Contribution of Asymmetric Synapse Loss to Lateralizing Clinical Deficits in Frontotemporal Dementias

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Background: Synapse loss has been found to be the major correlate of cognitive decline in Alzheimer disease (AD), and prefrontal synapse loss has been found in patients with frontotemporal dementia (FTD).

Objective: To see if our hypothesis that within each FTD case, regional synapse loss would correlate with lateralizing neuropsychologic and neurobehavioral deficits would be correct.

Design: We analyzed synaptophysin as a marker for synapse loss in snap-frozen brain samples, using an enzyme-linked immunosorbent assay technique. Quantitative results were obtained by comparing patient data with a standard curve made by analyzing serial dilutions of a recombinant synaptophysin protein fragment. A board-certified neuropsychologist and a board-certified neurologist, both unaware of the synaptophysin results, determined areas of primary neuropsychologic and neurobehavioral dysfunction. Relationships between areas of primary dysfunction and synapse loss were analyzed using the binomial test.

Patients: Six cases of FTD, 28 cases of AD, and 16 nondemented control subjects.

Results: Five of 6 FTD cases had regional synaptophysins correlating with lateralizing frontal or temporal deficits. Three of 6 correlated in 2 or more regions. Although our results were higher than that expected based on a pure-chance mechanism (50% vs 34%), statistical significance was not attained.

Conclusions: We found a trend for an association between synapse loss and lateralizing neuropsychologic and neurobehavioral deficits in FTD. Studies in larger numbers of FTD cases are planned with the goal of attaining statistically significant conclusions.

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SYNAPSE LOSS in Alzheimer disease (AD) was initially reported in 1987 and was first correlated with cognitive decline in 1990. In a 1991 landmark study by Terry and colleagues, synapse loss was found to be the major correlate of cognitive impairment in AD. This has subsequently been confirmed by a number of studies.

A 1995 study by our group reported that a 2-site enzyme-linked immunosorbent assay (ELISA) for synaptophysin was a reliable method of quantitating synapse loss and confirmed decreases in frontal, temporal, and parietal lobes in AD. Similar findings have since been reported by other groups using the ELISA method.

There have been few studies investigating synapse loss in frontotemporal dementias (FTD). Liu and colleagues found that synapse loss was pronounced in the superficial layers of FTD prefrontal cortex compared with healthy control subjects and was similar to that in patients with AD. To our knowledge, however, synapse loss has not previously been correlated with the occasionally dramatic lateralizing neuropsychologic and neurobehavioral features seen in FTD.

The purpose of this study was to determine whether decreases in synaptophysin in FTD correlated with lateralizing clinical deficits. We hypothesized that, within each case, a decrease in either right or left frontal or temporal synaptophysin would correlate with neuropsychologic or neurobehavioral deficits on that side. We analyzed 6 cases of several types of FTD to test this hypothesis.

RESULTS

All cases showed the expected pattern of more severe impairments in executive function and memory, corresponding to a classic clinical pattern of frontotemporal dysfunction. Neuropsychologic and neurobehavioral evaluation disclosed left-sided deficits greater than right-sided defi-
PATIENTS AND METHODS

CASE SELECTION AND EVALUATION OF FTD CASES

Six cases of FTD were identified from the University of Texas Southwestern Alzheimer Disease Center (ADC) for whom we had results of bilateral frontal, temporal, and parietal synaptophysin analyses and antemortem neuropsychologic or neurobehavioral evaluation or both (Table 1 and Table 2). Comprehensive neuropsychologic evaluations (Table 2) were conducted in 4 cases undergoing initial examination at our ADC from January 1, 1988, through December 31, 1995, from 0.7 to 7.3 years before death, with a mean of 3.5 years (Table 1). Three cases (patients 1, 3, and 5) had undergone evaluation using the same battery of standard tests before 1995, and 1 case (patient 6) underwent a revised battery of measures. In these 4 cases, common and well-standardized measures were administered.19,20 Patient 4 underwent neuropsychologic examination at another site, but unfortunately, although we had the clinical report of findings, individual test scores were unavailable for review. Patient 2 showed such severe cognitive limitations that detailed testing was not possible. Tests were grouped by functional domain, and particular attention was paid to measures that have been shown to demonstrate lateralizing or focal cerebral dysfunction. Table 2 lists the cognitive domains assessed and some of the representative measures that were administered as part of each test battery. Although we did not have detailed neuropsychologic evaluations for patients 2 and 4, we had results of neuropsychologic and radiologic evaluation, enabling us to include them in this study, and we include short case histories for both.

Neuropsychologic determination of areas of primary dysfunction was performed by means of clinical interpretation by a board-certified clinical neuropsychologist (C.M.C.) who was unaware of synaptophysin results. All available neuropsychologic data were reviewed and subjected to clinical ratings to evaluate patterns of regional/lateralized cerebral dysfunction across cognitive domains (Table 2). Tests with known sensitivity to lateralized (ie, predominantly verbal vs nonverbal) or focal cerebral dysfunction based on the neuropsychological literature were weighted most heavily in the ratings. Clinical ratings were based on a scale of 0 to 4 points for each functional domain corresponding to frontal, temporal, and parietal regions (0 indicates normal; 1-1.5, mild; 2-2.5, moderate; 3-3.5, severe; and 4, profound deficit) within each hemisphere. Similar ratings have demonstrated usefulness in other populations.11,22 A board-certified ADC neurologist (A.M.L.) who was unaware of the synaptophysin results determined localized neurobehavioral findings. Each patient’s chart was reviewed with regard to localizing findings on neurologic and psychiatric examination, clinical history and course, and radiographic results. The reviewing clinician applied a plus or minus rating concerning clinical involvement of right and left frontal, temporal, and parietal lobes. Patients were designated as having primary frontal involvement on the basis of the presence of typical frontal symptoms such as executive dysfunction or upper motor neuron signs. Pre-dominance of expressive language impairment or apathy was considered to indicate left frontal dysfunction, whereas disinhibition predominating over language deficits was considered to be compatible with right frontal impairment. Pre-dominance of receptive language impairment was considered to be consistent with left temporal impairment. The clinical and neurobehavioral findings are summarized in Table 3.

Table 3. The evaluation of parietal involvement was based primarily on signs such as apraxia, agnosia, and neglect syndromes of the parietal lobes. Such symptoms were not prominent in any of these patients. Results of radiographic studies (computed tomography [CT], magnetic resonance imaging, or regional cerebral blood flow) are summarized in Table 3.

The duration of illness in these 6 FTD cases ranged from 4 to 10 years, with a mean of 7 years. There was no positive family history in any of the 6. Ages at death ranged from 65 to 85 years, with a mean of 73 years. The post-mortem interval (PMI; time from death to fixation and freezing of brain tissue) ranged from 5.0 to 19.8 hours, with a mean of 14.2 hours. Pathological evaluation revealed sparse diffuse plaques in the brain of patient 2 and sparse neuritic plaques insufficient for the diagnosis of AD according to criteria of the Consortium to Establish a Registry for Alzheimer’s Disease (CERAD)23 in the brain of patient 5. The other cases had no neuritic or diffuse plaques. The pathologic diagnosis was corticobasal ganglionic degeneration in patients 1, 2, and 6; Pick disease in patient 3; frontotemporal degeneration—not otherwise specified in patient 4; and sporadic multiple-system atrophy with dementia24 in patient 5.

Patient 2

This 67-year-old man had a 4-year history of progressive apathy, difficulty expressing himself, and episodic verbal and physical aggression. Results of examination disclosed psychomotor retardation and inappropriate affect. He was hypofluent and perseverative, with echolalia, acalculia, and dysnomia. He had motor apraxia, nonsustained clonus in the right foot, and a wide-based shuffling gait, with decreased arm swing bilaterally. Clinical Dementia Rating score was 3; Blessed score, 12; and modified Hachinski Ischemia Scale score, 5. Formal neuropsychologic testing was not possible because of the patient’s profound level of impairment. Head CT showed frontal and minimal temporal lobe atrophy. The patient died at 68 years of age, after a 5-year course.

In addition to the findings suggesting greater left hemisphere dysfunction in patient 5, only this patient also showed a significant discrepancy between verbal and performance IQ scores.

The synaptophysin concentrations in the 6 FTD cases were decreased in all lobes compared with the 16 controls, but the decrements were not as marked as in 28 AD cases. Synaptophysin values were lower in frontal lobes...
The 65-year-old man had a 4-year history of progressive irritability, forgetfulness, acalculia, and left upper extremity tremor. On examination, he demonstrated hypofluent speech, profound echopraxia, and echolalia. There was focal rigidity in bilateral biceps and triceps (greater in the left side than in the right side), and left upper extremity resting tremor. Coordination was decreased, particularly on the left side. Gait was slightly shuffling with stooped posture. Mini-Mental State Examination score was 23/30; Clinical Dementia Rating score, 2; Blessed score, 10; and modified Hachinski Ischemia Scale score, 4.

Results of neuropsychologic testing performed at another facility showed deficits in cognitive flexibility, problem solving, memory, attention, and visuospatial skills, consistent with primary anterior cerebral dysfunction, greater on the left side.

The MRI showed diffuse atrophy (greater on the right side than on the left), and single-photon emission CT showed decreased bilateral frontal flow. Dysphagia and mutism eventually developed. He died at 65 years of age, after a 4-year course.

CASE SELECTION AND EVALUATION OF AD CASES AND CONTROLS

For comparison, we used 28 AD cases from the ADC program who had been thoroughly studied clinically and pathologically. All 28 had received a clinical diagnosis of dementia. Ten were male and 18 were female; all were white. Age at onset ranged from 58 to 90 years, with a mean age of 78 years. Twenty had senile (aged ≥65 years) and 8 had presenile (aged < 65 years) onset. Duration of disease ranged from 2 to 18 years, with a mean of 10.4 years. Pathologically, all had histologic alterations compatible with AD, according to CERAD criteria. The PMI ranged from 3.3 to 26.0 hours, with a mean of 14.6 hours. The 16 controls were obtained primarily from the University of Texas Southwestern Medical School Willed Body Program. Controls underwent clinical evaluation using a modification of the Retrospective Postmortem Cognitive Assessment tool, and none met criteria for cognitive impairment. Ages of controls ranged from 60 to 86 years, with a mean age of 72 years. Fifteen were men and 3 were women; 14 were white and 2 were African American. The PMI ranged from 5.0 to 23.0 hours, with a mean of 8.5 hours. No pathologic diagnoses were made in 5 controls, and mild age-related neurofibrillary degeneration was diagnosed in 11. The age-related neurofibrillary degeneration consisted of neurofibrillary tangles predominantly in the entorhinal or hippocampal region only. Braak stages were 1 and 2 in these controls. There were no neuritic plaques in any control; all had a CERAD grading of 0.

IMMUNOHISTOCHEMICAL ANALYSIS

Immunohistochemical analysis was performed in a standard fashion at room temperature on an automated immunostainer (BioTek Solutions TechMate 1000; Ventana BioTek Systems, Tucson, Ariz) using heat-induced epitope retrieval and standard avidin-biotin complex technique. Antibodies and dilutions used included polyclonal rabbit anti-ubiquitin (Dako, Carpinteria, Calif) at a 1:200 dilution and PHF-1, a monoclonal antibody to tau protein (gift of Peter Davies, PhD) at a 1:100 dilution. Ubiquitin-stained sections were stained using a new fuchsin-type chromogen (BT Red; Ventana BioTek Systems); and PHF-1–stained sections were stained using diaminobenzidine (brown chromogen). Sections were counterstained with hematoxylin.

SYNAPTOPHYSIN QUANTITATION

At the time of autopsy, neocortical gray matter was dissected from the middle frontal, superior temporal, and inferior parietal regions bilaterally, snap frozen in liquid nitrogen, and stored at −70°C. Frozen tissue samples were subsequently thawed, weighed, and homogenized at a constant ratio of 1 g of tissue per 10 mL of buffer (10M Tris, 150mM sodium chloride, 2mM ethylene glycoltetraacetic acid, 2mM dithiothreitol; pH, 7.4), containing a cocktail of protease inhibitors (Roche Diagnostics Corporation, Indianapolis, Ind). Glycerol (10% vol/vol) was then added in the homogenates, and aliquots were stored at −70°C until assayed.

At the time of assay, homogenates were thawed on ice and diluted in blocking buffer (0.1M Tris buffer [pH, 8.0], 5% nonfat dry milk, and 0.2% polysorbate 20 [Tweens 20; Sigma-Aldrich Corp, St Louis, Mo). We used a 2-site, 2-antibody sandwich ELISA technique, first binding monoclonal antibody to synaptophysin (Chemicon International, Temecula, Calif) (1:1000 dilution, incubated overnight at 4°C) directly to the plate, followed by blocking buffer, the test samples (incubated overnight at 4°C), a rabbit polyclonal antibody to synaptophysin (Dako) (1:400 dilution), and then alkaline phosphatase-conjugated goat anti-rabbit IgG (Bio-Rad Laboratories, Hercules, Calif) (1:1000 dilution), with paranitrophenyl phosphate as the chromogen. Plates were read on a microtiter plate reader (Bio-Rad Laboratories) using a 405-nm filter. Each test sample was analyzed in triplicate. Serial dilutions of a recombinant synaptophysin protein fragment were used to construct a standard curve from which the concentration of synaptophysin in the test sample was determined. Results of the assay are expressed in picomoles of synaptophysin per 10 mg of brain.

STATISTICAL ANALYSIS

We used the binomial test to statistically analyze the results in Table 3. Because of the small sample size, other methods of analysis, parametric and nonparametric, were not useful.

on the sides corresponding to greater neurobehavioral or neuropsychologic deficits in 4 of 6 FTD cases (patients 2, 5, and 6 on the left side, and patient 4 on the right side) (Figure 1). Two of these corresponded to radiographic predominance (patients 1 and 4). Similar correlation was found in temporal lobes in 2 cases (patients 3 and 5, on the left side) (Figure 2), and radiographic correspondence was found in 1 case (patient 3). In the parietal lobes, synaptophysin values were lower on the sides corresponding to greater clinical parietal deficits in 3 cases (patients 3, 5, and 6 on the left side) (Figure 3), and radiographic correspondence was found in 2 cases (patients 3 and 6). Three of 6 cases (patients 3, 5, and 6) had synapse loss in 2 or more areas in the direction predicted by results of neuropsychologic, neurobehavioral, or radiographic evaluation. Only patient 1
failed to show correlation in any lobe between synapto-
physin level and neurobehavioral, neuropsychologic, or
radiographic indices.

Although our study is small, we were able to ana-
lyze statistically the results in Table 3 using the bino-
mial test. In our study, 3 (50%) of 6 cases had synapse
loss in 2 or more brain areas in the direction predicted
by clinical evaluation. Under a pure-chance mecha-
nism, the probability of observing 3 or more of 6 FTD
cases with 2 or more brain areas in the predicted direc-
table.

Table 1. Disease Duration, Postmortem Information, and Pathologic Findings*

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Evaluation-to-Death Interval, y</th>
<th>Total Course, y</th>
<th>Age at Death, y</th>
<th>PMI, h</th>
<th>AD Pathologic Findings</th>
<th>Pathologic Diagnosis</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>4.0</td>
<td>8</td>
<td>70</td>
<td>5.0</td>
<td>0</td>
<td>CBGD</td>
</tr>
<tr>
<td>2</td>
<td>0.7</td>
<td>5</td>
<td>68</td>
<td>15.8</td>
<td>Sparse DP</td>
<td>CBGD</td>
</tr>
<tr>
<td>3</td>
<td>2.0</td>
<td>7</td>
<td>70</td>
<td>19.5</td>
<td>0</td>
<td>Pick disease</td>
</tr>
<tr>
<td>4</td>
<td>2.5</td>
<td>4</td>
<td>65</td>
<td>8.3</td>
<td>0</td>
<td>FTD-NOS</td>
</tr>
<tr>
<td>5</td>
<td>7.3</td>
<td>10</td>
<td>85</td>
<td>16.8</td>
<td>Sparse NP</td>
<td>SMSTD</td>
</tr>
<tr>
<td>6</td>
<td>4.5</td>
<td>8</td>
<td>72</td>
<td>19.8</td>
<td>0</td>
<td>CBGD</td>
</tr>
<tr>
<td>Mean</td>
<td>3.5</td>
<td>7</td>
<td>73</td>
<td>14.2</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

AD Cases (n = 28)

| Mean (range) | NA | 10.4 (2.0-18.0) | 78 (58-90) | 14.6 (3.3-26.0) | NA | NA |

Nondemented Controls (n = 16)

| Mean (range) | NA | NA | 72 (60-86) | 8.5 (5.0-23.0) | NA | NA |

*PMI indicates postmortem interval; AD, Alzheimer disease; FTD, frontotemporal dementia; CBGD, corticobasal ganglionic degeneration; DP, diffuse plaques; FTD-NOS, frontotemporal degeneration—not otherwise specified; NP, neuritic plaques; SMSTD, sporadic multiple system tauopathy with dementia; and NA, not applicable. Groups are described in the “Patients and Methods” section.

Table 2. Neuropsychologic Test Results*

<table>
<thead>
<tr>
<th>Cognitive Domain, Test</th>
<th>FTD Patient No.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

|                        | 1              | 3          | 5          | 6†          |

- FTD indicates frontotemporal dementia; WAIS, Wechsler Adult Intelligence Scale; VIQ, Verbal IQ; PIQ, Performance IQ; FSIQ, Full-scale IQ; WCST, Wisconsin Card Sorting Test; WMS, Wechsler Memory Scale; and ellipses, not applicable.
- †Underwent the WAIS-Revised and WMS-Revised.
- ‡DC indicates patient exceeded maximum time and was unable to complete.
tion is 34.4%. Although our results are higher than chance, statistical significance was not attained.

**COMMENT**

Historically, the FTD disorders have been divided into Pick disease and non-Pick lobar atrophy.29,30 Both have grossly appreciable atrophy of the frontal and temporal lobes and microscopic upper cortical microvacuolation,31,32 but only Pick disease has round to oval argyrophilic, tau-positive, and ubiquitin-variable neuronal cytoplasmic inclusions in the hippocampal dentate gyrus and neocortex termed Pick bodies. Non-Pick lobar atrophy has recently been subclassified on the basis of the presence or absence of newly discovered immunohistochemically distinct inclusions.33-35 In the nonfamilial non-Pick lobar atrophies, there are at least 3 separate diagnostic categories. These include motor neuron–type dementia (frontal lobe dementia with ubiquitinated inclusions), which has ubiquitin-positive, tau-negative inclusions in the hippocampal dentate nucleus and in neocortical neuronal layers II and III; corticobasal ganglionic degeneration, which has tau-positive neuronal inclusions and glial plaques, along with ballooned neurons, in neocortex and subcortical regions; and frontotemporal degeneration—not otherwise specified, which to date and by definition has no specific inclusions. Although the neuropathologic findings are distinctive in these disorders, the FTDs are rare and have similar clinical presentations and therefore are often studied together.

Previously published studies of synapse loss in FTD using the technique of optical densitometric analysis of immunohistochemical preparations found decreased synaptophysin concentrations in superficial layers of the frontal lobes only in FTD,12-14 compared with decreases in frontal, temporal, and parietal lobes in AD, whereas we found decreases in all these regions. Liu et al14 found a 40% decrease in superficial frontal cortex in FTD and a 13% decrease in deeper layers. Our ELISA method evaluates transcortical synaptophysin, and we found that concentrations of synaptophysin in full-thickness frontal cortex detected by ELISA were 68% of that of control synaptophysin concentration, equivalent to a 32% decrease. This is similar to the frontal synaptophysin decrement found by Liu et al,14 if an average decrement is calculated from their decrements in superficial and deep cortical layers (−40% and −13%, respectively; average, −27%). On the other hand, they found a negligible decrease in quantities of synaptophysin in superficial (−8%) and deep parietal cortex (−7%), whereas we found a transcortical parietal synaptophysin concentration of 48% (−52%). Perhaps the difference in technique used in our study contributes to the different results obtained. In addition, in their group of FTD patients, these authors excluded Pick disease and motor neuron type dementia and most likely excluded corticobasal ganglionic degeneration cases by their use of silver stains in their neuropathological workup. Therefore, it appears that their

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**Table 3. Lateralizing Clinical Deficits Compared With Synaptophysin Concentration**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Lateralizing Deficit</th>
<th>Synaptophysin Concentration, pmol/10 mg of Brain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Neurophysiologic</td>
<td>Neurobehavioral</td>
</tr>
<tr>
<td>1</td>
<td>RF</td>
<td>BF and BT</td>
</tr>
<tr>
<td>2</td>
<td>LT</td>
<td>LT</td>
</tr>
<tr>
<td>3</td>
<td>LA</td>
<td>LT</td>
</tr>
<tr>
<td>4</td>
<td>NA</td>
<td>RF</td>
</tr>
<tr>
<td>5</td>
<td>LF, LT, LP</td>
<td>LF, LT</td>
</tr>
<tr>
<td>6</td>
<td>LF, LT, LP</td>
<td>LF, LT</td>
</tr>
</tbody>
</table>

*RF indicates right frontal lobe; LF, left frontal lobe; RT, right temporal lobe; LT, left temporal lobe; RP, right parietal lobe; LP, left parietal lobe; BF, bilateral frontal lobes; BT, bilateral temporal lobes; ellipses, not performed; and NA, not available.
†Indicates low regional cerebral blood flow.
‡Indicates atrophy detected by means of computed tomography or magnetic resonance imaging.

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**Figure 1.** Bilateral frontal lobe synaptophysin concentrations. R indicates right-sided clinical deficits; L, left-sided clinical deficits; and heavy lines, correlation. Patient 3 had no lateralizing frontal clinical deficit.

**Figure 2.** Bilateral temporal lobe synaptophysin concentrations. Abbreviations and markings are explained in the legend to Figure 1. Patients 1, 2, and 4 had no lateralizing temporal clinical deficit.
FTD group is composed of frontotemporal degeneration—not otherwise specified cases only. Perhaps the heterogeneity of pathologic diagnoses in our FTD cases also contributes to the differences in our results.

The variation in the concentration of synaptophysin from case to case can be striking and precludes direct case-to-case comparisons, although this issue has not been specifically addressed in the literature. In the present study, in the FTD cases, the concentration of synaptophysin in the right frontal lobe ranged from 429 to 7487 pmol/10 mg of brain, a 17-fold difference; in the nondemented controls it varied in the right temporal lobe from 1548 to 24460 pmol/10 mg of brain, a 16-fold difference (Table 4). Differences across regions within a case are on the order of 10-fold. Case-to-case variations in amounts of synaptophysin have been ascribed to differences in premorbid levels (synaptic “reserve”), differences in the intervals between clinical evaluation and death, and differences in PMIs. The issue of premorbid levels can only be investigated if antemortem and antemortem brain samples are available for analysis and comparison, and such investigation is therefore not generally possible in human brain disease. The interval between clinical evaluation and death varies from 0.7 to 7.3 years in our 6 FTD cases (Table 1), but the decrements in synaptophysin levels in our cases do not correlate with these periods. The PMIs, which vary from 5.0 to 19.8 hours, could play a role in case-to-case variation in synaptophysin concentrations, but analysis of this relationship reveals no correlation. Indeed, we (C.L.W. and E.H.B., unpublished data, 1995) and others have found no discernible decline in levels of synaptophysin in brains with a PMI of up to 36 hours or longer.

There was a great deal of overlap in synaptophysin concentrations across all 3 groups (Table 4). However, between groups, the synaptophysin concentrations of the temporal lobe were consistently higher than concentrations in the frontal and parietal lobes. In addition, within a case, the concentration of synaptophysin in each lobar region was relatively equivalent from side to side, at least within the same range of magnitude, except for patient 3 in the temporal (right, 1219 pmol/10 mg of brain; left, 454 pmol/10 mg of brain) and parietal (right, 1062 pmol/10 mg of brain; left, 118 pmol/10 mg of brain) lobes. Our procedure for relating synaptophysin values to lateralizing neuropsychologic or neurobehavioral deficits within and across cases suggests a new way of analyzing these types of data. Fifty percent of our FTD cases had 2 or more brain areas in the predicted direction, which was better than chance alone (34.4%). Although this difference is not statistically significant, it does indicate that there is a trend toward the predictions having a higher-than-chance level of correlating with the synaptophysin concentration.

Neuropsychologic evaluation is important in the clinical diagnosis of FTD. The Lund-Manchester criteria are heavily weighted toward neuropsychologic variables, as are the clinical diagnostic criteria for frontotemporal lobar degeneration. The use of a detailed battery of measures that assesses multiple cognitive domains is critical. Tests need to be included that provide for an appreciation of relative lateralized dysfunction and delineation of deficits in the anterior-posterior plane to adequately characterize patients with dementia. In cases of FTD, measures of executive function (ie, problem solving, reasoning, and mental flexibility) tend to be most prominently impaired.

### Table 4. Synaptophysin Concentrations in FTD and AD Cases Compared With Control Subjects*

<table>
<thead>
<tr>
<th>Brain Region</th>
<th>RF/LF</th>
<th>RT/LT</th>
<th>RP/LP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FTD cases (n = 6)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>3248/1762</td>
<td>2720/2711</td>
<td>2023/1496</td>
</tr>
<tr>
<td>Range</td>
<td>429-7487/927-3147</td>
<td>1219-5062/454-4763</td>
<td>937-3770/118-2590</td>
</tr>
<tr>
<td>Average of sides</td>
<td>2505</td>
<td>2716</td>
<td>1760</td>
</tr>
<tr>
<td>% of controls</td>
<td>68</td>
<td>37</td>
<td>48</td>
</tr>
<tr>
<td><strong>AD cases (n = 28)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>1892/1662</td>
<td>2414/2454</td>
<td>1260/1151</td>
</tr>
<tr>
<td>Range</td>
<td>67-11390/31-8527</td>
<td>47-13270/91-9316</td>
<td>31-7679/6-6259</td>
</tr>
<tr>
<td>Average of sides</td>
<td>1777</td>
<td>2434</td>
<td>1206</td>
</tr>
<tr>
<td>% of controls</td>
<td>48</td>
<td>33</td>
<td>33</td>
</tr>
<tr>
<td><strong>Controls (n = 16)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>3878/3539</td>
<td>7480/7139</td>
<td>3760/3591</td>
</tr>
<tr>
<td>Range</td>
<td>620-9179/538-8038</td>
<td>1548-24460/1977-17190</td>
<td>908-10510/34-13240</td>
</tr>
<tr>
<td>Average of sides</td>
<td>3709</td>
<td>7310</td>
<td>3676</td>
</tr>
</tbody>
</table>

*FTD indicates frontotemporal dementia; AD, Alzheimer disease. Other abbreviations are given in the first footnote to Table 3. Unless otherwise indicated, data are given as picomoles of synaptophysin per 10 mg of brain.
with additional evidence of lateralized deficits, such as prominent language or visuospatial impairment, as previously indicated.17 Although neuropsychologic tests cannot not exclusively tap the functioning of 1 lobe in isolation, the finding that the neuropsychologic patterns showed agreement with regional synaptophysin concentrations in 5 of 6 of the FTD cases in at least 1 lobe is indeed promising and parallels the relationship between neuropsychologic function and single-photon emission CT that has been reported in FTD.30 The association between synaptophysin concentrations and neuropsychologic patterns is particularly impressive, since the cognitive evaluations were conducted an average of 3.5 years before synaptophysin concentration was measured. This suggests that patterns of lateralized or localized cerebral dysfunction may show direct relationships to the underlying neuropathologic findings and that such associations remain robust for quite some time after clinical examination. Similar relationships between level of dementia and degree of synapse loss have been shown in AD,2,6 and synapse loss has been shown in the frontal lobe in FTD.10,11 However, this is one of the first studies to demonstrate the asymmetry of synapse loss in FTD as well as the association between regional synapse loss and localized neuropsychologic and neurobehavioral decline in patients with autopsy-confirmed FTD.

In addition, the finding that decrements in synaptophysin concentrations can localize with regional neuropsychologic and neurobehavioral deficits reveals a new way of approaching these data. Although huge differences in the magnitude of synaptophysin loss between cases, a lateralizing difference may prove significant within a case, similar to the within-subject comparison of neuropsychologic test results that have lateralizing or localizing properties or both.17,18 Although the pathogeneses of FTD and AD remain largely unknown and may well be multifactorial, synapse loss appears to be a common link. Studies in larger numbers of cases of FTD are planned to draw statistically significant conclusions.

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