

The neural basis of semantic memory: Evidence from semantic dementia

R. Rhys Davies^a, Glenda M. Halliday^b, John H. Xuereb^c,
Jillian J. Kril^d, John R. Hodges^{b,e,*}

^a Department of Clinical Neurosciences, University of Cambridge, Addenbrooke's Hospital Hills Road, Cambridge CB2 2QQ, UK

^b Prince of Wales Medical Research Institute, University of New South Wales, Randwick, New South Wales, Australia

^c Department of Pathology, University of Cambridge, Addenbrooke's Hospital Hills Road, Cambridge CB2 2QQ, UK

^d Disciplines of Medicine and Pathology, The University of Sydney, Sydney, New South Wales, Australia

^e MRC Cognition and Brain Sciences Unit, 15 Chaucer Road, Cambridge CB2 7EF, UK

Received 30 March 2007; received in revised form 7 February 2008; accepted 14 February 2008

Available online 25 March 2008

Abstract

Semantic dementia (SD) is a syndrome of progressive impairment in semantic memory. Fifty-eight brain regions were measured in seven post mortem SD cases, ten normal controls and two disease controls (diagnosis frontotemporal dementia and motor neuron disease, FTD–MND). Manual segmentation of the whole brain has not previously been undertaken in a series of SD cases, either post mortem or during life. Widespread volume loss relative to controls was found in SD, with anterior temporal lobe regions bearing the brunt (>60% atrophy of temporopolar and perirhinal cortices bilaterally). Comparison of regional volumes in SD and FTD–MND found greater atrophy in SD only in temporopolar and perirhinal volumes. The sole region showing atrophy relative to controls in FTD–MND but not SD was motor cortex. Posterior temporal and frontal regions were not consistently affected and no significant asymmetry of atrophy was found. In summary, whole-brain regional evaluation in SD, in comparison with normal controls and FTD–MND, found anterior temporal atrophy encompassing the perirhinal cortex with relative sparing of adjacent posterior temporal regions.

© 2008 Elsevier Inc. All rights reserved.

Keywords: Semantic memory; Perirhinal cortex; Semantic dementia; Frontotemporal dementia; Motor neuron disease

1. Introduction

Semantic dementia (SD) is a syndrome of progressive impairment in conceptual knowledge associated with anomia, impaired comprehension and speech that is fluent but lacking in content (Bozeat et al., 2000; Hodges et al., 1992; Snowden et al., 1989). Other cognitive domains, including

day-to-day memory, are relatively preserved (Hodges and Patterson, 1996; Hodges et al., 1992, 1999).

In terms of neuropathology, most SD cases (72%) conform to a single subtype of FTD, with intra-neuronal deposits containing the protein ubiquitin (Davies et al., 2005). Such deposits are also described in motor neuron disease (MND) and are sometimes termed MND inclusions (Jackson et al., 1996). Patient with clinical features of FTD (typically behavioural disturbance and reduced fluency of speech) with signs of MND are increasingly recognized, and may be labelled 'FTD–MND' (Lomen-Hoerth et al., 2002, 2003; Neary et al., 1990; Rakowicz and Hodges, 1998).

Manual tracing methods and automated voxel-based morphometry (VBM) in SD show asymmetric atrophy of the temporal lobe, worse on the left than the right (Chan et al., 2001; Galton et al., 2001b; Mummery et al., 2000).

* Corresponding author at: Prince of Wales Medical Research Institute, Barker Street, Randwick, Sydney, NSW 2031, Australia.
Tel.: +61 2 9399 1132; fax: +61 2 9399 1005.

E-mail addresses: rrd22@cam.ac.uk (R.R. Davies),
G.Halliday@powmri.edu.au (G.M. Halliday),
jhx1000@cus.cam.ac.uk (J.H. Xuereb),
jilliank@med.usyd.edu.au (J.J. Kril),
j.hodges@powmri.edu.au (J.R. Hodges).

Comparisons of atrophy in SD and AD, moreover, find relatively greater atrophy in anterior (rostral) than posterior (caudal) temporal regions in SD (Chan et al., 2001; Davies et al., 2004). Regional measurements with reference to cytoarchitectonic boundaries found the most severe atrophy in perirhinal cortex (PRC), incorporating Brodmann areas (BA) 35 and 36 in the collateral sulcus and extending over the temporal pole (Davies et al., 2004; Saleem and Tanaka, 1996; Suzuki and Amaral, 2003). Volume loss was also noted in the anterior entorhinal cortex (ERC), to which PRC projects, but not in the posterior ERC (Davies et al., 2004; Suzuki and Amaral, 1994). Semi-quantitative assessment of neuronal loss in twelve SD cases likewise found the most severe abnormality in the antero-medial temporal lobe, in the region of the PRC (Davies et al., 2005).

By contrast, a single case study quantified atrophy and neuronal loss in language-associated gyri, finding involvement of the angular and the posterior temporal gyri (BA 37 and 39) bilaterally and involvement of the lateral temporal gyri (BA 20, 21 and 22) on the right, the case having been one of the minority with SD in which right sided atrophy predominated (Harasty et al., 1996b). Functional abnormalities in the posterior temporal lobe (BA 37) were also found in a PET activation study in SD employing a semantic association task, although this area was not atrophic as assessed by VBM (Mummery et al., 1999).

A difficulty in assimilating existing studies that differ in the emphasis of atrophy reported is that the measurements have often been limited to selected regions (Chan et al., 2001; Davies et al., 2004; Galton et al., 2001b). Whole-brain assessments in SD, to date, have been confined to automated analyses in the form of VBM (Mummery et al., 2000; Williams et al., 2005). This method, however, may be insensitive to differences between small regions, especially those adjacent to CSF (Good et al., 2002; Mummery et al., 2000). Warping and smoothing required for image processing are particularly problematic when, as in SD, the disease causes marked anatomical distortion. The neural basis of semantic memory remains controversial in part because patients with isolated semantic impairment from focal brain lesions do not exist.

Our primary aim was to assess regional atrophy, in comparison with normal controls, across entire post mortem brain

specimens in SD, to illuminate the neural basis of semantic memory. A second aim was to compare regional atrophy in SD with a disease control group, namely FTD–MND, contrasting in neuropsychological impairments but similar in microscopic neuropathology. The third aim was to examine data on regional volumes and disease duration by factor analysis to identify underlying patterns.

2. Materials and methods

2.1. Cases

Cases were obtained from neuropathological series of dementia patients in Cambridge, England and Sydney, Australia. Both series were collected as part of multidisciplinary research programmes closely linked to specialist tertiary referral dementia clinics serving similar catchment populations. The effort at both centres to enrol patients with young onset and atypical dementias into brain donor programmes yielded a 90% success rate for obtaining declarations of intent during life. The provision of on-call services by the brain banks ensured that tissue donation occurred in virtually 100% of these cases.

2.2. Clinical features

SD ($n = 7$) cases fulfilled international consensus criteria (McKhann et al., 2001; Neary et al., 1998). In brief, all presented with progressive impairment of the semantic basis of language and evidence of associative agnosia with sparing of other aspects of cognition. Of the 7 SD cases, 6 were studied in Cambridge and 1 in Sydney. All underwent detailed neuropsychological evaluation (see Table 1) and brain imaging at presentation. Two SD patients had mild behavioural disturbance at presentation but this was less prominent than their semantic memory deficit. The FTD–MND patients, both from Sydney ($n = 2$), fulfilled diagnostic criteria for the behavioural variant of FTD (changes in personality and social cognition) but did not undergo detailed neuropsychological testing. They showed clinical and electrophysiological evidence of MND and progressed rapidly, dying within 2 years of presentation (Neary et al., 1998, 1990). All clinical information

Table 1

Cognitive performance of 7 SD cases on the Cambridge Semantic Battery plus pyramids and palm trees (PPT), digit span and copy of Rey figure: maximum scores in parentheses

Case no.	MMSE (30)	Naming (48)	Word-picture matching (48)	PPT (52)	Digit span	Rey copy (36)
1 ^a	20	10	30	-	6	34
2	13	3	36	39	7	36
3	24	31	43	44	8	34
4	20	10	23	34	6	24
5	13	4	26	36	6	31
6	23	39	44	47	6	34
7	23	26	43	41	6	36

MMSE, minimal state examination.

^a Case from Sydney.

pertains to the initial assessment when the syndromic diagnosis was reached. Reliable data on patients' cognitive and behavioural deficits in the immediate ante mortem period were unavailable. For controls who were all from Sydney ($n = 10$), questionnaires, were sent to relatives and general practitioners in life, and again at the time of death, enquiring about medication use, alcohol consumption, medical history (e.g. stroke, head injury) and evidence of cognitive dysfunction. Controls with significant comorbidities and evidence of alcohol abuse were excluded, as were individuals with evidence of dementia ($CDR < 0.5$) (Morris, 1993). All control brains were also without significant macroscopic or microscopic neuropathological abnormality (Table 2). These controls have been used in a number of other volumetric and cellular studies (Halliday et al., 2003, 1998; Harasty et al., 1996b, 1999; Kril et al., 2005).

All of the SD cases were reported in a larger qualitative neuropathological study of 18 SD cases (Davies et al., 2005). The remaining 11 cases were processed in a standard manner with snap freezing of one hemisphere and formalin fixation of the other which does not allow detailed morphometric analysis of the type reported here. Several also appeared in a range of clinical and neuropsychological papers (Bozeat et al., 2000; Galton et al., 2001a,b; Thompson et al., 2004). Two of the SD cases and both FTD–MND cases were included in the Sydney–Cambridge FTD clinico-pathological series (Hodges et al., 2004, 2003), the remaining 5 SD cases died after completion of the joint study but were reported in a former paper on the neuropathology of SD (Davies et al., 2005). The FTD–MND cases also featured in a study of brain volumes in FTD cases with prominent behavioural disturbance (Kril et al., 2005).

2.3. Brain preparation and identification of regions of interest

The volumetric methods used in this study are published in detail elsewhere (Halliday et al., 2003; Harasty et al., 1996a). Briefly, each brain was weighed at autopsy (maximum post mortem delay 38 h) and following fixation (14–28 days in 10% for Cambridge cases, or 15% for Sydney cases, neutral buffered formalin) the fixed brain volume was determined by fluid displacement using Archimedes's principle. In brief, volumes were measured using a standard container (a plastic desiccator) filled with water to the same level before (a) and after (b) submersion of the fixed brain. Volume was calculated using the formula; brain volume = $(a + \text{weight of brain} - b) / \text{density of fluid}$ (i.e. 1). Brains were retained in fluid (fixative) from the time of autopsy and care was taken to ensure that the ventricles remained filled with fluid during the volumetric measurement. Prior work has established inter and intra-individual case variation in volume of <2%. The cerebellum and brainstem were then separated from the cerebrum by sectioning through the rostral midbrain. The length of each hemisphere was measured using calipers. After embedding in 4% agar, the cerebrum was sliced coro-

Table 2
Individual patient details: age at death, pathological diagnoses and hemispheric volumes

Case no.	Clinical syndrome	Pathological diagnosis	Sex	Age at death (years)	PMI (h)	Symptom duration (years)	Cause of death	Left hemisphere volume (ml)	Right hemisphere volume (ml)
1	SD	FTLD-U	M	69	6	3	Pulmonary embolus	526	526
2	SD	FTLD-U	M	73	8	14	Pneumonia	383	441
3	SD	FTLD-U	M	61	3	10	Pneumonia	540	556
4	SD	FTLD-U	F	67	12	7	Pneumonia	446	386
5	SD	FTLD-U	F	71	6	14	Respiratory failure	442	479
6	SD	FTD (Pick's)	M	74	4	16	Sepsis	429	517
7	SD	AD	M	65	3	6	Gastric haemorrhage	508	526
8	FTD–MND	FTLD-U	M	58	2	3	Pneumonia	469	482
9	FTD–MND	FTLD-U	M	53	3	2	Pneumonia	535	538
1	Control	Nil	M	58	26	0	MI	758	755
2	Control	Nil	M	46	23	0	MI	690	700
3	Control	Nil	M	54	25	0	Blood loss	600	577
4	Control	Nil	M	71	27	0	Post-operative complications	581	584
5	Control	Nil	M	51	10	0	Sepsis	554	555
6	Control	Nil	F	57	19	0	Respiratory failure	622	619
7	Control	Nil	F	70	8	0	Respiratory failure	518	515
8	Control	Nil	F	64	16	0	Sepsis	568	572
9	Control	Nil	F	69	4	0	Ruptured AAA	605	592
10	Control	Nil	F	50	6	0	MI	554	561

PMI, post mortem interval; MI, myocardial infarct; AAA, abdominal aortic aneurysm.

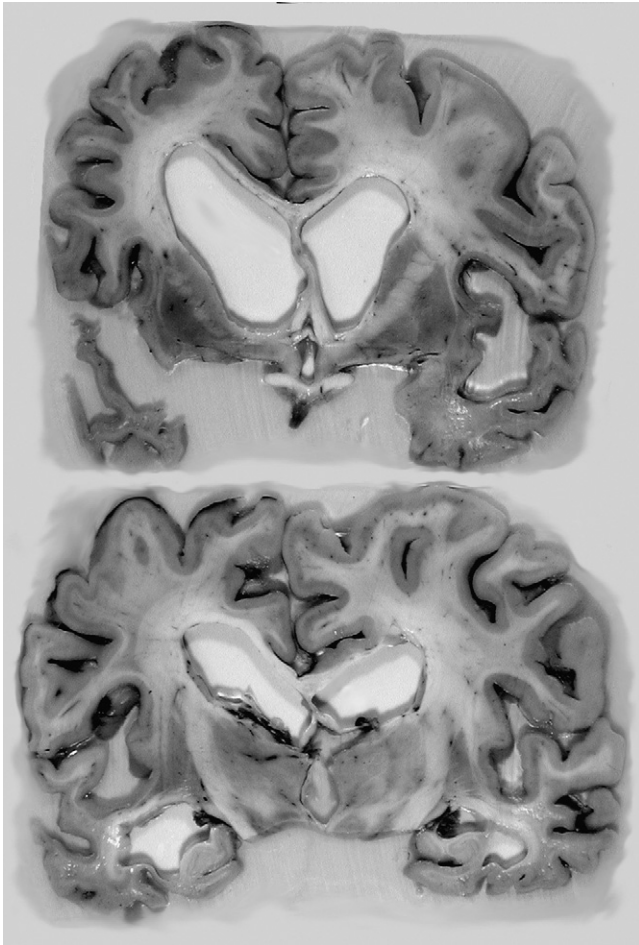


Fig. 1. Coronal slices through semantic dementia brain showing severe anterior and inferior temporal atrophy encompassing the perirhinal cortex.

nally using a rotary slicer, photographed and printed (1× magnification, Fig. 1). Average slice thickness was determined by dividing the hemisphere length by the number of slices.

Gyral boundaries and internal brain landmarks most consistently associated with cytoarchitectonic boundaries, in accordance with human brain atlases, were used to identify regions across all cases (Damasio, 1995; Harasty et al., 1996a; Mai et al., 1997). Twenty-four cortical regions, four subcortical grey matter regions and white matter were identified in the left and right hemisphere of each brain (58 regions in total). Cortical regions were: frontal lobe—frontal pole, orbitofrontal cortex, inferior frontal gyrus, superior and middle frontal gyri (superior frontal region), motor cortices; Temporal lobe—temporal pole, PRC, entorhinal cortex, posterior parahippocampal cortex, fusiform gyrus, inferior temporal gyrus, middle temporal gyrus, superior temporal gyrus, posterior temporal region (BA 37); Limbic/paralimbic structures—amygdala, hippocampus, insula, anterior cingulate cortex, posterior cingulate cortex; parietal lobe—somatosensory cortex, superior parietal lobule, supra-marginal gyrus, angular gyrus; occipital lobe. The subcortical

delineations were white matter, caudate, putamen, globus pallidus and thalamus (Halliday et al., 1998; Kril et al., 1997).

The segmentation of individual regions is detailed in a recent paper (Halliday et al., 2003). The only departure from that method was the inclusion of PRC, defined according to the landmarks of Insausti et al. (1998). The most anterior portion of PRC coincided with the anterior limit of the collateral sulcus while the its posterior limit coincided with that of the putamen. The medial boundary of PRC (in slices not containing ERC) was the medial aspect of the temporal lobe itself. Where ERC was present, the medial limit of PRC was the border with ERC—the midpoint of the medial bank of the collateral sulcus. The PRC's lateral boundary was the lateral edge of the collateral sulcus. Adjacent regional delineations affected by the inclusion of PRC were as follows: (1) ERC (see above); (2) posterior parahippocampal cortex occupied the gyrus adjacent to the hippocampus from just posterior to the putamen; (3) the anterior portion of the fusiform cortex occupied the occipitotemporal gyrus lateral to PRC and, in slices posterior to PRC, it occupied the whole of the gyrus with its lateral border abutting the cortex of the inferior temporal gyrus.

2.4. Volume determination

Volumes of the regions of interest were determined by a point counting procedure after the area corresponding to each region was identified on the brain slice photographs. Each photograph (1× magnification) was randomly overlaid with a grid of 3848 points with each point representing 16 mm² of the slice area. The points falling on each region were counted. Volumes were calculated by multiplying the sum of the points falling on a given structure by the volume represented by each point (volume/point = cerebrum volume/total number of points counted or 16 mm² × average slice thickness/1000; both averaged 0.05 ml and varied by <2% between methods). The average number of slices cut per brain was 50 ± 4 (range 43–58) and the average number of points counted per brain was 21,543 ± 3770 (range 13,406–28,553). This method is routinely used by us to measure regional volumes post mortem (Double et al., 1996a,b; Halliday et al., 2003, 1998; Harasty et al., 1999; Kril et al., 1997) and approximates current point counting procedures used in MRI studies of brain volumes. As previously described (Halliday et al., 2003), four trained raters counted all regions of interest in one male control brain. The coefficient of error for each regional volume was calculated as an indicator of accuracy of the measurement. The lower the value, the more accurately the mean value attained reflects the true mean. The coefficient of error for each brain region was <0.05 (range 0.021–0.048, average 0.032 ± 0.008). This confirms that the volume method used is highly reliable and reproducible for the subregions identified. The intraclass correlation coefficient for a subregional volume measured by these four raters was 0.959. For the newly introduced region, the PRC, there was no significant

difference between the values generated by two raters using a paired *t*-test.

2.5. Statistical analysis

For the purposes of standardization, volume data were expressed as a proportion of the control mean for each sex, given that regional brain volumes vary considerably between normal male and female subjects (~200 ml or 15% of cerebrum volume) (Cordato et al., 2000; DeCarli et al., 1994; Double et al., 1996a; Mueller et al., 1998). Many *in vivo* studies give values corrected for intracranial cavity volume to account for inter-individual variation, including sex differences, but estimation of intracranial volume at autopsy is technically complex and not possible if brain retrieval is performed away from the research centre (as occurred in most of the cases here).

Two-way analysis of variance (ANOVA) was used to determine differences between diagnostic groups and hemispheres. Post hoc Bonferroni correction for multiple comparisons was performed to identify group-differences in regional volume. Corrected *p*-values of <0.05 were accepted as significant. Analyses inclusive of all SD cases were performed followed by analyses in which the SD cases were confined to those carrying a pathological diagnosis from the FTD spectrum.

Factor analysis (principal component) was performed to identify relationships between regional cortical atrophy and disease duration in SD; regional volumes submitted to the factor analyses were those in which ANOVA had detected significant atrophy and only those with standard coefficient loadings >0.65 were considered significant. A further benefit of expressing volume data as proportions of the mean was that larger regions, with correspondingly greater variance did not have an undue effect on the factor analysis. Spearman rank correlations were performed for related variables to understand these relationships.

3. Results

3.1. Demographic data

The seven SD cases (5 male, 2 female) and two FTD–MND (both male) were compared with 10 cognitively normal controls (5 male and 5 female). The SD cases were somewhat older, on average, than the two control groups (SD mean 68 ± 4 and range 61–74 years, FTD–MND mean 55 ± 3 and range 53–58 years, control mean 59 ± 9 and range 46–71 years). This was a consequence of two additional SD cases, both older, coming to post mortem examination after the initial selection of cases and age-matched controls (see Table 2). The two FTD–MND patients had illness durations of 2 and 3 years, shorter than those with SD (range 3–16 years) in keeping with the literature on survival in FTD–MND. There was one SD case with Alzheimer-type pathology, i.e. not patho-

logical FTD. Excluding this case did not significantly affect the results for the vast majority of regions (those where it did are reported below).

As expected for FTD, overall brain volume was significantly reduced in the cases with SD (average $26 \pm 10\%$ atrophy, $F_{\text{diagnosis}} = 51.4$, $p < 0.0001$). Analyses incorporating diagnosis (all SD cases versus controls) and hemisphere (left versus right), covarying for duration, found no significant hemispheric difference for any region analysed, or for whole hemisphere volumes. Diagnosis was, therefore, the only variable that significantly affected regional tissue volume.

3.2. Frontotemporal regions of atrophy in SD

The most severe atrophy in the SD cases examined occurred in temporal lobe structures (Table 3), the most atrophic of all being the temporal pole and PRC, where cortical tissue was reduced on average by 59–66% ($F_{\text{diagnosis}} > 80$, $p < 0.0001$). Significant atrophy was also observed in ERC, inferior and middle temporal cortices, as well as in amygdala and hippocampus (34–40% atrophy, $F_{\text{diagnosis}} > 6$, $p < 0.03$). When the case with AD was excluded, significant atrophy was also observed in the posterior parahippocampal cortex and superior temporal cortex ($p < 0.05$). In contrast, few frontal regions were consistently atrophic, although considerable atrophy of the frontal pole (21% loss, $F_{\text{diagnosis}} = 16.7$, $p = 0.0003$) and the anterior cingulate gyrus (43% loss, $F_{\text{diagnosis}} = 63.8$, $p < 0.0001$) was observed. Further limbic structures showing significant atrophy were insula and posterior cingulate cortex (42–26% loss, $F_{\text{diagnosis}} > 41$, $p < 0.0001$).

3.3. Other atrophic regions in SD

Other regions implicated in language processing, the supramarginal and angular gyri, also showed atrophy (21–51% loss, $F_{\text{diagnosis}} > 11$, $p < 0.003$). Significant atrophy of striatum and globus pallidus was also present (28–43% loss, $F_{\text{diagnosis}} > 19$, $p < 0.0002$), as was white matter atrophy (31% loss, $F_{\text{diagnosis}} = 42.9$, $p < 0.0001$). Unexpectedly, there was significant atrophy of the occipital lobe ($22 \pm 14\%$ loss, $F_{\text{diagnosis}} = 25.8$, $p < 0.0001$).

3.4. Comparison with FTD–MND

The majority of regions involved in SD were also atrophic in the FTD–MND patients. Regions significantly atrophic in both SD and FTD–MND relative to controls were frontal pole, temporal pole, PRC, supramarginal gyrus, amygdala, hippocampus, insula, anterior cingulate, caudate nucleus, globus pallidus and white matter (in SD–22–69% atrophy, $F_{\text{diagnosis}} > 12.5$, $p < 0.0001$; in FTD–MND–22–47% atrophy, $F_{\text{diagnosis}} > 12.5$, $p < 0.01$). As expected, the motor cortices were significantly atrophic only in the FTD–MND cases (29% atrophy, $F_{\text{diagnosis}} = 5.1$, $p = 0.012$, post hoc

Table 3

Mean regional volumes (\pm standard deviation) for the control group, with percentage of regional control volume found in SD and in FTD–MND

	Control volume (ml)	SD (all pathologies) % control mean	SD (FTD pathologies) % control mean	FTD–MND % control mean
Frontal cortices				
Frontal pole	43.24 \pm 5.81	79.36 \pm 15.46*	77.58 \pm 16.07*	71.81 \pm 12.53*
Orbitofrontal	10.43 \pm 2.93	86.55 \pm 24.55	89.24 \pm 25.52	80.34 \pm 17.32
Inf. frontal	5.83 \pm 1.53	100.15 \pm 22.80	97.40 \pm 23.30	93.79 \pm 27.07
Sup. frontal	14.56 \pm 3.01	70.71 \pm 18.20	69.04 \pm 18.88	69.66 \pm 15.81
Motor	20.7 \pm 3.67	105.27 \pm 21.5	106.33 \pm 22.98	71.49 \pm 12.21*
Temporal cortices				
Temporal pole	11.40 \pm 2.86	34.46 \pm 15.44**	30.80 \pm 11.31**	70.74 \pm 13.11* [§]
Perirhinal	2.50 \pm 0.50	40.91 \pm 12.26**	39.61 \pm 12.84**	69.77 \pm 8.86* [§]
Entorhinal	1.21 \pm 0.68	63.13 \pm 21.45*	57.13 \pm 16.34*	80.56 \pm 23.26
Post. parahipp.	1.58 \pm 0.57	80.27 \pm 18.43	78.48 \pm 18.89*	62.66 \pm 2.70*
Fusiform	2.86 \pm 1.13	83.46 \pm 27.99	76.83 \pm 22.28	90.52 \pm 22.75
Inf. temporal	6.33 \pm 1.26	60.74 \pm 20.33**	55.45 \pm 15.84**	81.07 \pm 20.32
Mid. temporal	8.70 \pm 1.48	63.52 \pm 20.84**	60.67 \pm 29.67**	78.01 \pm 8.47
Sup. temporal	11.55 \pm 1.93	88.65 \pm 21.95	85.67 \pm 21.46*	81.86 \pm 13.49
Post. temporal	11.24 \pm 3.48	78.68 \pm 37.6	77.79 \pm 40.39	104.10 \pm 14.80
Parietal cortices				
Somatosensory	12.48 \pm 2.37	109.90 \pm 21.20	110.74 \pm 22.20	83.12 \pm 4.91
Sup. lobule	18.48 \pm 3.83	105.83 \pm 21.50	109.73 \pm 20.76	88.22 \pm 8.15
Angular	13.87 \pm 2.61	79.00 \pm 17.38*	78.39 \pm 18.40*	83.94 \pm 7.62
Supramarginal	14.56 \pm 4.09	49.16 \pm 15.57**	48.29 \pm 16.72**	53.32 \pm 2.10*
Occipital cortex				
	87.52 \pm 9.61	77.81 \pm 14.43**	75.34 \pm 13.78	94.54 \pm 16.03
Limbic structures				
Amygdala	1.82 \pm 0.32	59.73 \pm 25.22**	55.95 \pm 24.43**	63.09 \pm 21.41*
Hippocampus	4.90 \pm 1.07	65.59 \pm 17.87**	62.04 \pm 16.74**	71.13 \pm 15.85*
Insula	4.70 \pm 1.15	57.97 \pm 6.66**	56.79 \pm 6.38**	75.24 \pm 6.50*
Ant. cingulate	6.16 \pm 1.09	56.73 \pm 14.84**	57.90 \pm 15.77**	71.81 \pm 12.29*
Post. cingulate	4.89 \pm 1.14	54.14 \pm 15.80**	54.39 \pm 17.16**	86.83 \pm 16.13
White matter				
	258.78 \pm 41.7	69.04 \pm 11.02**	66.81 \pm 10.15**	77.80 \pm 3.80*
Subcortical structures				
Caudate	4.52 \pm 0.95	69.07 \pm 20.56**	65.10 \pm 19.42**	70.99 \pm 7.11*
Putamen	5.31 \pm 1.37	72.07 \pm 11.86**	69.84 \pm 11.06**	84.94 \pm 9.27
Globus pallidus	2.44 \pm 17.7	57.20 \pm 12.41**	55.16 \pm 11.48**	62.99 \pm 12.47**
Thalamus	7.34 \pm 1.2	98.35 \pm 14.38	96.87 \pm 15.08**	90.60 \pm 7.97

Patient data are expressed as a percentage of control mean for each gender. Values significantly different from controls are marked.

* $p > 0.0001$, < 0.05 after correction for multiple comparisons controls vs. patient group.** $p < 0.0001$ after correction for multiple comparisons controls vs. patient group.[§] $p < 0.05$ after correction for multiple comparisons SD vs. FTD–MND groups.

$p < 0.02$). The key comparison of SD and FTD–MND found only two regions to be significantly more atrophic in SD. These were the temporal pole (69% loss in SD versus 29% loss in FTD/MND, $F_{\text{diagnosis}} = 48.7$, $p < 0.0001$, post hoc $p = 0.001$) and PRC (60% loss in SD versus 30% loss in FTD/MND, $F_{\text{diagnosis}} = 48.6$, $p < 0.0001$, post hoc $p = 0.0039$).

3.5. Patterns of atrophy: relationship to SD duration

A principal components (factor) analysis identified three major factors. Factor 1 (Eigenvalue = 4.4) accounted for 40% of the variance and incorporated many of the most severely atrophic cortical regions. Atrophy of the temporal pole (0.88), PRC (0.74), inferior temporal (0.83), supramarginal (0.72) and posterior cingulate (0.74) cortices and globus pallidus

(0.76) was marked and showed significant inter-dependence. The second factor (Eigenvalue = 2.6) accounted for 24% of the variance and was the only factor related to SD duration. It identified a relationship between atrophy of ERC (0.79) and SD duration (0.77). Spearman rank correlation confirmed this finding ($Rho = -0.67$, $p = 0.03$). The third factor (Eigenvalue = 1.7) accounted for 16% of the variance. The only region whose volume identified with this factor was the amygdala (0.86), suggesting that atrophy of the amygdala in SD occurs independently of volume loss elsewhere in the brain.

4. Discussion

The findings of this study strongly support the view that the anterior temporal lobe plays a key role in semantic

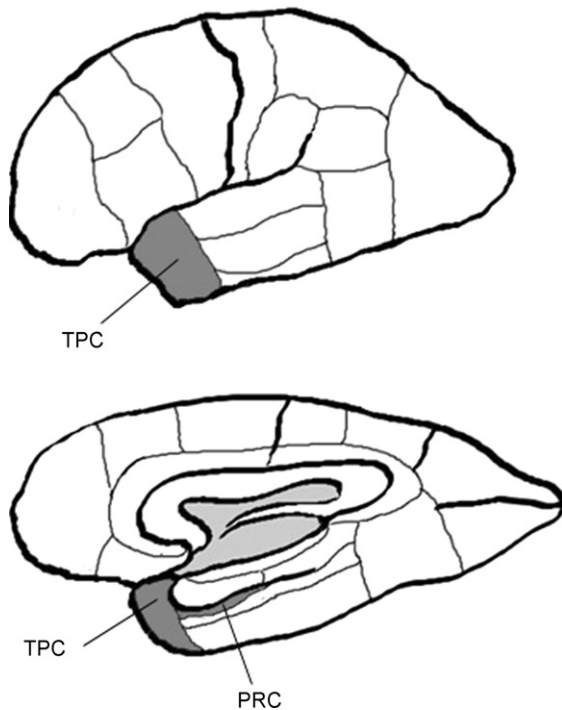


Fig. 2. Schematic lateral and medial views of the left cerebral hemisphere. The lines show the boundaries of the measured regions are shown. The intraventricular surfaces are shaded in light grey. The temporal pole and perirhinal cortex along the banks of the collateral sulcus are shaded in dark grey—being the regions that showed greatest atrophy in semantic dementia (40% of mean control volumes) and the only regions to show significantly greater atrophy in semantic dementia than in frontotemporal dementia with motor neuron disease.

processing. This is the first report of manual segmentation of the entire brain in SD, and the first quantitative data from a series of post mortem confirmed SD cases. Regions showing greatest atrophy were the temporal pole and PRC (59–65% atrophy, Figs. 1 and 2). Cytoarchitectonic and connective evidence suggests that these two regions are closely related (Saleem and Tanaka, 1996; Suzuki and Amaral, 2003). Indeed, the portion of PRC occupying the anterior collateral sulcus and the adjacent ventromedial aspect of the temporal pole have together been termed ‘total perirhinal cortex’ (Insausti et al., 1998). Furthermore, despite the paucity of studies concentrating on human PRC, it has long been a region of keen interest in experimental psychology (Murray and Richmond, 2001; Squire and Zola, 1996; Zola-Morgan et al., 1989). Recent studies have established that PRC-lesioned primates show profound deficits in higher-level object processing of a kind that may be analogous to human semantic memory (Lee et al., 2005; Murray and Richmond, 2001).

In keeping with the use of ‘temporal variant FTD’ as a synonym of SD, other temporal regions showing significant atrophy included amygdala, hippocampus, ERC and the cortices of the inferior and middle temporal gyri. Atrophy of the superior temporal and the posterior parahippocampal cortex, however, was significant only when the case with patho-

logical AD was excluded from the analyses. The remaining limbic and paralimbic regions also showed significant atrophy, namely cingulate cortex (anterior and posterior) and insula. By contrast, frontal lobe regions, with the exception of the frontal pole, were largely unaffected. The parietal language-associated areas, the angular gyrus and, in particular, the supramarginal gyrus, showed marked atrophy. Other parietal and posterior temporal regions were relatively well preserved.

The extensive loss of white matter volume, at 31%, was surprising in the context of conventional understanding that FTD is a disease of grey matter, with white matter degeneration only occurring as a consequence of loss of fibres following neuronal death. Increasingly, however, white matter abnormalities are recognized in FTD (Krill et al., 2005). An additional factor that may be relevant is age-difference across the groups: mean control age was 59 years while mean age for the SD cases was 68 years. Although previous studies have shown that increasing age, over the age range of the cases here, has only a slight effect on grey matter volumes, the effect on white matter volume may be considerable (Double et al., 1996a; Ge et al., 2002; Guttmann et al., 1998). Arguing against this as a primary explanation, however, is the significant loss of white matter volume in the FTD–MND patients, whose mean age was 55 years.

Another novel finding for SD, although recognized in the wider spectrum of FTD was the marked atrophy of the basal ganglia, most severe in the globus pallidus (Broe et al., 2003). The significant volume loss in occipital cortex was more surprising and at odds with the observation of cellular preservation of occipital cortex in SD (Davies et al., 2005). Although associative visual agnosia forms part of the clinical syndrome of SD, visuo-perceptual processing is generally intact in all forms of FTD, especially the more rudimentary visual functions in which the occipital lobe is implicated. Presumably, the finding is a reflection of widespread atrophy in advanced neurodegeneration. It seems unlikely to simply be an artefact of segmentation: while other cortical regions were defined with reference to gyral patterns and deep brain structures, occipital cortex was unique in having an intrinsic marker, the stria of Genari.

The first notable negative finding in the main SD versus controls analyses was that removal of the single case with AD pathology produced little difference to the regional results, affirming that clinical syndrome is determined by the distribution of brain volume loss, irrespective of the nature of the pathology.

The lack of consistent asymmetry to the atrophy, given previous *in vivo* MRI findings, was also somewhat surprising. Although the left cerebral hemisphere was smaller in five of the seven SD cases, one case had equal hemispheric volumes bilaterally and the right hemisphere was smaller in another. Clinically, atrophy may be strikingly asymmetric at presentation, with the left hemisphere usually more involved than the right (Thompson et al., 2003). Formal measurement, how-

ever, has typically found severe bilateral, though asymmetric, volume loss in affected regions (Davies et al., 2004; Galton et al., 2001a; Thompson et al., 2003). Our results, based on end-stage cases, suggest that the less severely affected hemisphere ‘catches up’ as the disease progresses.

Two specific regions, previously reported to show volume loss in SD, did not show significant atrophy in this data-set. These were orbitofrontal cortex and fusiform cortex. The orbitofrontal cortex is recognized as a site of atrophy in the behavioural variant of FTD (Rankin et al., 2004) and functional imaging also implicates the adjacent ventro-lateral prefrontal cortex in semantic processing (Thompson-Schill, 2003). More recently, a correlational VBM study in FTD patients found orbitofrontal volume was correlated not with behavioural disturbance but rather with semantic performance (Williams et al., 2005). Differences in segmentation may account for the apparently conflicting results. The demarcation of orbital cortex from underlying white matter and the grey matter of the basal forebrain on *post mortem* specimens is unarguable, however, these boundaries may be less clear on MRI. Previous reports of orbitofrontal atrophy in SD may not relate specifically to loss of cortical tissue.

Several imaging studies have found particular atrophy of the fusiform gyrus in SD and, also, that semantic deficits correlate with fusiform atrophy (Galton et al., 2001b). The lack of fusiform atrophy reported here must therefore be addressed. Part of the explanation rests in nomenclature. Our use of the term PRC stems from the idea that it forms a meaningful cytoarchitectonic and functional unit, however, PRC occupies part of the anterior fusiform gyrus (Insausti et al., 1998). It is likely that previous reports of fusiform atrophy in SD relate to its anterior portion. By contrast, more posterior medial temporal regions are relatively spared.

The introduction of the FTD–MND group for comparison gave a rare opportunity to quantify brain structures in cases with differing cognitive deficits caused by the same type of neurodegenerative pathology. Despite the logistical challenges, the clinical and pathological heterogeneity of FTD may form a starting point for future studies of a similar nature. Several regions showed atrophy in both syndromes, including frontal pole, supramarginal gyrus, occipital cortex, white matter, caudate, globus pallidus and most of the limbic regions, suggesting that these regions are unlikely to be critical to the semantic breakdown seen in SD.

The differences between SD and FTD–MND, however, were striking and focused on a small number of specific regions, in contrast to the wide-ranging anatomical differences between the SD cases and the normal controls. Thus, the sole cortical region to show atrophy relative to controls in FTD–MND, and not to show atrophy in SD was, reassuringly, motor cortex. Finally, direct comparison of FTD–MND and SD found significant regional differences only in the temporal pole and PRC. These regions showed atrophy compared with controls in both SD and FTD–MND, suggesting they are vulnerable in all instances of FTD. However, both regions were

significantly more atrophic in SD than FTD–MND (60% versus 30% atrophy, Fig. 2), strongly supportive of the view they have a key role in semantic processing.

The third facet to the experiment was the factor analysis. The first factor, responsible for 40% of the variance in the data was related to the many of the most severely atrophic regions, which we might speculate form a semantic network that underwent atrophy in parallel (involving in particular the temporal pole, PRC, inferior temporal cortex and supramarginal gyrus). The second factor, accounting for 24% of the variance, was related to disease duration unlike factor 1. This implies that the temporal pole, PRC and other ‘factor 1’ regions have already undergone considerable atrophy by the time the first symptoms of SD emerge. The only region whose atrophy correlated with factor 2 was ERC. The ERC may thus form part of a second wave of regional atrophy occurring during the period of overt clinical progression.

The third factor correlated only with atrophy of the amygdala and represented 16% of the total variance. Damage to the amygdala has been invoked as an explanation of behavioural disturbance in FTD. The fact that atrophy of the amygdala seems to occur independently of atrophy in other (possibly ‘semantic’) regions would be consistent with the observation that behavioural disturbance occurs in some but not all SD patients, seemingly unrelated to the severity of the semantic impairment. This, however, is at best a partial explanation as the two SD patients noted to show behavioural disturbance at presentation were, in fact, those in whom the amygdala showed least atrophy. Of course, the more relevant information, unfortunately unavailable, would be the severity of behavioural disturbance in the ante mortem period.

In conclusion, whole brain regional assessment in post mortem specimens from patients presenting with SD found widespread bilateral atrophy. The recurring theme, however, was the dominant atrophy of the anterior temporal lobe (temporal pole and PRC) in SD. These regions showed the greatest proportional atrophy of all the regions in which significant volume loss was detected in the overall analysis. They were also the only two regions in which atrophy was significantly greater in SD brains than in pathological FTD specimens in whom semantic impairment had not been present. Furthermore, their atrophy was highly correlated with the strongest factor in the principal components analysis undertaken to identify themes in the SD volume data-set as a whole. Previous reports of PRC atrophy in SD have measured brain regions selectively, while this study made no prior assumptions about which regions would show atrophy. The findings add significantly to the evidence of atrophy of temporal pole and PRC in SD and further implicate these regions in semantic memory function.

Conflict of interest

We declare that there are no conflicts of interest concerning financial, personal or other issues.

Acknowledgements

R.R.D. was funded the Wellcome Trust (Clinical Training Fellowship) and the Sackler Foundation. G.M.H. and J.J.K. are in receipt of a project grant from the National Health and Medical Research Council of Australia. J.R.H. holds an UK Medical Research Council programme grant. We thank Angela O'Sullivan and Kate Dawson for their work in supporting the patients.

References

- Bozeat, S., Lambon Ralph, M.A., Patterson, K., Garrard, P., Hodges, J.R., 2000. Non-verbal semantic impairment in semantic dementia. *Neuropsychologia* 38, 1207–1215.
- Broe, M., Hodges, J.R., Schofield, E., Kersaitis, C., Shepherd, C.E., Kril, J.J., GM, H., 2003. Staging disease severity in pathologically confirmed cases of frontotemporal dementia. *Neurology* 60 (6), 1005–1011.
- Chan, D., Fox, N.C., Scihill, R.I., Crum, W.R., Whitwell, J.L., Leschziner, G., 2001. Patterns of temporal lobe atrophy in semantic dementia and Alzheimer's disease. *Ann. Neurol.* 49, 433–442.
- Cordato, N.J., Halliday, G.M., Harding, A.J., Hely, M.A., Morris, J.G., 2000. Regional brain atrophy in progressive supranuclear palsy and Lewy body disease. *Ann. Neurol.* 47, 718–728.
- Damasio, H., 1995. *Human Brain Anatomy in Computerized Images*. Oxford University Press, New York.
- Davies, R., Graham, K.S., Xuereb, J.H., Williams, G.B., Hodges, J.R., 2004. The human perirhinal cortex and semantic memory. *Eur. J. Neurosci.* 20 (9), 2441–2446.
- Davies, R.R., Hodges, J.R., Kril, J., Patterson, K., Halliday, G., Xuereb, J., 2005. The pathological basis of semantic dementia. *Brain* 128 (9), 1984–1995.
- DeCarli, C., Murphy, D.G., Gillette, J.A., Haxby, J.V., Teichberg, D., Schapiro, M.B., Horwitz, B., 1994. Lack of age-related differences in temporal lobe volume of very healthy adults. *AJNR: Am. J. Neuroradiol.* 15, 689–696.
- Double, K.L., Halliday, G.M., Kril, J.J., Cullen, K., Brooks, W.S., Creasey, H., Broe, G.A., 1996a. Topography of brain atrophy during normal aging and Alzheimer's disease. *Neurobiol. Aging* 17, 513–521.
- Double, K.L., Halliday, G.M., McRitchie, D.A., Reid, W.G., Hely, M.A., Morris, J.G., 1996b. Regional brain atrophy in idiopathic Parkinson's disease and diffuse Lewy body disease. *Dementia* 7, 304–313.
- Galton, C.J., Gomez-Anson, B., Antoun, N., Scheltens, P., Patterson, K., Graves, M., Sahakian, B.J., Hodges, J.R., 2001a. The temporal lobe rating scale: application to Alzheimer's disease and Frontotemporal dementia. *J. Neurol. Neurosurg. Psychiatry* 70, 165–173.
- Galton, C.J., Patterson, K., Graham, K.S., Lambon-Ralph, M., Williams, G., Antoun, N., Sahakian, B.J., Hodges, J.R., 2001b. Differing patterns of temporal atrophy in Alzheimer's disease and semantic dementia. *Neurology* 57, 216–225.
- Ge, Y., Grossman, R.I., Babb, J.S., Rabin, M.L., Mannon, L.J., Kolson, D.L., 2002. Age-related total gray matter and white matter changes in normal adult brain. Part I: volumetric MR imaging analysis. *AJNR: Am. J. Neuroradiol.* 23, 1327–1333.
- Good, C.D., Scihill, R.I., Fox, N.C., Ashburner, J., Friston, K.J., Chan, D., Crum, W.R., Rossor, M.N., Frackowiak, R.S., 2002. Automatic differentiation of anatomical patterns in the human brain: validation with studies of degenerative dementias. *Neuroimage* 17, 29–46.
- Guttmann, C.R., Jolesz, F.A., Kikinis, R., Killiany, R.J., Moss, M.B., Sandor, T., Albert, M.S., 1998. White matter changes with normal aging. *Neurology* 50, 972–978.
- Halliday, G.M., Double, K.L., Macdonald, V., Kril, J.J., 2003. Identifying severely atrophic cortical subregions in Alzheimer's disease. *Neurobiol. Aging* 24, 797–806.
- Halliday, G.M., McRitchie, D.A., Macdonald, V., Double, K.L., Trent, R.J., McCusker, E., 1998. Regional specificity of brain atrophy in Huntington's disease. *Exp. Neurol.* 154, 663–672.
- Harasty, J., Halliday, G.M., Kril, J.J., 1996a. Reproducible sampling regimen for specific cortical regions—application to speech associated areas. *J. Neurosci. Methods* 67, 43–51.
- Harasty, J.A., Halliday, G.M., Code, C., Brooks, W.S., 1996b. Quantification of cortical atrophy in a case of progressive fluent aphasia. *Brain* 119, 181–190.
- Harasty, J.A., Halliday, G.M., Kril, J.J., Code, C., 1999. Specific temporoparietal gyral atrophy reflects the pattern of language dissolution in Alzheimer's disease. *Brain* 122, 675–686.
- Hodges, J.R., Davies, R., Xuereb, J., Casey, B., Broe, M., Bak, T., Kril, J., Halliday, G., 2004. Clinicopathological correlates in frontotemporal dementia. *Ann. Neurol.* 56 (3), 399–406.
- Hodges, J.R., Davies, R., Xuereb, J., Kril, J., Halliday, G., 2003. Survival in frontotemporal dementia. *Neurology* 61, 349–354.
- Hodges, J.R., Patterson, K., 1996. Non-fluent progressive aphasia and semantic dementia: a comparative neuropsychological study. *J. Int. Neuropsychol. Soc.* 2, 511–524.
- Hodges, J.R., Patterson, K., Oxbury, S., Funnell, E., 1992. Semantic dementia: progressive fluent aphasia with temporal lobe atrophy. *Brain* 115, 1783–1806.
- Hodges, J.R., Patterson, K., Ward, R., Garrard, P., Bak, T., Perry, R., Gregory, C., 1999. The differentiation of semantic dementia and frontal lobe dementia (temporal and frontal variants of frontotemporal dementia) from early Alzheimer's disease: a comparative neuropsychological study. *Neuropsychology* 13, 31–40.
- Insausti, R., Juottonen, K., Soininen, H., Insausti, A.M., Partanen, K., Vainio, P., Laakso, M.P., Pitkanen, A., 1998. MR volumetric analysis of the human entorhinal, perirhinal, and temporopolar cortices. *Am. J. Neuroradiol.* 19, 659–671.
- Jackson, M., Lennox, G., Lowe, J., 1996. Motor neurone disease: inclusion dementia. *Neurodegeneration* 5, 339–350.
- Kril, J.J., Halliday, G.M., Svoboda, M.D., Cartwright, H., 1997. The cerebral cortex is damaged in chronic alcoholics. *Neuroscience* 79, 983–998.
- Kril, J.J., Macdonald, V., Patel, S., Png, F., Halliday, G.M., 2005. Distribution of brain atrophy in behavioral variant frontotemporal dementia. *J. Neurol. Sci.* 232, 83–90.
- Lee, A.C.H., Bussey, T.J., Murray, E.A., Saksida, L.M., Epstein, R., Kapur, N., Hodges, J.R., Graham, K.S., 2005. Perceptual deficits in amnesia: challenging the medial temporal lobe 'mnemonic' view. *Neuropsychologia* 43, 1–11.
- Lomen-Hoerth, C., Anderson, T., Miller, B., 2002. The overlap of amyotrophic lateral sclerosis and frontotemporal dementia. *Neurology* 59, 1077–1079.
- Lomen-Hoerth, C., Murphy, J., Langmore, S., Kramer, J.H., Olney, R.K., Miller, B., 2003. Are amyotrophic lateral sclerosis patients cognitively normal? *Neurology* 60, 1094–1097.
- Mai, J.K., Assheuer, J., Paxinos, G., 1997. *Atlas of the Human Brain*. Academic Press, San Diego.
- McKhann, G.M., Albert, M.S., Grossman, M., Miller, B., Dickson, D., Trojanowski, J.Q., 2001. Clinical and pathological diagnosis of frontotemporal dementia: report of the Working Group on Frontotemporal Dementia and Pick's Disease. *Arch. Neurol.* 58, 1803–1809.
- Morris, J.C., 1993. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology* 43, 2412–2414.
- Mueller, E.A., Moore, M.M., Kerr, D.C., Sexton, G., Camicioli, R.M., Howieson, D.B., Quinn, J.F., Kaye, J.A., 1998. Brain volume preserved in healthy elderly through the eleventh decade. *Neurology* 51, 1555–1562.
- Mummery, C.J., Patterson, K., Price, C.J., Ashburner, J., Frackowiak, R.S.J., Hodges, J.R., 2000. A voxel based morphometry study of semantic

- dementia: the relationship between temporal lobe atrophy and semantic dementia. *Ann. Neurol.* 47, 36–45.
- Mummery, C.J., Patterson, K., Wise, R.J.S., Vandenberghe, R., Price, C.J., Hodges, J.R., 1999. Disrupted temporal lobe connections in semantic dementia. *Brain* 122, 61–73.
- Murray, E.A., Richmond, B.J., 2001. Role of perirhinal cortex in object perception, memory, and associations. *Curr. Opin. Neurobiol.* 11, 188–193.
- Neary, D., Snowden, J.S., Gustafson, L., Passant, U., Stuss, D., Black, S., Freedman, M., Kertesz, A., Robert, P.H., Albert, M., Boone, K., Miller, B.L., Cummings, J., Benson, D.F., 1998. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology* 51, 1546–1554.
- Neary, D., Snowden, J.S., Mann, D.M.A., Northen, B., Goulding, P.J., Macdermott, N., 1990. Frontal lobe dementia and motor neuron disease. *J. Neurol. Neurosurg. Psychiatry* 53, 23–32.
- Rakowicz, Z., Hodges, J.R., 1998. Dementia and aphasia in motor neuron disease: an under recognised association. *J. Neurol. Neurosurg. Psychiatry* 65, 881–889.
- Rankin, K.P., Rosen, H.J., Kramer, J.H., Schauer, G.F., Weiner, M.W., Schuff, N., Miller, B.L., 2004. Right and left medial orbitofrontal volumes show an opposite relationship to agreeableness in FTD. *Dement. Geriatr. Cogn. Disord.* 17 (4), 328–332.
- Saleem, K.S., Tanaka, K., 1996. Divergent projections from the anterior inferotemporal area TE to the perirhinal and entorhinal cortices in the macaque monkey. *J. Neurosci.* 16, 4757–4775.
- Snowden, J.S., Goulding, P.J., Neary, D., 1989. Semantic dementia: a form of circumscribed cerebral atrophy. *Behav. Neurol.* 2, 167–182.
- Squire, L.R., Zola, S.M., 1996. Structure and function of declarative and nondeclarative memory systems. *Proc. Natl. Acad. Sci. U.S.A.* 93, 13515–13522.
- Suzuki, W.A., Amaral, D.G., 1994. Topographic organization of the reciprocal connections between the monkey entorhinal cortex and the perirhinal and parahippocampal cortices. *J. Neurosci.* 14, 1856–1877.
- Suzuki, W.A., Amaral, D.G., 2003. Where are the perirhinal and parahippocampal cortices? A historical overview of the nomenclature and boundaries applied to the primate medial temporal lobe. *Neuroscience* 120, 893–906.
- Thompson-Schill, S.L., 2003. Neuroimaging studies of semantic memory: inferring “how” from “where”. *Neuropsychologia* 41, 280–292.
- Thompson, S.A., Graham, K.S., Williams, G., Patterson, K., Kapur, N., Hodges, J.R., 2004. Dissociating person-specific from general semantic knowledge: roles of the left and right temporal lobes. *Neuropsychologia* 42, 359–370.
- Thompson, S.A., Patterson, K., Hodges, J.R., 2003. Left/right asymmetry of atrophy in semantic dementia: behavioural cognitive implications. *Neurology* 61, 1196–1203.
- Williams, G.B., Nestor, P.J., Hodges, J.R., 2005. The neural correlates of semantic and behavioural deficits in frontotemporal dementia. *NeuroImage* 24, 1042–1051.
- Zola-Morgan, S., Squire, L.R., Amaral, D.G., Suzuki, W.A., 1989. Lesions of perirhinal and parahippocampal cortex that spare the amygdala and hippocampal formation produce severe memory impairment. *J. Neurosci.* 9, 4355–4370.