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The clinical profile of right temporal lobe atrophy

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Frontotemporal lobar degeneration is currently associated with three syndromic variants. Disorders of speech and language figure prominently in two of the three variants, and are associated with left-sided frontotemporal atrophy. The detailed characterization of these syndromes contrasts with the relative paucity of information relating to frontotemporal lobar degeneration primarily affecting the right cerebral hemisphere. The objective of this study was to identify the clinical profile associated with asymmetrical, predominantly right-sided, temporal lobe atrophy. Twenty patients with predominant right temporal lobe atrophy were identified on the basis of blinded visual assessment of the MRI scans. The severity of right temporal lobe atrophy was quantified using volumetric analysis of the whole temporal lobes, the amygdala and the hippocampus. Profiles of cognitive function, behavioural and personality changes were obtained on each patient. The pattern of atrophy and the clinical features were compared with those observed in a group of patients with semantic dementia and predominant left-sided temporal lobe atrophy. The mean right temporal lobe volume in the right temporal lobe atrophy group was reduced by 37%, with the mean left temporal lobe volume reduced by 19%. There was marked atrophy of the right hippocampus and right amygdala, with mean volumes reduced by 41 and 51%, respectively (left hippocampus and amygdala volumes were reduced by 18 and 33%, respectively). The most prominent cognitive deficits were impairment of episodic memory and getting lost. Prosopagnosia was a symptom in right temporal lobe atrophy patients. These patients also exhibited a variety of behavioural symptoms including social disinhibition, depression and aggressive behaviour. Nearly all behavioural disorders were more prevalent in the right temporal lobe atrophy patient group than the semantic dementia group. Symptoms particular to the right temporal lobe atrophy patient group included hyper-religiosity, visual hallucinations and cross-modal sensory experiences. The combination of clinical features associated with predominant right temporal lobe atrophy differs significantly from those associated with the other syndromes associated with focal degeneration of the frontal and temporal lobes and it is, therefore, proposed that this right temporal variant should be considered a separate syndromic variant of frontotemporal lobar degeneration.

Keywords: dementia; frontotemporal lobar degeneration; frontotemporal dementia; right temporal lobe

Abbreviations: DRC = Dementia Research Centre; FTLD = frontotemporal lobar degeneration; NHNN = National Hospital for Neurology and Neurosurgery; RTLA = right temporal lobe atrophy; VUMC = VU University Medical Centre

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Introduction

Focal degeneration of the frontal and temporal lobes is associated with distinct clinical syndromes characterized by dysexecutive syndrome, memory impairment, disorders of speech and language and changes in behaviour. Guidelines for the diagnosis of the three prototypical syndromic variants of frontotemporal lobar degeneration (FTLD) have been outlined by Neary *et al*. (1998). In two of the three variants the predominant deficit involves speech or language, and in these instances there is asymmetrical, primarily left-sided, frontotemporal atrophy, consistent with the lateralization of verbal skills to the left hemisphere. The progressive nonfluent aphasia variant is associated with atrophy of the left perisylvian region (Mesulam, 2001), whereas in the semantic dementia variant the anterior and medial portions of the left temporal lobe are particularly affected (Chan *et al*., 2001; Galton *et al*., 2001).

The extensive clinical and anatomical characterization of the syndromes associated with left-sided frontotemporal atrophy contrasts with the paucity of information concerning focal atrophy of the right temporal lobe. Clinical data relating to right temporal lobe atrophy exist primarily in the form of individual case reports, typically involving patients presenting with prosopagnosia in whom right frontotemporal damage was demonstrated on structural or functional imaging (Tyrrell *et al*., 1990; Evans *et al*., 1995; Gainotti *et al*., 2003). Five patients with right-sided FTLD were described by Edwards-Lee and colleagues (1997) as part of a study of 'temporal variant' frontotemporal dementia. In this study, the five cases of right temporal variant frontotemporal dementia were characterized by aggressivity, impulsivity, behavioural disinhibition and, in some cases, hyper-religiosity. Subsequent studies by the same investigators have shown that patients with right-sided frontotemporal dementia also exhibit loss of empathy and diminution of interpersonal skills (Perry *et al*., 2001). To date, the most extensive study of 'right temporal variant' frontotemporal dementia is that conducted by Thompson *et al*. (2003), in which the most prominent symptoms documented were difficulty in recognizing faces, loss of insight, changes in affect and abnormal social conduct.

Although, the number of published cases with focal right temporal lobe atrophy is relatively limited, several studies have been able to establish an association between damage to the right frontal and temporal regions and disorders of behaviour, using a variety of techniques including volumetric MRI analysis, voxel-based morphometry and SPECT functional imaging to identify right-sided damage in patients with FTLD (Rosen *et al*., 2002, 2005; Mendez *et al*., 2006). In these studies a variety of symptoms were noted, including disinhibition, obsessive–compulsive behaviour and depression, and it has been suggested that there is a deficit of emotional processing underlying these behavioural disturbances, resulting from disruption to a neuronal circuit within the right hemisphere which includes the orbitofrontal cortex, the anterior temporal cortex and the amygdala (Rosen *et al*., 2002).

The relative under-reporting of patients with selective right temporal lobe atrophy is likely to reflect the nature of the clinical features associated with right temporal lobe damage. The disorders of speech and language associated with focal left frontotemporal damage are clearly identifiable as neurological deficits, which in turn facilitate early investigation and diagnosis. Conversely, the relative preservation of speech and language functions, and the relative preponderance of behavioural disorders, in right-sided frontotemporal damage may detract from early recognition and diagnosis of the condition as a neurological disorder. Under-recognition of symptoms relating to right hemisphere pathology has been noted in studies of patients presenting with left and right hemisphere strokes, resulting in significant delays in the provision of stroke interventional therapies to the latter patient group. In this instance the discrepancy is attributed to the involvement of language and dominant hand function in left hemisphere strokes, as well as to the presence of neglect and loss of awareness of symptoms in patients with right hemisphere strokes (Foerch *et al*., 2005).

This study aimed to establish the clinical correlates of right temporal lobe pathology by identifying a group of patients in whom right temporal lobe atrophy was the predominant feature on visual inspection of MRI scans. Volumetric measurements of the whole temporal lobe, hippocampus and amygdala in the right temporal lobe atrophy patient group were compared with those obtained in a group of age-matched, cognitively normal, control subjects in order to quantify the severity of the right-sided temporal atrophy. Following the process of patient identification, the associated clinical features were detailed by retrospective analysis of the case notes and available neuropsychological test data. Finally, identification of the clinical profile associated with right temporal lobe atrophy was facilitated by comparison of the clinical features with those present in patients with semantic dementia and associated predominant left temporal lobe atrophy.

Methods

Clinical data on right temporal lobe atrophy (RTLA) patients were acquired from the Dementia Research Centre (DRC), The National Hospital for Neurology and Neurosurgery (NHNN), London, UK and from the Alzheimer Centre, VU University Medical Centre (VUMC), Amsterdam, The Netherlands. Fifteen patients with RTLA were identified at the DRC by unbiased visual inspection of scans acquired on 1800 subjects initially by an experienced rater (D.C.), blinded to all clinical details. These 1800 scans represent a database held by the Dementia Research Centre and consist of volumetric MRI scans acquired on patients referred to the Specialist Cognitive Disorders Clinic, as well as scans acquired on cognitively intact control subjects. Clinical diagnoses in this patient group encompassed a number of different neurodegenerative disorders including Alzheimer's disease and frontotemporal lobar degeneration.

Five additional RTLA patients were identified at the VUMC. These patients were derived from a group of 36 subjects with temporal lobe atrophy as the predominant finding on unbiased visual inspection of MRI scans (F.B.) taken from 525 consecutive subjects that had been referred to the Alzheimer Centre, VUMC.

All MRI data were analysed at the DRC. MRI sections in the coronal plane through the entire anteroposterior extent of the frontal and temporal lobes were displayed on a Sun workstation (Sun Microsystems, Mountain View, California, USA) and confirmation of the presence of RTLA was made on visual inspection by two further

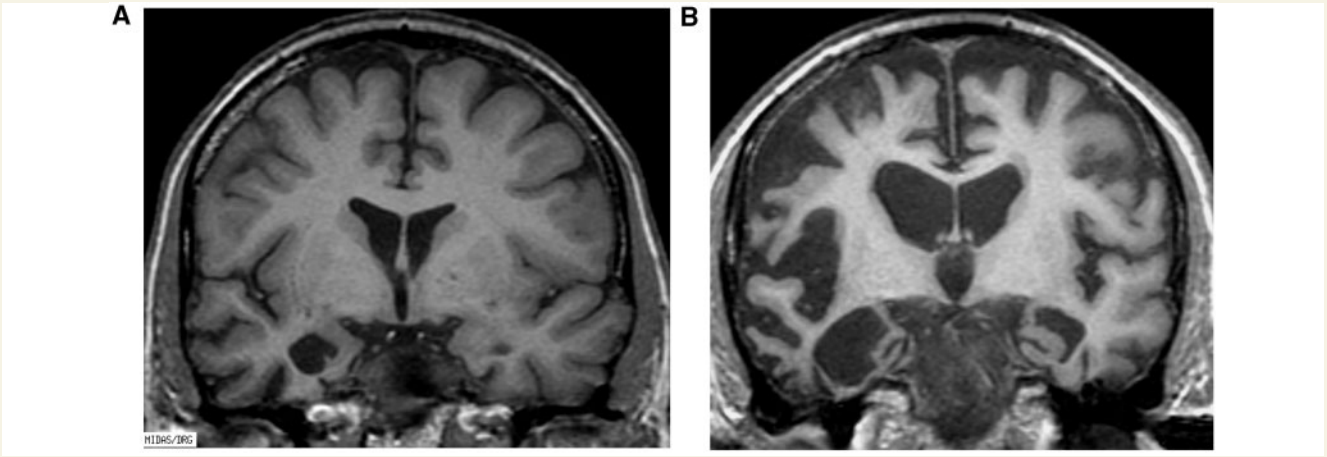

Figure 1 Right temporal lobe atrophy. (**A**) Mild atrophy, with particular involvement of the inferomedial temporal lobe. (**B**) Severe atrophy, with bilateral, asymmetrical, temporal lobe atrophy affecting primarily the right temporal lobe structures.

observers (N.C.F. and J.M.S.), again blinded to patient name, diagnosis and clinical details. Subjects were included in the study only if both observers agreed on the presence of RTLA. For the purposes of this study, RTLA encompassed cases in which atrophy appeared confined to the right temporal lobe, as well as those instances in which there was asymmetrical, predominantly right-sided, temporal lobe atrophy. This definition excluded those cases in which there was bilateral, symmetrical, temporal lobe atrophy as well as those with bilateral, but predominantly left-sided, temporal lobe atrophy.

Volumetric MRI and neuropsychological data on the comparison groups of ten control subjects and ten semantic dementia patients have been documented in a previous publication (Chan *et al*., 2001).

Volumetric MRI analysis

Volumetric MRI on all DRC patients was obtained using a 1.5T MRI scanner (General Electric, Milwaukee, Wisconsin, USA). Scans included a sagittal T_1-weighted scout sequence and an axial dual-echo sequence (T_2-weighted and proton-density weighted). Volumetric imaging in the coronal plane was achieved using a spoiled gradient echo technique with a 24 cm field of view and 256×128 matrix to provide 124 contiguous 1.5 mm slices. Scan acquisition parameters were: TR = 3500 ms, TE = 5 ms, NEX = 1, FLIP angle 35°. VUMC scans were performed on a 1.0 T MRI scanner. Sections included coronal 3D T_1-weighted GE, axial turbo-FLAIR, axial T_2 weighted and coronal heavily T_2-weighted turbo-SE sequences.

The MIDAS image analysis tools (Freeborough *et al*., 1997) were used for brain region segmentation. These include manual editing tools that allow simultaneous multiplanar display and editing, such that sagittal sections through a region may be viewed while outlining that region in the coronal plane. Regions were outlined using a mouse-driven cursor. Editing appears in real time in all planes to improve measurement reproducibility. All measurements were performed by raters blinded to the clinical diagnosis. The MRI scan of each individual was presented twice in random order, once conventionally and once flipped across a plane parallel to the mid-sagittal plane, in order to ensure blinding to structure laterality; structures were outlined on the right of each scan image as seen on the computer screen. All measurements were normalized to the total intracranial volume, to compensate for inter-individual differences in head size (Whitwell *et al*., 2001), and all volumes are therefore expressed as fractions of the total intracranial volume.

The whole temporal lobe, amygdala and hippocampus were measured on each subject, as described by Chan *et al*. (2001).

Statistical analysis

SPSS Version 8.0 (SPSS, Chicago, IL) was used for statistical calculations. *T*-tests were employed to determine the significance of mean differences between the RTLA, semantic dementiaand control groups.

Results

Patient details

The RTLA group comprised thirteen men and seven women, mean age 61.9 years [standard deviation (SD) 7.3; range 52–85]. All RTLA patients were right-handed. The mean duration of illness by the time of initial assessment was 4.1 years (SD 2.0; range 2–10). The mean Mini Mental State Examination Score (Folstein *et al*., 1975) at time of initial assessment was 22.7 (SD 5.3; range 10–30) (Table 1).

Six out of the twenty RTLA patients had a positive family history of dementia affecting at least one first degree family member. In two of these patients there was a strong likelihood of familial FTLD, although pathogenic mutations have not been identified in either instance. In one case, several of the affected family members carried a clinical diagnosis of FTLD whereas in the other case six family members had dementia characterized by prominent behavioural disturbances.

Neuropathological data were available in two of the 20 cases described in this study, both on postmortem examination of brain tissue. In one patient the final diagnosis was of FTLD associated with ubiquitin-positive, tau-negative inclusion bodies and in the other patient the histological diagnosis was mixed Alzheimer and cortical Lewy body disease.

Table 1 Demographic data and Mini-Mental State Examination (MMSE) scores for the RTLA patient group

Patient characteristics	
Men/Women	13/7
Handedness	20 right: 0 left
Age	
Mean (SD), years	61.9 (7.3)
Range, years	52–85
Illness duration	
Mean (SD), years	4.1 (2.0)
Range, years	2–10
MMSE	
Mean (SD)	22.7 (5.3)
Range	10–30

Data are taken from the time of initial patient assessment.

The healthy control group comprised four men and six women, mean age 59.7 years (SD 6.3). The semantic dementia group consisted of six men and four women, of mean age 63.2 years (SD 5.9). There were no significant differences in age between the three study groups (RTLA versuss controls, $P = 0.45$; RTLA versus semantic dementia, $P = 0.45$).

Clinical case reports

A selection of case reports are presented below. In all cases, the descriptions of the MRI appearances represent the blinded visual assessments by experienced neuroradiologists (J.M.S. for NHNN patients, F.B. for VUMC patients). The results of EEG and formal neuropsychological testing, both performed within four months of the initial assessment, are documented.

Case 1: Patient DRC4

DRC4 was a right-handed housewife who was initially referred aged 55 years. She presented 3 years earlier with progressive word-finding difficulty and within months several abnormalities of behaviour were observed. Her husband commented that she had become 'childlike' and was frequently inappropriate in social situations. She became obsessed with the possibility that strangers were mistaking her for a daytime TV chat show host. Despite washing her hands repeatedly her personal hygiene deteriorated. She became excessively fond of the colours silver and gold, to the point where all her light switches at home had to be repainted in these colours. She lost interest in her previous hobbies and listened repeatedly to the same small selection of popular classical music pieces. One year after the onset of symptoms she had difficulty recognizing the faces of famous actors and other well-known personalities.

There was no past medical history of note. Her father had previously been diagnosed with cognitive impairment related to chronic alcoholism. Neurological examination was normal. The EEG revealed absent alpha rhythm with excess slow wave activity posteriorly. The initial MRI showed bilateral temporal lobe atrophy, markedly more severe on the right side, but no frontal lobe atrophy and no atrophy of posterior cortical regions.

Case 2: Patient DRC5

DRC5 was a right-handed electronics engineer who was initially referred aged 57 years. There was a 3-year history of impairment of memory for appointments and other day-to-day events, difficulty in recognizing faces and getting lost when driving on familiar routes. Over 2 years, there was an additional history of personality change, exemplified by fiscal extravagance, social disinhibition, irascibility and aggressivity. He also developed a preference for sweet foods and experienced a sudden loss of libido. Subsequently he began to exhibit some obsessional behaviour, in particular excessive cleaning behaviour. There was no past medical history of note. His mother was diagnosed as having Alzheimer's disease in her late 60s and died aged 90 years. Neurological examination was normal. The EEG showed preserved alpha rhythm with widespread excesses of theta and additional focal epileptiform discharges arising from the left frontotemporal region. The initial MRI was reported as showing asymmetrical cerebral atrophy with increased prominence of the right perisylvian fissure in conjunction with atrophy of the right amygdala and mild atrophy of the right hippocampus. Postmortem examination of the brain provided a pathological diagnosis of mixed Alzheimer and cortical Lewy body disease.

Case 3: VUMC1

VUMC1 was a right-handed widow aged 64 years at the time of initial assessment. Her problems began 10 years earlier when she began to complain of atypical headaches. At this time her behaviour changed; she would behave inappropriately in social situations, often making rude comments about strangers. Having previously been a tolerant person she began to make racist remarks. She developed a fixed daily routine and became obsessive about her health. She became emotionally 'flat'. Motor restlessness alternated with periods of apathy and depression. Her level of personal hygiene deteriorated. She felt that she was being watched by her neighbours. Subsequently she developed a tendency to speak using frequently repeated stereotyped sentences but despite this continued to play language games without difficulty. Her memory for events gradually deteriorated and she had difficulty in recognizing family members with some additional problems recognizing objects. She got lost in familiar places within the city where she had always lived. She lost the ability to perform financial administrative tasks. There was a strong family history of dementia associated with prominent behavioural problems, involving a brother, four aunts (all sisters of her mother) and a daughter of one of these aunts. The family declined to undergo genetic counselling and testing. General neurological examination was normal. The MRI scan showed asymmetrical temporal lobe atrophy. The right temporal lobe was markedly atrophic, with mild involvement of the left temporal lobe and basal frontal areas. Additionally, there were confluent ischaemic vascular white matter lesions, located predominantly in the parietal regions but with additional lesions in the frontal lobes.

Case 4: Patient VUMC2

VUMC2 was a right-handed man aged 85 years when he presented with a 4-year history of impairment of face recognition and

subsequent slowly progressive impairment of episodic memory. He also demonstrated difficulties with topographical orientation in unfamiliar environments. He lost interest in previous hobbies but played dice-based and language-based games. He became increasingly voluble and ate to excess, although no change in food preference was noted. He became increasingly self-centred and demonstrated a lack of empathy, leaving his spouse during an illness. He became obsessed with eating times and exhibited a degree of motor restlessness.

His medical history included narcolepsy, hypertension, emphysema, and glaucoma. There was no family history of note. Neurological examination was normal.

The MRI scan revealed end stage right temporal lobe atrophy, with prominent but still advanced left sided temporal lobe atrophy. There was additional mild frontal cortical atrophy. There was an anteroposterior gradient of hippocampal atrophy, with volume loss being most prominent anteriorly. The EEG showed a normal background rhythm.

Summary of clinical features

Eighteen out of the 20 (90%) RTLA patients exhibited impairment of episodic memory; in seven cases (35%) memory impairment was the initial symptom. 'Getting lost' was a problem observed in 13 patients (65%). Prosopagnosia was a symptom reported in 12 cases (60%) and was the presenting symptom in four patients (20%). Disorders of speech and language were observed in seven cases (35%).

Disinhibition of social conduct was the most frequently described 'behavioural' symptom, being present in 13 cases (65%). In three patients disinhibited behaviour was the initial complaint (15%). Ten patients (50%) exhibited obsessional behaviour, with behavioural rigidity—typically with respect to daily routine—noted in seven cases (35%). Depression was a prominent feature in nine patients (45%) and aggressive behaviour was present in eight patients (40%). Apathy was a prominent feature in seven patients (35%).

Alteration of eating habits was noted in over half of the cases; eight patients (40%) developed a change in food preference at some stage during their illness, always in favour of sweet foods. In addition, symptoms of hyperorality were present in four patients (20%). Loss of libido was a feature in six cases (30%). Although, sexually inappropriate comments were noted as part of the behavioural disinhibition in a number of patients, none of the RTLA patients experienced an increase in libido.

In seven patients (35%), there was a marked somatic element to the presentation; all complained of atypical chronic pains for which no clear underlying disorder could be identified.

Several additional symptoms were noted in a minority of cases; hyper-religiosity was a prominent feature of the presentation in three patients (15%). Two patients (10%) experienced complex visual hallucinations of animate objects and two patients (10%) described unusual 'cross-modal' experiences in response to various sensory stimuli, in that the subjective experience of these stimuli by these patients involved a different sensory modality.

Formal neuropsychological testing

All patients underwent formal neuropsychological testing as part of their routine clinical assessment. As a consequence there was variability in the tests applied, with additional differences in test protocol between the DRC and VUMC sites. The neuropsychological data obtained from the 15 patients seen at the DRC are summarized in Table 2 and the data from the five VUMC patients are provided in Table 3. Two patients (DRC14 and VUMC5) had severe cognitive and behavioural problems by the time of diagnosis and were largely unable to comply with formal testing.

A comparison with the clinical features of semantic dementia

The prevalence of the various neurological and neuropsychiatric symptoms in the RTLA and semantic dementia patient groups is summarized in Table 2. In addition to the impairment of word comprehension that represents a core symptom of semantic dementia (and present in all semantic dementia patients), 90% of semantic dementia patients also presented with impairment of episodic memory. In contrast to the RTLA cases, none of the semantic dementia patients had problems getting lost and

Table 2 A summary of the clinical features associated with the RTLA and semantic dementia patient group

	RTLA (percent affected)	SD (percent affected)
Cognitive functions		
Episodic memory	90	90
Topographical disorientation	65	0
Prosopagnosia	60	10
Problems with naming	35	100
Problems with calculation	5	10
Problems with spelling	10	0
Behaviour		
Apathy	35	20
Disinhibition	65	30
Obsessional behaviour	50	40
Behavioural rigidity	35	60
Loss of insight	15	0
Loss of empathy	25	20
Aggression	40	30
Personality		
Hyper-religiosity	15	0
Loss of libido	30	10
Decline in personal care	30	30
Mood		
Depression	45	30
Somatization disorder	30	0
Eating habits		
Over-eating	20	30
Altered food preference	40	40
Other		
Visual hallucinations	10	0
Abnormal perception of sensory stimuli	15	0

Table 3 Summary of neuropsychological test results for DRC patients

	DRC1	DRC2	DRC3	DRC4	DRC5	DRC6	DRC7	DRC8	DRC9	DRC10	DRC11	DRC12	DRC13	DRC14	DRC15
MMSE	28	30	23	22	25		25	16		25	22	30	12	24	30
VIQ	84	112	64	73	97	85	91	91	73	NT	92	101	65	61	90
PIQ	72	117	60	70	92	80	99	NT	Unable	NT	83	107	77	Refused	83
Recognition															
Memory[a]				NT						NT					
Words (long)	<5%	<50%			<1%										<1%
Faces (long)	<1%	<5%			<1%										<1%
Words (short)			12/25			19/25	16/25	21/25	14/25		20/25	25/25	22/25	Refused	
Faces (short)			11/25			23/25	15/25	20/25	11/25		NT	25/25	20/25	Refused	
Face recognition	NT	NT	NT		NT			NT		NT		NT	NT		
Famous faces				3/12			1/15		0/15		2/15				0/15
Naming skills			Imp	NT	Normal		Imp	Imp	No score	NT	Normal	Normal	Imp		
GNT	<25%	>75%				<5%									<1%
Visuoperceptual skills				NT	NT		NT			NT			NT	NT	NT
Object decision	Imp	20/20	0/20			19/20		0/20	0/20		15/20	19/20			
Fragmented letters															
Silhouettes															
Visuospatial skills															
Cube analysis	Imp			NT	NT		NT			NT		NT	NT		
Dot counting		20/20	0/10			8/10		10/10	3/10		10/10			10/10	
Frontal lobe function			NT	NT	NT					NT					
Weigl	Fail	Pass				Fail	Pass	Fail	Fail		Pass	Pass	Fail	Fail	Pass
Wisconsin	Fail														

a Warrington Recognition Memory Tests.
VIQ = verbal IQ; PIQ = performance IQ; GNT = Graded Naming Test; NT = not tested; imp = impaired performance.

Table 4 Summary of neuropsychological test results for VUMC patients

	VUMC1	VUMC2	VUMC3	VUMC4	VUMC5
MMSE	28	25	21	19	26
Recognition memory	Visual association test:[a] Learning visual associations: weak; Recognition visual associations: preserved; RMT[b] faces: impaired (<1%)	Visual association test:[a] Impaired; RBMT story recall: Impaired encoding; CAMCOG address: preserved	Several tests impaired	Visual association test[a] impaired; CAMCOG address: impaired	NT
Face recognition	Benton face recognition: impaired	NT	NT	NT	NT
Naming skills	Naming animals: preserved	Naming animals: grossly impaired	Grossly impaired	Naming animals: impaired	NT
Visuoperceptual skills	Hooper visual organization test: impaired	Naming animals: impaired recognition	Object recognition impaired; impaired clock watching	Naming animals: impaired recognition	NT
Visuospatial skills	Copying, clock drawing: preserved	Copying: preserved	Preserved copying and construction of 3D figures	Copying: preserved	NT
Frontal lobe function	Trailmaking, Stroop: impaired	Trailmaking, BADS: preserved	Trailmaking: impaired; Proverbs: impaired (concreteness of thought); Labyrinths: preserved	Trailmaking: impaired	NT

a Visual Association Test of Lindeboom *et al*. (2002).
b Warrington Recognition Memory Test.
NT = not tested.

disinhibition of behaviour was reported in only three of these patients (30%). Loss of insight was not a symptom documented for any of the semantic dementia patients. With one exception, all of the various neuropsychiatric symptoms were more frequently reported in the RTLA patient group, the exception being behavioural rigidity, which was present in 60% of the semantic dementia patients (noted in 35% of the RTLA patients). Hyper-religiosity, abnormal sensory experiences and visual hallucinations were not documented in the semantic dementia patient group.

Formal neuropsychological testing

All patients underwent formal neuropsychological testing as part of their routine clinical assessment. As a consequence there was a variability in the tests applied, with additional differences in test protocol between the DRC and VUMC sites. The neuropsychological data obtained from the fifteen patients seen at the DRC are summarized in Table 3 and the data from the five VUMC patients are provided in Table 4. Two patients (DRC14 and VUMC5) had severe cognitive and behavioural problems by the time of diagnosis and were largely unable to comply with formal testing.

Quantitative MRI analysis

Volumetric analysis revealed differences between control and RTLA groups for all measured structures. In the RTLA patients, there was evidence of asymmetry with greater right-sided atrophy of temporal lobe structures for all temporal lobe regions ($P < 0.001$), and in all cases the discrepancy between right- and left-sided temporal lobe volumes exceeded 10%, emphasizing the radiological uniformity of the RTLA patient group. The whole brain and regional temporal lobe volumes (temporal lobe, hippocampus and amygdalae), measured in the three patient groups, are presented in Fig. 2(A–D). The regional volume measurements are summarized in Table 5. All measurements are corrected for total intracranial volume.

Discussion

The most common symptoms associated with RTLA were impairment of episodic memory, getting lost and behavioural disturbance. Prosopagnosia was a symptom reported by 60% of RTLA patients. Depression and aggressive behaviour were features of the presentation in 45 and 40% of patients, respectively.

One of the most striking observations made in this study was the frequency with which disorders of behaviour represented the initial symptoms, predating in nine patients (45%) the occurrence of the cognitive deficits which prompted referral for neurological opinion. In six out of these nine cases the initial reported problem was associated with a change in personality, with patients developing inappropriate or aggressive behaviour. It is, however, important to note that the battery of neuropsychological tests applied to this patient cohort did not encompass assessments of visuospatial function or processing of emotional material; given the role of the right hemisphere in visuospatial functions (Vallar, 1997) and emotional processing (Rosen *et al*., 2002; Tranel *et al*., 2002), the possibility remains that deficits in these domains may precede abnormalities of behaviour. Future prospective studies of this patient group will need to include such assessments in order to address this outstanding issue.

In addition to the right temporal lobe atrophy, a number of the study patients had a degree of frontal lobe atrophy and left

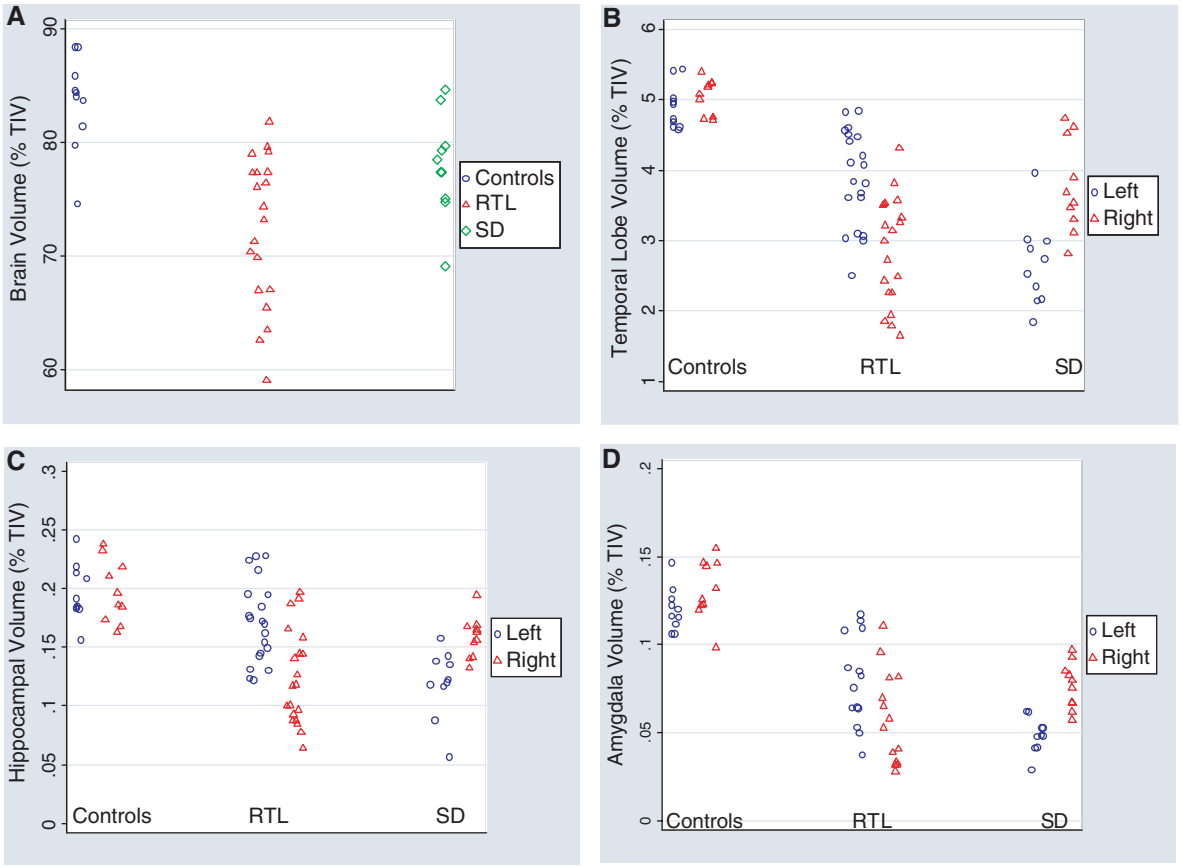

Figure 2 Regional brain volumes (expressed as percentage of total intracranial volume) for the three study groups. (**A**) Brain Volume (% TIV); (**B**) Temporal lobe volume (% TIV); (**C**) Hippocampal volume (% TIV) and (**D**) Amygdala volume (% TIV). RTL, right temporal lobe atrophy patients; SD, semantic dementia patients.

temporal lobe atrophy on visual inspection of the MRI scans. However, at present there is no agreed protocol for obtaining volumetric data in order to quantify frontal lobe atrophy and as a consequence, the potential contribution of frontal lobe pathology to the clinical presentation cannot be easily established. In view of this, it is important to note that the symptoms reported in this patient group are representative of asymmetrical, predominantly right-sided, frontotemporal lobe atrophy and not necessarily of atrophy restricted to the right temporal lobe.

In order to compensate in part for this difficulty, comparison was made between the clinical features apparent in the RTLA patient group and those observed in patients with semantic dementia, in whom the atrophy was predominantly left-sided but with some additional frontal lobe atrophy. The majority (65%) of the RTLA patients described problems getting lost, whereas this symptom was not reported by any of the semantic dementia patients. With the exception of behavioural rigidity (observed in 60% of semantic dementia patients and 35% of RTLA patients), all other neuropsychiatric symptoms were more prevalent in the RTLA patient group. Both patient groups were equally associated with alterations in eating habits; 40% of patients in both groups developed a change of dietary preference in favour of sweet foods and 20% of patients in both groups displayed excessive eating (hyper-orality). Hyper-religiosity, visual hallucinations and abnormal responses to sensory stimuli were symptoms not documented in the semantic dementia patient group.

The majority of case reports of patients with predominant right temporal lobe damage have focused on prosopagnosia as the clinical feature of interest. Tyrrell *et al*. (1990) described a patient who presented with prosopagnosia in addition to memory impairment, difficulty with naming and a visuoperceptual disorder. Evans *et al*. (1995) reported a patient with progressive prosopagnosia who also had problems getting lost, in the context of relative preservation of episodic memory, naming and visuoperceptual function. Gainotti *et al*. (2003) described a patient with a slowly progressive defect in the recognition of familiar people, who presented additionally with symptoms of depression and irritability. The three cases described by Joubert *et al*. (2006) exhibited severe deficits in their ability to recognize, name or provide semantic information on famous individuals, regardless of the mode of presentation of data. However, a detailed report by Gorno-Tempini *et al*. (2004) of a patient with right anterior temporal lobe degeneration draws attention not only to the presence of prosopagnosia but also to marked behavioural changes and atypical semantic disorders.

Table 5 Summary of volumetric MRI analysis. Figures quoted represent the mean values obtained in each patient group (SD in parentheses)

	Control subjects	RTLA subjects	SD subjects	ANOVA	*t*-test RTLA versus CON	*t*-test SD versus CON	*t*-test RTLA versus SD	% RTLA/CON	%SD/CON
Male/Female	4/6	13/7	6/4						
Handedness (r/l)	9/1	20/0	9/1						
	Mean (SD)	Mean (SD)	Mean (SD)						
Age	60 (6)	62 (7)	63 (6)	0.477	0.34	0.21	0.76		
TIV (mm^3)	1 427 396 (1 82 579)	1 433 496 (92 312)	1 368 202 (1 48 237)	0.436	0.90	0.44	0.15		
Whole brain/TIV	83.7 (4.1)	72.37 (6.27)	77.8(4.5)	<0.001	<0.001	0.007	0.021	86.5	93.0
L amygdala/TIV	0.121 (0.013)	0.078 (0.025)	0.050(0.011)	<0.001	<0.001	<0.001	0.003	64.2	40.9
R amygdala/TIV	0.132 (0.017)	0.059 (0.027)	0.076(0.013)	<0.001	<0.001	<0.001	0.079	44.6	57.4
L hippocampus/TIV	0.19 (0.02)	0.17 (0.034)	0.12(0.03)	<0.001	0.078	<0.001	<0.001	88.7	63.2
R hippocampus/TIV	0.20 (0.03)	0.12 (0.04)	0.16(0.02)	<0.001	<0.001	0.001	0.014	62.7	80.7
L temporal lobe/TIV	4.90 (0.31)	3.89 (0.69)	2.67(0.61)	<0.001	<0.001	<0.001	<0.001	79.4	54.5
R temporal lobe/TIV	5.03 (0.22)	2.88 (0.78)	3.76(0.63)	<0.001	<0.001	<0.001	0.004	57.3	74.8
Difference between left and right									
	CON	RTLA	SD						
Amygdala	0.034	<0.001	<0.001						
Hippocampus	0.144	<0.001	0.004						
Temporal Lobe	0.135	<0.001	0.003						

All measurement values are expressed as percentages of the total intracranial volume (TIV). L = left; R = right; RTLA = right temporal lobe atrophy; SD = semantic dementia; CON = control; %RTLA/CON = mean RTLA volume as fraction of mean control volume; % SD/CON = mean SD volume as fraction of mean control volume; % RTLA/SD = mean RTLA volume as fraction of mean SD volume.

The behavioural disorders in patients with predominant right temporal lobe atrophy are also emphasized in those studies, which describe a series of patients with predominant right temporal lobe pathology. Five patients with right-sided frontotemporal dementia were described by Edwards-Lee *et al*. (1997). Three of these patients had previously been documented in the paper by Miller *et al*. (1993), although at that time the nature of the temporal lobe involvement had not been fully recognized. These patients were noted to have an unusual affect with additional disinhibition and irritability. Several exhibited obsessional behaviour and features of atypical depression. Additional symptoms of note included alterations in sexual and dietary habit and hyper-religiosity. Prosopagnosia was documented in only one subject.

Eleven patients with predominant right temporal lobe atrophy were described by Thompson *et al*. (2003). A retrospective review of the case notes of these patients identified an increased prevalence of behavioural disorders, disturbances of social conduct and loss of insight when compared with cases with predominant left temporal lobe atrophy. A high proportion (91%) of their 'right temporal variant' frontotemporal dementia patients presented with prosopagnosia (60% in our study) whereas only 18% of patients demonstrated difficulties with navigation (65% in our study).

Our study differs from these previous studies in one key respect, in that the presence of right temporal lobe atrophy on MRI, determined independently of any pre-existing knowledge of clinical features or presumptive clinical diagnosis, was the sole criterion for patient selection. By contrast, the patients described by Tyrrell *et al*. (1990), Evans *et al*. (1995) and Gainotti *et al*. (2003) were selected on the basis of their progressive prosopagnosia; damage to the right temporal lobe was detailed at a subsequent stage. The patients with 'right temporal variant frontotemporal dementia' described by Edwards-Lee *et al*. (1997) were initially identified on clinical grounds, with right-sided temporal lobe damage subsequently demonstrated on SPECT scanning. Similarly, the 'right temporal variant' frontotemporal dementia patients documented by Thompson *et al*. (2003) were selected on clinical presentation, and were subsequently segregated from left temporal variant frontotemporal dementia following review of the MRI scans.

The core symptoms of right temporal lobe atrophy

'Getting lost'

After impairment of episodic memory, the most frequently reported neurological problem involved 'getting lost', affecting 65% of RTLA patients. The importance of this symptom within the clinical profile of RTLA is underscored by its absence in the comparison group of patients with semantic dementia associated with predominant left temporal lobe atrophy, as well as previous observations that patients with 'prototypical frontotemporal dementia' are less likely to get lost in familiar surroundings than patients with Alzheimer's disease or vascular dementia.

The symptom of 'getting lost' may arise as a consequence of disorders affecting a number of different cognitive processes, each in turn implicating different brain regions, ranging from the posterior parietal cortex through to the medial temporal lobe (Aguirre and D'Esposito, 1999). In this study, it is postulated that it may represent a disorder of right medial temporal lobe function, with the right hippocampus being centrally involved. The relative preservation of posterior cortical regions would argue against this symptom being a manifestation of a visuospatial disorder or a form of visual agnosia such as landmark agnosia.

Patients with hippocampal damage exhibit disproportionately severe spatial memory deficits (Henke *et al*., 1999; Holdstock *et al*., 2000), in keeping with the cognitive map theory of hippocampal function which is based on observations that the hippocampus in animals is involved in maintaining environmental representations (O'Keefe and Nadel, 1978; Holdstock *et al*., 2000). In humans, evidence that processing of environmental representations is primarily lateralized to the right medial temporal lobe is provided by functional neuroimaging studies which have demonstrated activation of the right hippocampus during recall of routes (Maguire *et al*., 1997) and of the right parahippocampal gyrus during perception of spatial scenes (Epstein and Kanwisher, 1998). Patients who have undergone right temporal lobectomy demonstrate impairment of recall of object location (Pigott and Milner 1993; Bohbot *et al*., 1998), with the severity of impairment in proportion to the extent of right hippocampal damage (Nunn *et al*., 1999).

Prosopagnosia

Impaired face recognition was found in 60% of RTLA patients. This contrasts both with the documentation by Thompson *et al*. (2003) of this symptom in over 90% of their patients with right frontotemporal atrophy, and with the report of impaired face recognition in only one of the five 'right variant' FTLD patients described by Edwards-Lee *et al*. (1997). The results of this study also bears comparison to the various case reports of patients with progressive prosopagnosia who are found on subsequent imaging studies to have selective damage to the right temporal lobe (Gentileschi *et al*., 1999; Gainotti *et al*., 2003).

There are several possible explanations for the discrepancies in the reported association between right temporal pathology and prosopagnosia. First, impaired face recognition may not be cited as a specific problem by the patients and their carers. Mention has already been made of the relative under-reporting of non-verbal symptoms, and this may be compounded by the tendency of patients to conceive of impairment of face recognition as an aspect of 'poor memory' rather than as a separate cognitive disorder. Second, it is possible that clinical interviewers may not question patients and carers specifically about the symptom, in the absence of any tendered information suggestive of this disorder. Finally, it may be that the occurrence of prosopagnosia is dependent upon the pathological involvement of a region (or regions) within the right temporal lobe that is specifically involved in the identification of familiar faces. Accordingly, damage to this subregion would be necessary and sufficient to result in prosopagnosia, and one possible explanation is that this region is spared in the RTLA patients of this study and in those described by Edwards-Lee

et al. (1997), in whom prosopagnosia was not apparent. With respect to the region(s) in question, the anterior portion of the right temporal lobe has been implicated in the attribution of semantic meaning to face identification in order to generate the component of familiarity (Gainotti *et al*., 2003). However, other studies have suggested that the critical region may lie more posteriorly within the cortex, with the right fusiform gyrus involved, in particular (Joubert *et al*., 2003). Further detailed imaging studies focusing on the distribution of damage within the right temporal lobe in patients with and without prosopagnosia will be required.

Behavioural disorders

Various abnormalities of behaviour were identified which included behavioural disinihibition, apathy, obsessional behaviour, behavioural rigidity, loss of insight, loss of empathy and aggressive behaviour. With the exception of behavioural rigidity, all of these symptoms were more frequently observed in this group than in the comparison semantic dementia patient group.

This difference in the prevalence of behavioural disorders in patients with predominant right- and left-sided temporal lobe atrophy is consistent with previous studies suggesting that certain behaviours, especially those associated with emotional processing, are lateralized to the right hemisphere and in particular the right frontal and temporal lobe regions (Rosen *et al*., 2005).

Additional symptoms associated with RTLA

Analysis of the case notes of the RTLA patients uncovered a number of additional and phenomenologically distinct symptoms in a minority of cases. Although the prevalence of these additional symptoms is comparatively low, the absence of similar symptoms in the semantic dementia patient group and the unusual nature of these symptoms warrants brief discussion.

Two out of 20 RTLA patients (10%) experienced visual hallucinations. The fearful aspect of the hallucinations recounted by the RTLA patients, involving visions of snakes and headless figures, contrasts with the typically undisturbing hallucinations associated with Lewy body dementia. The anterior distribution of cortical pathology in the RTLA cases also contrasts with the predominantly posterior distribution of cortical damage associated with Lewy body dementia.

Hyper-religiosity was a symptom reported by 15% of RTLA patients. Only one of the three affected RTLA patients exhibited one of the other symptoms of Geschwind syndrome (the behavioural triad of hyper-religiosity, hypergraphia and hyposexuality), in this instance hyposexuality. Little at present is known about the anatomical correlates of hyper-religiosity although some information pertaining to possible cerebral lateralization is provided by a study of patients with refractory epilepsy which observed that smaller volumes of the right hippocampus were associated with an increase in religious behaviour (Wuerfel *et al*., 2004).

A number of RTLA patients exhibited abnormal responses to somatic and other sensory stimuli. Three patients complained of persistent pains that remained undiagnosed despite extensive investigations. Although it is possible that these symptoms may represent a form of somatization disorder, it is worth noting that only one of the three patients exhibited other features of depression, and that all three patients exhibited obsessional behaviour. One possible explanation is that the chronic pains described by these patients represent an inappropriately heightened emotional awareness of minor, and undiagnosed, somatic complaints, magnified by concomitant obsessional behaviour. In this context, similarities exist between these patients and a report by Gabbay *et al*. (2003) of a patient with acquired damage to the frontotemporal region who developed a body dysmorphic disorder manifest as a morbid preoccupation with a perceived cosmetic defect. Furthermore, a retrospective study of 450 patients who have undergone temporal lobe epilepsy surgery revealed that somatoform disorders were significantly more common following right, rather than left, temporal lobectomy (Naga *et al*., 2004).

A different form of abnormal response to sensory stimuli was also observed in two RTLA patients. Patient DRC3 saw the entire visual scene as coloured red, except when walking. Patient DRC7 derived pleasure from loud noises and from certain smells. The experiences of these two patients echoes those documented by Edwards-Lee *et al*. (1997) in one of their patients with right temporal variant frontotemporal dementia; this patient reported that sounds and colours reverberated painfully in his head. In contrast with the patients with undiagnosed somatic complaints, the experiential nature of these symptoms appears cross-modal in nature, although the descriptions differ from that of true synaesthesiae.

Conclusion

Asymmetrical, predominantly right-sided, frontotemporal atrophy is associated with a clinical profile in which memory impairment of episodic memory and the symptom of 'getting lost' are frequently combined with disorders of behaviour, with prosopagnosia reported in 60% of patients. The early occurrence of behavioural symptoms, allied with the relative sparing of speech and language functions, may result in under-reporting and misdiagnosis of this condition. Although the clinical presentation of RTLA is heterogeneous, overall the symptom complex differs sufficiently from the currently recognized syndromic variants of frontotemporal lobar degeneration to warrant acknowledgement of RTLA as a separate clinical subtype of FTLD.

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