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Patterns of cortical thinning in the language variants of frontotemporal lobar degeneration

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ABSTRACT

Background: Frontotemporal lobar degeneration (FTLD) is a clinically, genetically, and pathologically heterogeneous neurodegenerative disorder. Two subtypes commonly present with a language disorder: semantic dementia (SemD) and progressive nonfluent aphasia (PNFA).

Methods: Patients meeting consensus criteria for PNFA and SemD who had volumetric MRI of sufficient quality to allow cortical thickness analysis were recruited from a tertiary referral clinic: 44 (11 pathologically confirmed) patients with SemD and 32 (4 pathologically confirmed) patients with PNFA and 29 age-matched and gender-matched healthy controls were recruited. Cortical thickness analysis was performed using the Freesurfer software tools.

Results: Patients with SemD had significant cortical thinning in the left temporal lobe, particularly temporal pole, entorhinal cortex, and parahippocampal, fusiform, and inferior temporal gyri. A similar but less extensive pattern of loss was seen in the right temporal lobe and (with increasing severity) also in left orbitofrontal, inferior frontal, insular, and cingulate cortices. Patients with PNFA had involvement particularly of the left superior temporal lobe, inferior frontal lobe, and insula, and (with increasing severity) other areas in the left frontal, lateral temporal, and anterior parietal lobes. Similar patterns were seen in the pathologically confirmed cases. Patterns of cortical thinning differed between groups: SemD had significantly more cortical thinning in the temporal lobes bilaterally while PNFA had significantly more thinning in the frontal and parietal lobes.

Conclusions: The language variants of frontotemporal lobar degeneration have distinctive and significantly different patterns of cortical thinning. Increasing disease severity is associated with spread of cortical thinning and the pattern of spread is consistent with progression of clinical deficits. Neurology® 2009;72:1562–1569

GLOSSARY

FDR = False Discovery Rate; FTLD = frontotemporal lobar degeneration; GNT = Graded Naming Test; PNFA = progressive nonfluent aphasia; SemD = semantic dementia.

Frontotemporal lobar degeneration (FTLD) is the second most common young onset degenerative dementia.1 Two of its subtypes characteristically present with language impairment2: semantic dementia (SemD) and progressive nonfluent aphasia (PNFA). Pathologically, SemD is usually a TDP-43 proteinopathy4,5 while PNFA is most commonly associated with tau pathology.6-8 Previous imaging studies comparing PNFA and SemD have examined the neuroanatomic differences between the two syndromes using a variety of techniques including manual volumetry and voxel-based morphometry of structural MRI and functional (PET/SPECT) imaging2,9,10. SemD has been associated with asymmetric left greater than right temporal lobe atrophy while PNFA has been most commonly associated with left inferior frontal lobe and
superior temporal lobe atrophy. The measurement of cortical thickness is a relatively new technique for assessing the brain substrates of neurodegenerative disease and can provide complementary information to other imaging techniques about the neuroanatomy of the language variants of FTLD: thickness measures allow the regional distribution and quantification of gray matter cortical loss to be specifically assessed in contrast to gyral or lobar volumetric studies which combine gray and white matter within regional volumes. There are currently few studies that have examined cortical thinning in the language syndromes of FTLD and its value as a potential biomarker. The objective of this study was to look at the cross-sectional patterns of cortical thickness in a large cohort of patients with PNFA and SemD including a subgroup with pathologically confirmed FTLD.

METHODS

Subjects. Patients were recruited from the Specialist Cognitive Disorders Clinic of the National Hospital of Neurology and Neurosurgery, London, UK. All patients attending the clinic were assessed by an experienced cognitive neurologist (M.N.R., N.C.F., J.D.W.) and had a detailed clinical history, physical examination, and formal neuropsychometry. Based on this initial assessment and independent of any brain imaging findings, a diagnosis of either SemD or PNFA was made. A retrospective review of the clinical patient database (1992 to 2006) was performed and all patients with a single volumetric 1.5 T MRI brain scan of sufficient quality to allow cortical thickness analysis and who had consented to allow their MRI data to be used for research were included in the study. A clinical diagnosis of SemD was based on modified Neary criteria as per Adlam et al. with patients having fluent speech, marked anomia, impaired word comprehension, and deficits in nonverbal semantic domains, while a clinical diagnosis of PNFA was based on modified Neary criteria with patients having a speech production impairment characterized by apraxia of speech and agrammatism. These criteria allow patients with SemD and PNFA to be separated on clinical or neuropsychological grounds; patients who did not meet criteria for either SemD or PNFA as described above were not included in the study (e.g., patients who would fit the descriptions of the logopenic/phonologic variant of primary progressive aphasia were excluded). Forty-four patients with SemD (59% male, mean age at scan 64.1 [SD 7.5] years, mean duration 4.3 [1.8] years) and 32 patients with PNFA (66% male, mean age at scan 65.8 [7.7] years, mean duration 4.4 [2.0] years) met criteria for inclusion with no significant difference between the groups in terms of gender, age at scan, or duration of disease. A control group of 29 cognitively normal subjects group-matched for gender and age was also included (60% male, mean age at scan 65.2 [8.7] years). Eleven patients with SemD were pathologically confirmed: 64% male, mean age at scan 65.9 (5.9) years, mean duration 4.7 (2.5) years, with ubiquitous positive, tau-negative pathology in all cases. Four PNFA patients were pathologically confirmed: 75% male, mean age at scan 62.7 (7.0) years, mean duration 4.4 (0.6) years, with tau-positive pathology in all cases (two patients had corticobasal degeneration and two had classic Pick disease). Research ethics approval to perform this study was obtained from the National Hospital for Neurology and University College London Hospitals Research Ethics Committees.

Image acquisition and analysis. All patients had volumetric MRI acquired on a 1.5 T GE Signa scanner (General Electric, Milwaukee, WI). Patients were scanned on four different scanners (all 1.5 T GE) over the 15-year time period of scan acquisition but for all scanners T1-weighted volumetric images were obtained with a 24-cm field of view and 256 × 256 matrix to provide 124 contiguous 1.5-mm-thick slices in the coronal plane. Scanners used in each of the groups were as follows—SemD: scanner 1, 55%, 2, 30%, 3, 9%, 4, 7%; PNFA: 1, 44%, 2, 38%, 3, 0%, 4, 19%; controls: 1, 59%, 2, 31%, 3, 10%, 4, 0%—and in order to account for the different scanner use we included scanner type as a covariate in the statistical analysis. Cortical reconstruction and thickness estimation was performed with the Freesurfer image analysis suite, version 4.0.3 (http://surfer.nmr.mgh.harvard.edu/) on a 64-bit Linux CentOS 4 Cluster managed by a Sun Grid Engine. Briefly, the process involves initially generating an automatic gray matter, white matter, and CSF classification. The results of these segmentations were visually inspected, and if needed, manually edited by adding control points. Finally, an automatic reconstruction of the cortex was produced and cortical thickness estimated by computing the average shortest distance between the white matter boundary and the pial surface. Surface maps were generated following registration of all subjects’ cortical reconstructions to a common average surface and then smoothed using a surface-based Gaussian kernel of 20 mm full width half-maximum. The standard Freesurfer processing stream was used apart from two modifications. First, we used locally generated brain masks for the skull-stripping process. This brain mask was produced using a semiautomated segmentation procedure that involved selection of thresholds, followed by a series of erosions and dilations, providing a brain region separated from surrounding CSF, skull, and dura. Secondly, we modified the white matter mask by incorporating the ventricle segmentations from the Freesurfer volume processing stream—this was necessary because of mislabeling of CSF in the standard white matter mask, particularly in cases where the ventricles were large.

Statistical analysis. A vertex-by-vertex analysis using a general linear model was performed to examine differences in cortical thickness between the patient groups and the control group. Cortical thickness, C, was modeled as a function of group, controlling for age, sex, and the scanner used by including them as nuisance covariates. C = β0 + β1 SemD + β2 PNFA + β3 controls + β4 age + β5 sex + β6 scanner + μ + ε (where μ is a constant, and ε is error) with the contrasts of interest being the two-tailed t tests between the estimates of the group parameters, i.e., β1, and β2, β3, and β4. Maps showing the significant differences between the disease groups and controls were generated, correcting for multiple comparisons by thresholding the images of t statistics to control the False Discovery Rate (FDR) at a 0.05 significance level.

As well as the surface maps, the Freesurfer processing stream also generates thickness measures from 33 cortical regions of interest as described in Desikan et al. In order to take into account the severity of disease, we used the mean cortical thickness in these regions of interest in a separate statistical model to investigate regional differences in thinning between the PNFA and
SemD groups. Overall severity was taken into account by normalizing in each patient by the average over all their regions. FDR was controlled at a 0.05 significance level.

In order to examine changes in cortical thickness as the disease progressed, we used performance on naming tests as a measure of disease severity. Other markers of disease severity such as estimated disease duration may be uninformative and subject to recall bias, while global indices of cognitive function such as the Mini-Mental State Examination are insensitive and may not be relevant to the specific deficits produced by the language-based dementias. In contrast, impaired naming ability is observed in both language variants of FTLD and central to the clinical syndrome in each case, and performance can be easily quantified: naming performance is therefore a suitable index of clinical severity that can be applied across individuals and groups. The standard naming test performed in our patients is the Graded Naming Test but this is a difficult naming test and when patients become very anomic and unable to score on this test (e.g., in patients with moderate to severe SemD) the easier Oldfield Naming Test is usually performed. In order to compare scores between these two tests, a group of 55 patients with a neurodegenerative disease and 55 cognitively normal controls have previously performed both tests and a conversion table was generated, allowing an equivalent score to be calculated (unpublished PhD data). Twenty-eight patients with SemD and 28 patients with PNFA performed one of the two naming tests within 6 months of the time of the scan and were therefore used for the whole group analysis.

RESULTS Whole group analysis. Compared with the healthy control group, in the SemD group there was thinning of the cortex in an asymmetric pattern, most prominently affecting the temporal lobes on the left more than the right (figure 1A). The areas of greatest thinning were anterior and inferior in the temporal lobes: on the left, the most affected areas were the temporal pole (reduced by 51% relative to control mean thickness), entorhinal cortex (46%), parahippocampal (30%), fusiform (27%), and inferior temporal (26%) gyri. On the right, a similar but less extensive pattern of thinning was seen, particularly affecting the entorhinal cortex (reduced by 25% relative to control mean thickness), temporal pole (19%), and parahippocampal (14%) areas. Areas outside the temporal cortices were also affected, although to a lesser extent; in particular, thinning was seen in the left orbitofrontal, insular, inferior frontal, and (particularly anterior) cingulate cortices (figure 1A).

In the PNFA group, the most significant areas of thinning were in the superior areas of the left temporal lobe (banks of the superior temporal sulcus [reduced by 14% relative to control mean thickness], superior temporal lobe [10%], and transverse temporal gyrus [9%]) as well as both left inferior frontal (pars opercularis, 9% and triangularis, 9%) and superior frontal lobes (9%) (figure 1B). Cortical thinning was also seen in the left insula (although there is no region of interest cortical label for this area in Freesurfer and therefore no measure of the extent of thinning). There were no significant areas of thinning in the right hemisphere.

Comparing the two disease groups directly, areas that were significantly thinner in the SemD group were also thinner in the PNFA group compared to controls. In each of these severity subgroups and in the whole SemD and PNFA groups, comparing each to the controls and expressing the disease-control difference as a percentage of the mean control group thickness. Mean cortical thickness for each lobe in the different severity groups is also shown in the table.

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<th>Table Comparison of disease groups by naming score and cortical thickness in each lobe</th>
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*p < 0.05 disease group vs controls.

SemD = semantic dementia; PNFA = progressive nonfluent aphasia.
the temporal pole, parahippocampal, entorhinal, fusiform, inferior temporal, middle temporal, and superior temporal gyri in the left temporal lobe and corresponding areas (except the superior temporal gyrus) in the right temporal lobe. Areas that were significantly thinner in the PNFA group were mainly in the left hemisphere: inferior frontal (pars opercularis and triangularis), middle, and superior frontal gyri, precentral gyrus, transverse temporal gyrus, and notably in the parietal lobe (superior, inferior areas and supramarginal gyrus). Areas in the right hemisphere that were significantly thinner in the PNFA group were in the frontal lobe (inferior, middle, and superior areas) and parietal lobes (superior, inferior areas and supramarginal gyrus).

**Pathologically confirmed subgroup analysis.** A similar pattern of cortical thinning was seen in the pathologically confirmed SemD group compared to the whole SemD group (figure 2A) with asymmetric left greater than right thinning of the temporal lobe cortices.

The smaller pathologically confirmed PNFA group showed only one area of significant thinning in the left insula (figure 2B), which is seen more clearly on the inflated cortical map (figure 2B).

**Modeling severity using performance on naming task.** In SemD, there was greater thinning of the temporal lobe cortices as the disease became more severe (as assessed by the severity of anomia) (table). In the
least affected group, the predominant thinning was in the anterior and inferior parts of the left temporal lobe with a similar but less affected area in the right temporal lobe (figure 3). As the disease became more severe, there was involvement of more posterior and superior parts of the left temporal lobe, parts of the left frontal lobe (orbitofrontal and inferior gyri), and the insula and cingulate gyrus. A similar pattern of evolution with increasing disease severity was observed in the right temporal lobe cortex.

In PNFA, there was also greater thinning of the cortices as the disease became more severe (table). In the least affected group, the areas of thinning were in the left inferior frontal gyrus, insula, and areas of the superior temporal lobe. As the disease became more severe, these areas became thinner and there was additional involvement of the lateral left temporal lobe, anterior parietal lobe, and middle and superior parts of the frontal lobe (figure 4).

DISCUSSION We have described distinct patterns of cortical thinning in a large cohort of patients with SemD and patients with PNFA. Our findings of predominantly asymmetric left greater than right temporal lobe atrophy in SemD and predominantly left-sided superior temporal, inferior frontal lobe, and insular atrophy in PNFA are consistent with previous reports using other image analysis techniques. These findings further suggest that increasing disease severity is associated with distinct patterns of evolution of cortical thinning beyond these core regions: into the left frontal, insular, and cingulate cortices in SemD, and into left middle and superior frontal lobe and anterior left parietal lobe in PNFA.

The initial and canonical feature of SemD is progressive degradation of semantic knowledge resulting in anomia and impaired single word comprehension. Theories of semantic memory localization suggest the anterior left temporal lobe plays a critical role and this would be consistent with the early involvement of this core area even in the least affected SemD group. In PNFA, the initial clinical feature is often apraxia of speech, which has been associated with left insula involvement and aggramatism, which has been associated with left inferior frontal lobe damage. Other regions of superior temporal cortex involved in the PNFA group here, in particular the superior temporal sulcus and
transverse temporal gyrus, mediate the analysis, transcoding, and short-term storage of speech signals. Damage involving these areas might contribute to impairments of phonologic encoding, working memory, and grammar processing that are often prominent in this group, suggesting testable hypotheses for future work. In the pathologically confirmed subgroup of patients with PNFA, the most significant area of thinning was in the insular cortex, consistent with previous findings that this area is critical for the development of speech production deficits in PNFA.

Our findings concerning the effects of disease severity on cortical thinning in SemD and PNFA are based on the analysis of stratified cross-sectional data indexed using a key neuropsychological function (naming performance), rather than longitudinal measurements in individual patients. However, allowing this caveat, the stratified cross-sectional findings are consistent with available data on patterns of disease evolution in SemD and PNFA. In SemD, disease progression is associated with the development of impairments of behavior and social cognition and symptoms attributable to right temporal lobe dysfunction such as prosopagnosia. These clinical features are consistent with the thinning of frontal (particularly left orbitofrontal), insula, right temporal, and posterior temporal cortices observed in the more severely affected SemD group here. In PNFA, disease progression is associated with increasing difficulties with speech repetition and often the emergence of non-language symptoms such as limb apraxia and dyscalculia, consistent with spread through the temporal lobes posteriorly to involve the left parietal lobe. There are few longitudinal imaging studies of either SemD or PNFA. Although other studies have generally used estimated disease duration as a surrogate of severity, the patterns of disease spread described previously are qualitatively similar to those observed here: namely, increasing involvement of right temporal and posterior temporal and left inferior frontal areas in SemD, and more dorsal posterior left temporal and parietal areas in PNFA. However, the data concerning PNFA in particular should be interpreted with caution, given that pathologic confirmation was available in only a minority of cases. The PNFA syndrome is likely to be pathologically heterogeneous, and involvement of parietal and other posterior cortical areas may be produced by specific pathologic substrates rather than
neurodegenerative diseases, although their clinical utility has not been widely evaluated and the various techniques not yet adequately compared. From the neurobiological perspective, this technique can potentially provide important complementary information about cortical areas (such as the superior temporal sulcus region) that are likely to be crucial in the pathophysiology of the language-based dementias but difficult to assess using conventional imaging modalities on anatomic or geometric grounds. Evaluation of the sensitivity and specificity of cortical thickness techniques, hypothesis-driven correlation with behavioral, pathologic, and other neuroimaging data, and longitudinal studies in degenerative disease are clear directions for future work.

**AUTHOR CONTRIBUTIONS**

Statistical analysis was performed by Gerard Ridgway, Dementia Research Centre, ION, London, UK.

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**REFERENCES**

New Guidelines Examine Safety of Women with Epilepsy and Pregnancy

New evidence-based practice guidelines developed by the American Academy of Neurology in full collaboration with the American Epilepsy Society show the relative safety for women with epilepsy to become pregnant, but caution against taking one particular epilepsy drug, which can cause birth defects. The guidelines were published in the April 27, 2009, online issue of Neurology® and were presented at the AAN’s Annual Meeting in Seattle. The guidelines were also published electronically in Epilepsia, the journal of the International League Against Epilepsy. They represent an update of the 1998 guideline, “Management Issues for Women with Epilepsy.”
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