Journal of Alzheimer's Disease 30 (2012) 407–411
DOI 10.3233/JAD-2012-111556
IOS Press

Rates of Hemispheric and Lobar Atrophy in the Language Variants of Frontotemporal Lobar Degeneration

Jonathan D. Rohrer[a], Matthew J. Clarkson[a,b], Raivo Kittus[a], Martin N. Rossor[a], Sebastien Ourselin[a,b], Jason D. Warren[a] and Nick C. Fox[a,*]
[a]*Dementia Research Centre, Institute of Neurology, University College London, Queen Square, London, UK*
[b]*Centre for Medical Image Computing (CMIC), University College London, London, UK*

Accepted 10 February 2012

Abstract. Frontotemporal lobar degeneration (FTLD) is a neurodegenerative disorder which presents with either behavioral or language impairment. The two language syndromes are known as progressive nonfluent aphasia (PNFA) and semantic dementia (SEMD). While cross-sectional imaging patterns of brain atrophy are well-described in FTLD, fewer studies have investigated longitudinal imaging changes. We measured longitudinal hemispheric and lobar atrophy rates using serial MRI in a cohort of 18 patients with PNFA and 17 patients with SEMD as well as 14 cognitively-normal control subjects. We subsequently calculated sample size estimates for clinical trials. Rates of left hemisphere atrophy were greater than rates of right hemisphere atrophy in both PNFA and SEMD with no significant differences between the groups. The disease groups showed asymmetrical atrophy (more severe on the left) at baseline with significantly increasing asymmetry over time. Within a hemisphere, the fastest rate of atrophy varied between lobes: in SEMD temporal > frontal > parietal > occipital, while in PNFA frontal > temporal/parietal > occipital. In SEMD, using temporal lobe measures of atrophy in clinical trials would provide the lowest sample sizes necessary, while in PNFA left hemisphere atrophy measures provided the lowest sample size. These patterns provide information about disease evolution in the FTLD language variants that is of both clinical and neurobiological relevance.

Keywords: Frontotemporal dementia, primary progressive aphasia

INTRODUCTION

Frontotemporal lobar degeneration (FTLD) is a genetically and pathologically heterogeneous neurodegenerative disorder in which patients present with either behavioral or language impairment [1]. The two language subtypes are semantic dementia (SEMD) and progressive nonfluent aphasia (PNFA) [1–3]. MRI studies have demonstrated that these groups have characteristic patterns of cross-sectional brain atrophy: SEMD is associated with asymmetrical (usually left greater than right) anteroinferior temporal lobe atrophy and PNFA is associated with mainly left inferior frontal and perisylvian atrophy [4–7]. There are fewer studies of longitudinal imaging changes in the FTLD language subtypes [8–13]. Here we used serial MRI to investigate rates of hemispheric and lobar atrophy in the language variants of FTLD in order to investigate patterns of cell loss over time and to determine whether such measures could be feasible imaging biomarkers for disease-modification trials in comparison to previously investigated markers such as rates of whole brain atrophy or ventricular enlargement.

METHODS

From the Dementia Research Centre patient database, we extracted all cases with a clinical

*Correspondence to: Prof. Nick C. Fox, Dementia Research Centre, Institute of Neurology, Queen Square, London WC1N 3BG, UK. Tel.: +44 207 829 8773; Fax: +44 207 676 2066; E-mail: nfox@dementia.ion.ucl.ac.uk.

ISSN 1387-2877/12/$27.50

diagnosis of PNFA or SD. All patients had attended the tertiary Cognitive Disorders Clinic at the National Hospital for Neurology and Neurosurgery, Queen Square, London, UK and had given consent to be involved in clinical research. The clinical records were reviewed and all patients fulfilling clinical criteria for either PNFA or SEMD independent of imaging features [2] and who had also had more than one volumetric MR scan with an inter-scan interval between 9 months and 2 years were included in the study. Patients who would fit criteria for logopenic aphasia (LPA) were not included in the study [2]. In total, 18 patients with PNFA (1 with pathologically-confirmed Pick's disease and 2 with known mutations in the progranulin gene) and 17 patients with SEMD (4 with pathologically-confirmed type 1 FTLD-TDP) fulfilled criteria. A control group of 14 cognitively-normal subjects were also included. There were no significant differences in age, gender, or interscan interval between any of the groups (Table 1). The groups partly overlap with cohorts on whom data on rates of whole brain atrophy and ventricular enlargement in PNFA and SEMD [9, 13] as well as rates of temporal lobe atrophy in SEMD [9] have been previously published. Ethical approval for the study was obtained from the National Hospital for Neurology and Neurosurgery Local Research Ethics Committee. Written research consent was obtained from all patients participating in the study.

All subjects had been scanned on a 1.5T GE Signa scanner (General Electric, Milwaukee, WI) with T1-weighted volumetric images 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. Image analysis was performed using the MIDAS software package [14]. A rapid, semi-automated technique of brain segmentation which involves interactive selection of thresholds, followed by a series of erosions and dilations was performed for each scan. This yields a brain region which is separated from surrounding cerebrospinal fluid (CSF), skull, and dura. Serial scans were co-registered and volume change was calculated directly using the boundary shift integral (BSI) [15]. BSI-derived whole-brain volume changes (BBSI) were expressed as annualized volume change as a percentage of the baseline brain volume. Ventricles were also segmented and rates of ventricular enlargement calculated using the BSI.

For all patients and controls, we calculated left and right cerebral hemisphere volumes and rates of atrophy as well as left/right hemisphere volume ratios and rates of change of this hemispheric asymmetry ratio. Scans and associated brain regions were initially transformed into standard space by registration to the Montreal Neurological Institute (MNI) Template [16]. Left and right hemispheric regions were defined using the MNI average brain which was split by dividing the whole volume along a plane coincident with the interhemispheric fissure. An intersection of each individual's brain region and the hemispheric regions defined on the MNI template was generated to provide a measure of brain volume in left and right hemispheres and left/right volume ratios were also calculated. Hemispheric atrophy was expressed as the difference in hemisphere volume between the repeat and baseline scans divided by the baseline hemisphere volume. Lobar grey matter volumes were calculated using the Freesurfer analysis suite version 4.5 (http://surfer.nmr.mgh.harvard.edu) on a 64-bit Linux CentOS 4 Sun Grid Engine Cluster. Lobar atrophy was expressed as the difference in lobar volume

Table 1
Mean (standard deviation) demographic and baseline volumetric MRI data

	Controls		SEMD		PNFA	
Number of subjects	14		17		18	
Male:female ratio	8 : 6		9 : 8		12 : 6	
Duration of disease (years)	N/A		4.5 (1.5)		5.2 (2.3)	
Age at baseline scan (years)	65.1 (10.2)		65.0 (8.7)		66.2 (7.2)	
Interscan interval (years)	1.3 (0.3)		1.1 (0.3)		1.2 (0.3)	
Baseline brain volume (ml)	1150.6 (98.2)		1090.2 (96.4)		1065.6 (144.7)*	
Baseline ventricular volume (ml)	29.9 (26.9)		42.6 (17.5)		45.2 (22.0)	
Baseline left/right hemisphere ratio	1.00 (0.01)		0.94 (0.01)*		0.95 (0.03)*	
	Left	*Right*	*Left*	*Right*	*Left*	*Right*
Baseline hemisphere volume (ml)	581.4 (45.4)	579.5 (47.8)	523.0 (44.1)*	555.4 (52.5)	513.6 (60.2)*	537.8 (64.0)
Baseline frontal lobe volume (ml)	76.0 (6.2)	76.9 (6.5)	73.3 (7.0)	77.2 (7.3)	67.4 (11.0)*,[1]	74.1 (9.1)
Baseline temporal lobe volume (ml)	50.6 (5.9)	49.8 (5.2)	31.2 (5.6)*,[1]	40.8 (6.0)*,[1]	42.5 (7.6)*	46.9 (5.4)
Baseline parietal lobe volume (ml)	52.7 (4.2)	54.2 (2.5)	47.8 (3.5)*	53.4 (4.8)	47.9 (7.5)*	51.8 (6.3)
Baseline occipital lobe volume (ml)	21.3 (1.8)	22.1 (3.4)	20.8 (2.7)	22.2 (2.8)	20.8 (2.7)	22.1 (2.9)

*$p < 0.05$ significant difference between disease group and controls, [1]$p < 0.05$ significant difference between SEMD and PNFA.

between the repeat and baseline scans divided by the baseline lobar volume. Annualized rates of hemisphere and lobar atrophy were subsequently calculated by dividing by the interscan interval.

The two disease groups and the healthy control group were compared statistically based on contrasts between the group means using a linear regression model in STATA10 (Stata Corporation, College Station, TX). 95% bias-corrected bootstrap confidence intervals with 1000 replicates were used. Wilcoxon signed-rank test was used to look at within-disease group comparisons. We used standard methods to calculate sample sizes for detection of a moderate treatment effect (30% reduction in atrophy adjusting for control atrophy rate), including baseline and one follow-up assessment at 12 months with 90% power and 5% two-tailed significance level [17].

RESULTS

Baseline imaging (Table 1)

At baseline, brain volumes were significantly smaller in PNFA than controls but there was no significant difference in ventricular volume. In SEMD there were no significant differences from controls in either brain or ventricular volume.

The left hemisphere volumes were smaller than controls in both disease groups (10% smaller in SEMD, 12% smaller in PNFA) with no significant difference in the right hemisphere volumes. Left/right hemisphere asymmetry ratios were significantly lower than control ratios in PNFA and SEMD at baseline but not significantly different between the two disease groups.

At baseline, both temporal lobes and the left parietal lobe were significantly smaller than controls in SEMD, while in PNFA, the left frontal, temporal, and parietal lobes were smaller than controls. In both groups, the left hemisphere lobar volumes were all significantly smaller than the right. Comparing the groups directly, the left frontal lobe was significantly smaller in PNFA compared to SEMD with both temporal lobes significantly smaller in SEMD compared to PNFA.

Longitudinal imaging (Table 2)

Rates of whole brain atrophy and ventricular enlargement were greater in both SEMD and PNFA compared to controls with no significant differences between the disease groups.

Both left and right hemisphere rates of atrophy were greater than controls in both disease groups. Furthermore, left hemisphere rates of atrophy were significantly greater than right hemisphere rates for both PNFA ($p = 0.002$) and SEMD ($p = 0.0004$). The left/right hemisphere asymmetry ratio significantly increased in the SEMD group over time with a non-significant trend toward an increase in the PNFA group. However, two PNFA patients started with right greater than left asymmetry (both of whom were known to be left-handed) and when these patients were excluded from the analysis, there was a significant increase in the left/right hemisphere asymmetry ratio also in the PNFA group.

In both SEMD and PNFA, left and right frontal, temporal, and parietal lobe rates of atrophy were significantly greater than controls with the left occipital lobe rate of atrophy also greater in SEMD. In both hemispheres in SEMD, the temporal lobe had the fastest rate of atrophy followed by the frontal lobe, then parietal lobe, and lastly the occipital lobe. In both hemispheres in PNFA, the frontal lobe had the fastest rate of atrophy, followed by the temporal and parietal lobes (temporal greater on the left, parietal greater on the right), with

Table 2
Rates of whole brain atrophy, ventricular enlargement, hemispheric atrophy and change in left/right hemisphere ratio

Outcome measure	Mean rate of atrophy[1] (standard deviation)					
	Controls		SEMD		PNFA	
Brain BSI (%/yr)	0.4 (0.4)		2.5 (1.5)*		2.6 (1.2)*	
Ventricle BSI (ml/yr)[1]	0.7 (1.2)		6.9 (4.4)*		6.6 (3.4)*	
L/R hemisphere ratio change (%/yr)	0.4 (0.8)		1.1 (0.8)*		0.9 (1.1)	
	Left	*Right*	*Left*	*Right*	*Left*	*Right*
Hemisphere (%/yr)	0.2 (1.0)	–0.1 (1.0)	4.2 (3.2)*	3.1 (2.8)*	4.3 (1.6)*	3.4 (2.0)*
Frontal lobe (%/yr)	0.8 (1.4)	0.7 (1.6)	4.3 (2.0)*	2.8 (2.5)*	5.7 (2.8)*	4.5 (2.3)*,[1]
Temporal lobe (%/yr)	0.5 (1.4)	0.8 (1.0)	7.1 (2.3)*	6.6 (2.9)*,[1]	5.3 (3.6)*	3.4 (3.5)*
Parietal lobe (%/yr)	0.5 (1.5)	0.2 (1.1)	3.5 (2.9)*	2.0 (2.9)*	4.3 (2.3)*	3.5 (3.2)*
Occipital lobe (%/yr)	–0.2 (2.9)	0.4 (3.5)	1.8 (3.1)*	1.3 (2.9)	1.0 (3.0)	1.2 (3.8)

[1]Enlargement rate for ventricle boundary shift integral (BSI), *$p < 0.05$ significant difference between disease group and controls, [1]$p < 0.05$ significant difference between SEMD and PNFA.

the slowest rate of atrophy in the occipital lobe. Significant differences between the disease groups were seen in the frontal and temporal lobes with a significantly greater rate of atrophy in the right temporal lobe (and a trend to greater rate in the left) in SEMD compared with PNFA, and, in contrast, a significantly greater rate of atrophy in the right frontal lobe (and a trend to greater rate in the left) in PNFA compared with SEMD. Within group, lobar rates of atrophy were greater in the left hemisphere compared to the right for the frontal and temporal lobes for PNFA, and for the frontal and parietal lobes for SEMD, with no significant difference between the parietal lobe rates in PNFA or between the temporal lobe rates in SEMD.

Sample size estimates (Table 3)

In SEMD, estimated sample sizes were smallest using temporal lobe atrophy rates. However in the PNFA group, the smallest were for the left hemisphere rate with whole brain, ventricle, right hemisphere, and frontal lobe volumes providing similar sample sizes.

DISCUSSION

Here we present quantitative longitudinal brain imaging data for language variants of FTLD, showing that both groups have asymmetrical (predominantly left-sided) cerebral atrophy at baseline with increasing asymmetry as the disease progresses. Overall rates of progression for whole brain or hemispheric atrophy rates were similar in both groups. However, lobar atrophy rates varied between the groups with the temporal lobes fastest in SEMD and left frontal lobe fastest in PNFA. These findings corroborate and extend previous neuroimaging data in the language subtypes.

Baseline brain volumes reveal the asymmetrical nature of both PNFA and SEMD but with differing lobar involvement in the two diseases. Both diseases predominantly affect the left hemisphere with each of the left hemisphere lobes significantly smaller than the right hemisphere lobes at baseline. However in SEMD, the disease is focused particularly in the temporal lobe with significant involvement at baseline in both left and right temporal lobes as well as the left parietal lobe. In contrast in PNFA, the left frontal, temporal, and parietal lobes are significantly smaller than controls at baseline. These patterns of baseline volume loss are consistent with the lobar rates of atrophy; each lobe appears to atrophy at a different rate in both diseases with left lobar rates greater than right lobar rates and the greatest rates in the temporal lobes in SEMD and in left frontal and temporal in PNFA.

The basis for increasing cerebral asymmetry with disease evolution in the language variants of FTLD is a further unresolved issue with neurobiological implications. This longitudinal change in left/right hemisphere ratio is not attributable simply to an arithmetical effect, which would follow if both hemispheres atrophied at a similar fixed rate: rather, the increase in hemisphere asymmetry was underpinned by a genuine disproportionate increase in left hemisphere atrophy. On face value this finding appears to run counter to the widely held view that focal dementias become 'global' brain diseases over time, with more or less uniform involvement as an endpoint. To address this issue will require detailed regional analysis of the profile of longitudinal changes within as well as between hemispheres, as well as systematic sampling of atrophy rates throughout the course of the disease. One interpretation is that, at least during the phase of mid-stage disease, atrophy spread occurs via a mainly intrahemispheric network of connected brain regions, tending to 'focus' the effects

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

	Sample size per treatment arm (30% reduction in atrophy rate[1] adjusting for control atrophy rate with 90% power and 5% two-tailed significance level in a trial for completers of a 12 month study)			
	SEMD		PNFA	
Brain BSI	120		70	
Ventricle BSI	118		78	
	Left	*Right*	*Left*	*Right*
Hemisphere	150	179	36	77
Frontal lobe	77	331	77	86
Temporal lobe	30	59	137	424
Parietal lobe	219	607	86	104
Occipital lobe	561	2425	1460	5269

[1]Enlargement rate for ventricle boundary shift integral (BSI).

of the pathological process within the more damaged (left) hemisphere. This interpretation would be consonant with other emerging evidence of network-specific damage in FTLD syndromes [18] and suggests testable hypotheses about the mechanism of brain damage in FTLD more generally.

These findings have implications for the design of future trials of disease-modifying therapy in FTLD [12, 19]. SEMD will be an attractive candidate target for such trials because it is a relatively well-defined clinico-pathological entity: we have previously shown using manual measurements that in SEMD, smaller sample sizes may be needed in clinical trials if MR measures of regions of interest (temporal lobes) are used rather than measures of whole brain or ventricular volume change [9]. The present findings support this finding, even when using an automated technique (Freesurfer) and in comparison to the other lobes. Measures of rate of atrophy for the left hemisphere in PNFA would yield practically useful sample sizes and in this study are superior to whole brain, ventricle, and frontal lobe measures. Taken together with the previous data in SEMD (and in contrast to the situation for relatively homogeneous entities such as Alzheimer's disease), the findings underline the need for stratification of both clinical diagnosis and imaging biomarkers within the FTLD spectrum.

ACKNOWLEDGMENTS

This work was undertaken at UCLH/UCL who received a proportion of funding from the Department of Health's NIHR Biomedical Research Centres funding scheme. The Dementia Research Centre is an Alzheimer's Research UK Co-ordinating Centre. This work was also funded by the Medical Research Council UK.

Authors' disclosures available online (http://www.j-alz.com/disclosures/view.php?id=1176).

REFERENCES

[1] Seelaar H, Rohrer JD, Pijnenburg YA, Fox NC, van Swieten JC (2011) Clinical, genetic and pathological heterogeneity of frontotemporal dementia: A review. *J Neurol Neurosurg Psychiatry* **82**, 476-486.

[2] Gorno-Tempini ML, Hillis AE, Weintraub S, Kertesz A, Mendez M, Cappa SF, Ogar JM, Rohrer JD, Black S, Boeve BF, Manes F, Dronkers NF, Vandenberghe R, Rascovsky K, Patterson K, Miller BL, Knopman DS, Hodges JR, Mesulam MM, Grossman M (2011) Classification of primary progressive aphasia and its variants. *Neurology* **76**, 1006-1014.

[3] Hodges JR, Patterson K (2007) Semantic dementia: A unique clinicopathological syndrome. *Lancet Neurol* **6**, 1004-1014.

[4] Chan D, Fox NC, Scahill RI, Crum WR, Whitwell JL, Leschziner G, Rossor AM, Stevens JM, Cipolotti L, Rossor MN (2001) Patterns of temporal lobe atrophy in semantic dementia and Alzheimer's disease. *Ann Neurol* **49**, 433-442.

[5] Schroeter ML, Raczka K, Neumann J, Yves von Cramon D (2007) Towards a nosology for frontotemporal lobar degenerations-a meta-analysis involving 267 subjects. *Neuroimage* **36**, 497-510.

[6] Rohrer JD, Warren JD, Modat M, Ridgway GR, Douiri A, Rossor MN, Ourselin S, Fox NC (2009) Patterns of cortical thinning in the language variants of frontotemporal lobar degeneration. *Neurology* **72**, 1562-1569.

[7] Lindberg O, Ostberg P, Zandbelt BB, Oberg J, Zhang Y, Andersen C, Looi JC, Bogdanović N, Wahlund LO (2009) Cortical morphometric subclassification of frontotemporal lobar degeneration. *AJNR Am J Neuroradiol* **30**, 1233-1239.

[8] Whitwell JL, Anderson VM, Scahill RI, Rossor MN, Fox NC (2004) Longitudinal patterns of regional change on volumetric MRI in frontotemporal lobar degeneration. *Dement Geriatr Cogn Disord* **17**, 307-310.

[9] Rohrer JD, McNaught E, Foster J, Clegg SL, Barnes J, Omar R, Warrington EK, Rossor MN, Warren JD, Fox NC (2008) Tracking progression in frontotemporal lobar degeneration: Serial MRI in semantic dementia. *Neurology* **71**, 1445-1451.

[10] Brambati SM, Rankin KP, Narvid J, Seeley WW, Dean D, Rosen HJ, Miller BL, Ashburner J, Gorno-Tempini ML (2009) Atrophy progression in semantic dementia with asymmetric temporal involvement: A tensor-based morphometry study. *Neurobiol Aging* **30**, 103-111.

[11] Krueger CE, Dean DL, Rosen HJ, Halabi C, Weiner M, Miller BL, Kramer JH (2010) Longitudinal rates of lobar atrophy in frontotemporal dementia, semantic dementia, and Alzheimer's disease. *Alzheimer Dis Assoc Disord* **24**, 43-48.

[12] Knopman DS, Jack CR Jr, Kramer JH, Boeve BF, Caselli RJ, Graff-Radford NR, Mendez MF, Miller BL, Mercaldo ND (2009) Brain and ventricular volumetric changes in frontotemporal lobar degeneration over 1 year. *Neurology* **72**, 1843-1849.

[13] Gordon E, Rohrer JD, Kim LG, Omar R, Rossor MN, Fox NC, Warren JD (2010) Measuring disease progression in frontotemporal lobar degeneration: A clinical and MRI study. *Neurology* **74**, 666-673.

[14] Freeborough PA, Fox NC, Kitney RI (1997) Interactive algorithms for the segmentation and quantitation of 3-D MRI brain scans. *Comput Methods Programs Biomed* **53**, 15-25.

[15] Freeborough PA, Fox NC (1997) The boundary shift integral: An accurate and robust measure of cerebral volume changes from registered repeat MRI. *IEEE Trans Med Imaging* **16**, 623-629.

[16] Mazziotta JC, Toga AW, Evans A, Fox P, Lancaster J (1995) A probabilistic atlas of the human brain – theory and rationale for its development. *Neuroimage* **2**, 89-101.

[17] Fox NC, Cousens S, Scahill R, Harvey RJ, Rossor MN (2000) Using serial registered brain magnetic resonance imaging to measure disease pro- gression in Alzheimer disease: Power calculations and esti- mates of sample size to detect treatment effects. *Arch Neurol* **57**, 339-344.

[18] Seeley WW, Crawford RK, Zhou J, Miller BL, Greicius MD (2009) Neurodegenerative diseases target large-scale human brain networks. *Neuron* **62**, 42-52.

[19] Knopman DS, Kramer JH, Boeve BF, Caselli RJ, Graff-Radford NR, Mendez MF, Miller BL, Mercaldo N (2008) Development of methodology for conducting clinical trials in frontotemporal lobar degeneration. *Brain* **131**(Pt 11), 2957-2968.