Tracking progression in frontotemporal lobar degeneration: Serial MRI in semantic dementia

Neurology 2008;71;1445-1451
DOI: 10.1212/01.wnl.0000327889.13734.cd

This information is current as of January 7, 2009

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://www.neurology.org/cgi/content/full/71/18/1445

Neurology® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright © 2008 by AAN Enterprises, Inc. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.
Tracking progression in frontotemporal lobar degeneration
Serial MRI in semantic dementia

J.D. Rohrer, MRCP
E. McNaught, BASc
J. Foster, BA
S.L. Clegg, BSc
J. Barnes, PhD
R. Omar, MRCP
E.K. Warrington, FRCP
M.N. Rossor, MD, FRCP
J.D. Warren, PhD, FRACP
N.C. Fox, MD, FRCP

ABSTRACT

Background: Semantic dementia is a sporadic neurodegenerative disorder characterized by the progressive erosion of semantic processing and is one of the canonical subtypes of frontotemporal lobar degeneration. This study aimed to characterize the pattern of global and regional longitudinal brain atrophy in semantic dementia and to identify imaging biomarkers that could underpin therapeutic trials.

Methods: Twenty-one patients with semantic dementia (including eight pathologically confirmed cases) underwent whole-brain and region-of-interest analyses on volumetric brain MRI scans at two time points. Sample size estimates for trials were subsequently calculated using these data.

Results: Mean (SD) whole-brain atrophy rate was 39.6 (31.9) mL/y [3.2 (12.0) mL/y in controls], with ventricular enlargement of 8.9 (4.4) mL/y [1.0 (1.0) mL/y in controls]. All patients had a smaller left temporal lobe at baseline [left mean 31.9 (6.9) mL, right mean 49.2 (9.5) mL; p < 0.0001]; however, the mean rate of atrophy was significantly greater in the right temporal lobe [right 3.9 (1.7) mL/y, left 2.8 (1.2) mL/y; p = 0.02]. Similarly, whereas the left hippocampus was smaller at baseline, the mean atrophy rate was significantly greater in the right hippocampus. Using the atrophy rates generated, sample size requirements for clinical trials were found to be smaller for temporal lobe measurement.

Conclusions: These findings show that the rate of tissue loss in the right temporal lobe overtakes the left temporal lobe as semantic dementia evolves, consistent with the later development of symptoms attributable to right temporal lobe dysfunction. Furthermore, our findings demonstrate that MRI measures of temporal lobe volume loss could provide a feasible and sensitive index of disease progression in semantic dementia. Neurology® 2008;71:1445–1451

GLOSSARY

BBSI = boundary shift integral–derived whole-brain volume change; BSI = boundary shift integral; FTLD = frontotemporal lobar degeneration; MMSE = Mini-Mental State Examination; MR = magnetic resonance; NT = not tested; PIQ = performance IQ; VIQ = verbal IQ.

Frontotemporal lobar degeneration (FTLD) is a clinically, pathologically, and genetically diverse group of disorders that together constitute the second most common degenerative cause of dementia in those younger than 65 years. Semantic dementia is one of the canonical clinical subtypes of FTLD,\textsuperscript{1,2} presenting with a fluent aphasia, anomia, and single word comprehension impairment secondary to a verbal semantic deficit. However, deficits in nonverbal domains are also present from early in the disease,\textsuperscript{3,4} the most common being an associative visual agnosia. Typically, patients have a cross-sectional brain imaging profile of asymmetrical anteroinferior temporal lobe atrophy more marked on the left.\textsuperscript{5,6} Similarly, functional imaging using fluorodeoxyglucose-PET has shown asymmetrical hypometabolism of the temporal lobes, worse on the left.\textsuperscript{7,8} At postmortem, patients with semantic dementia characteristically have ubiquitin-positive/TDP-43–positive,
tau-negative neuronal inclusions.\textsuperscript{9,12,13} Hence, semantic dementia forms a unique clinicopathologic syndrome and may therefore offer a prime opportunity for targeting drug trials directed at tissue pathology in FTLD. To realize this opportunity, it will be necessary to develop biomarkers of disease progression suitable for use in therapeutic trials, such as quantitative measures of global and regional longitudinal brain atrophy calculated from MRI.\textsuperscript{14}

Longitudinal imaging studies in semantic dementia are limited, and the size of the groups studied is generally small.\textsuperscript{15-18} Clinical studies of semantic dementia suggest that patients who present with predominantly left-sided temporal lobe atrophy develop clinical and radiologic features of right temporal lobe damage as the disease evolves.\textsuperscript{15,18,19} However, detailed volumetric analyses of the evolution of brain atrophy in semantic dementia are lacking. This study was therefore designed with two aims: to characterize profiles of whole-brain and temporal lobe atrophy longitudinally in semantic dementia, and to determine whether such measures could constitute feasible imaging biomarkers for therapeutic trials in semantic dementia.

METHODS Patients were recruited from the tertiary-level Cognitive Disorders Clinic of the National Hospital of Neurology and Neurosurgery, London, United Kingdom. Seventy-four patients with a clinical diagnosis of semantic dementia were seen between 1992 and 2006, with all patients meeting modified Neary criteria as per Adlam et al.,\textsuperscript{1} i.e., fluent speech, marked anomia, impaired word comprehension, and deficits in nonverbal semantic domains. All patients with two volumetric T1-weighted magnetic resonance (MR) scans of sufficient quality to allow region-of-interest analysis were included in the study; 21 semantic dementia patients met these criteria (12 men, 9 women; mean (SD) age at first scan 64.2 (7.2) years) with a mean interval of 18 (11) months between scans. Disease duration (from first symptoms) ranged between 1.5 and 7.6 years, with a mean of 3.9 years. A control group consisting of 20 cognitively normal subjects (12 men, 8 women; mean age at first scan 63.9 (9.1) years; no evidence of a difference from the semantic dementia group, \( p = 0.45 \)) also had longitudinal scans [mean interval 20 (11) months; no evidence of a difference from the semantic dementia group, \( p = 0.24 \)].

Eight of the semantic dementia patients have come to post-mortem [4 men, 4 women; mean age at first scan 64.5 (6.1) years; mean disease duration 4.1 (1.8) years; no evidence of a difference from total semantic dementia group], and all have shown ubiquitin-positive, tau-negative pathology\textsuperscript{20}: subgroup analyses were performed on these pathologically confirmed semantic dementia cases.

Neuropsychological assessment. Baseline neuropsychological data, including the Mini-Mental State Examination (MMSE) score,\textsuperscript{21} are shown in appendix e-1 on the Neurology\textsuperscript{22} Web site at www.neurology.org and in table 1.

Brain image analysis. All patients had MRI on a 1.5-Tesla GE Signa scanner (General Electric, Milwaukee, WI). T1-weighted volumetric images were obtained with a 24-cm field of view and 256 \( \times \) 256 matrix to provide 124 contiguous 1.5-mm-thick slices in the coronal plane (echo time = 5 msec, repetition time = 12 msec, inversion time = 650 msec). Visual assessment of the MR images revealed that all patients had left greater than right temporal lobe atrophy at baseline (figure 1), with characteristic predominantly anteroinferior atrophy of the left temporal lobe. Whole-brain, ventricular, temporal lobe, and hippocampal segmentations were performed using the software package MIDAS.\textsuperscript{23} For each of the regional segmentations, the operator was blinded to the subject’s identity, whether in the disease or control group, whether measurements were being performed on the baseline or registered-repeat image, and (for temporal lobes and hippocampi) the left-right orientation of the scan.

Whole-brain segmentation. A rapid, semiautomated technique of brain segmentation that involves interactive selection of thresholds, followed by a series of erosions and dilations, was performed for each scan.\textsuperscript{24} This yields a brain region that is separated from the surrounding CSF, skull, and dura. Whole-brain volume change was calculated in two ways: first, change was calculated by subtracting the outlined brain volume on the repeat scan from the baseline brain volume and then adjusted to an annualized rate according to the interscan interval; and second, the serial scans were coregistered and volume change was calculated directly using the boundary shift integral (BSI).\textsuperscript{25} BSI-derived whole-brain volume changes (BBSI) were expressed as annualized volume change in milliliters per year.

Regional segmentation. Scans were transformed into standard space by registration to the Montreal Neurological Institute template,\textsuperscript{26} and then an affine (12 df) registration was performed to align the repeat scan onto the baseline image.\textsuperscript{27}

Temporal lobes. Both temporal lobes were segmented for all subjects by a single rater with intrarater variability of 0.4% and intraclass correlation coefficient of 0.99. The average segmentation time per temporal lobe was 30 minutes. Initially, each scan was reflected across the mid-sagittal plane, producing two scans, each a mirror image of the other. This enabled the temporal lobe to be consistently measured on the right hand side of the presented image, whether the temporal lobe was left or right. The baseline and registered-repeat scans were presented simultaneously in random order. The operator traced around all the boundaries of the temporal lobe with two orthogonal views available. A consistent threshold of 60% of mean brain intensity was applied to exclude lower intensity voxels, which correspond predominantly to CSF. The caudal boundary was defined as the coronal slice where the thalamus and fornix first become distinct structures and is generally where the longest length of the fornix is observable. An arbitrary cutoff point was used for the temporal lobe stem, determined by a straight line connecting the most inferior and medial point of the sylvian fissure to the superior lateral-most point of the medial temporal lobe, adjacent to the stem. However, if this demarcating line clearly eliminated any subcortical structures, an alternative cutoff was used. In these cases, a straight line was drawn from the same inferomedial portion of the sylvian fissure, now connecting to the most superior surface of the subcortical structure (i.e., hippocampus or amygdala), after which the demarcating line followed the curve of this structure back to the superior lateral-most point of the medial

Downloaded from www.neurology.org at SWETS SUB SERVICE on January 7, 2009
Copyright © by AAN Enterprises, Inc. Unauthorized reproduction of this article is prohibited.
<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Years from onset</th>
<th>MMSE*</th>
<th>VIQ*</th>
<th>PIQ*</th>
<th>Verbal memory</th>
<th>Visual memory</th>
<th>Naming</th>
<th>Single word comprehension</th>
<th>Executive function</th>
<th>Reading</th>
<th>Arithmetic</th>
<th>Spelling</th>
<th>Limb praxis†</th>
<th>Visuospatial skills</th>
</tr>
</thead>
<tbody>
<tr>
<td>SD1</td>
<td>5.9</td>
<td>5</td>
<td>54</td>
<td>62</td>
<td>Unable</td>
<td>&lt;5th</td>
<td>&lt;5th</td>
<td>&lt;5th</td>
<td>Fail</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
<td>Normal</td>
</tr>
<tr>
<td>SD2</td>
<td>4.1</td>
<td>19</td>
<td>54</td>
<td>85</td>
<td>Unable</td>
<td>&lt;5th</td>
<td>&lt;5th</td>
<td>&lt;5th</td>
<td>Pass</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
<td>Normal</td>
</tr>
<tr>
<td>SD3</td>
<td>2.5</td>
<td>7</td>
<td>69</td>
<td>85</td>
<td>&lt;5th</td>
<td>50th-75th</td>
<td>&lt;5th</td>
<td>&lt;5th</td>
<td>Fail</td>
<td>&lt;5th</td>
<td>&lt;5th</td>
<td>&lt;5th</td>
<td>NT</td>
<td>Normal</td>
</tr>
<tr>
<td>SD4</td>
<td>3.7</td>
<td>8</td>
<td>68</td>
<td>92</td>
<td>5th-10th</td>
<td>&lt;5th</td>
<td>&lt;5th</td>
<td>&lt;5th</td>
<td>NT</td>
<td>&lt;5th</td>
<td>5th-10th</td>
<td>&lt;5th</td>
<td>NT</td>
<td>Normal</td>
</tr>
<tr>
<td>SD5</td>
<td>4.8</td>
<td>20</td>
<td>NT</td>
<td>96</td>
<td>&lt;5th</td>
<td>&lt;5th</td>
<td>&lt;5th</td>
<td>10th-25th</td>
<td>Fail</td>
<td>50th-75th</td>
<td>&lt;5th</td>
<td>NT</td>
<td>NT</td>
<td>Normal</td>
</tr>
<tr>
<td>SD6</td>
<td>3.7</td>
<td>28</td>
<td>114</td>
<td>110</td>
<td>10th-25th</td>
<td>10th-25th</td>
<td>&lt;5th</td>
<td>10th-25th</td>
<td>Pass</td>
<td>10th-25th</td>
<td>&gt;75th</td>
<td>NT</td>
<td>Normal</td>
<td>&gt;5th</td>
</tr>
<tr>
<td>SD7</td>
<td>6.1</td>
<td>16</td>
<td>NT</td>
<td>100</td>
<td>Unable</td>
<td>&lt;5th</td>
<td>&lt;5th</td>
<td>&lt;5th</td>
<td>Fail</td>
<td>&lt;5th</td>
<td>&lt;5th</td>
<td>NT</td>
<td>NT</td>
<td>&gt;5th</td>
</tr>
<tr>
<td>SD8</td>
<td>3.9</td>
<td>19</td>
<td>74</td>
<td>101</td>
<td>&lt;5th</td>
<td>50th-75th</td>
<td>&lt;5th</td>
<td>10th-25th</td>
<td>Pass</td>
<td>&lt;5th</td>
<td>&lt;5th</td>
<td>&lt;5th</td>
<td>NT</td>
<td>&gt;75th</td>
</tr>
<tr>
<td>SD9</td>
<td>2.9</td>
<td>NT</td>
<td>61</td>
<td>76</td>
<td>Un able</td>
<td>5th-10th</td>
<td>&lt;5th</td>
<td>&lt;5th</td>
<td>NT</td>
<td>&lt;5th</td>
<td>5th-10th</td>
<td>&lt;5th</td>
<td>NT</td>
<td>&gt;75th</td>
</tr>
<tr>
<td>SD10</td>
<td>1.8</td>
<td>26</td>
<td>77</td>
<td>81</td>
<td>Un able</td>
<td>Un able</td>
<td>&lt;5th</td>
<td>&lt;5th</td>
<td>NT</td>
<td>10th-25th</td>
<td>&gt;75th</td>
<td>NT</td>
<td>Normal</td>
<td>&gt;75th</td>
</tr>
<tr>
<td>SD11</td>
<td>1.7</td>
<td>20</td>
<td>94</td>
<td>106</td>
<td>10th-25th</td>
<td>10th-25th</td>
<td>&lt;5th</td>
<td>10th-25th</td>
<td>Pass</td>
<td>50th-75th</td>
<td>&lt;5th</td>
<td>NT</td>
<td>NT</td>
<td>10th-25th</td>
</tr>
<tr>
<td>SD12</td>
<td>5.1</td>
<td>18</td>
<td>60</td>
<td>93</td>
<td>&lt;5th</td>
<td>10th</td>
<td>&lt;5th</td>
<td>&lt;5th</td>
<td>Fail</td>
<td>50th-75th</td>
<td>5th-10th</td>
<td>5th-10th</td>
<td>NT</td>
<td>&gt;75th</td>
</tr>
<tr>
<td>SD13</td>
<td>3.8</td>
<td>25</td>
<td>85</td>
<td>98</td>
<td>&lt;5th</td>
<td>25th-50th</td>
<td>&lt;5th</td>
<td>10th-25th</td>
<td>Pass</td>
<td>25th-50th</td>
<td>25th-50th</td>
<td>50th-75th</td>
<td>NT</td>
<td>&gt;75th</td>
</tr>
<tr>
<td>SD14</td>
<td>5.3</td>
<td>27</td>
<td>100</td>
<td>92</td>
<td>&lt;5th</td>
<td>&lt;5th</td>
<td>&lt;5th</td>
<td>&lt;5th</td>
<td>Pass</td>
<td>25th-50th</td>
<td>NT</td>
<td>50th-75th</td>
<td>NT</td>
<td>&gt;75th</td>
</tr>
<tr>
<td>SD15</td>
<td>3.7</td>
<td>22</td>
<td>91</td>
<td>90</td>
<td>&lt;5th</td>
<td>&lt;5th</td>
<td>5th-10th</td>
<td>&lt;5th</td>
<td>5th-10th</td>
<td>50th-75th</td>
<td>50th-75th</td>
<td>50th-75th</td>
<td>NT</td>
<td>&gt;75th</td>
</tr>
<tr>
<td>SD16</td>
<td>2.9</td>
<td>11</td>
<td>67</td>
<td>79</td>
<td>&lt;5th</td>
<td>&lt;5th</td>
<td>&lt;5th</td>
<td>&lt;5th</td>
<td>NT</td>
<td>&lt;5th</td>
<td>&lt;5th</td>
<td>5th-10th</td>
<td>NT</td>
<td>&gt;75th</td>
</tr>
<tr>
<td>SD17</td>
<td>7.3</td>
<td>15</td>
<td>NT</td>
<td>NT</td>
<td>&lt;5th</td>
<td>&lt;5th</td>
<td>&lt;5th</td>
<td>&lt;5th</td>
<td>NT</td>
<td>&lt;5th</td>
<td>25th-50th</td>
<td>&lt;5th</td>
<td>NT</td>
<td>&gt;75th</td>
</tr>
<tr>
<td>SD18</td>
<td>3.9</td>
<td>26</td>
<td>87</td>
<td>120</td>
<td>&lt;5th</td>
<td>&lt;5th</td>
<td>&lt;5th</td>
<td>&lt;5th</td>
<td>Pass</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
<td>&gt;75th</td>
</tr>
<tr>
<td>SD19</td>
<td>2.5</td>
<td>26</td>
<td>73</td>
<td>99</td>
<td>10th-25th</td>
<td>&lt;5th</td>
<td>&lt;5th</td>
<td>&lt;5th</td>
<td>Pass</td>
<td>10th-25th</td>
<td>50th-75th</td>
<td>&lt;5th</td>
<td>Normal</td>
<td>&gt;75th</td>
</tr>
</tbody>
</table>

Patients SD14 to SD21 are pathologically confirmed.

*Mini-Mental State Examination (MMSE) value represents a score out of 30; IQ score = average of 100; other values represent a percentile score.

Assessment of ability to copy meaningless and meaningful hand gestures.

VIQ = Verbal IQ; PIQ = Performance IQ; NT = Not tested.
temporal lobe. The accessory gyrus was included as soon as the CSF was just visible between the medial side and the temporal stem on the coronal view. The baseline and repeat images were then edited in adjacent views to ensure that the arbitrary cutoff points were consistent between scans.

Ventricles and hippocampi were also manually segmented, with rates of ventricular enlargement and hippocampal atrophy calculated using manual segmentation and BSI. Detailed methods are described in appendix e-2.

Statistics and sample size calculations. STATA 8 (StataCorp, College Station, TX) was used for statistical analysis. Two-sample t tests allowing unequal variances were used to compare the rates of brain atrophy between the groups. After measurement of rates of atrophy for the whole brain and regions of interest, we used standard methods to calculate sample sizes for a trial including baseline and one follow-up assessment with 90% power to detect a treatment effect and 5% two-tailed significance level. Sample sizes to detect a 30% reduction in atrophy were calculated in two ways: first, without adjustment for the control atrophy rate, and second, adjusted for control atrophy rate.

RESULTS Psychometric data. The psychometric data are summarized in table 1. All but two of the patients (SD12 and SD17) had psychometric testing within 6 months of the baseline scan. All of the patients had severe anomia and impaired single word comprehension, supporting the clinical diagnosis of semantic dementia. Furthermore, all patients whose reading was tested had a surface dyslexia, a characteristic feature of semantic dementia. Similarly, many of the patients had a surface dysgraphia. Executive function was variably impaired, but posterior functions (visuospatial and visuoperceptual skills, arithmetic and limb praxis) were relatively intact, again supportive of a diagnosis of semantic dementia. Performance was relatively poor on tests of episodic memory (although worse on verbal rather than visual tests). However, patients with semantic dementia often fail formal tests of episodic memory for reasons other than an actual amnestic deficit, i.e., failure on verbal tests is usually due to underlying verbal semantic impairment and failure on visual tests that involve recognition of faces or objects is due to an associative visual agnosia.

Rates of volume change. Rates of whole-brain atrophy. The mean (SD) baseline whole-brain volume was 1,110 (107) mL in the semantic dementia group and 1,182 (97) mL in the controls. The whole-brain atrophy rate was significantly greater for the semantic dementia group compared with the controls (p = 0.0002; table 2). Individual atrophy rates for the semantic dementia group are shown in figure 2. Using the BBSI rates, a relatively smaller atrophy rate was found in the disease group, with a smaller variability in both groups (figure e-1A). Expressed as a percentage, the mean annualized rate of whole-brain atrophy using the BBSI was 2.5% (1.5%), vs 0.4% (0.4%) in the controls.

Rates of ventricular enlargement. The mean (SD) baseline ventricular volume was 43.1 (19.7) mL in the semantic dementia group and 28.7 (23.4) mL in the controls. The mean annualized rate of ventricular enlargement was significantly greater in the semantic dementia group compared with the controls using both manual ventricular measurement and ventricular BSI (p < 0.0001; figure e-1B).

Rates of temporal lobe atrophy. The mean (SD) baseline left temporal lobe volume was 31.9 (6.9) mL in the semantic dementia group and 61.3 (5.8) mL in the controls, whereas the mean baseline right temporal lobe volume was 49.2 (9.5) mL in the semantic dementia group and 64.8 (6.8) mL in the controls. The mean baseline left temporal lobe volume was significantly smaller than the right in the semantic dementia group (35% smaller, p < 0.0001). The mean annualized rates of both left and right temporal lobe atrophy were significantly greater in the semantic dementia group compared with controls (p < 0.0001). However, the right
temporal lobe atrophy rate for the semantic dementia group was significantly greater than the left temporal lobe atrophy rate \( (p = 0.02) \). Furthermore, right and left temporal lobe atrophy rates were correlated \( (R^2 = 0.31, p = 0.008; \text{figure c-2}) \).

**Rates of hippocampal atrophy.** The mean (SD) baseline left hippocampal volume was 1.92 (0.43) mL in the semantic dementia group and 2.57 (0.27) mL in the controls, whereas the mean baseline right hippocampal volume was 2.41 (0.43) mL in the semantic dementia group and 2.73 (0.29) mL in the controls. The mean baseline left hippocampal volume was significantly smaller than the right in the semantic dementia group \( (p = 0.0006) \). The mean annualized rate of both left and right hippocampal atrophy was significantly greater in the semantic dementia group compared with controls \( (p < 0.05) \). Similar to the temporal lobes, the right hippocampal atrophy rate for the semantic dementia group was significantly greater than the left hippocampal atrophy rate \( (p = 0.04) \). As with BBSI, there was a smaller variability using the boundary shift integral–derived hippocampal volume change.

**Pathologically confirmed semantic dementia subgroup.** We also analyzed the data from the subgroup of eight patients who had pathologic confirmation of disease (which in all cases was ubiquitin-positive, tau-negative pathology). There was no evidence for differences between the pathologically confirmed and non-pathologically confirmed semantic dementia groups in any of the volumetric measures of change, apart from the manual ventricular measurement, where the pathologically confirmed semantic dementia group’s rate of ventricular enlargement was smaller than that of the non-pathologically confirmed semantic dementia group \( (p = 0.01) \).

**Psychometric data.** No correlations were found between MMSE, verbal IQ score, or performance IQ, either with baseline volumes or with rates of atrophy. This may be because these scores (particularly MMSE) are poor measures of disease severity in semantic dementia.

**Survival data.** For the pathologically confirmed semantic dementia subgroup, the mean total duration of disease from symptom onset until death was 12.5 years, with a range of 8.7 to 18.7 years (median 11.8 years). Published data relating to this issue are limited: although one study of survival in frontotemporal lobar degeneration\(^7\) reported the mean length of disease in semantic dementia as 6.9 years, a recent reevaluation of that same cohort suggested this was an underestimate and quoted a longer median survival from diagnosis to death of 12 years,\(^7\) which is very similar to our study. We did not find any evidence for correlations between the total duration of disease and rates of volume change in any of the measured brain regions.

**Sample size calculations.** Sample size requirements for clinical trials that have 90% statistical power to detect 30% difference in rate of volume change are summarized in table 3. The lowest sample size estimates were for right and left temporal lobe atrophy rates.
Here we describe profiles of longitudinal global and regional brain atrophy in a large and well-defined cohort of patients with semantic dementia. Although all patients had asymmetrical left greater than right temporal lobe and hippocampal atrophy at baseline (and as a group there was a significantly smaller left temporal lobe and hippocampus at baseline), our findings show that at this stage in clinically established semantic dementia (mean 4 years after symptom onset), the right temporal lobe and right hippocampus are losing volume more quickly than the left. Semantic dementia is a relatively uncommon disease, and candidate biomarkers for therapeutic trials must therefore be robust to small sample sizes. We found that temporal lobe atrophy rates measured from serial MRI offer an attractive imaging biomarker of disease progression in semantic dementia, with calculated sample sizes using manual segmentation feasible for clinical trials in semantic dementia. However, although manual segmentation of temporal lobe has good intrarater reliability, it is relatively time-consuming and requires training of the segmenter. Development of more automated measurements would be useful, and there are a number of possible approaches (e.g., template-based segmentation of temporal lobes); these would need to be validated in semantic dementia scans, but if reliable they may be easier and quicker to implement in a multicenter clinical trial.

Our study also demonstrates quantitatively different rates of atrophy of the right and left temporal lobes in semantic dementia. For the semantic dementia group, the mean rate of atrophy was higher for the right than for the left temporal lobe, despite a smaller left temporal lobe volume at baseline. A similar pattern was found for the hippocampi. This may at first sight seem counterintuitive given the greater atrophy of left temporal lobe at baseline. However, it may simply reflect the extent of damage in the left temporal lobe at a later disease stage with relatively less to lose than the (by now, also affected) right temporal lobe. These findings suggest that rate of atrophy of the right temporal lobe overtakes that of the left (at least in terms of total number of milliliters lost per year) as the disease evolves, and there is less left temporal lobe tissue to lose. There is limited evidence from postmortem studies that at the endpoint of disease, temporal lobe atrophy is bilateral and can be fairly symmetric.\(^*\) Our study, with only two time points per individual, cannot address within-subject nonlinearity of rates of loss. It would be interesting to assess with multiple time points how atrophy rates of the temporal lobes change. The evidence of increasing right temporal lobe losses is also consistent with clinical findings of symptoms attributable to right temporal lobe dysfunction (e.g., prosopagnosia) later in the disease.\(^\dagger\) It would also provide a disease model for the less common scenario of right "temporal lobe variant" FTLD that subsequently involves the left temporal lobe. Furthermore, in the current study, rates of right and left temporal lobe atrophy were correlated with each other (but not with total disease duration), arguing for an intrinsic rate of lobar atrophy that shows individual variation and is controlled by unidentified factors that operate on both temporal lobes or between temporal lobes. This profile of anatomically restricted disease spread in semantic dementia could help to guide the search for disease mechanisms linked to biochemical, immunologic, and pathologic characteristics expressed in temporal lobe tissue. More detailed study of volume change at the level of individual gyri is required to establish the mechanism of such "catch-up" lobar atrophy.

In addition to its considerable pathobiological interest, the identification of profiles of lobar atrophy has important implications for the design of future therapeutic trials in semantic dementia (and other FTLD syndromes) once disease-modifying treatments become available. Our findings show that "conventional" imaging biomarkers such as whole-brain or hippocampal atrophy rates that have been applied successfully in a particular disease such as Alzheimer’s may not be optimal for diseases with distinct pathogenesis and regional involvement: the biomarker must be tailored to the disease. Furthermore, biomarkers that are intuitively appealing from

---

**Table 3** Sample size required per treatment arm using different measurement methods, based on 90% power to detect a difference

<table>
<thead>
<tr>
<th>Outcome measure*</th>
<th>Not adjusted for control rate</th>
<th>Adjusted for control rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole brain</td>
<td>148</td>
<td>175</td>
</tr>
<tr>
<td>Brain BSI</td>
<td>86</td>
<td>118</td>
</tr>
<tr>
<td>Ventricles</td>
<td>57</td>
<td>73</td>
</tr>
<tr>
<td>Ventricle BSI</td>
<td>71</td>
<td>89</td>
</tr>
<tr>
<td>Left temporal lobe</td>
<td>44</td>
<td>60</td>
</tr>
<tr>
<td>Right temporal lobe</td>
<td>44</td>
<td>55</td>
</tr>
<tr>
<td>Left hippocampus</td>
<td>235</td>
<td>1,099</td>
</tr>
<tr>
<td>Left hippocampal BSI</td>
<td>77</td>
<td>104</td>
</tr>
<tr>
<td>Right hippocampus</td>
<td>81</td>
<td>180</td>
</tr>
<tr>
<td>Right hippocampal BSI</td>
<td>78</td>
<td>81</td>
</tr>
</tbody>
</table>

*Sample sizes are based on atrophy rates calculated either on differences in manually segmented volumes or on the boundary shift integral (BSI).

*Enlargement rate for ventricles and ventricle BSI.
the pathobiological standpoint (e.g., left temporal lobe volume in semantic dementia) may not be optimal in established disease: here, right temporal lobe atrophy rate provided at least as sensitive a biomarker of disease progression in semantic dementia as left temporal lobe atrophy rate, suggesting that the use of left vs right temporal lobe measures should be guided by disease stage. There is an interaction and a trade-off between the frequency of the disease process and the magnitude of a clinically meaningful effect (which dictate sample size), the use of biomarkers that are anatomically optimal, and the practicality of measuring these biomarkers in the trial setting (e.g., the measurement of temporal lobe vs ventricular volumes in semantic dementia). Further work is needed to resolve this trade-off for semantic dementia and other non-Alzheimer dementias.

ACKNOWLEDGMENT

The authors thank Valerie Anderson for help with temporal lobe segmentation and to Lois Kim, PhD (Statistician at Dementia Research Centre, Institute of Neurology, London), for help with statistical analysis.

Received April 24, 2008. Accepted in final form July 22, 2008.

REFERENCES

Tracking progression in frontotemporal lobar degeneration: Serial MRI in semantic dementia
Neurology 2008;71;1445-1451
DOI: 10.1212/01.wnl.0000327889.13734.cd

This information is current as of January 7, 2009

Updated Information & Services
including high-resolution figures, can be found at:
http://www.neurology.org/cgi/content/full/71/18/1445

Supplementary Material
Supplementary material can be found at:
http://www.neurology.org/cgi/content/full/71/18/1445/DC1

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
Volumetric MRI
http://www.neurology.org/cgi/collection/volumetric_mri
Frontotemporal dementia
http://www.neurology.org/cgi/collection/frontotemporal_dementia

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
http://www.neurology.org/misc/Permissions.shtml

Reprints
Information about ordering reprints can be found online:
http://www.neurology.org/misc/reprints.shtml