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## Frontal Paralimbic Network Atrophy in Very Mild Behavioral Variant Frontotemporal Dementia

**William W. Seeley, MD, Richard Crawford, BS, Katya Rascovsky, PhD, Joel H. Kramer, PsyD, Michael Weiner, MD, Bruce L. Miller, MD, and Maria Luisa Gorno-Tempini, MD, PhD**

*Department of Neurology and Memory and Aging Center (Drs Seeley, Rascovsky, Kramer, Miller, and Gorno-Tempini and Mr Crawford) and Department of Radiology and San Francisco Veterans Affairs Hospital Magnetic Resonance Imaging Unit (Dr Weiner), University of California at San Francisco.*

### Abstract

**Background:** Behavioral variant frontotemporal dementia (bvFTD) strikes hardest at the frontal lobes, but the sites of earliest injury remain unclear.

**Objective:** To determine atrophy patterns in distinct clinical stages of bvFTD, testing the hypothesis that the mildest stage is restricted to frontal paralimbic cortex.

**Design:** A bvFTD cohort study.

**Setting:** University hospital dementia clinic.

**Participants:** Patients with bvFTD with Clinical Dementia Rating (CDR) scale scores of 0.5 (n=15), 1 (n=15), or 2 to 3 (n=15) age and sex matched to each other and to 45 healthy controls.

**Main Outcome Measures:** Magnetic resonance voxel-based morphometry estimated gray matter and white matter atrophy at each disease stage compared with controls.

**Results:** Patients with a CDR score of 0.5 had gray matter loss in frontal paralimbic cortices, but atrophy also involved a network of anterior cortical and subcortical regions. A CDR score of 1 showed more extensive frontal gray matter atrophy and white matter losses in corpus callosum and brainstem. A CDR score of 2 to 3 showed additional posterior insula, hippocampus, and parietal involvement, with white matter atrophy in presumed frontal projection fibers.

**Conclusions:** Very mild bvFTD targets a specific subset of frontal and insular regions. More advanced disease affects white matter and posterior gray matter structures densely interconnected with the sites of earliest injury.

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Behavioral variant frontotemporal dementia (bvFTD) is the most common clinical syndrome associated with frontotemporal lobar degeneration pathology. This bvFTD has been associated with frontal, temporal, and insular degeneration accompanied by early deficits in personal and

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**Correspondence:** William W. Seeley, MD, UCSF Memory and Aging Center, 350 Parnassus Ave, Suite 706, San Francisco, CA 94143-1207 (wseeley@memory.ucsf.edu).

**Author Contributions:** Dr Seeley had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Seeley, Miller, and Gorno-Tempini. *Acquisition of data:* Seeley and Weiner. *Analysis and interpretation of data:* Seeley, Crawford, Rascovsky, Kramer, Miller, and Gorno-Tempini. *Drafting of the manuscript:* Seeley, Crawford, Miller, and Gorno-Tempini. Critical revision of the manuscript for important intellectual content: Seeley, Crawford, Rascovsky, Kramer, Weiner, Miller, and Gorno-Tempini. *Statistical analysis:* Seeley and Kramer. *Obtained funding:* Seeley, Weiner, and Miller. *Administrative, technical, and material support:* Crawford and Weiner. *Study supervision:* Miller and Gorno-Tempini.

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social conduct, emotion, and insight.<sup>1,2</sup> The syndrome progresses relentlessly, with an interval of 3 to 5 years from diagnosis to death.<sup>3-5</sup>

Although the brain regions affected in bvFTD have been characterized without specific regard to disease stage,<sup>2,6-9</sup> information is lacking about where the neurodegeneration begins. In Alzheimer disease, early pathologic changes target the medial temporal lobe.<sup>10</sup> Early bvFTD, however, has proved difficult to study, and whether the disease begins focally, affecting 1 or 2 neighboring brain regions,<sup>11</sup> or whether it affects a network of regions from early in its course is still unknown.<sup>6</sup> Patients with little or no atrophy on magnetic resonance imaging (MRI) have been described, but their underlying diagnoses remain uncertain.<sup>12</sup>

Converging evidence implicates the dorsomedial and orbital frontoinsular cortices in bvFTD. In particular, neuroimaging studies have highlighted pregenual anterior cingulate (ACC) and frontoinsula (FI) cortex involvement through structural,<sup>2,6</sup> metabolic,<sup>8,13,14</sup> perfusion,<sup>9</sup> and neurotransmitter receptor<sup>14</sup> imaging analyses. Still, this body of work (for a review and meta-analysis, see Schroeter et al<sup>15</sup>) has not resolved the question of where bvFTD begins. Group studies often combine patients of varying clinical stages, rendering a picture of FTD as a diffuse frontal disorder. Few studies have attempted to refine the early anatomical picture. Broe et al<sup>16</sup> examined gross atrophy patterns among 7 patients who died with clinically mild to moderate bvFTD. Four showed tissue loss restricted to dorsomedial frontal, orbital frontoinsular, and anterior hippocampal regions. A single presymptomatic P301L tau mutation carrier was found to have pregenual ACC and dorsolateral prefrontal hypometabolism.<sup>17</sup> A recent volumetric region-of-interest MRI analysis stratified patients according to overall frontal atrophy severity.<sup>11</sup> Among 3 patients classified as having mild disease, no single subregion was atrophic, whereas 6 moderately affected patients showed only orbitofrontal and right insular atrophy. These studies, although tantalizing, need to be extended through larger studies of bvFTD in its earliest clinical stages.

In the present study, we used a cross-sectional approach to identify brain structures atrophied in very mild, mild, and moderate to severe bvFTD, stratifying patients on clinical grounds according to the Clinical Dementia Rating (CDR) scale. On the basis of recent neuropathologic observations<sup>16,18</sup> and previous bvFTD imaging studies,<sup>2,6,8,9,13,14</sup> we hypothesized that the ACC and FI would be among the few regions focally affected in patients with very mild bvFTD.

## METHODS

### PARTICIPANTS

We searched the University of California at San Francisco Memory and Aging Center database for patients with a research diagnosis of FTD<sup>1</sup> (also known as bvFTD), a high-quality MRI, and a CDR score.<sup>19</sup> Fifty-eight patients met these criteria; 13 had coexisting motor neuron disease (MND). All were evaluated with an extensive protocol described previously.<sup>2</sup> Neuroimaging abnormalities were not required for diagnosis.<sup>1</sup> Among the 58 candidate patients, 15 had a CDR score of 0.5 (very mild dementia). For 14 of these 15, the CDR score was determined within 6 months of imaging (mean separation, 20.4 days; range, 0-65 days). We included 1 patient with a longer interval (MRI 372 days after CDR score was determined) whose Mini-Mental State Examination (MMSE) score and clinical status had not changed significantly between imaging (MMSE score, 28) and CDR score determination (MMSE score, 29). We then matched 15 patients with a CDR score of 1 (mild) or 2 to 3 (moderate to severe) to our group with a CDR score of 0.5, seeking comparable distributions of age, sex, and the presence of MND (Table 1). We chose a uniform group size of 15 so that patterns of atrophy typical of each group would not be influenced by statistical power. All patients with a CDR score of 1 or higher had a CDR score determined within 6 months of imaging (CDR score of

1: mean, 27.5 days; range, 0-98 days; CDR score of 2 to 3: mean, 21.8 days; range, 0-147 days). For 2 patients in the group with a CDR score of 2 to 3, the total CDR score was estimated as 2 to 3 based on an ongoing requirement for full-time care; therefore, CDR subscale scores were not available for these patients. Forty-five healthy control subjects were matched to the patient groups (Table 1). All procedures were approved by the University of California at San Francisco Committee on Human Research, and informed consent was obtained from all participants (or their surrogates) according to the Declaration of Helsinki.

## NEUROPSYCHOLOGICAL BATTERY

The neuropsychological battery has been described elsewhere.<sup>2</sup> General intellectual functioning was assessed with the MMSE. Memory tests included the California Verbal Learning Test–Short Form and 10-minute free recall of the modified Rey-Osterrieth complex figure. Language was assessed with the abbreviated (15-item) Boston Naming Test and semantic fluency (animals generated in 1 minute). Copy of the modified Rey-Osterrieth figure provided a measure of visuospatial functioning. Executive function tests included phonemic fluency (D words generated in 1 minute), design fluency (Delis-Kaplan Executive Functions System–Trial 1), a modified version of the Trails B test, backward digit span, and the Stroop interference task. Patients were asked to perform 5 simple arithmetic calculations.

Group differences in continuous demographic and neuropsychological variables were assessed with 1-way analyses of variance and post hoc Tukey tests for pairwise group comparisons, correcting for multiple comparisons. Dichotomous measures were evaluated using  $\chi^2$  analyses.

## VOXEL-BASED MORPHOMETRY

**Image Acquisition**—Structural MRI was performed with a 1.5-T Magnetom VISION system (Siemens Inc, Iselin, New Jersey). A volumetric magnetization-prepared rapid gradient echo MRI (repetition time, 10 milliseconds; echo time, 4 milliseconds; inversion time, 300 milliseconds) was used to obtain a T1-weighted image of the entire brain (15° flip angle, coronal orientation perpendicular to the double spin echo sequence, 1.0×1.0-mm<sup>2</sup> in-plane resolution of 1.5-mm slab thickness).

**Preprocessing and Analysis**—Voxel-based morphometry (VBM) is a whole-brain MRI analysis technique used to assess local changes in brain tissue content. It includes an image-preprocessing step followed by statistical analysis. Both were implemented in the SPM2 software package ([www.fil.ion.ucl.ac.uk/spm](http://www.fil.ion.ucl.ac.uk/spm)). Preprocessing followed the optimized VBM protocol.<sup>20</sup> A study-specific template and prior probability maps were created. Voxel values were modulated by multiplying them by the jacobian determinants derived from the spatial normalization step, and all images were smoothed with a 12-mm isotropic gaussian kernel. Identical procedures were applied to gray matter (GM) and white matter (WM) compartments.

Statistical analysis was applied to 4 groups: control subjects and patients with bvFTD with a CDR score of 0.5 (very mild bvFTD), 1 (mild bvFTD), and 2 to 3 (moderate to severe bvFTD). Age and sex were entered into the model as nuisance covariates, and total intracranial volume was used as a global correction factor. Comparisons of interest were each patient group vs controls. Exploratory head-to-head bvFTD group comparisons were also performed. The statistical threshold was set at  $P < .05$ , whole brain corrected for familywise error.

## RESULTS

### GROUP DEMOGRAPHIC AND NEUROPSYCHOLOGICAL FEATURES

Consistent with our study design, groups were similar in age, sex, and educational level (Table 1), and patient groups did not differ statistically in the rate of coexisting MND (CDR score of

0.5, 5 of 15 patients; CDR score of 1, 5 of 15 patients; CDR score of 2-3, 3 of 15 patients;  $\chi^2=0.86$ ;  $P=.65$ ). Symptom duration did not differ significantly across bvFTD groups, suggesting that mildly affected patients represent a more indolent disease course, having relatively few symptoms despite a symptomatic interval similar to that seen in patients with later-stage disease. As indicated in Table 2, patients with very mild bvFTD showed greatest impairment on the CDR subscale for judgment and problem solving, followed by community affairs and home and hobbies. Memory and orientation were the least affected across stages, with no patient showing a subscale score greater than 1 except in moderate to severe disease.

Neuropsychological performance differed with stage (Table 1). At a CDR score of 0.5, patients with bvFTD showed mild executive and memory deficits that were slightly worse at a CDR score of 1. A CDR score of 2 to 3 involved posterior cortical functions (calculations and drawing) consistent with biparietal atrophy identified with VBM, although worsening executive function could also have contributed to these deficits. Overall, lower MMSE scores were correlated with more advanced disease stage, as indicated by the CDR (MMSE vs CDR box score sum: Pearson  $r=-0.53$ ,  $P=.001$ ,  $n=39$ ).

### VBM-ESTIMATED GM

Patients with a CDR score of 0.5 showed circumscribed GM atrophy in a network of anterior brain regions (Figure 1 and eTable; available at: <http://manuscripts.archneurology.com>), including paralimbic (ACC, FI, dorsal anterior insula, and lateral orbitofrontal cortex), frontal neocortical (dorsolateral, rostromedial, and frontal polar), limbic (right hippocampus), and subcortical (ventral striatum and dorsomedial thalamus) areas, as well as the precentral gyrus. Extent of right hemisphere involvement exceeded that on the left.

Among patients with a CDR score of 1, atrophy was more confluent, extensive, and bilateral within regions affected in very mild disease. Most of the medial frontal surface and new lateral frontal regions (Brodmann areas 9/45) were involved, and striatal-thalamic atrophy was diffuse. In the group with a CDR score of 2 to 3, nearly the entire frontal lobe was affected bilaterally, and GM loss was seen within posterior reaches of the insula, posterior hippocampi, parietal lobes, and right cerebellum. No posterior cingulate or precuneus atrophy was detected. Sparse temporal atrophy was seen across stages. Head-to-head comparisons between bvFTD groups revealed a difference only between patients with very mild and severe disease, in whom greater left caudate atrophy was seen ( $P<.05$ , whole brain corrected for familywise error).

### VBM-ESTIMATED WM

Patients with bvFTD who had a CDR score of 0.5 showed minimal WM loss, with only small subfrontal and basal pontine foci detected (Figure 2). With a CDR score of 1, atrophy involved the subfrontal, parahippocampal, and midcallosal WM and extended into the cerebral peduncles and the pontine base. A CDR score of 2 to 3 showed WM loss that affected the entire corpus callosum and extensive subcortical WM reaching from subfrontal to parahippocampal and parietal areas. More severe WM loss was also seen in the midbrain and brainstem, with pontine involvement affecting the middle cerebellar peduncles (Figure 2).

### IMPACT OF FTD-MND ON VBM FINDINGS

Finally, to assess whether GM or WM findings in MND-relevant areas (precentral gyrus, cerebral peduncles, and pontine base) were being driven solely by patients with bvFTD-MND, we reanalyzed the main contrasts after removing the patients with MND from each group. After removing the patients with bvFTD-MND from the very mild (CDR score of 0.5) group, the right precentral gyrus no longer showed significant GM atrophy. Results from MND-relevant regions showed no other changes, at any disease stage, after this manipulation. Furthermore, extending this reanalysis to the entire brain for each group, only the left parietal region in the

moderate to severe group no longer reached significance vs controls when patients with bvFTD-MND were excluded. Otherwise, the regions atrophied at each disease stage (eTable) were unchanged, although the extent (total number of contiguous, significantly atrophied voxels) was slightly reduced in some regions because of lowered statistical power.

## COMMENT

To our knowledge, this is the first neuroimaging study to identify bvFTD atrophy patterns specific to clinical stage. Fifteen patients with a CDR score of 0.5 showed atrophy within a multifocal, distributed frontal insular network. In keeping with our hypotheses, this early bvFTD network featured the ACC, FI, and orbitofrontal and cingulofrontal transition zones. These areas have been highlighted in small autopsy studies<sup>16,18,21,22</sup> of bvFTD, in which some patients died early in the illness. In addition, in very mild disease, we found atrophy in small regions of dorsolateral and polar frontal neocortex, dorsal insula, striatum, thalamus, and anterior hippocampus. In patients with a CDR score of 1, additional frontal neocortical GM regions were atrophied, whereas those with a CDR score of 2 to 3 showed atrophy in the posterior hippocampi, posterior insulae, and parietal lobes.

Why does early FTD target a focal paralimbic frontal insular circuit? Recently, we have observed that bvFTD is associated with severe, selective, and disease-specific injury to von Economo neurons (VENs), a class of large bipolar projection neurons unique to humans, great apes, and possibly selected whales.<sup>18,23,24</sup> von Economo neurons are 30% more abundant in the right hemisphere and reside mainly in the ACC, FI, and orbitofrontal and cingulofrontal transition zones.<sup>25,26</sup> Furthermore, we and others<sup>27,28</sup> have shown with functional MRI that ACC and FI activity levels correlate tightly with each other in task-free settings as part of a normal human intrinsic connectivity network. This network closely mirrors the group of regions, identified in this study, that are targeted in very mild bvFTD. This group of findings suggests that early bvFTD targets a specific anterior network that may bridge limbic, paralimbic, and neocortical centers and integrate them through the caudate and thalamus. von Economo neurons are a distinguishing feature at the core of this network and may support human social cognition,<sup>18,25</sup> but further studies are needed to determine if and how VENs render the FTD network vulnerable.

Previous imaging and pathologic studies of more advanced or mixed bvFTD stages suggest that, with time, the disease encompasses most of the frontal lobe<sup>2,6,8,9,13,16</sup> and may spread to posterior neocortex.<sup>22,29,30</sup> A positron emission tomography study<sup>29</sup> found diffuse frontal and insular hypometabolism in patients with CDR scores of 0.5 to 1 that progressed to involve lateral parietal and temporal regions 20 months later. These findings agree with stage-wise pathologic analyses<sup>16,22</sup> and with our data. However, positron emission tomography may represent a more sensitive measure than MRI because, in contrast to the positron emission tomography study,<sup>29</sup> we found parietal involvement only in moderate to severe bvFTD.

Both bvFTD-related WM atrophy and the timing of WM changes have received limited previous attention.<sup>31,32</sup> We found later-stage WM contraction not only in tissue subjacent to degenerating GM but also in midbrain and pontine regions that carry dense frontal, cingulate, and insular efferent and afferent projections, a finding not attributable to MND-related degeneration alone. A recent diffusion tensor imaging study<sup>33</sup> showed prominent superior longitudinal fasciculus involvement in bvFTD, in keeping with our findings, although the functional status of the patients was not specified. Our data suggest that early frontal GM damage induces WM degeneration, which in turn erodes GM in later-affected posterior regions.

The present study has 2 main limitations. First, no clinical staging system for bvFTD has been established. We chose the CDR because it is a widely used, validated instrument for



characterizing dementia. The CDR, however, was developed for Alzheimer disease and emphasizes memory more than a bvFTD-specific staging system might. Despite this limitation, the CDR produced bvFTD groups that differed anatomically in keeping with our hypotheses. Second, although it was not a primary aim of this study, we attempted to make inferences about longitudinal change based on cross-sectional data from clinically stratified patients. Previous longitudinal studies of bvFTD were performed on relatively small sample sizes, yielding similar but less anatomically refined results.<sup>30,34,35</sup> Consistent with our cross-sectional findings, a recent longitudinal tensor-based morphometry study<sup>36</sup> on a subset of the patients studied herein showed cingulofrontal and frontoinsular volume loss during a 1-year interval.

In contrast to some previous reports,<sup>22,37,38</sup> this study did not detect significant temporal polar atrophy in any disease stage. The literature, however, suggests that bvFTD often shows predominantly frontal insular degeneration,<sup>2,6,13,15</sup> at least when it is distinguished from right hemisphere–predominant semantic dementia, in which early behavioral features result from temporal pole disease.<sup>39,40</sup> Our clinical experience suggests that temporal atrophy, although universal in semantic dementia, occurs in only a subset of patients with bvFTD, perhaps impeding statistical detection by a technique such as VBM.

The healthy brain safeguards an anterior paralimbic frontal-subcortical network that is crucial for processing emotional salience and orchestrating visceral-autonomic responses.<sup>27,28,41,42</sup> Early injury to this network, as demonstrated in very mild bvFTD, may strip the brain of its ability to integrate internal and external stimuli with response options to produce adaptive, context-sensitive behavior.<sup>42,43</sup> Further insights into bvFTD pathogenesis will require careful study of the cells and regions first injured by the disease.

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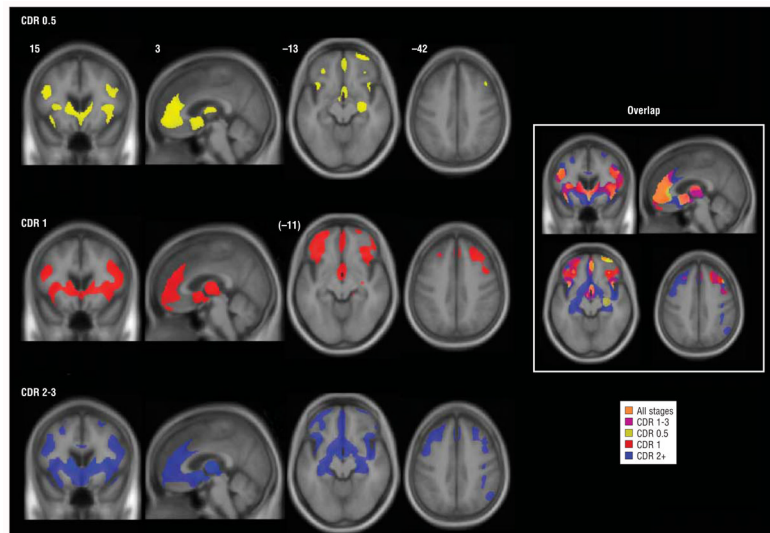
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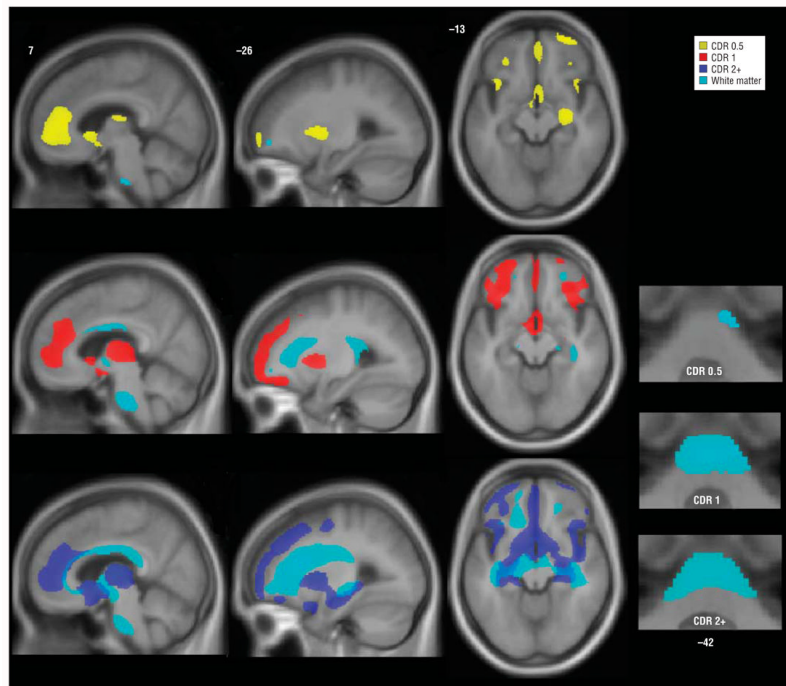
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**Figure 1.**

Stage-specific gray matter atrophy in behavioral variant frontotemporal dementia. Maps of significantly atrophied voxels (each group vs controls:  $P < .05$ , whole brain corrected) are overlaid on the study-specific brain template, using an inclusive gray matter mask for visualization purposes only. On the right, the same color scheme is overlaid on a single image to show overlap of stage-related atrophy patterns. The right side of the axial and coronal images corresponds to the right side of the brain. Numbers indicate the MNI (Montreal Neurological Institute) coordinate of the template brain magnetic resonance image shown. CDR indicates Clinical Dementia Rating; CDR 1-3, mild to severe; CDR 0.5, very mild; CDR 1, mild; and CDR 2+, moderate to severe.



**Figure 2.** Stage-specific white matter atrophy in behavioral variant frontotemporal dementia. Areas of white matter loss are overlaid on gray matter atrophy maps for each stage. Bottom right images show basal pontine white matter loss that involves the middle cerebellar peduncles at later stages. Images are otherwise displayed as in Figure 1. Numbers indicate the MNI (Montreal Neurological Institute) coordinate of the template brain magnetic resonance image shown. CDR indicates Clinical Dementia Rating, CDR 0.5, very mild; CDR 1, mild; and CDR 2+, moderate to severe.

Table 1  
Demographic and Neuropsychological Variables for bvFTD Patient Groups and Controls<sup>a</sup>

Variable	Patients With bvFTD			Overall ANOVA
	Controls	CDR Score of 0.5	CDR Score of 1	
Age, y	68.3 (7.9)	65.9 (8.3)	64.3 (8.9)	$F_{3,86}=2.16$
Educational level, y	16.4 (2.4)	14.7 (3.3)	15.9 (2.3)	$F_{3,86}=3.00$
Male/female, No.	23/22	9/6	10/5	$\chi^2_{3,86} = 1.66$
Duration of symptoms, y		5.8 (4.8)	4.7 (3.6)	$F_{2,42}=0.54$
CDR box score sum	0.0 (0.0)	3.6 (2.3), <sup>bc</sup>	6.1 (1.4), <sup>cd</sup>	$F_{2,42}=46.8^e$
MMSE score [range] (maximum score, 30)	29.5 (0.7) [27-30]	26.7 (3.1) [20-30] <sup>c</sup>	23.3 (7.9) [2-29], <sup>cf</sup>	$F_{3,84}=33.9^e$
CVLT-SF, 4 trials, score (maximum score, 28)	29.5 (3.8)	19.6 (4.4), <sup>cf</sup>	18.1 (7.0), <sup>cf</sup>	$F_{3,75}=52.0^e$
CVLT-SF, 10-minute recall, score (maximum score, 9)	7.3 (1.6)	3.0 (1.9), <sup>cf</sup>	4.1 (2.4), <sup>cf</sup>	$F_{3,71}=47.9^e$
Modified Rey-Osterrieth copy score (maximum score, 17)	15.8 (1.4)	14.6 (1.8) <sup>c</sup>	14.9 (1.8) <sup>c</sup>	$F_{3,80}=11.0^e$
Modified Rey-Osterrieth delay score (maximum score, 17)	12.5 (3.1)	7.1 (4.1), <sup>cf</sup>	5.7 (4.0), <sup>cf</sup>	$F_{3,79}=37.6^e$
Digit span backward score	5.3 (1.2)	3.9 (1.1) <sup>f</sup>	3.7 (1.9) <sup>f</sup>	$F_{3,81}=11.2^e$
Modified Trails B score (correct lines in 1 minute)	32.4 (12.2)	13.5 (15.5) <sup>f</sup>	11.8 (14.3) <sup>f</sup>	$F_{3,76}=19.4^e$
Stroop interference task score (correct in 1 minute)	55.1 (15.3)	33.0 (24.9) <sup>f</sup>	28.6 (16.9) <sup>f</sup>	$F_{3,71}=13.8^e$
Design fluency score (correct in 1 minute)	11.2 (2.5)	6.1 (4.0) <sup>f</sup>	5.5 (2.7) <sup>f</sup>	$F_{3,69}=26.9^e$
Phonemic fluency score (D words generated in 1 minute)	15.5 (4.6)	8.2 (5.7) <sup>f</sup>	5.8 (4.2) <sup>f</sup>	$F_{3,81}=31.5^e$
Semantic fluency score (animals generated in 1 minute)	22.8 (5.3)	10.0 (6.3), <sup>cf</sup>	8.8 (5.4) <sup>f</sup>	$F_{3,83}=57.5^e$
Abbreviated BNT score (maximum score, 15)	14.6 (0.7)	11.2 (3.7) <sup>f</sup>	11.3 (4.5) <sup>f</sup>	$F_{3,83}=17.4^e$
Calculations score (maximum score, 5)	4.8 (0.4)	4.1 (1.2) <sup>c</sup>	3.5 (1.8) <sup>f</sup>	$F_{3,82}=16.9^e$

Abbreviations: ANOVA, analysis of variance; BNT, Boston Naming Test; bvFTD, behavioral variant frontotemporal dementia; CDR, Clinical Dementia Rating; CVLT-SF, California Verbal Learning Test-Short Form; MMSE, Mini-Mental State Examination.

<sup>a</sup>Data are presented as mean (SD) unless otherwise indicated.

<sup>b</sup> $P < .05$  vs CDR score of 1.

<sup>c</sup> $P < .05$  vs CDR score of 2 to 3.

<sup>d</sup> $P < .05$  vs CDR score of 0.5.

<sup>e</sup> $P < .01$  across groups.

<sup>f</sup> $P < .05$  vs controls.

**Table 2**

Clinical Dementia Rating (CDR) Subscale Scores in Very Mild, Mild, and Moderate to Severe Behavioral Variant Frontotemporal Dementia CDR Subscale CDR Score, Median (Range) Very Mild Mild Moderate to Severe<sup>a</sup>

CDR Subscale	CDR Score, Median (Range)		
	Very Mild	Mild	Moderate to Severe <sup>a</sup>
Memory	0.5 (0-1)	1.0 (0.5-1)	1.0 (1-3)
Orientation	0.0 (0-1)	0.5 (0-1)	1.0 (1-2)
Judgment and problem solving	1.0 (0-2)	1.0 (1-3)	2.0 (2-3)
Community affairs	0.5 (0-2)	1.0 (1-2)	2.0 (2-3)
Home and hobbies	0.5 (0-2)	1.0 (1-2)	2.0 (2-3)
Personal care	0.0 (0-2)	1.0 (0-2)	2.0 (0-3)

<sup>a</sup> n = 13 (see the "Participants" subsection of the "Methods" section).

Regions of Gray Matter Loss in Very Mild, Mild, and Moderate to Severe bvFTD

Region	BA	CDR Score					
		0.5		1		2-3	
		x, y, z	z Score	x, y, z	z Score	x, y, z	z Score
Paralimbic							
R pregenual ACC	24	2, 36, 14	5.79	4, 38, 20	5.66	2, 28, 18	6.68
L pregenual ACC	24	-2, 36, 12	5.83	-2, 38, 16	5.06	-2, 32, 16	6.61
R paracingulate	32	2, 44, 20	5.79	2, 44, 30	5.92	2, 44, 28	6.81
L paracingulate	32	-2, 48, 22	5.38	-2, 46, 28	5.98	-2, 46, 24	5.96
R rostromedial SFG	10	2, 53, -4	5.89	-2, 58, 2	5.83	1, 53, -3	6.82
L rostromedial SFG	10	-2, 54, -4	5.52	-2, 54, -2	5.57	-2, 54, -4	6.62
R subgenual ACC	25	2, 8, -4	5.44	4, 8, -8	5.43	4, 8, -6	7.05
L subgenual ACC	25	-4, 12, -6	4.85	-4, 8, -6	5.20	-4, 10, -6	6.88
R frontal insula	47/12	42, 17, -10	5.46	36, 18, -8	5.58	42, 16, -12	6.80
L frontal insula	47/12	-39, 17, -13	5.44	-38, 20, -10	5.18	-39, 17, -13	6.92
R dorsal anterior insula	NA	39, 23, 5	5.61	35, 18, 5	6.97	35, 16, 7	7.22
L dorsal anterior insula	NA	-34, 24, 4	4.98	-32, 22, 4	6.05	-36, 24, 4	6.68
R lateral orbital gyrus	47/11	33, 36, -13	4.66	34, 36, -13	5.72	42, 16, -12	6.80
L lateral orbital gyrus	47/11	-29, 38, -13	4.86	-29, 38, -14	6.00	-30, 38, -15	5.60
R posterior insula	NA					44, -10, -4	6.55
L posterior insula	NA					-40, -12, -2	5.40
Neocortical							
R frontal pole	11	28, 61, -15	5.85	24, 61, -13	4.81	33, 63, -6	6.10
L frontal pole	11	-31, 61, -2	5.67	-29, 61, -2	6.78	-27, 61, -3	6.31
R MFG, ventral	46	30, 52, 18	5.18	38, 52, 6	5.43	36, 44, 28	5.37
L MFG, ventral	46	-42, 52, 9	4.84	-42, 53, 7	5.87	-45, 53, 4	6.60
R IFG, opercularis	44	38, 14, 33	5.13	38, 15, 33	6.57	38, 13, 34	6.76
L IFG, opercularis	44	-44, 13, 28	5.70	-44, 11, 27	6.25	-43, 10, 25	6.69
R precentral gyrus	4	47, -6, 33	4.97	47, -6, 34	6.25	47, -6, 34	5.25
L STS	21	-53, -30, -8	4.82	-54, -29, -4	5.51	-54, -29, -4	5.51
R IFG, triangularis	45	45, 36, 17	4.60	45, 34, 20	5.60	44, 34, 24	4.87
L IFG, triangularis	45			-48, 36, 26	4.96	-56, 28, 18	6.85
R MFG, dorsal	9	26, 34, 40	5.55	26, 34, 40	5.55	30, 26, 40	5.92
L MFG, dorsal	9	-40, 25, 46	4.82	-40, 25, 46	4.82	-42, 28, 45	5.28
Dorsomedial SFG	9			0, 36, 38	6.02	0, 36, 38	6.91
L SFG	8			-24, 19, 47	4.72	-25, 21, 47	5.80
R middle temporal gyrus	21			48, -18, -4	4.99	50, -18, -6	5.40
L angular gyrus	22					-50, -51, 26	4.75
R inferior parietal lobule	39					48, -59, 44	5.37
Limbic							
R anterior hippocampus/amygdala	NA	29, -13, -13	5.64	30, -14, -10	4.74	-30, -14, -10	6.12
L anterior hippocampus/amygdala	NA					28, -14, -16	5.86
R posterior hippocampus	NA					27, -26, -10	5.68
L posterior hippocampus	NA					-28, -32, -6	5.60
Subcortical							
L caudate	NA	-7, 15, 6	6.15	-8, 13, 9	7.23	-10, 15, 7	7.88
R caudate	NA	9, 13, 9	6.15	9, 13, 9	6.97	9, 12, 7	7.65
R putamen	NA	30, 4, 8	5.51	27, 6, 8	6.57	29, 8, 10	7.27
L putamen	NA	-22, 3, 6	5.63	-22, 5, 4	6.40	-22, 11, 4	7.23
Medial thalamus	NA	2, -8, 10	4.98	2, -8, 8	6.65	2, -8, 8	7.55
R lateral cerebellum	NA					48, -67, -48	4.65



Abbreviations: ACC, anterior cingulate; bvFTD, behavioral variant frontotemporal dementia; BA, Brodmann area, CDR, Clinical Dementia Rating; IFG, inferior frontal gyrus; MFG, middle frontal gyrus; NA, not applicable; SFG, superior frontal gyrus; STS, superior temporal sulcus.