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ORIGINAL RESEARCH

Occupational attainment influences longitudinal decline in behavioral variant frontotemporal degeneration

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Abstract

To evaluate whether occupational attainment influences the trajectory of longitudinal cognitive decline in behavioral variant frontotemporal degeneration (bvFTD). Single-center, retrospective, longitudinal study. Sixty-three patients meeting consensus criteria for bvFTD underwent evaluation at the University of Pennsylvania Frontotemporal Degeneration Center. All patients were studied longitudinally on letter-guided fluency, category-naming fluency and Boston Naming Test (BNT). Occupational attainment was defined categorically by assigning each individual's occupation to a professional or non-professional category. Linear mixed-effects models evaluated the interaction of neuropsychological performance change with occupational status. Regression analyses were used to relate longitudinal decline in executive function to baseline MRI grey matter atrophy. Higher occupational status was associated with a more severe slope of cognitive decline on letter-guided fluency and category-naming fluency, but not BNT. Faster rates of longitudinal decline on letter-guided and category-naming fluency were associated with more severe baseline grey matter atrophy in right dorsolateral and inferior frontal regions. Our longitudinal findings suggest that bvFTD individuals with higher lifetime cognitive experience demonstrate more rapid decline on measures of executive function. This finding converges with cross-sectional evidence suggesting that lifetime cognitive experiences contribute to heterogeneity in clinical progression in bvFTD.

Keywords Frontotemporal degeneration · Cognitive reserve · Occupation · MRI

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Introduction

Models of cognitive reserve posit that lifetime cognitive experiences such as education, occupation and leisure activities are related to cognitive strategies and neural connectivity that support brain functioning in the face of neurodegenerative disease, and therefore may play a moderating role in the rate of longitudinal cognitive decline (Steffener and Stern 2012). In Alzheimer's disease (AD), it has been suggested that individuals with higher education and occupational attainment associated with cognitive reserve are able to compensate in part for the consequences of underlying neurodegenerative disease pathology and thus slow or delay the emergence of clinical symptoms (Stern 2009). Once symptomatic, however, a more rapid clinical course may ensue (Stern et al. 1999) with a shorter duration of clinical disease (Stern et al. 1995).

While it has been established that cognitive reserve may contribute to the observed patterns of longitudinal progression in patients with AD, few studies have evaluated how lifetime cognitive experiences influence progression in frontotemporal degeneration (FTD). Cross-sectional studies of FTD have demonstrated that individuals with higher occupational attainment and education levels have longer survival (Massimo et al. 2015) and more dense inferior frontal cortex grey matter (GM) (Placek et al. 2016). We interpreted this evidence as support for cognitive reserve, although this could also be related to brain reserve or earlier detection of symptoms in FTD patients with higher education and occupational levels. However, these findings were in clinically heterogeneous cohorts of FTD patients and did not assess the longitudinal trajectory of decline in individuals.

The most common syndrome associated with FTD is the behavioral variant (bvFTD), manifesting as significant impairments in executive function and regulation of social behavior (Rascovsky et al. 2011). Early frontal disease may limit access to cognitive resources like strategic planning and mental flexibility that are hypothesized to contribute to mechanisms of compensation in individuals with high cognitive reserve (Puente et al. 2015). Therefore, bvFTD patients with high cognitive reserve who have high occupational attainment may rely heavily on these resources during daily professional activities, and thus they may be at a disadvantage early in the course of disease due to their limited executive resources and present earlier with a longer disease course. The possible role of cognitive reserve on cognitive performance in FTD has been investigated in a small number of studies, but these are cross-sectional in nature (Fairjones et al. 2011; Premi et al. 2015). Longitudinal studies are essential to address the causal impact of occupational attainment on the rate of cognitive decline, but these are rare in FTD (Grossman et al. 2008; Ramanan et al. 2016; Ranasinghe et al. 2016) and have not previously considered factors related to cognitive reserve. Moreover, cognitive reserve in bvFTD has been related to prefrontal cortex (Placek et al. 2016), a brain region implicated in executive functioning, but this study was cross-sectional in design. In the present study, we examine: (1) the effects of occupational attainment on longitudinal cognitive decline in bvFTD, and (2) the anatomic basis for longitudinal change in these patients. To determine whether there are differing effects depending on executive resource demand, we assessed patients on two executive function tasks involving lexical retrieval that are resource demanding and a confrontation naming task requiring lexical retrieval with less demand on executive resources.

Methods

Patients

A total of 63 patients with a clinical diagnosis of probable bvFTD (Rascovsky et al. 2011) and at least one sufficient neuropsychological assessment on each verbal fluency and confrontation naming test were included in this study. Patients with a diagnosis of motor neuron disease or amyotrophic lateral sclerosis (MND/ALS), Corticobasal Degeneration (CBD) and Progressive Supranuclear Palsy (PSP) were excluded due to their known, shorter clinical survival associated with motor factors (Hu et al. 2009; Xie et al. 2008) and to minimize potential motor-related confounds on verbally-mediated cognitive tasks. Likewise, patients with clinical evidence for primary progressive aphasia (PPA) or another form of language impairment, as identified using the Philadelphia Brief Assessment of Cognition (PBAC) (Avants et al. 2014; Libon et al. 2007a) were also excluded because their language difficulty makes it challenging to assess true performance on verbal measures of executive function. All patients were initially evaluated at the University of Pennsylvania Frontotemporal Degeneration Center by experienced cognitive neurologists (DJI, MG) using published consensus criteria (Rascovsky et al. 2011), subsequently confirmed by a multidisciplinary consensus committee based on history and neurological examination including a detailed mental status evaluation (Folstein et al. 1975; Libon et al. 2007b). Medical and psychiatric causes of dementia were excluded by clinical exam, blood tests, and clinical neuroimaging. All subjects completed a written informed consent procedure in accordance with the Declaration of Helsinki and approved by the institutional review board of the University of Pennsylvania.

The subject's occupation of longest duration was classified and ranked as previously described (Massimo et al. 2015), based on US census categories. Patients were categorically-defined as non-professionals and professionals, as used in previous studies of cognitive reserve (Stern et al. 1999). The non-professional group consisted of craftsmen, foreman, laborers and operative service workers. The professional group consisted of managers, administrators, clerical, sales and technical workers. Patients classified as "no occupation" were omitted because of their heterogeneity (i.e., this group consisted of unemployed subjects and homemakers). We also recorded years of education. Education was dichotomized into low (< 16 years) and high (≥ 16 years equivalent to college graduate or higher). We report our educational analyses in Supplement S-1.

Participants were relatively early in the course of their disease, with a disease duration since symptom onset of about 3 years. Table 1 summarizes the demographic features of these patients.

Cognitive assessments

To evaluate the hypothesized role of frontal contributions we report two verbally-mediated measures of executive functioning widely recognized to involve planning, mental organization and working memory and a control, non-frontal measure involving lexical retrieval with minimal executive resource demands. For example, verbal fluency involves mental search and working memory, two dimensions of executive function (Cook et al. 2014). Confrontation naming is a task involving picture naming, that relies largely on semantic knowledge and less on executive resources.

The baseline visit is defined as the date of the initial evaluation on the cognitive measure (e.g., letter-guided fluency, category-naming fluency or Boston Naming Test (BNT). While time to baseline visit from symptom onset may vary from individual to individual for a variety of clinical reasons, we did not observe differences in lag time (i.e. symptom onset until baseline visit) by occupational status ($t = 0.07$, $df = 13$; $p = .94$) suggesting that any group differences in longitudinal neuropsychological performance is not confounded by factors that influence time to diagnosis (e.g., socioeconomic factors). See Table 2 for mean performance at baseline.

We evaluated 63 well-characterized bvFTD patients across 243 letter-guided fluency observations (median = 3; mean months between visits = 23.54), 145 category-naming observations (median = 2; mean months between visits = 26.04) and 112 observations on BNT (median = 1; mean months between visits = 29.54). Follow up time and number of outcomes collected could vary for a variety of reasons including intercurrent illness, death, unwillingness to participate due to disease progression and transportation issues (Table 3).

Letter-guided fluency

Patients were asked to name as many unique words beginning with the letter 'F' as possible in 60 s. The number of responses was recorded.

Category-naming fluency

Patients were asked to produce as many unique names of animals as possible in 60 s. The total names produced was recorded.

Table 1 Mean (standard deviation) demographic features of behavioral variant frontotemporal degeneration patients (N = 63)

	Professionals	Non-professionals	p-value
Sex, male/female	36/14	12/1	0.12
Baseline age, years	62.5 (±7.4)	62.0 (±13.5)	0.89
Education, years	17.1 (±2.7)	12.8 (±2.3)	< 0.0001
Baseline MMSE, max 30	24.2(±5.7)	22.2 (±5.1)	0.24
Baseline disease Duration, years	3.1 (±2.0)	3.2 (±4.0)	0.94
Final visit MMSE	20.6 (±8.3)	20.2 (±6.6)	0.90
Final visit disease duration, years	5.2 (±2.7)	6.5 (±4.3)	0.32

Table 2 Baseline neuropsychological performance

	Professionals	Non-professionals	p-value
Mean (*SD*) letter-guided fluency score at baseline	8.0 (±5.1)	5.1 (±3.0)	0.01*
Mean (*SD*) category-naming fluency score at baseline	12.3 (±6.1)	10.7 (±4.0)	0.39
Mean (*SD*) Boston naming test score at baseline (max = 30)	22.6 (±6.9)	24.3 (±3.2)	0.21

Table 3 Anatomic locus of peak voxels in clusters relating longitudinal decline in executive function to grey matter density in behavioral variant frontotemporal degeneration

Peak voxels where grey matter is correlated with decline in executive function				
Location (Brodmann area)	Cluster coordinates[a]			Cluster size (voxels)
	X	Y	Z	
Letter-guided fluency				
Dorsomedial prefrontal cortex (8)	6	38	36	158
Inferior frontal gyrus (44)	48	8	24	147
Anterior cingulate (32)	−2	30	32	130
Dorsomedial prefrontal cortex (8)	24	34	42	94
Inferior frontal gyrus (6/44)	60	2	6	58
Category-naming fluency				
Dorsolateral prefrontal cortex (9)	44	2	40	105
Middle temporal gyrus (21)	54	-40	0	62

[a]Peak locus of these clusters are derived from Montreal Neurological Institute (MNI) space converted to Talairach space using MNI2TAL

Boston naming test (BNT)

Visual confrontation naming was assessed with a 30-item version of the BNT(Kaplan et al. 1983). The stimuli were equally divided into high-frequency, mid-frequency and low-frequency items. Patients were given as much time as they needed to respond. The total number of correct responses was recorded.

Neuroimaging acquisition and analysis

MRI was available in 55 patients. Participants underwent a structural T1-weighted MPRAGE MRI acquired from a SIEMENS 3.0T Trio scanner with an 8-channel coil using the following parameters: repetition time = 1620msec; echo time = 3msec; slice thickness = 1.0 mm; flip angle = 15°; matrix = 192 × 256, and in-plane resolution = 0.9 × 0.9 mm. The MRI was collected on average 2.9 months (SD = 3.6) of the baseline verbal fluency measure. T1 image preprocessing was performed using Advanced Normalization Tools (ANTs) which provides a state-of-the-art pipeline as previously reported(Tustison et al. 2014). Briefly, we first perform N4 bias correction of all images to minimize image inhomogeneity effects that could otherwise yield artificial intensity variation and bias segmentation priors. We then perform brain extraction using a combination of template-based and segmentation strategies. This involves registering a dilated template brain to each individual subject brain that can then be used to guide brain segmentation from the full MRI volume. We then perform Atropos six-tissue class (cortex, deep grey, brainstem, cerebellum, white matter, and cerebrospinal fluid/other) segmentation using an optimized combination of prior knowledge from N4 bias-correction and template-based priors to guide the segmentation process (Tustison et al. 2010). Finally, to make group-level inferences we use a diffeomorphic and symmetric registration algorithm to warp each grey matter map to a a standard template space derived from scans of the Open Access Series of Imaging Studies (OASIS) dataset (Marcus et al. 2007) that is comprised of a demographically-comparable cohort of aging healthy controls with no report of neurological or psychiatric impairment. The resulting grey matter images were then downsampled to 2 mm isotropic voxels and smoothed using a 4 mm FWHM Gaussian kernel. We report voxelwise analyses of grey matter (GM) density.

Statistical methods

Descriptive statistics were calculated for demographic and for clinical variables we assumed unequal variances. Linear mixed-effects models (Laird and Ware 1982) independently evaluated the influence of occupation on three outcome measures that included letter-guided fluency, category-naming fluency and BNT. The fixed-effects in the linear mixed-effects models included occupation, baseline scores, and time. To focus on the influences of lifetime cognitive experiences on longitudinal decline we report time by occupation category interactions. Time was defined as the duration in years between initial evaluation and follow-up testing. All models additionally covaried for baseline letter-guided fluency, category-naming fluency or BNT performance. Subject-specific random intercepts were used to account for the correlation between repeated measures. For each model, we report an overall pseudo-R^2 statistic to summarize the overall fit of the model (Singer and Willett 2003) and we also report an adjusted-R^2-like pseudo-R^2 statistic (which we refer to for brevity as "within-person pseudo-R^2") to assess the proportion of within-person variation in outcomes explained by time which was computed using the estimated variance of the residual error from the unconditional means and growth models (Singer and Willett 2003). We adopted Cohen's (1988) guideline for the within-person pseudo-R^2 statistics to report standardized effect sizes. All analyses were conducted using the statistical software package SAS version 9.3 (SAS Institute Inc., Cary, North Carolina). All statistical tests were two-sided.

Voxelwise analyses of GM density were performed using the non-parametric randomise tool implemented in the FMRIB Software Library (FSL: http://fsl.fmrib.ox.ac.uk) with 10,000 permutations, as previously reported (Winkler et al. 2014). To identify regions of reduced GM density we compared bvFTD relative to 55 demographically matched healthy controls who self-report no psychiatric or neurological history (mean age = 61.2, mean education = 16 years).

We report clusters that survive family-wise error (FWE) correction of $p < .05$ and a minimum of 200 adjacent voxels. To examine the neuroanatomical basis of longitudinal decline in neuropsychological performance across the range of occupational attainment in our cohort, we extracted individual subjects slopes from the fitted regression models of the significant behavioral findings including: letter-guided fluency and category-naming fluency. These slopes were derived from statistical models that evaluated an occupation by time interaction; therefore, the slope values used in our imaging regression account for occupational status. Nuisance covariates were included for baseline letter-guided fluency or category-naming fluency score. We report clusters that survive $p < .01$ and a minimum of 50 adjacent voxels.

Results

Baseline characteristics

As summarized in Table 2, baseline performance on category-naming fluency and BNT did not differ between professional and non-professional groups. At baseline, professionals had higher scores on letter-guided fluency.

Longitudinal characteristics

As summarized in Fig. 1, professionals' annual decline on letter-guided fluency was 0.9 words/minute and non-professionals declined annually at a rate of 0.2 words/minute, indicating that professionals declined at a rate that is more than four times faster than non-professionals ($t = 3.22$, $df = 178$; $p = .001$; overall pseudo-$R^2 = 0.58$; within-person pseudo-$R^2 = 0.30$). Given the difference between professional and non-professional at baseline, we generated an additional regression model that included a baseline by occupation group interaction and our key longitudinal effect remained significant.

Professionals declined annually on category-naming fluency at a rate of 1.78 words/minute and non-professionals declined at a rate of 0.75 words/minute, again indicating that the professionals declined more than twice the rate of non-professionals ($t = 3.12$, $df = 80$; $p = .002$; overall pseudo-$R^2 = 0.76$; within-person pseudo-$R^2 = 0.43$) (see Fig. 1).

Professionals' annual decline on BNT was 0.86 words/minute and non-professional declined annually by 1.22 words/minute, indicating little difference on the rate of decline on BNT between professionals and non-professionals ($t = 0.82$, $df = 47$; $p = .41$; overall pseudo-$R^2 = 0.70$; within-person pseudo-$R^2 = 0.60$). Comparable data for this and the analyses above are presented in Supplement S-1: Longitudinal performance on letter-guided fluency, category-naming fluency and BNT between education groups.

The overall pseudo-R^2 statistics indicate a good overall fit for all regression models. Based on Cohen's (1988) guideline for the within-person pseudo-R^2 statistics, our results suggest that time has a large effect on the outcomes (Cohen 1988; Kwok et al. 2008).

Imaging results

Figure 2 illustrates reduced GM density in frontal and temporal areas in bvFTD relative to healthy controls. Regression analyses evaluating each individual's slope to baseline GM density identified that more rapid cognitive decline on letter-guided fluency was related to less dense GM in the dorsomedial and

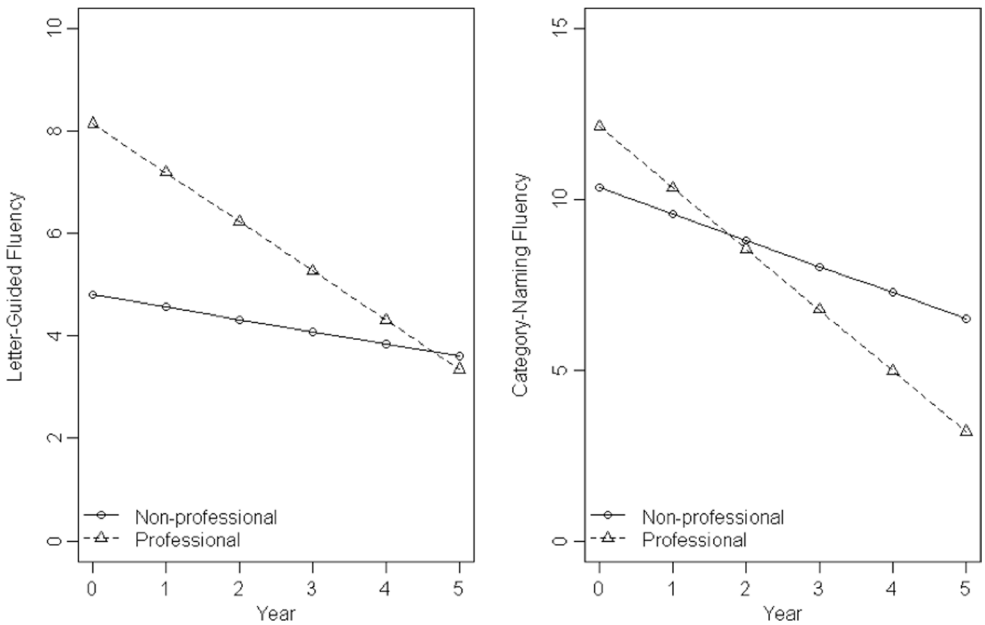

Fig. 1 Longitudinal decline on letter-guided fluency and category-naming fluency by professional status. *Note: Year 0 is the time of the first evaluation on letter-guided fluency and category-naming fluency

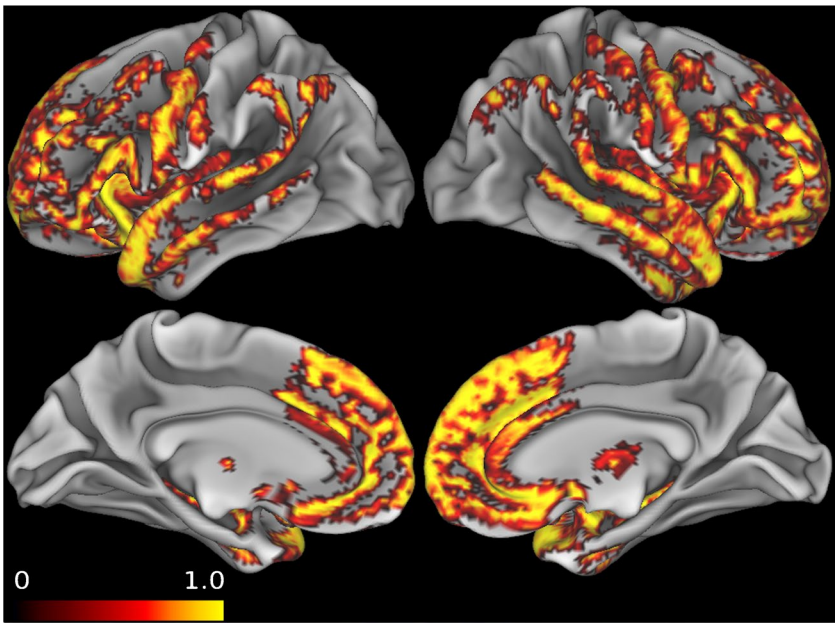

Fig. 2 Significant grey matter atrophy in behavioral variant frontotemporal degeneration

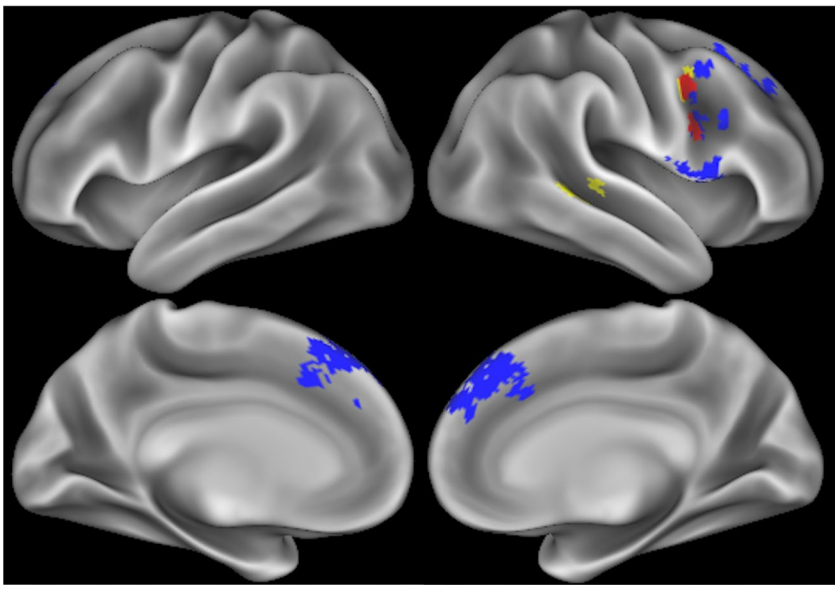

Fig. 3 Regressions relating longitudinal decline on executive cognitive measures to grey matter density. *Note: Significant regressions relating decline in letter-guided fluency (blue) and category-naming fluency (yellow) to reduced baseline grey matter density. Area of significant overlap (red)

inferior frontal regions as well as anterior cingulate (Fig. 3, blue). We also found that reduced density in the dorsolateral prefrontal cortex and middle temporal gyrus at baseline was associated with a more rapid decline on category-naming fluency (Fig. 3, yellow). Areas of significant overlap include right inferior frontal cortex and dorsolateral regions (Fig. 3, red).

Discussion

This study investigated the relationship between lifetime cognitive experiences, including occupational attainment on longitudinal decline in bvFTD. We found that higher occupational attainment was associated with more rapid decline on two executive measures but not on a naming task that have minimal executive resource demands. We also found that a more rapid rate of decline on measures of executive function is related to increased atrophy in right dorsolateral and inferior frontal regions. These findings add to the known sources of heterogeneity in bvFTD and are consistent with the idea that the rate of longitudinal decline in bvFTD depends in part on lifetime cognitive experiences. In the sections below we discuss the potential mechanisms behind this source of heterogeneity.

Our observation that lifetime cognitive experiences were related to cognitive decline was restricted to measures of

executive function. Executive function, a frontal-mediated family of cognitive processes, includes mental flexibility, planning and strategic processing (Alvarez and Emory 2006; Rabinovici et al. 2015). These cognitive skills are likely heavily used by professionals in order to maintain their level of functioning. Non-professionals are arguably less dependent and less practiced on executive function and may use these resources less, and thus non-professionals may have a lower level of executive function at onset and experience less evidence of decline as disease progresses.

Previous studies investigating the influences of lifetime cognitive experiences in FTD have focused on pathology-confirmed FTD spectrum disorders and were cross-sectional in nature. These studies associated high education and occupational attainment with longer survival (Massimo et al. 2015). We speculate that cognitive deficits may become apparent earlier in individuals in a higher occupational category with cognitively demanding jobs than individuals in lower occupational categories, resulting in a lengthier disease duration. Moreover, the concept of brain reserve may also be an important moderator between pathology and cognitive performance. Indeed, in pathology-confirmed FTD, we observed higher GM density in individuals with high occupational attainment and this was associated with superior performance on executive measures (Placek et al. 2016). However, there are considerable biological differences within a FTD cohort that may impact the rate of decline in an individual, including phenotype, anatomic extent and distribution of disease, as well as genetic and epigenetic factors (Irwin et al. 2014; McMillan et al. 2015). It is thus important to study rate of progression longitudinally within an individual. To our knowledge, this is the first study to investigate cognitive reserve in bvFTD in a longitudinal cohort.

Individuals with a neurodegenerative disease are thought to accumulate histopathologic abnormalities many years prior to the emergence of clinical symptoms (Jack et al. 2010). In patients with AD, one possibility is that individuals with high levels of education and occupational attainment may be able to compensate and maintain performance longer in the face of accumulating pathology due in part to practiced strategizing and superior executive functioning (Stern 2003). Strategizing of this sort appears to depend in part on prefrontal brain regions (Peter et al. 2016; Possin et al. 2012). In bvFTD, from this perspective, there is early prefrontal disease that may limit access to executive resources that are thought to contribute to minimizing symptoms early in the disease. Indeed, we found that more disease in inferior frontal gyrus and dorsolateral regions were associated with faster rate of longitudinal decline. Previous studies have demonstrated compensatory responses in the frontal cortex which may act as a buffer in response to cognitive decline (Chang et al. 2016; Franzmeier et al. 2017; Pudas et al. 2017). For example, consistent with the compensation-related utilization of neural-network hypothesis (CRUNCH), high-performing healthy older adults, tend to recruit bilateral prefrontal regions to cope with task demands (Bauer et al. 2015; Cabeza et al. 2002). We hypothesize that prefrontal disease early in the course of bvFTD may severely limit the ability to draw upon compensatory resources and thus results in greater decline. Moreover, it is likely that 'reserve' moderation depends on a combination of integrity of brain structure and compensatory processes.

Understanding the mechanisms of reserve could shed light into the compensatory processes that are used to maintain function in face accumulating neurodegenerative disease. Thus, it would be important to develop an in-depth understanding of cognitive processes that underlie compensation so that their mechanisms of action can be targeted. For example, other studies have demonstrated executive function underlies an important compensatory role (Martins et al. 2015; Puente et al. 2015). From this perspective, future research might include cognitive interventions that could potentially target aspects of executive function such as attention and mental flexibility that are compromised in bvFTD.

Our findings should be interpreted in light of several limitations. FTD is a relatively uncommon condition, and our findings are based on a relatively small sample of patients, and therefore require confirmation in a larger sample of participants. We examined patients with relatively mild disease of approximately 3 years duration, this limits our generalizability to later stages of disease. Further, we use the MMSE to evaluate the global cognitive status of FTD patients. It will be important for future studies to evaluate global cognition using a clinical scale that captures severity while addressing issues more sensitive to FTD such as The Clinical Dementia Rating-FTLD scale (CDR-FTLD) (Knopman et al. 2008). While our study was longitudinal in nature, we were able to use only a limited number of neuropsychological measures because our protocol has been modified over time. The three measures used in this study were all verbal tasks, therefore, an evaluation of performance on non-verbal tasks specifically designed to assess the effects of CR on executive function is necessary.

Occupational categories were dichotomized and this restricted our sensitivity to measure the influence of specific occupational groups on cognitive reserve, and further research into occupational complexity is likely to provide additional insights into the relationship between work conditions and cognitive performance. We did not include homemakers in our analysis because this group did not fit into prescribed categories, however, future studies should include this important category. While we did not assess leisure activities in this study, future work should explore the influence of mental and physical activities on cognitive decline in FTD. Future work would benefit from including longitudinal measures of both neuroimaging and neuropsychological data

to determine the contribution of cognitive reserve status to cognitive decline in bvFTD.

With these caveats in mind, our findings suggest that bvFTD patients, who are professionals, decline faster on measures of executive functioning than bvFTD patients who are non-professionals. This may be due in part to early prefrontal disease in bvFTD that limits professionals' ability to utilize compensatory strategies.

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Compliance with ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

Alvarez, J. A., & Emory, E. (2006). Executive function and the frontal lobes: a meta-analytic review. *Neuropsychology Review, 16*(1), 17–42. https://doi.org/10.1007/s11065-006-9002-x.

Avants, B. B., Libon, D. J., Rascovsky, K., Boller, A., McMillan, C. T., Massimo, L., … Grossman, M. (2014). Sparse canonical correlation analysis relates network-level atrophy to multivariate cognitive measures in a neurodegenerative population. *Neuroimage, 84*, 698–711. https://doi.org/10.1016/j.neuroimage.2013.09.048.

Bauer, E., Sammer, G., & Toepper, M. (2015). Trying to put the puzzle together: age and performance level modulate the neural response to increasing task load within left rostral prefrontal cortex. *Biomed Research International, 2015*, 415458. https://doi.org/10.1155/2015/415458.

Cabeza, R., Anderson, N. D., Locantore, J. K., & McIntosh, A. R. (2002). Aging gracefully: compensatory brain activity in high-performing older adults. *Neuroimage, 17*, 1394–1402.

Chang, Y. T., Huang, C. W., Chen, N. C., Lin, K. J., Huang, S. H., Chang, Y. H., … Chang, C. C. (2016). Prefrontal lobe brain reserve capacity with resistance to higher global amyloid load and white matter hyperintensity burden in mild stage Alzheimer's disease. *PLoS One, 11*(2), e0149056. https://doi.org/10.1371/journal.pone.0149056.

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd edn.). Mahwah: Erlbaum.

Cook, P. A., McMillan, C. T., Avants, B. B., Peelle, J. E., Gee, J. C., & Grossman, M. (2014). Relating brain anatomy and cognitive ability using a multivariate multimodal framework. *Neuroimage, 99*, 477–486. https://doi.org/10.1016/j.neuroimage.2014.05.008.

Fairjones, S. E., Vuletich, E. J., Pestell, C., & Panegyres, P. K. (2011). Exploring the role of cognitive reserve in early-onset dementia. *American Journal Alzheimers Disease and Other Dementias, 26*(2), 139–144. https://doi.org/10.1177/1533317510397328.

Folstein, M. F., Folstein, S. F., & McHugh, P. R. (1975). "Mini mental state." A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research, 12*, 189–198.

Franzmeier, N., Duering, M., Weiner, M., Dichgans, M., Ewers, M., & Alzheimer's Disease Neuroimaging, I (2017). Left frontal cortex connectivity underlies cognitive reserve in prodromal Alzheimer disease. *Neurology*. https://doi.org/10.1212/WNL.0000000000003711.

Grossman, M., Xie, S. X., Libon, D. J., Wang, X., Massimo, L., Moore, P., … Trojanowski, J. Q. (2008). Longitudinal decline in autopsy-defined frontotemporal lobar degeneration. *Neurology, 70*(22), 2036–2045. https://doi.org/10.1212/01.wnl.0000303816.25065.bc.

Hu, W. T., Seelaar, H., Josephs, K. A., Knopman, D. S., Boeve, B. F., Sorenson, E. J., … Grossman, M. (2009). Survival profiles of patients with frontotemporal dementia and motor neuron disease. *Archives of Neurology, 66*(11), 1359–1364. https://doi.org/10.1001/archneurol.2009.253.

Irwin, D. J., McMillan, C. T., Suh, E., Powers, J., Rascovsky, K., Wood, E. M., … Grossman, M. (2014). Myelin oligodendrocyte basic protein and prognosis in behavioral-variant frontotemporal dementia. *Neurology, 83*(6), 502–509. https://doi.org/10.1212/WNL.0000000000000668.

Jack, C. R. Jr., Knopman, D. S., Jagust, W. J., Shaw, L. M., Aisen, P. S., Weiner, M. W., … Trojanowski, J. Q. (2010). Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol, 9*(1), 119–128. https://doi.org/10.1016/S1474-4422(09)70299-6.

Kaplan, E., Goodglass, H., & Weintraub, S. (1983). *The Boston naming test*. Philadelphia: Lea and Febiger.

Knopman, D. S., Kramer, J. H., Boeve, B. F., Caselli, R. J., Graff-Radford, N. R., Mendez, M. F., … Mercaldo, N. (2008). Development of methodology for conducting clinical trials in frontotemporal lobar degeneration. *Brain, 131*(Pt 11), 2957–2968. https://doi.org/10.1093/brain/awn234.

Kwok, O. M., Underhill, A. T., Berry, J. W., Luo, W., Elliott, T. R., & Yoon, M. (2008). Analyzing longitudinal data with multilevel models: an example with individuals living with lower extremity intra-articular fractures. *Rehabilitation Psychology, 53*(3), 370–386. https://doi.org/10.1037/a0012765.

Laird, N. M., & Ware, J. H. (1982). Random-effects models for longitudinal data. *Biometrics, 38*, 963–974.

Libon, D. J., Massimo, L., Moore, P., Coslett, H. B., Chatterjee, A., Aguirre, G. K., … Grossman, M. (2007a). Screening for frontotemporal dementias and Alzheimer's disease with the Philadelphia brief assessment of cognition: a preliminary analysis. *Dementia and Geriatric Cognitive Disorders, 24*(6), 441–447. https://doi.org/10.1159/000110577.

Libon, D. J., Massimo, L., Moore, P., Coslett, H. B., Chatterjee, A., Aguirre, G. K., … Grossman, M. (2007b). Differentiating the frontotemporal dementias from Alzheimer's disease: the Philadelphia brief assessment of cognition. *submitted*.

Marcus, D. S., Wang, T. H., Parker, J., Csernansky, J. G., Morris, J. C., & Buckner, R. L. (2007). Open access series of imaging studies (OASIS): cross-sectional MRI data in young, middle aged, nondemented, and demented older adults. *Journal of Cognitive Neuroscience, 19*(9), 1498–1507. https://doi.org/10.1162/jocn.2007.19.9.1498.

Martins, R., Joanette, Y., & Monchi, O. (2015). The implications of age-related neurofunctional compensatory mechanisms in executive function and language processing including the new Temporal Hypothesis for Compensation. *Frontiers in Human Neuroscience, 9*, 221. https://doi.org/10.3389/fnhum.2015.00221.

Massimo, L., Zee, J., Xie, S. X., McMillan, C. T., Rascovsky, K., Irwin, D. J., … Grossman, M. (2015). Occupational attainment

influences survival in autopsy-confirmed frontotemporal degeneration. *Neurology, 84*(20), 2070–2075. https://doi.org/10.1212/WNL.0000000000001595.

McMillan, C. T., Russ, J., Wood, E. M., Irwin, D. J., Grossman, M., McCluskey, L., … Lee, E. B. (2015). C9orf72 promoter hypermethylation is neuroprotective: neuroimaging and neuropathologic evidence. *Neurology, 84*(16), 1622–1630. https://doi.org/10.1212/WNL.0000000000001495.

Peter, J., Kaiser, J., Landerer, V., Kostering, L., Kaller, C. P., Heimbach, B., … Kloppel, S. (2016). Category and design fluency in mild cognitive impairment: performance, strategy use, and neural correlates. *Neuropsychologia, 93*(Pt A), 21–29. https://doi.org/10.1016/j.neuropsychologia.2016.09.024.

Placek, K., Massimo, L., Olm, C., Ternes, K., Firn, K., Van Deerlin, V., … McMillan, C. T. (2016). Cognitive reserve in frontotemporal degeneration: neuroanatomic and neuropsychological evidence. *Neurology, 87*(17), 1813–1819. https://doi.org/10.1212/WNL.0000000000003250.

Possin, K. L., Chester, S. K., Laluz, V., Bostrom, A., Rosen, H. J., Miller, B. L., & Kramer, J. H. (2012). The frontal-anatomic specificity of design fluency repetitions and their diagnostic relevance for behavioral variant frontotemporal dementia. *Journal of International Neuropsychological Society, 18*(5), 834–844. https://doi.org/10.1017/S1355617712000604.

Premi, E., Archetti, S., Pilotto, A., Seripa, D., Paghera, B., Padovani, A., & Borroni, B. (2015). Functional genetic variation in the serotonin 5-HTTLPR modulates brain damage in frontotemporal dementia. *Neurobiol Aging, 36*(1), 446–451. https://doi.org/10.1016/j.neurobiolaging.2014.07.008.

Pudas, S., Josefsson, M., Rieckmann, A., & Nyberg, L. (2017). Longitudinal evidence for increased functional response in frontal cortex for older adults with hippocampal atrophy and memory decline. *Cerebral Cortex*. https://doi.org/10.1093/cercor/bhw418.

Puente, A. N., Lindbergh, C. A., & Miller, L. S. (2015). The relationship between cognitive reserve and functional ability is mediated by executive functioning in older adults. *Clin Neuropsychology, 29*(1), 67–81. https://doi.org/10.1080/13854046.2015.1005676.

Rabinovici, G. D., Stephens, M. L., & Possin, K. L. (2015). Executive dysfunction. *Continuum (Minneap Minn), 21*(3 Behavioral Neurology and Neuropsychiatry), 646–659. https://doi.org/10.1212/01.CON.0000466658.05156.54.

Ramanan, S., Bertoux, M., Flanagan, E., Irish, M., Piguet, O., Hodges, J. R., & Hornberger, M. (2016). Longitudinal executive function and episodic memory profiles in behavioral-variant frontotemporal dementia and Alzheimer's disease. *Journal of the International Neuropsychological Society*, 1–10. https://doi.org/10.1017/S1355617716000837.

Ranasinghe, K. G., Rankin, K. P., Lobach, I. V., Kramer, J. H., Sturm, V. E., Bettcher, B. M., … Miller, B. L. (2016). Cognition and neuropsychiatry in behavioral variant frontotemporal dementia by disease stage. *Neurology, 86*(7), 600–610. https://doi.org/10.1212/WNL.0000000000002373.

Rascovsky, K., Hodges, J. R., Knopman, D., Mendez, M. F., Kramer, J. H., Neuhaus, J., … Miller, B. L. (2011). Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain, 134*(Pt 9), 2456–2477. https://doi.org/10.1093/brain/awr179.

Singer, J. D., & Willett, J. B. (2003). *Applied longitudinal data analysis: Modeling change and event occurrence*. New York: Oxford University Press.

Steffener, J., & Stern, Y. (2012). Exploring the neural basis of cognitive reserve in aging. *Biochimica et Biophysica Acta, 1822*(3), 467–473. https://doi.org/10.1016/j.bbadis.2011.09.012.

Stern, Y. (2003). The concept of cognitive reserve: a catalyst for research. *Journal of Clinical and Experimental Neuropsychology, 25*(5), 589–593. https://doi.org/10.1076/jcen.25.5.589.14571.

Stern, Y. (2009). Cognitive reserve. *Neuropsychologia, 47*(10), 2015–2028. https://doi.org/10.1016/j.neuropsychologia.2009.03.004.

Stern, Y., Tang, M. X., Denaro, J., & Mayeux, R. (1995). Increased risk of mortality in Alzheimer's disease patients with more advanced educational and occupational attainment. *Annals of Neurology, 37*, 590–595.

Stern, Y., Albert, S., Tang, M. X., & Tsai, W. Y. (1999). Rate of memory decline in AD is related to education and occupation: cognitive reserve? *Neurology, 53*(9), 1942–1947.

Tustison, N. J., Avants, B. B., Cook, P. A., Zheng, Y., Egan, A., Yushkevich, P. A., & Gee, J. C. (2010). N4ITK: improved N3 bias correction. *IEEE Transactions on Medical Imaging, 29*(6), 1310–1320. https://doi.org/10.1109/TMI.2010.2046908.

Tustison, N. J., Cook, P. A., Klein, A., Song, G., Das, S. R., Duda, J. T., … Avants, B. B. (2014). Large-scale evaluation of ANTs and FreeSurfer cortical thickness measurements. *Neuroimage, 99*, 166–179. https://doi.org/10.1016/j.neuroimage.2014.05.044.

Winkler, A. M., Ridgway, G. R., Webster, M. A., Smith, S. M., & Nichols, T. E. (2014). Permutation inference for the general linear model. *NeuroImage, 92*, 381–397. https://doi.org/10.1016/j.neuroimage.2014.01.060.

Xie, S. X., Forman, M. S., Farmer, J., Moore, P., Wang, Y., Wang, X., … Grossman, M. (2008). Factors associated with survival probability in autopsy-proven frontotemporal lobar degeneration. *Journal of Neurology, Neurosurgery, and Psychiatry, 79*(2), 126–129. https://doi.org/10.1136/jnnp.2006.110288.