Neural Correlates of Caregiver Burden in Cortical Basal Syndrome and Frontotemporal Dementia

K.M. Knutson^a G. Zamboni^{a,b} M.C. Tierney^a J. Grafman^a

^aCognitive Neuroscience Section, National Institutes of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Md., USA; ^bDipartimento di Neuroscienze, Università di Modena e Reggio Emilia, Modena, Italy

Key Words

Corticobasal syndrome • Frontotemporal dementia •
Magnetic resonance imaging • Voxel-based morphometry •
Caregiver burden

Abstract

Aims: To determine areas of atrophy in patients that are associated with caregiver burden. **Methods:** We measured caregiver burden, dementia and neuropsychiatric scores in 22 patients with corticobasal syndrome (CBS) and 25 with frontotemporal dementia (FTD), and in 14 healthy controls. We used voxel-based morphometry to correlate caregiver burden with gray matter loss. **Results:** Increased dementia and behavioral disturbances contributed to higher burden scores in CBS patients, while behavioral disturbances alone significantly affected burden scores in frontal-variant FTD (FTD-fv) patients. In CBS patients, caregiver burden scores correlated with atrophy in left inferior and middle temporal gyri. **Conclusions:** Caregivers of FTD-fv patients had significantly higher burden scores than caregivers of CBS patients. Damage to areas important in semantic knowledge appears critical in increased burden for CBS caregivers.

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Introduction

Both corticobasal syndrome (CBS) and frontotemporal dementia (FTD) are neurodegenerative diseases that place tremendous burdens on primary caregivers [1, 2]. De Vugt et al. [3] report that when a spouse cares for a partner with dementia, it can lead to reductions in the quality of the marriage characterized by reduced communication, restriction of freedom, lack of intimacy and fewer joint activities due to the patients' apathy. De Vugt et al. [4] found that the caregivers who reported many behavioral problems in their partners with dementia had significantly more distress, health problems and stress. Disinhibition has also been found to be correlated with caregiver burden in FTD patients [5].

CBS and FTD seem to affect males and females at equal rates [1, 6–8]. CBS generally strikes at an older age than FTD which frequently starts before the age of 65 [9]. CBS was first described in 1968 by Rebeiz et al. [10]. Cortical atrophy in CBS affects the bilateral posterior inferior, middle and superior frontal lobes, superior premotor cortex, posterior temporal and parietal lobes, insula and supplemental motor area. Clinically, CBS is marked by motor impairments including rigidity and apraxia, and occasionally alien limb, sensory loss, myoclonus, tremor and dystonia, along with dementia [1, 11, 12]. CBS can present in several ways: as a predominantly motor

Table 1. Demographic characteristics, total intracranial volumes and test scores for the patient groups and normal controls

	CBS (n = 22)	FTD-fv (n = 25)	Controls (n = 14)
Mean age, years	67.86 ± 8.72	59.84 ± 8.33	60.57 ± 6.35
Mean education, years	14.41 ± 3.05	14.92 ± 3.30	17.14 ± 3.46
Gender (female/male)	11/11	13/12	7/7
Mean TIV, liters	1.41 ± 0.22	1.40 ± 0.21	1.46 ± 0.17
Mean MDRS-2 total raw scores	110.86 ± 22.33	97.12 ± 31.30	139 ± 2.94 (n = 13 ¹)
Mean NPI total scores	4.95 ± 4.10	35.08 ± 15.01	n.a.
Mean ZBI scores	25.00 ± 8.98	40.92 ± 14.59	n.a.

TIV = Total intracranial volume; MDRS-2 = Mattis Dementia Rating Score, 2nd edition; NPI = Neuropsychiatric Inventory; ZBI = Zarit Burden Inventory; n.a. = not assessed.

¹ MDRS-2 was not obtained for one normal control.

disorder, a predominantly dementia disorder or as progressive aphasia [13]. The better known predominantly motor type has been found to have more gray matter atrophy in the premotor cortex, while the predominantly dementia type has more atrophy in the superior, middle and inferior frontal gyri, posterior temporal and parietal lobes and the insula [1]. There may also be problems with executive functions [14] in CBS.

In FTD, atrophy is found mainly in the frontal and anterior temporal lobes. Inappropriate social behavior is a diagnostic feature [8, 15]. Behavioral abnormalities can occur along the course of all the FTD syndromes, although they are predominant in the frontal variant of FTD (FTD-fv). These behavioral abnormalities include changes in personal and social conduct, emotional blunting, loss of insight [9], apathy [5, 16] and may include disinhibition, irritability and agitation [2, 17]. Patients with FTD can be tactless, childish, rigid and demanding. They violate social boundaries and have little insight into their behaviors [18]. Caregivers of FTD patients at home experienced more emotional burden due to the neuropsychiatric disturbances of the patients than caregivers of FTD patients in nursing homes [5]. Distress scores for caregivers of FTD patients are higher than for caregivers of patients with Alzheimer's disease (AD) [17].

Zarit et al. [19] found that factors inherent to the caregiver of a dementia patient such as the caregiver's problem-solving abilities, social support especially from family members [20; although see 21], and the quality of the relationship between the patient and the caregiver before the onset of the disease affected the levels of caregiver burden. Zarit et al. [22] also state that caregivers feel bur-

dened by behaviors such as waking the caregiver at night, being constantly restless or talkative, and being incontinent, but that there is variability in the caregivers' ability to tolerate various behaviors.

We wanted to replicate the correlations between caregiver burden and neuropsychological and demographic variables found in previous studies on FTD and CBS patients, and in addition, use voxel-based morphometry (VBM) to find neural correlates of atrophy that predict higher levels of burden in the primary caregivers. To our knowledge, the neural correlates of caregiver burden in CBS and FTD-fv patients have not yet been investigated. We expected that the psychological burdens upon caregivers would be more important to them than the physical burdens, and that the psychological burdens upon the caregiver would be due mainly to behavioral disturbances in the patient. As multiple factors could contribute to caregiver burden, our study was mainly exploratory, but we did expect that caregiver burden scores that are related to behavioral disturbances in the patient would be mediated by increased atrophy in frontal and temporal lobes [23, 24].

Methods

Subjects

For this study, we included 47 patients (24 women; mean age 63.6 ± 9.34 years; mean education 14.68 ± 3.16 years) with clinically diagnosed CBS or FTD-fv; see table 1 for demographic information. They were referred by outside providers to the Cognitive Neuroscience Section of the National Institute of Neurological Disorders and Stroke (NINDS) at the National Institutes of

Health (NIH) and enrolled in an ongoing study to further characterize patients with CBS or FTD. All patients assigned durable power of attorney to their caregiver prior to enrollment, and assignees gave written informed consent for the study, which was approved by the NINDS Institutional Review Board. They received extensive clinical and neuropsychological evaluations and underwent brain magnetic resonance imaging (MRI) and positron emission tomography during a 1.5-week-long visit at the NIH. The diagnosis was confirmed according to published criteria [8, 9, 25] and was reached through a consensus decision between a neurologist and a neuropsychologist based on the clinical history, the neurological examination, and the results of neuroimaging and neuropsychological evaluations. Patients with evidence of head injury, depression, other types of dementia or other conditions affecting their ability to complete the testing such as an inability to speak were excluded. In addition, 14 healthy elderly controls volunteered to participate in the study and received some of the same clinical and neuropsychological evaluations given to the patients except for those intended to be filled out by caregivers since they had no caregivers. They also underwent brain MRI scans at the NIH. The healthy controls gave informed consent and were paid for their participation.

Behavioral Assessment

Caregiver burden was measured by the Zarit Burden Interview (ZBI) [19], a commonly used measure of caregiver burden in dementia. The ZBI contains 22 items asking for the caregiver's feelings of anger, embarrassment, strain, effects on social life, guilt and financial burden. Each item is scored from 0 = 'never' to 4 = 'nearly always'. The range of possible scores varies from 0 (no burden) to 88 (very high burden). Example items include: 'Do you feel strained when you are around your relative?' and 'Do you feel your health has suffered because of your involvement with your relative?' A cutoff score of 24 has been determined to be appropriate when used to identify caregivers in need of intervention due to high levels of stress and risk of depression [26]. The Mattis Dementia Rating Scale, 2nd edition (MDRS-2) [27], which gives a measure of dementia severity (where lower scores mean greater dementia) and UCLA Neuropsychiatric Inventory (NPI) [28] scores were also obtained. The NPI assesses behavioral disturbances/neuropsychiatric symptoms in 10 areas: delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability and aberrant motor behavior. The scores are calculated by summing the severity of the symptoms (1 = mild, 2 = moderate, 3 = marked) multiplied by the frequency, from 1 to 4, in each of the 10 scales. Higher scores indicate more behavioral disturbances/neuropsychiatric symptoms. The ZBI and NPI were completed by the patients' caregivers, and the MDRS-2 was administered to the patients and controls by an examiner.

Imaging

General Electric 1.5-tesla MRI scanners (GE Medical Systems, Milwaukee, Wisc., USA) and standard quadrature head coils were used to obtain all but 3 volumes. Two of the others were obtained on 3-tesla Philips MRI scanners and the other on a 1.5-tesla Philips scanner. For the GE scanners, a T_1 -weighted spoiled gradient echo sequence was used to generate at least 120 contiguous 1.5-mm-thick axial slices (TR = 6.1 ms; TE = min. full; flip angle = 20°; FOV = 240 mm; in-plane resolution = 0.9375 mm × 0.9375 mm). For the 1.5-tesla Philips scanner, a T_1 -weighted spoiled

gradient echo sequence was used to generate 160 contiguous 1.5-mm-thick axial slices (TR = min.; TE = min. full; flip angle = 9°; FOV = 240 mm; in-plane resolution = 0.9 mm × 0.9 mm). For the 3-tesla Philips scanner, the same sequence was used except that 140 slices were obtained.

Statistical Analysis

Independent *t* tests were performed using SPSS (version 11 for the Mac, Cupertino, Calif., USA) to check for demographic (age at testing, years of education, gender, total intracranial volume, TIV) and dementia and behavioral disturbance differences (MDRS-2 and NPI total scores), along with ZBI scores between groups. Pearson's one-tailed correlation analyses were conducted within each patient group between ZBI, MDRS-2, NPI total scores and duration of disease (based on the estimated number of years between the appearance of the first symptoms and the date of testing). To further explore the relationship of caregiver burden with the other variables, we conducted separate stepwise multiple regression analyses for patients, in which ZBI scores were the dependent variable and MDRS-2 scores, NPI total scores, patient gender, duration of disease, years of education and caregiver gender were the independent variables. *p* to enter the equation was set at 0.05. Also, a Pearson's one-tailed correlational analysis was conducted within each patient group using each patient's intensity value at the peak voxel resulting from the group VBM analysis and that patient's MDRS-2 and NPI scores.

VBM: Processing and Analysis

In order to measure areas of atrophy in the patients' brains, we used VBM. First, anatomical images were manually reoriented to position the anterior commissure at the center. Next, segmentation of the data was performed with SPM5 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm5>) using a unified segmentation algorithm [29] and all default options unless otherwise specified. Structural MR images were segmented into gray matter, white matter and cerebrospinal fluid. The segmented and modulated normalized gray matter images were smoothed with a 12-mm full-width at half maximum filter. To identify gray matter atrophy in each of the patient groups as compared to controls, multiple regression *t* tests were performed with an absolute threshold mask of 0.05 and age, gender, scanner manufacturer (GE or Philips) and TIV as covariates of no interest. Whole-brain family-wise error (FWE; *p* = 0.05 with an extent threshold of 30 voxels) correction for multiple comparisons was used. Then, within each of the patient groups, an analysis was performed to identify gray matter changes that correlated with the burden upon the primary caregiver. Regressors corresponding to age, gender, TIV and scanner manufacturer were added as covariates of no interest. The relationship between voxel values and the total caregiver burden was examined using a negative one-sided *t* test, assuming that increasing degree of caregiver burden would be associated with decreased tissue density in the patient. Following Ridgway et al. [30], a positive one-sided *t* test was also performed as a quality control check. The correlational analyses were limited to areas within the explicit mask containing areas of significant gray matter differences between the control group and the relevant patient group. Within this mask, we accepted a voxel level statistical threshold of *p* < 0.001 uncorrected at the voxel level with an extent threshold of 30 voxels. SPM coordinates were converted to anatomical regions using MEDx (Medical Numerics, Germantown, Md., USA).

Results

Comparisons between FTD-fv and CBS Patient Groups

As expected due to the typically later onset of CBS, the CBS group was significantly older when tested than the FTD-fv group [$t(45) = 3.22$, $p = 0.002$]. The CBS group was also older than the control group [$t(34) = 2.70$, $p = 0.011$]. There was no significant difference in age between the FTD-fv group and the control group. The control group had significantly more years of education than the CBS group [$t(34) = 2.49$, $p = 0.018$] and the FTD-fv group [$t(37) = 1.98$, $p = 0.055$]. There were no significant differences in years of education or caregiver gender between the two patient groups. There were no significant differences between any of the three groups (CBS, FTD-fv or controls) for gender or TIV (table 1).

There was a significant difference in behavioral disturbances/neuropsychiatric symptoms as measured by NPI across patient groups [$t(28) = 9.64$, $p < 0.001$], reflecting the greater amounts of behavioral disturbances/neuropsychiatric symptoms in FTD-fv patients compared to CBS patients. Further analysis showed that FTD-fv patients had significantly higher scores than CBS patients in every NPI subcategory [$t_s(24) > 2.08$, $p_s < 0.05$] except for depression [$t(45) = 0.33$, n.s.].

While the MDRS-2 means were not significantly different between the CBS and FTD-fv patient groups, the scaled scores for the FTD-fv group averaged less than 3 indicating a severe impairment. As could be expected, the normal controls scored significantly better on the MDRS-2 than the patient groups [CBS, $t(33) = 4.49$, $p < 0.001$; FTD-fv, $t(36) = 4.78$, $p < 0.001$; table 1]. No significant correlations were found between MDRS-2 and NPI total scores for either of our patient groups. No significant correlations were found between disease duration and ZBI, NPI or MDRS-2 scores.

Caregiver Burden Results

There was a significant difference in caregiver burden as measured by ZBI scores between patient groups [$t(45) = 4.43$, $p < 0.001$], reflecting higher burden ratings for the caregivers of FTD-fv patients.

In the CBS patient group, ZBI and MDRS-2 scores were mildly correlated ($r = -0.391$; $p = 0.036$; one-tailed) as were ZBI and NPI total scores ($r = 0.375$; $p < 0.043$; one-tailed), revealing that caregivers of CBS patients with increased dementia severity and more behavioral disturbances had a slightly greater tendency to have higher caregiver burden scores; however, no significant model emerged from the

stepwise multiple regression for the CBS patient group, suggesting that differences in dementia severity, behavioral disturbances, patient and caregiver gender, disease duration or education do not significantly explain the variance in caregiver burden for CBS patients.

In the FTD-fv patient group, ZBI and MDRS-2 scores were not significantly correlated ($r = -0.277$; n.s.), showing that caregiver burden for FTD-fv patients is not related simply to the patient's level of dementia. Instead, within the FTD-fv group, ZBI scores were significantly correlated with NPI total scores ($r = 0.445$; $p = 0.013$; one-tailed), demonstrating that greater behavioral disturbances/neuropsychiatric symptoms in FTD-fv patients led to increased caregiver burden. Stepwise multiple regression analyses confirmed that NPI total scores entered into the equation for the FTD-fv patient group and explained 16% of the variance in caregiver burden [$F(1, 24) = 5.68$, $p = 0.026$].

VBM Results

As expected, both the CBS patients and the FTD-fv patients showed atrophy in the cerebral cortex especially in frontal and temporal areas when compared to the control group (fig. 1 and 2).

For CBS patients, a significant correlation between gray matter atrophy and ZBI scores was found in the anterior portion of the left inferior temporal gyrus (ITG) (Brodmann's area 20) extending into the middle temporal gyrus (MTG) (Brodmann's area 21) with a cluster size of 423 voxels [$T(1, 16) = 6.84$; peak Montreal Neurological Institute voxel coordinates of $-36, -4, -46$]. This region survived an FWE-corrected statistical threshold of $p < 0.05$ (fig. 3).

For FTD-fv patients, there was no significant correlation between gray matter atrophy and ZBI scores at the uncorrected statistical threshold of $p < 0.001$. However, when an exploratory analysis was performed using an uncorrected $p < 0.005$ and an extent threshold of 30 voxels, the results showed an area of atrophy composed of 96 voxels in the right orbital gyrus (Brodmann's area 11) that correlated with ZBI scores [$T(1, 19) = 3.42$; peak Montreal Neurological Institute voxel coordinates of $10, 54, -18$].

For each patient group, correlations between each patient's intensity value at the peak voxel resulting from the group analysis and MDRS-2 and NPI scores were performed. Results showed a significant correlation for the peak voxel intensities and MDRS-2 scores only for FTD-fv patients ($r = 0.41$; $p = 0.022$; one-tailed), not for CBS patients ($r = -0.13$; n.s.), meaning that for FTD-fv patients, atrophy in the orbital gyrus was associated not

Fig. 1. Patterns of significant gray matter loss identified in the CBS group compared to the control group (FWE-corrected $p < 0.05$, minimum cluster size 30 voxels), superimposed onto the mean of 152 T_1 -weighted images from SPM5. The crosshairs are centered at 14, 10, 14 in Montreal Neurological Institute coordinates.

Fig. 2. Patterns of significant gray matter loss identified in the FTD-fv group compared to the control group (FWE-corrected $p < 0.05$, minimum cluster size 30 voxels), superimposed onto the mean of 152 T_1 -weighted images from SPM5. The crosshairs are centered at 14, 10, 14 in Montreal Neurological Institute coordinates.

only with caregiver burden, but also with dementia severity. No significant correlations between peak voxel intensities and NPI total scores were found, meaning that the density value of the atrophied region was associated specifically with burden and not with behavioral impairment. Further analysis using the subscores of the NPI found no correlations for CBS patients, but for FTD-fv patients, correlations between the NPI subscores of apathy ($r = 0.57$; $p = 0.001$; one-tailed) and of aberrant (repetitive) motor behaviors ($r = 0.45$; $p = 0.012$; one-tailed) were significantly correlated with the intensity values at the peak voxel in the right orbital gyrus.

Discussion

While dementia severity (as measured by MDRS-2 scores) was similar across patient groups, caregivers of FTD-fv patients had significantly higher burden scores than the caregivers of CBS patients. Caregivers of FTD-fv patients scored well above the threshold for needing assessment and intervention, while caregivers of CBS patients scored near the cutoff. Others have found similarly high burden scores for FTD-fv patients compared to AD

Fig. 3. Region of reduced gray matter density associated with the caregiver burden scores in CBS patients. The significant cluster is in the left ITG extending into the MTG (uncorrected $p < 0.001$, minimum cluster size 30 voxels), superimposed onto the mean of 152 T_1 -weighted images from SPM5. The crosshairs are centered at -36, -4, -46 in Montreal Neurological Institute coordinates.

[5, 31]. ZBI scores for FTD patients did not differ between our study and another recent study [31] [$t(48) = 0.508$, n.s.], but caregivers of FTD-fv patients in our study had a significantly higher ZBI mean score than the caregivers of AD patients reported in the other study who had a ZBI mean score of 21.0 ± 12.73 [$t(47) = 5.27$, $p < 0.001$], reflecting that caregivers found it more burdensome to care for FTD-fv patients than AD patients. FTD-fv is marked by inappropriate social behavior while CBS is marked by motor impairment, so it is not surprising that the FTD-fv patient caregivers rated themselves as having a greater burden to bear, especially since the ZBI includes questions on the caregiver's social life and levels of embarrassment and anger, all of which may be affected by inappropriate social behavior in the patient. Our finding of increased behavioral disturbances/neuropsychiatric symptoms (as measured by NPI scores), including significantly more delusions, hallucinations, agitation, anxiety, euphoria/elation, apathy/indifference, disinhibition, irritability/lability and aberrant motor behavior, in FTD-fv patients compared to CBS patients likely contributes to increased caregiver burden for caregivers of FTD-fv patients. Our finding is generally consistent with the study of Riedijk et al. [5], which also found greater levels of neuropsychiatric symptoms in FTD patients compared to AD patients, and that of Leinonen et al. [32], which found greater caregiver burden for those caring for dementia patients with psychiatric or behavioral symptoms than for dementia patients without these symptoms.

Only in our CBS patients was there a mild significant correlation between dementia severity and caregiver burden, as higher levels of dementia severity led to more caregiver burden. The relationship for FTD-fv patients was lower and not significant perhaps because the caregiver burden was fairly high for all of the FTD-fv patients and because inappropriate social behavior, neuropsychiatric symptoms and behavioral changes were more important factors in caregiver burden for FTD-fv patients. Boutoleau-Bretonniere et al. [31] also found no correlation between caregiver burden scores and dementia severity for FTD-fv patients.

Another goal of this study was to examine CBS and FTD-fv patients for regions of gray matter atrophy that correlated with their caregivers' levels of burden. For the CBS group, gray matter atrophy in the left ITG and MTG was correlated with increased caregiver burden. The left ITG is important in semantic retrieval [33–35]. The temporal cortex is commonly atrophied in semantic dementia, leading to a loss of conceptual knowledge and an impairment of semantic memory that affects language processing

and includes a loss of word meaning and empty speech content [36]. As mentioned above, within the CBS patient group, there was a mild correlation between dementia severity and higher caregiver burden. A decline in semantic memory abilities due to atrophy in the left ITG and MTG may contribute to the impaired cognition seen in CBS patients, which then led to increases in caregiver burden; however, further analysis is needed to clarify the role that loss of semantic memory abilities plays in caregiver burden for CBS patients as we did not directly measure semantic memory ability in this study. Post hoc VBM analyses showed that left ITG atrophy was found even when the analysis included MDRS-2 scores or NPI total scores as covariates of no interest, meaning that atrophy in this region is associated with burden independent of dementia or behavioral symptoms. This is consistent with the results of the peak voxel intensity analysis which showed no correlation between MDRS-2 or NPI scores and the intensity of the peak voxel in ITG for CBS patients.

For the FTD-fv group, an area of atrophy in the right orbital gyrus was significantly correlated with caregiver burden only when a less stringent p value was used [37, 38 also used more liberal p values for post hoc analyses in their VBM studies]. Patients with lesions in the orbitofrontal cortex have been found to be more aggressive and violent than patients with lesions in other brain areas [39]. Similarly, patients with lesions in the right orbitofrontal cortex have been found to be more angry, ready to fight, panicky, depressed with little energy, and to have altered sex practices [40]. Perhaps increased levels of caregiver burden result from the FTD-fv patients' tendencies toward increased social and emotional impairments due to atrophy in the orbitofrontal cortex. On the other hand, as similar areas in the orbitofrontal regions have been found to be engaged in reward processing [41, 42], burden levels for the FTD-fv patients' caregivers may also be increased because the patients engage in behavior without regard to whether it is rewarded or not. A post hoc VBM analysis showed that right orbital gyrus atrophy was also found when the analysis included MDRS-2 as a covariate of no interest, but the T value was greater (3.42 vs. 3.22) and the cluster size larger (96 vs. 39) when we did not control for MDRS-2. This and the significant correlation between the peak voxel's intensity values and MDRS-2 scores along with two NPI subscores in FTD-fv patients suggests that caregiver burden, dementia severity, apathy and repetitive motor behavior are mildly related to the orbital gyrus atrophy in FTD-fv patients.

In summary, results indicate that for CBS patients, increased dementia severity due to deterioration in areas

important in semantic function led to higher caregiver burden. For FTD-fv patients, increased neuropsychiatric and behavioral symptoms such as disinhibition and mood abnormalities contribute to caregiver burden. Our results support the idea that some of the burden upon caregivers of CBS and FTD-fv patients is correlated with atrophy in specific brain regions. Ultimately, knowing the 'neural correlates' of caregiver burden and identifying whether atrophy is present in these areas during a visual inspection of an MRI might aid clinicians in identifying caregivers at risk of high burden levels.

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