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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.

1. Introduction

Predisposition to dementia may be expressed prior to clinical symptomology, 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 (Borroni 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 FLTD 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 FLTD 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