well-characterized patients with quantified neuroimaging data, the lateralization effect was localized to the temporal lobes and included verbal and mathematical ability. Patients whose professions placed high demands on language and mathematics had relatively preserved left temporal relative to right temporal volumes. Thus, occupation selection occurring in early adulthood is related to lateralized brain asymmetry in patients who develop FTLD decades later in the relatively deficient hemisphere. The finding suggests that verbal and mathematical occupations may have been pursued due to developmental right-lateralized functional impairment that precedes the neurodegenerative process. Alternatively, long-term engagement of activities associated with these occupations contributed to left-lateralized reserve, right-lateralized dysfunction, or both.

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## 1. Introduction

Predisposition to dementia may be expressed prior to clinical symptomatology, with significant implications for diagnosis and treatment. In Alzheimer's disease (AD), predisposition can be predicted decades prior to clinical manifestation from analysis of diary writings (Snowdon et al., 1996). Additionally, prodromal signs can be observed in the form of mild cognitive impairment years before those patients convert to dementia (Petersen et al., 2001). In keeping with the theory of cognitive reserve (Stern, 2006), certain life

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experiences have been attributed to protective effects that forestall the symptoms of dementia despite an ongoing degenerative process. The expression of AD may be attenuated by years of education (Stern et al., 1994), whereby individuals with higher levels of education present with few or no symptoms of Alzheimer's despite levels of postmortem pathology that are similar in severity to those seen in lower education individuals who are symptomatic (Roe, Xiong, Miller, & Morris, 2007). Higher occupational attainment is also associated with reserve capacity in the attenuation of AD symptoms (Stern et al., 1994). Additionally, there is evidence for an association between specific occupational factors (interpersonal skills, physical demands) and Alzheimer's-related parietal regional cerebral blood flow (Stern et al., 1995), further supporting the theory of cognitive reserve.

Frontotemporal lobar degeneration (FTLD) is as common a cause of dementia as AD in people under 65 years of age (Knopman, Petersen, Edland, Cha, & Rocca, 2004; Ratnavalli, Brayne, Dawson, & Hodges, 2002). This disease is characterized by either (a) early and progressive change in personality, characterized by difficulty in modulating behavior, often resulting in inappropriate responses or activities, or (b) early and progressive change in language, characterized by problems with expression of language or severe naming difficulty and problems with word meaning (McKhann et al., 2001). Atrophy in FTLD often begins asymmetrically, with the cognitive and behavioral changes associated with the lateralized origin of atrophy (Boone et al., 1999; Edwards-Lee et al., 1997; Thompson, Patterson, & Hodges, 2003).

There is a high degree of variability in the clinical manifestations of FTLD, dependent upon origin of the hemispheric degeneration, the extent of disease progression, and individual differences that may relate to cognitive reserve and cognitive style. Furthermore, the FTLD phenotype may manifest early in life, with one study reporting that healthy individuals carrying tau gene mutations were impaired on tests sensitive to frontal lobe function decades prior to potential onset of the disease (Geschwind et al., 2001). In support of cognitive reserve in FTLD patients, inverse relationships between years of education and job skill level with frontal pathology, as measured by regional cerebral metabolic rate and regional cerebral blood flow, have been observed (Borrioni et al., 2009; Perneczky, Diehl-Schmid, Drzezga, & Kurz, 2007). There is some evidence to suggest a relationship between pre-symptomatic abilities and laterality of degeneration in FTLD. In a small case series, verbal learning disabilities were noted to be elevated in patients who later developed primary progressive aphasia, a subtype of FTLD with left-lateralized degeneration (Mesulam & Weintraub, 1992).

Case studies have described FTLD patients who chose professions dependent upon the activity of one hemisphere and eventually developed atrophy that was greatest in the contralateral hemisphere. Alajouanine (1948) reported a case of progressive cerebral atrophy with a progressive non-fluent aphasia in the composer Maurice Ravel. More recently, visual artists and musicians, individuals with professions that are heavily dependent on the right hemisphere, have been reported with aphasia due to left temporal atrophy (Mell, Howard, & Miller, 2003; Miller, Boone, Cummings, Read, & Mishkin, 2000; Seeley et al., 2008). These case studies suggest that FTLD patients who are highly skilled in music or the visual arts may have a propensity to left hemisphere degeneration, either due to premorbid brain vulnerability or to long-term effects of prolonged mental activity. In this study, we assessed whether this association would generalize to a large sample of FTLD patients whose occupations engaged varying degrees of capacity in different skill sets.

We assembled occupation and neuroimaging data from a sample of 588 FTLD patients from nine neurology clinics specialized in the diagnosis of this condition. The patients' occupations were

coded according to a standard database (United States Department of Labor, 2006) containing detailed information regarding the attributes of each occupation, reduced via principle component analysis to verbal, physical, mechanical, mathematic, and visuospatial components. We examined the relationship between these occupation attributes and localized brain abnormalities in two analyses. The first used visual ratings of relative atrophy or hypometabolism in all 588 FTLD patients and the second used quantitative cerebral volumes in a subset of 96 FTLD patients with high quality structural neuroimaging data and more detailed dementia severity information.

## 2. Methods

### 2.1. Participants

Chart reviews were conducted for 812 patients diagnosed with FTLD at dementia clinics specializing in FTLD assessment and research. Inclusion criteria were composed of a diagnosis of FTLD following the criteria of Neary et al. (1998), a primary occupation outside of the home, and abnormal findings on structural and/or functional diagnostic neuroimaging. One hundred and three patients were excluded due to the absence of occupation data, where no career was coded at intake or the patient was a homemaker. Patients who served in the military as the primary occupation were excluded because the United States Department of Labor Standard Occupational Classification Network (O\*Net; United States Department of Labor, 2006) does not collect data on military occupations. An additional 121 patients were excluded due to the absence of neuroimaging data or failure to detect any abnormalities on diagnostic imaging.

Five-hundred eighty-eight patients (354 males) were included in this study (133 were contributed from the UCSF Memory & Aging Center; 107, Mayo Clinic, Jacksonville; 102, MRC Cognition & Brain Sciences Unit, Cambridge; 87, Department of Psychiatry of the Technische Universität München; 44, University of Texas Southwestern Medical Center; 39, Rancho Los Amigos/USC Alzheimer's Disease Center, Los Angeles; 39, Sunnybrook Health Sciences Centre, Toronto; 24, West Los Angeles VA Medical Center; 13, Baycrest Centre, Toronto). Of the sample, 303 were diagnosed with frontotemporal dementia, 120 with primary progressive (non-fluent) aphasia, and 142 with semantic dementia (Neary et al., 1998). An additional 23 patients with disorders that are part of the spectrum of FTLD (McKhann et al., 2001) were studied, including 12 with a primary diagnosis of progressive supranuclear palsy, 8 with corticobasal degeneration, and 3 with amyotrophic lateral sclerosis (ALS) with FTLD. Of these 588 patients, 32 had died and had autopsy-confirmation of pathology consistent with FTLD, including ubiquitin-positive, tau-negative inclusions with or without degeneration of the motor neurons, or tau-positive Pick bodies, or tau-positive inclusions associated with related disorders (progressive supranuclear palsy or cortical basal degeneration), or dementia lacking distinctive histology.

The charts of 30 patients did not indicate the number of years of education. To avoid exclusion of these cases due to list wise deletion in statistical analyses, these missing data values were replaced with the typical number of years of education for each respective profession as indicated by the O\*Net database (United States Department of Labor, 2006). To confirm that this data replacement did not bias the results, we repeated the analyses excluding patients without education data. Because this did not significantly affect the results, we present data from the full sample. Four hundred forty-eight patients were right-handed, 37 left-handed, six ambidextrous; 97 charts contained no handedness information. In a preliminary analysis, we included handedness as a covariate in a sub sample of 491

patients. Handedness was not a significant covariate, nor did its inclusion significantly affect the results. As such, we present data from the full sample without handedness as a covariate.

Data from 96 of the UCSF patients who had undergone high-resolution structural neuroimaging were subjected to more in-depth analyses. This sample, while smaller than the above sample, afforded the advantages of uniformly quantified neuroimaging, multiple measures of disease severity (disease duration, clinically rated severity with the clinical dementia rating scale (CDR; Morris, 1993), and global atrophy) and a comparison group of matched AD patients from the same clinic. 42 of these 96 patients were diagnosed with frontotemporal dementia, 14 with primary progressive (non-fluent) aphasia, and 20 with semantic dementia (Neary et al., 1998). Eleven additional patients were included with a primary diagnosis of progressive supranuclear palsy, six with corticobasal degeneration, and three with ALS with FTLD. The duration of illness, calculated as the difference between age at MRI and clinically determined age of onset, was available for 86 patients. Dementia severity, measured by the CDR scale (Morris, 1993) within three days of acquiring brain imaging, was available for 89 patients. These data, along with demographic data, are presented in Table 1. As a comparison group, 30 patients diagnosed with probable AD according to the NINCDS-ADRDA criteria (McKhann et al., 1984) were included. These patients were comparable in age and years of education to the FTLD group (see Table 2). Structural neuroimaging data from 37 healthy comparison subjects, matched in age and education to the patients (see Table 2) was used to calculate the degree of atrophy. All patients and healthy controls were right-handed.

*Coding of occupation and derivation of occupation component scores.* Patients' occupations were coded according to O\*Net, the United States Department of Labor Standard Occupational Classification Network (United States Department of Labor, 2006). This database provides a classification for all workers into one of over 796 occupations according to their occupational definition. For patients engaged in more than one occupation, the occupation with the longest duration was included in the analysis, consistent with most studies of occupation and dementia (e.g., Helmer et al., 2001; Potter, Plassman, Helms, Foster, & Edwards, 2006; Stern et al., 1995; Sutedja et al., 2007).

O\*Net 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. An alternative international standard occupation classification system (the ISCO-88) was ill suited for comparing occupation characteristics across occupations. While a cultural bias in occupation attributes due to our use of the O\*Net cannot be ruled out, we have no basis to expect this from patients attending academic dementia clinics in Canada, Germany, the United Kingdom and the United States.

O\*Net contains 128 descriptor variables concerning abilities, skills, and general work activities comparable across all occupations derived from surveys of workers and job analysts. We used principle component analysis to reduce the 128 variables to composite scores describing broad characteristics of occupations that were in turn related to the degree of hemispheric abnormalities in FTLD patients (see below). A principle component analysis was conducted on the occupation ratings variables with all 796 O\*Net occupations treated as "participants". A scree test (Cattell, 1966) revealed that the sixth component was nearly indistinguishable in slope from the subsequent components, supporting an interpretation of a five-component solution. The five components account for approximately 70% of the variance. As such, five components were retained and an orthogonal rotation was then performed to maximize the variance of the squared loadings within the components. The five components comprised verbal (accompanied by social

capacities and general intellectual demands), physical, mechanical, mathematical, and visuospatial capacities (see Supplemental Table 1). On the basis of component saturation (the absolute magnitude of the loadings), the five components are considered a stable representation of the population parameter (Guadagnoli & Velicer, 1988; Stevens, 2002).

The five components derived from the principal component analysis are largely consistent with the Dictionary of Occupational Titles (United States Employment Service, 1991) factor analyses of worker functions and worker characteristics that has also been used in studies of dementia (Cain, 1981; Link, Lennon, & Dohrenwend, 1993; Potter et al., 2006; Smyth et al., 2004; Stern et al., 1994). One major difference between the Dictionary of Occupational Titles factor scores is the division of mental, managerial and interpersonal factors. The present analysis combines these attributes along the common thread of verbal behavior. Although our verbal component contains items related to social capacities, these have a common pathway through verbal behavior. In the workplace, occupations with high verbal demands as characterized by O\*Net (e.g., administration) are inherently interpersonal, and vice versa. Accordingly, occupations rated low on this component (e.g., manufacturing worker) have little or no interpersonal requirements (see Supplemental Table 2). Both analyses also found a physical component, although the present analysis does not distinguish the physical from the motor (e.g., Link et al., 1993). The mathematical component was unique to the component structure of occupations from the O\*Net database. Overall, the commonalities between the analyses are remarkable considering the component scores were derived from a set of data that differed in the number and type of descriptor variables, method of measurement, and occupation classification.

In order to calculate the component scores for each occupation, each of the 128 occupation attributes were multiplied by the corresponding loading and summed for each of the five components. These values were then standardized, each with a mean of zero and standard deviation of one. Scaling of the computed scores was such that higher values indicated greater levels of engagement in the parameter. As a result, each patient had five occupation scores, reflecting each of the occupational dimensions. Examples of the occupational scores that were highest and lowest for each of the five components can be found in Supplemental Tables 2A and 2B.

*Imaging.* In order to estimate the degree of imaging abnormalities for the larger sample of patients, imaging data were derived from different imaging platforms depending on availability in this multi-centre study, including SPECT, fluoro-deoxy-glucose PET, or structural MRI. While different platforms and analysis methods are differentially sensitive to pathology and may have increased the noise in the data, there is no reason to expect that the combination of such methods would produce a systematic bias into the investigation of the relationship between occupation and brain imaging data.

Degeneration was coded from the earliest scan in which abnormalities were detected as included in radiologists' reports where available ( $n=455$ ), as rated by a neurologist with expertise in FTLD ( $n=37$ ), or, for those patients included in the second set of analyses ( $n=96$ ; see below), volumetric measures of MRIs. All coding was accomplished blind to occupation data. Patients were classified according to location of greatest abnormality in terms of hemisphere and lobe (right, left, frontal, temporal). When abnormalities were bilateral, but with evidence of asymmetry, this was reflected in the coding (e.g., if a patient was characterized with frontal atrophy, left greater than right, they were coded as left frontal). When atrophy was judged to be symmetrical across hemisphere or lobes (e.g., bifrontal atrophy), patients were classified as showing bilateral atrophy. Although this method is coarse, it was the only way to harmonize the imaging data for the present study across centers.

**Table 1**  
Patient group means and standard deviations for demographic and neuropsychological data.

	Left temporal			Right temporal			Left frontal			Right frontal			Alzheimer's		
	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n
Age	62.66	8.49	32	61.00	6.04	24	61.17	10.05	23	61.41	9.14	17	62.17	10.62	30
Education	16.44	3.32	32	15.71	2.66	24	16.04	2.23	23	15.47	2.45	17	15.10	3.88	30
Onset age	59.33	9.48	26	55.76	6.65	23	57.33	10.34	21	57.82	10.43	16	57.54	10.52	24
Duration	4.12	3.10	26	5.48	3.62	23	4.71	3.73	21	3.69	1.78	16	5.17	3.83	24
CDR	.77	.50	31	1.21	.73	21	.60	.34	21	.78	.41	16	.95	.48	30
Global atrophy	-1.05	0.97	32	-1.38	0.89	24	-1.25	1.01	23	-1.72	1.04	17	-1.42	0.88	30
Gender (M/F)			20/12			13/11			10/13			12/5			16/14

**Table 2**  
Age and education by gender for healthy controls, FTL and AD patients.

		Healthy controls		FTLD		Alzheimer's disease	
		Mean	SD	Mean	SD	Mean	SD
Male	Age	63.91	10.31	61.73	8.84	66.06	11.38
	Education	17.27	2.10	16.56	2.67	15.93	4.86
	N	22		55		16	
Female	Age	64.00	8.64	61.59	7.84	57.71	7.87
	Education	15.60	1.76	15.22	2.72	14.14	2.11
	N	15		41		14	

Two-hundred seventy-three patients were coded as having left-lateralized degeneration, 122 right and 193 bilateral. These same patients were also rated on lobe of degeneration. 229 patients were classified as frontal, 210 as temporal, and 149 as frontotemporal. There were no differences in gender or years of education between these groups (all  $p$ 's > .30).

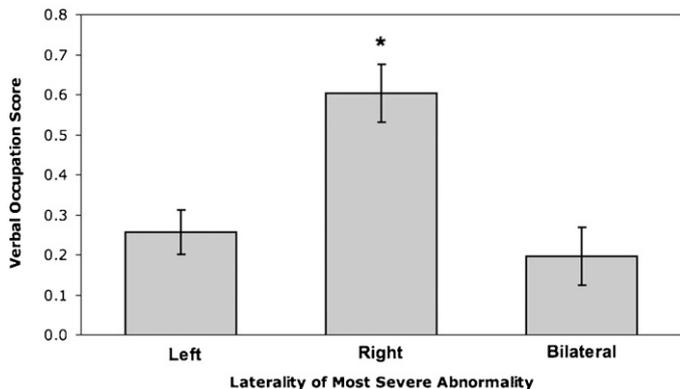
For the subset of 96 UCSF patients, AD patients, and healthy comparison subjects, MRI scans were acquired from a 1.5-T Magnetom VISION system (Siemens Inc., Iselin, NJ) equipped with a standard quadrature head coil. Sequences of the structural MRI included: (i) 2D FLASH MRI along three orthogonal directions, 3 mm slices, approximately 15 slices in each direction to acquire scout views of the brain for positioning subsequent MRI slices, (ii) A double spin echo sequence [repetition time/echo time 1/echo time 2 (TR/TE<sub>1</sub>/TE<sub>2</sub>) = 5000/20/80 ms] to acquire proton density and T<sub>2</sub>-weighted MRIs, 51 contiguous axial slices (3 mm) covering the entire brain and angulated -10° from the AC-PC line; 1.0 mm × 1.25 mm in-plane resolution, (iii) Volumetric magnetization prepared rapid gradient echo MRI [MPRAGE, repetition time/echo time/inversion time (TR/TE/TI) = 10/4/300 ms] to obtain T<sub>1</sub>-weighted images of the entire brain, 15° flip angle, coronal orientation perpendicular to the double spin echo sequence, 1.0 mm × 1.0 mm in-plane resolution and 1.5 mm slab thickness.

Images were processed using the BRAINS2 software package using a standard algorithm to produce lobar volumes (Magnotta et al., 2002). The T<sub>1</sub>-weighted images were spatially normalized and resampled to 1.0 mm<sup>3</sup> voxels so that the anterior-posterior axis of the brain was realigned parallel to the anterior commissure-posterior commissure line and the inter-hemispheric fissure aligned on the other two axes. Next, the outermost boundaries of the cortex, as well as the anterior commis-

sure and posterior commissure, were identified in order to warp the Talairach grid (Talairach & Tournoux, 1988) onto the current brain. The T<sub>2</sub>- and PD-weighted images were then realigned to the spatially normalized T<sub>1</sub>-weighted image using an automated image registration program (Woods, Cherry, & Mazziotta, 1992). The resampled images were then segmented into grey matter, white matter, and CSF using the co-registered images and a discriminate analysis method based on automated training class selection (Harris et al., 1999). This tissue classification algorithm uses a Bayesian classifier based on discriminate analysis in order to reduce the variability in signal intensity across individual image sets and correct for partial voluming. This step requires the manual tracing of venous blood and is subsequently able to perform "plug" selection for grey matter, white matter, and cerebrospinal fluid automatically. Lobar volumes are calculated using an automated Talairach-based method of regional classification that designates individual brain voxels as belonging to a particular lobe based on their location within this standardized space (Harris et al., 1999; Magnotta et al., 2002). This method of lobar classification in Talairach space has been validated for use in atrophied brains (Krueger et al., 2009; Magnotta et al., 2002). Total brain volumes were corrected for head size using the total intracranial volume (Arndt, Cohen, Alliger, Swayze, & Andreasen, 1991), and then converted to z-scores based on the mean and standard deviation derived from healthy controls. Measures of total brain volume are reported as standardized scores, where lower scores are indicative of greater atrophy. Site of greatest atrophy (left frontal, right frontal, left temporal, right temporal) was determined to be the lobe with the largest z-score deviation from normal healthy age and education matched healthy adults. Thus, we were able to identify the specific region of greatest atrophy in each patient. The

**Table 3**  
Occupation factor scores by patient group.

	Left temporal		Right temporal		Left frontal		Right frontal		Alzheimer's	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Verbal	0.31	1.00	0.72	0.63	0.25	1.14	0.22	0.85	0.53	0.82
Physical	-0.46	0.51	-0.51	0.64	-0.37	0.51	-0.39	0.64	-0.08	1.03
Mechanical	-0.69	0.72	-0.04	0.98	-0.41	0.82	-0.24	0.81	-0.25	1.01
Mathematical	-0.17	0.94	0.88	1.41	0.36	1.23	0.85	1.38	-0.03	0.99
Visuospatial	-0.21	0.75	-0.15	0.80	0.10	1.08	-0.04	0.68	0.09	0.99



**Fig. 1.** Verbal occupation component scores are significantly higher for the right-lateralized group than the left- and bilateral group scores (which were not different from each other).

ability to assign patients to discrete groups according to atrophy reflected a major advantage afforded by the precision of quantified MRI data over and above the clinical ratings as done for the larger sample.

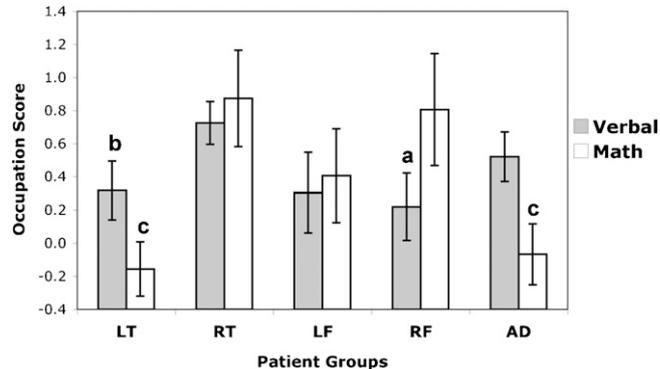
There were no significant differences in age, years of education, age of onset, duration of dementia, or degree of global atrophy (all  $p$ 's > .15; see Table 2) between any of the regional imaging abnormality groups. Differences were found among groups for dementia severity,  $F(4, 114) = 5.21$ ;  $p < .001$ . The left frontal group had significantly lower CDR scores than the right temporal, right frontal and AD patient groups, and the left temporal patients had significantly lower CDR scores than the right temporal and AD patient groups. These effects likely reflect the earlier clinical presentation of patients with language deficits due to left-lateralized degeneration (Rosen et al., 2004).

**Statistical analysis.** Multivariate analysis of covariance (MANCOVA) was conducted to determine the association between site of greatest imaging abnormality and occupation component scores while statistically controlling for potentially confounding factors (for the larger sample, differences in gender and education, for the smaller sample, differences in gender, education, and CDR scores). Follow-up comparisons for occupation scores across groups were adjusted for multiple comparisons with Tukey's least significant difference (LSD) at the .05 level.

### 3. Results

As seen in Fig. 1, verbal scores for patients with right-lateralized degeneration were higher than for patients with left- and bilateral degeneration, which were not different from each other. The reliability of these findings was supported by a main effect of laterality on verbal occupation scores adjusted for gender and years of education ( $F(2, 577) = 4.95$ ;  $p < .01$ ). Across occupation scores, the omnibus MANCOVA statistic showed a trend towards significance for a main effect of laterality (Wilks' Lambda  $F(10, 1146) = 1.59$ ;  $p = .10$ ) but there were no effects of lobe or laterality by lobe interactions. There were no significant effects involving other occupation component scores. See Supplemental Tables 3 and 4 for occupation scores by laterality and region.

There were significant effects of gender and years of education (Wilks' Lambda  $F_s(5, 573) = 20.25$  and  $27.19$ , respectively;  $p$ 's < .001). Men had significantly higher physical scores, mechanical scores, and mathematical scores ( $t$ 's(586) =  $-3.97$ ,  $-3.88$ , and  $-8.20$ , respectively,  $p$ 's < .001). Years of education positively correlated with verbal scores and mathematical scores ( $r$ 's(586) = .41 and .13,  $p$ 's < .001 and .01, respectively). Physical scores were negatively associated with years of education ( $r(586) = -.17$ ,  $p < .001$ ).



**Fig. 2.** FTLD patient groups indicate region with greatest abnormality. LT, left temporal lobe; RT, right temporal lobe; LF, left frontal lobe; RF, right frontal lobe; AD, Alzheimer's disease. (a) lower than RT; (b) lower than RT, AD; (c) lower than RF, RT.

Whereas the analysis of the larger sample revealed lateralization but not lobar effects, the analysis of the smaller sample, where regional changes were more accurately measured, revealed specific lobar effects. For the MANCOVA omnibus test, there was a significant effect of group (i.e. left frontal, right frontal, left temporal, right temporal, AD) when controlling for the influence of gender, years of education and dementia severity (Wilks' Lambda  $F(20, 356) = 1.91$ ;  $p < .01$ ; Table 3). The effect of verbal occupation scores approached significance,  $F(4, 111) = 2.25$ ;  $p < .07$ . There was a significant effect for mathematical scores,  $F(4, 111) = 4.27$ ;  $p < .01$ . As seen in Fig. 2, patients with atrophy that was most severe in the left temporal lobe had significantly lower verbal and mathematical occupation scores than patients with atrophy originating in the right temporal lobe. Their verbal occupation scores were lower than for patients with AD. AD patients shared low mathematical scores with the left temporal group. Significant effects were also noted for patients with right frontal lobe atrophy, who had lower verbal scores than the right temporal atrophy group, but shared the right temporal group's advantage in mathematical scores over the left temporal and AD groups.

These effects were significant after controlling for gender, education, and dementia severity, Wilks' Lambda  $F_s(5, 107) = 5.44$ ,  $13.74$ , and  $2.85$  respectively;  $p$ 's < .001, .001, and .05, respectively. The gender effect was due to higher mathematical scores for men than women ( $t(130) = 3.55$ ,  $p < .001$ ). Years of education positively correlated with verbal occupation scores ( $r(130) = .44$ ,  $p < .001$ ) and negatively correlated with physical scores ( $r(130) = -.24$ ,  $p < .01$ ). Dementia severity was positively correlated with mechanical workmanship ( $r(126) = .27$ ,  $p < .01$ ) and negatively with years of education ( $r(126) = -.32$ ,  $p < .001$ ).

### 4. Discussion

Occupation selection provides a unique view into cognitive style and practice of long-term behaviors predating the onset of symptoms. In this study, we used quantitatively derived occupation scores to measure long-term engagement in specific cognitive activities. We then related these occupation scores to relative degree of hemispheric and lobar pathology in subsequently developing FTLD. Two analyses were conducted. The first used clinically derived estimates of the site of most severe abnormality from heterogeneous imaging platforms that permitted assessment in a large sample of patients. The second was conducted in a subset of patients whose regional cerebral volumes were quantitatively measured. Although smaller, this sample permitted additional analysis of disease progression factors as well as comparison with a group of AD patients.

Both analyses demonstrated an association between verbal occupation attributes and the site of most severe pathology based on imaging. FTLD patients with right-lateralized degeneration engaged in occupations more reliant on verbal abilities than patients with left-lateralized degeneration. The quantitative neuroimaging data available for the second analysis allowed for more precise localization of this effect to the temporal lobe, accompanied by a similar effect for mathematical occupations. The right temporal atrophy patients were drawn towards occupations that placed demands on verbal and mathematical ability, managerial positions and complex problem solving, while left temporal patients were drawn away from such professions, or they may not have been promoted to positions requiring high verbal and mathematical skills (e.g., Schooler, Mulatu, & Oates, 1999). For verbal professions, the left temporal group's disadvantage was robust when they were compared with the AD group, although this was not the case for mathematical occupations.

This analysis also revealed effects specific to patients who had a predominance of right frontal atrophy, who were similar to the right temporal group in their bias towards mathematical occupations, but dissociated from the right temporal group in that they tended to select occupations with low verbal attributes. This suggests that the lateralized effect observed in the first set of analyses may not generalize to the frontal lobe, at least for verbal occupations. Indeed, any reserve capacity conferred by verbal occupations may be more specific to the temporal lobes, where function is more localized, rather than the frontal lobes, where function is more distributed.

Considering the numerous intervening variables likely to determine occupation selection and lateralization effects in FTLD, it is striking that statistically significant effects emerged. The influence of occupational engagement is likely to be distributed throughout the brain, with lateralized specialization contributing to some cognitive components. We emphasize the lateralized effects that were consistent across the two analyses. These convergent effects are not attributable to the inclusion of the subset of 96 well-characterized patients in the larger sample. An ancillary analysis of the larger sample excluding these patients did not significantly alter the pattern of results. Furthermore, results from both analyses indicate that differential effects of gender, years of education, age, disease duration, global atrophy, and symptom severity across groups cannot explain our effects.

Our findings that patients developed degeneration contralateral to the hemisphere putatively supporting their occupational skills are consistent with the pattern of findings from artists with left-lateralized volume loss due to FTLD (Miller et al., 2000). We did not observe elevated visuospatial scores in patients with left-lateralized damage specifically, however (although all five visual artists in our sample had left-lateralized atrophy), possibly due to the heterogeneity of functionally localizable skills among artistic professions, their low prevalence in the overall sample, or the poor characterization of artistic professions by the occupation components. Unlike the previous studies involving artists (e.g., Mell et al., 2003; Miller et al., 2000; Seeley et al., 2008), the present work demonstrates an association between region of most severe pathology and occupation in more prevalent, less specialized careers.

While functional localization at the lobar level is coarse by contemporary standards, occupational attributes as defined here may not demonstrate a finer grain of functional localization. The association of verbal occupation attributes with the left temporal neocortex is consistent with this region's specificity to phonological linguistic operations (Lambon Ralph, McClelland, Patterson, Galton, & Hodges, 2001). Mathematical occupation attributes were also associated with the left temporal neocortex. Indeed individuals with high mathematical competence may rely on linguistic representations to attain high arithmetic precision (Dehaene, Spelke,

Pinel, Stanescu, & Tsivkin, 1999; Grabner et al., 2007). Furthermore, early left hemisphere dysfunction has been associated with verbal and mathematical problem solving difficulties (Hynd, Semrud-Clikeman, Lorys, Novey, & Eliopoulos, 1990; Isaacs, Edmonds, Lucas, & Gadian, 2001; Larsen, Høien, Lundberg, & Odegaard, 1990).

It is unclear whether the findings are specific to FTLD neuropathology or whether they may generalize to asymmetric temporal lobe damage due to other etiologies. In order to test this, a sample of patients capable of engaging the workforce for 20+ years with progressive unilateral disease other than FTLD would be needed. This may be possible to assess in patients with unilateral AD. Our sample of AD patients, however, had relatively symmetrical changes.

The finding of an association between occupation and regions of most severe pathology are differentiated from those related to prodromal signs (Snowdon et al., 1996) or mild cognitive impairment preceding AD (Petersen et al., 2001), as indicated by the relative remoteness of occupational engagement. Rather, these findings suggest that occupational activities within a normal spectrum of behavior may relate to factors that ultimately influence the regions most affected in neurodegenerative disease. The determinants of lateralization of neurodegeneration in FTLD are unclear (Geschwind & Miller, 2001; Kertesz et al., 2000). Genetic influences may contribute to selective vulnerability, susceptibility to pathology resulting from an unknown early neurological insult or, possibly, cognitive style; yet individuals with similar genotypes do not necessarily develop the same lateralization of degeneration in FTLD (Kertesz et al., 2000).

An association between most severe pathology and occupation attributes may reflect a causal effect of occupation on lateralized brain degeneration, a premorbid bias towards occupations with certain characteristics among those vulnerable to FTLD, or an interaction of the two. Long-term practice effects of verbal behavior in the course of an occupation may offer neural protection to the left hemisphere by building reserve status. More generally, cognitive performance spanning decades may strengthen resistance to pathology within the supporting neuroanatomy, thereby building localizable neurocognitive reserve. Functional reorganization may extend across cortical representations reflecting patterns of work activity as observed with highly skilled musicians (Pantev et al., 2003) and taxi drivers (Maguire et al., 2000).

Alternately, occupational selection may be optimized to cognitive and physical predispositions, including, in the case of highly verbal and mathematical occupations, incipient right temporal dysfunction. The evidence from artists (Mell et al., 2003; Miller et al., 2000; Seeley et al., 2008) and from the present study suggests an enhancement of function associated with FTLD, especially in the temporal lobe. This process may be indicative of 'compensatory augmentation' (Kapur, 1996) by which left-lateralized functions excel in the context of reduced competition/interference from the right hemisphere. Accordingly, patients with primary progressive aphasia also had reading, spelling and arithmetic difficulties as children (Mesulam & Weintraub, 1992). These findings indicate a "tardative expression of a genetic or acquired vulnerability focused upon the left hemisphere language network" (Mesulam & Weintraub, 1992). This vulnerability could interact with other factors, such as the developmental organization of large-scale brain networks that are associated with vulnerability to disease (Seeley, Crawford, Zhou, Miller, & Greicius, 2009), which in turn support occupation attributes, and determine a site of least resistance in an emergent pathological process.

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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.2010.08.020.

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Supplemental Table 1: Occupation Factor Analysis Results

<u>Factor</u>	<u>Theme</u>	<u>Eigenvalue</u>	<u>Loading Range</u>		<u>No. Items</u>	<u>% Variance explained</u>
			<u>High</u>	<u>Low</u>		
1	Verbal	44.07	0.89	0.42	68	34.43
2	Physical	17.06	0.85	0.51	23	13.33
3	Mechanical	12.58	0.83	0.43	19	9.83
4	Mathematical	8.43	0.73	0.46	10	6.58
5	Visuospatial	7.29	0.64	0.44	8	5.69

Supplemental Table 2A: Highest Scoring Occupations by Component Scores

Verbal	Physical	Mechanical	Mathematical	Visuospatial
Coaches and Scouts	Athletes and Sports Competitors	Refrigeration Mechanics and Installers	Operations Research Analysts	Airline Pilots, Copilots, and Flight Engineers
Education Administrators, Elementary and Secondary School	Choreographers	Mobile Heavy Equipment Mechanics, Except Engines	Mathematicians	Police, Fire, and Ambulance Dispatchers
Athletic Trainers	Structural Iron and Steel Workers	Stationary Engineers and Boiler Operators	Aerospace Engineers	Commercial Pilots
Nursing Instructors and Teachers, Postsecondary	Municipal Fire Fighters	Rotary Drill Operators, Oil and Gas	Astronomers	Bus Drivers, Transit and Intercity
Chief Executives	Dancers	Electronics Engineering Technicians	Physicists	Police Identification and Records Officers
Education Administrators, Postsecondary	Commercial Divers	Avionics Technicians	Mathematical Technicians	Air Traffic Controllers
Social Work Teachers, Postsecondary	Police Patrol Officers	Respiratory Therapy Technicians	Numerical Tool and Process Control Programmers	Police Patrol Officers
First-Line Supervisors/Managers of Police and Detectives	Truck Drivers, Heavy and Tractor-Trailer	Anesthesiologists	Marine Architects	Taxi Drivers and Chauffeurs
Education Administrators, Preschool and Child Care Center/Program	Farmworkers and Laborers, Crop	Medical Equipment Repairers	Agricultural Engineers	Medical and Clinical Laboratory Technicians
Education Teachers, Postsecondary	Ship and Boat Captains	Automotive Specialty Technicians	Computer Software Engineers, Systems Software	Auditors

Supplemental Table 2B: Lowest Scoring Occupations by Component Scores

Verbal	Physical	Mechanical	Mathematical	Visuospatial
Watch Repairers	Electrical Engineering Technicians	Umpires, Referees, and Other Sports Officials	Psychiatric Aides	Tile and Marble Setters
Potters, Manufacturing	Computer Systems Analysts	Travel Guides	Funeral Attendants	Education Administrators, Elementary and Secondary School
Shoe Machine Operators and Tenders	Chemists	Talent Directors	Physical Therapist Assistants	Brickmasons and Blockmasons
Data Entry Keyers	Technical Writers	Agents and Business Managers of Artists, Performers, and Athletes	Surgical Technologists	Stationary Engineers and Boiler Operators
Cutters and Trimmers, Hand	Electronics Engineering Technicians	Human Resources Managers	Clergy	Athletic Trainers
Fabric Menders, Except Garment	Computer Programmers	Private Detectives and Investigators	Shuttle Car Operators	Dancers
Painting, Coating, and Decorating Workers	Computer Software Engineers, Applications	Crossing Guards	Massage Therapists	Tree Trimmers and Pruners
Photographic Process Workers	Medical Transcriptionists	Dancers	Bailiffs	Roofers
Gem and Diamond Workers	Court Reporters	Choreographers	Dental Hygienists	Plasterers and Stucco Masons
Sewers, Hand	Computer Support Specialists	Athletes and Sports Competitors	Flight Attendants	Fitness Trainers and Aerobics Instructors

Supplemental Table 3: Occupation scores by laterality

<u>Occupation Score</u>	<u>Laterality</u>	<u>Mean</u>	<u>SD</u>
Verbal	Left	0.26	0.92
	Right	0.60	0.79
	Bilateral	0.20	1.01
Mechanical	Left	-0.43	0.85
	Right	-0.27	0.94
	Bilateral	-0.27	0.85
Physical	Left	-0.10	0.89
	Right	-0.14	0.78
	Bilateral	-0.10	0.89
Visuospatial	Left	-0.29	0.81
	Right	-0.30	0.73
	Bilateral	-0.18	1.13
Mathematical	Left	0.14	1.15
	Right	0.14	1.22
	Bilateral	0.30	1.24

Supplemental Table 4: Occupation scores by region

<u>Occupation Score</u>	<u>Region</u>	<u>Mean</u>	<u>SD</u>
Verbal	Frontal	0.24	0.96
	Temporal	0.37	0.92
	Frontotemporal	0.31	0.93
Mechanical	Frontal	-0.34	0.84
	Temporal	-0.40	0.86
	Frontotemporal	-0.29	0.93
Physical	Frontal	-0.08	0.93
	Temporal	-0.07	0.84
	Frontotemporal	-0.21	0.81
Visuospatial	Frontal	-0.24	0.91
	Temporal	-0.28	0.87
	Frontotemporal	-0.26	0.99
Mathematical	Frontal	0.19	1.19
	Temporal	0.08	1.10
	Frontotemporal	0.36	1.32