

The temporal variant of frontotemporal dementia

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Summary

Frontotemporal dementia is a dementia syndrome with diverse clinical characteristics. Based upon clinical parameters and single photon emission computed tomography, we identified 47 frontotemporal dementia subjects. In 10 of these 47 the primary site of brain dysfunction was anterior temporal and orbital-frontal with other frontal regions relatively spared. In this temporal lobe variant (TLV) of frontotemporal dementia, five of the subjects had more severe left-sided, and five had more right-sided, hypoperfusion. The clinical, neuropsychological and neuropsychiatric features of predominantly left-sided (LTLV) and right-sided (RTLTV) TLV subjects are discussed and contrasted with more frontal presentations of frontotemporal dementia. In LTLV, aphasia was usually the first and most severe clinical abnormality. RTLTV patients presented with behavi-

oural disorders characterized by irritability, impulsiveness, bizarre alterations in dress, limited and fixed ideas, decreased facial expression and increased visual alertness. These findings suggest that: (i) frontotemporal dementia is clinically heterogeneous with bitemporal and inferior frontal lobe dysfunction contributing to the clinical presentation; (ii) behavioural disturbance and aphasia are the most prominent features of predominantly temporal subtypes of frontotemporal dementia; (iii) the right and left anterior temporal regions may mediate different behavioural functions. The results of this study suggests that TLV offers a valuable source of information concerning the behavioural disorders seen with combined anterior temporal and inferior frontal lobe dysfunction.

Keywords: temporal lobe variant; frontotemporal dementia

Abbreviations: FSIQ = Full Scale IQ; HMPAO = ^{99m}Tc-hexamethyl-propyleneamineoxime; LTLV = predominantly left-sided TLV; MMSE = Mini-Mental Status Examination; PIQ = Performance IQ; rCBF = regional cerebral blood flow; RTLTV = predominantly right-sided TLV; SPECT = single photon emission computed tomography; TLV = temporal lobe variant of frontotemporal dementia; VIQ = Verbal IQ; WCST = Wisconsin Card Sorting Test

Introduction

The temporal lobe variant (TLV) of frontotemporal dementia

Frontotemporal dementia represents a heterogeneous group of disorders with variable clinical and pathological manifestations (Miller *et al.*, 1991; Brun, 1993; Mitsuyama, 1993; Neary *et al.*, 1993; Frisoni *et al.*, 1995). Names coined for progressive dementia with bilateral degeneration of frontotemporal cortex include Pick's disease (Pick, 1892), progressive subcortical gliosis (Neumann and Cohn, 1967), frontal dementia of the non-Alzheimer type (Brun, 1987), dementia of the frontal type (Neary *et al.*, 1988), dementia lacking distinctive histology (Knopman *et al.*, 1990), Pick-complex disorder (Kertesz *et al.*, 1994), and disinhibition-

dementia-parkinsonism-amyotrophy syndrome (Lynch *et al.*, 1994). Recently, research criteria for this entity were established by the Lund-Manchester groups who coined the term 'frontotemporal dementia' (Brun *et al.*, 1994).

Another group of patients who may be a subtype of frontotemporal dementia are those who show unilateral frontal or temporal degeneration. Mesulam (1982) called attention to the left-sided variant of frontotemporal dementia when he described patients with progressive aphasia, 'without global dementia,' for whom he coined the term 'primary progressive aphasia'. Subsequently, Morris *et al.* (1984) described a familial form of primary progressive aphasia which they named hereditary dysphasic dementia. Many primary

progressive aphasia patients show pathological findings that resemble frontotemporal dementia (Caselli *et al.*, 1993; Neary *et al.*, 1993; Scheltens *et al.*, 1994; Snowden *et al.*, 1996). Primary progressive aphasia is associated with unilateral left cortical degeneration. We described five patients with 'right frontotemporal degeneration' and emphasized the behavioural disorders of these patients (Miller *et al.*, 1993). Although not fully recognized at the time, three of the individuals (whom we describe below) had predominantly temporal lobe involvement. Others have emphasized the behavioural disorders and visuo-perceptive abnormalities of patients with primarily right frontotemporal involvement (Tyrrell *et al.*, 1990; Evans *et al.*, 1995).

It is unknown whether frontotemporal dementia represents a single pathological process with variable clinical and pathological manifestations, or several separate disorders. The most common pathological features of patients with degeneration of anterior frontal or temporal regions are tissue atrophy, spongiosis, neuronal loss and gliosis (Brun, 1987; Knopman *et al.*, 1990). Pick bodies (Pick, 1892) and 'Pick-like bodies' (Chang *et al.*, 1995), are present in a minority of subjects. Some suggest that the presence of Pick-bodies at post-mortem indicates a distinct entity (Brun, 1993), while others argue that all frontotemporal dementia patients represent a single clinical-pathological category, the 'Pick-complex disorder' (Kertesz *et al.*, 1994). In support of the unitary disease hypothesis, recent genetic work has shown linkage to a small region on the short arm of chromosome 17 in patients with highly distinctive pathological variants of frontotemporal dementia; frontotemporal dementia with parkinsonism and motor neuron disease (Wilhelmsen *et al.*, 1994), frontotemporal dementia with progressive subcortical gliosis (Petersen *et al.*, 1995), striato-nigral degeneration (Wilhelmsen *et al.*, 1996) and hereditary dysphasic dementia (J. Morris, personal communication).

Although most of the literature on frontotemporal dementia emphasizes frontal involvement as the cause for clinical symptoms (Neary *et al.*, 1988; Miller *et al.*, 1991; Brun, 1993), frontotemporal dementia represents a clinically heterogeneous group and, in some patients, the sites of most severe degeneration are the temporal lobes (Miller *et al.*, 1993). Just as patients with focal frontal degeneration present a clinical model for understanding the frontal lobes, those with unilateral or bilateral temporal degeneration may be used to study the role of the anterior temporal lobes in cognition and behaviour.

Methods

Clinical overview

Forty-seven clinically diagnosed frontotemporal dementia patients received neurobehavioural, neuropsychological and imaging studies as previously described (Miller *et al.*, 1991). Subjects were seen through the UCLA Alzheimer Disease Center and the protocols were reviewed and approved

by the UCLA Human Subjects Protection Committee, and patients (or relatives) gave informed consent to participation. The Mini-Mental Status Examination (MMSE) (Folstein *et al.*, 1975) quantified severity of dementia and the Neuropsychiatric Inventory (Cummings *et al.*, 1994) rated psychiatric symptoms. All subjects were evaluated with comprehensive bedside mental status testing. Seven subjects were evaluated with the following neuropsychological tests: intelligence, i.e. Full Scale IQ (FSIQ), Verbal IQ (VIQ) and Performance IQ (PIQ) tests; attention Digit Span test; information processing speed (Digit Symbol, Trails A, Stroop A and B tests); language (FAS, Boston Naming); visual perception/construction (Rey-Osterrieth figure copying); verbal memory (shopping list Trial 5 and delayed memory); nonverbal visual memory (Rey-Figure 3-min delay); and executive function, i.e. Wisconsin Card Sort Test Categories (WCST), Stroop C and Trails B tests.

Single photon emission computed tomography (SPECT) imaging was performed with both ^{133}Xe (Kanno *et al.*, 1981) and $^{99\text{m}}\text{Tc}$ -hexamethyl-propyleneamineoxime (HMPAO) (Neirinckx *et al.*, 1987). These frontotemporal dementia patients had prominently frontal or temporal hypoperfusion with sparing of posterior parietal perfusion. Visual rating of SPECT (both ^{133}Xe and HMPAO) was used to classify frontotemporal dementia patients into groups with predominantly temporal or predominantly frontal dysfunction (10 in each group). MRI was used to rate right and left temporal and frontal atrophy.

All frontotemporal dementia patients, including the 10 with TLV, met the research criteria for frontotemporal dementia established by the Lund-Manchester Group (Brun *et al.*, 1994). Using these guidelines our diagnostic accuracy for frontotemporal dementia is high. Of the 47 frontotemporal dementia patients at UCLA, 10 have died subsequent to diagnosis and all showed pathology typical for frontotemporal dementia: frontal gliosis, neuronal loss and vacuolization of tissue; Pick bodies or 'Pick-like bodies' were present in six (Read *et al.*, 1995).

Neuroimaging (SPECT)

SPECT was performed with ^{133}Xe which gave absolute measures of regional cerebral blood flow (rCBF), and HMPAO which provided high resolution qualitative images. Patients were studied awake with eyes open and supine with low ambient light and noise. Following inhalation of 30 mCi (1100 MBq) of ^{133}Xe , rCBF was measured on a brain-dedicated unit (Headtome II, Shimadzu, Kyoto). The three slices acquired simultaneously were reconstructed into transaxial images which showed absolute rCBF. Each patient received 20 mCi (740 MBq) of HMPAO (Ceretek, Amersham, Arlington Heights, Ill., USA) injected intravenously (Neirinckx *et al.*, 1987). Scanning started 2 h after injection. HMPAO acquisitions were finished in 10 min and were followed by two body shifts of 16 mm each to scan the 32 mm of blind interslice space. Nine transaxial brain cuts were acquired in 30 min, covering an extension

of 14.4 cm, without blind regions. Parallel transaxial scans started at the orbitomeatal line.

Classification

SPECT images of 47 frontotemporal dementia patients were rated by two clinicians (T.E.-L. and B.L.M.) who were blind to patient names. A consensus classification of TLV was made in 10 of the frontotemporal dementia patients, based upon visual inspection. TLV patients had asymmetrical bitemporal and orbital-frontal involvement but relative sparing of cingulum, dorsolateral and polar frontal areas. Visual inspection was also used to sort scans into predominantly right or left-sided involvement (RTLTV or LTLV). Thus, while the term TLV is used, all subjects also had orbital-frontal hypoperfusion. Similarly, patients were clinically sorted into RTLTV and LTLV based upon asymmetrical hypoperfusion; all subjects showed bilateral temporal involvement.

Finally, to define the selective effect of temporal lobe dysfunction on behaviour, we compared these 10 TLV subjects with all subjects in our cohort in whom SPECT showed selective frontal hypoperfusion with temporal lobe sparing. Ten such subjects were found in whom the frontal lobes were diffusely involved while the temporal lobes were spared. Five showed predominantly right-sided frontal hypoperfusion, and in the other five it was predominantly left-sided.

Quantification

To strengthen the validity of our visual classification of subjects we compared left and right temporal and frontal perfusion in the 10 TLV subjects. Quantification was achieved by using automatically drawn adjacent regions-of-interest that covered the entire cortex. Regions-of-interest were circular and 1.9 cm in diameter. The lowest slice (orbitomeatal ± 2 cm) was used to quantify temporal lobe perfusion, while the second cut (orbitomeatal ± 6 cm) was used to measure frontal perfusion. The intra-observer coefficient of correlation with this standardized method was found to be 0.97. In the 10 subjects with predominantly frontal frontotemporal dementia, rCBF was also estimated in the frontal and temporal regions by a nurse-clinician (N.K.) blinded to the study hypotheses.

MRI

T₁- and T₂-weighted MRI scans were obtained with a 1.5 Tesla superconducting magnet. MRIs were visually inspected and rated by two clinicians blinded to patient status (G.A.R. and N.K.). Frontal and temporal lobe atrophy were rated on a 0–3 scale (none, mild, moderate and severe). Also, scans were evaluated for the presence of other pathology such as tumour or stroke.

Results

Patient histories: predominantly right temporal TLV

Patient RTLTV 1

A 59-year-old right-handed man made errors in calculations and over 2 years was demoted from an estimator to a handyman and was forced to retire. He wore unmatched shoes or socks, tucked his jacket into his pants, buttoned shirts inside out and put deodorant or shaving lotion in his hair. He waved to pictures on walls. Initially easygoing, he became stubborn and irritable. A religious awakening led him to spend hours in church; he argued with his wife and friends regarding his new religious ideas. He became emotional, cried when people left him and refused to attend his father's funeral. His eating habits changed; he nibbled constantly, repetitively spat, and ate coffee and banana peels.

He was alternately placid and irritable with a remote, bizarre and robot-like affect. MMSE was 22. Digit Span was seven and verbal output fluent. He showed a severe anomia, named only two animals in 1 min but had only mild difficulty with reading and memory. His calculations were poor but he copied drawings well. Head CT showed mild atrophy, most marked in the right temporal lobe. SPECT showed decreased rCBF of the anterior temporal regions, greater on the right than the left. He died 4 years after examination. An autopsy showed asymmetric, primarily right-sided temporal > frontal atrophy with no plaques, neurofibrillary tangles, Pick bodies or Lewy bodies. Neuronal loss and gliosis were noted in the temporal > frontal areas and were worse on the right than the left.

Patient RTLTV 2

A 56-year-old right-handed female was seen for a behavioural disturbance of 3-years duration. Initially she became apathetic and unconcerned with housekeeping. One year later she developed an agitated psychotic depression, accusing her husband of sexual infidelity, certain that he gave her AIDS. She became robot-like and bizarre. Sexually, she was aggressive and disinhibited. When upset she would pace and attempt to hit her husband or whined or manufactured tears to manipulate him. She spent many hours chain-smoking cigarettes and drinking coffee. Her memory deteriorated.

On examination she was agitated, irritable, bizarre and remote. She left the room when she found the conversation unpleasant. MMSE score was 24. Language and comprehension were normal. She had a memory disturbance, mildly impaired drawing ability and could not perform abstractions. FSIQ was within the borderline range (78) with VIQ (85) significantly higher than PIQ (70). Word-retrieval was normal (Boston Naming Test = 50/60) while basic attention was only mildly depressed (Digit Span = 9%). In contrast, information processing speed (Digit Symbol <1st%), constructional skill (Rey-Osterrieth <10; 1st%), learning and memory (shopping list Trial 5 and delayed recall = 1st%;

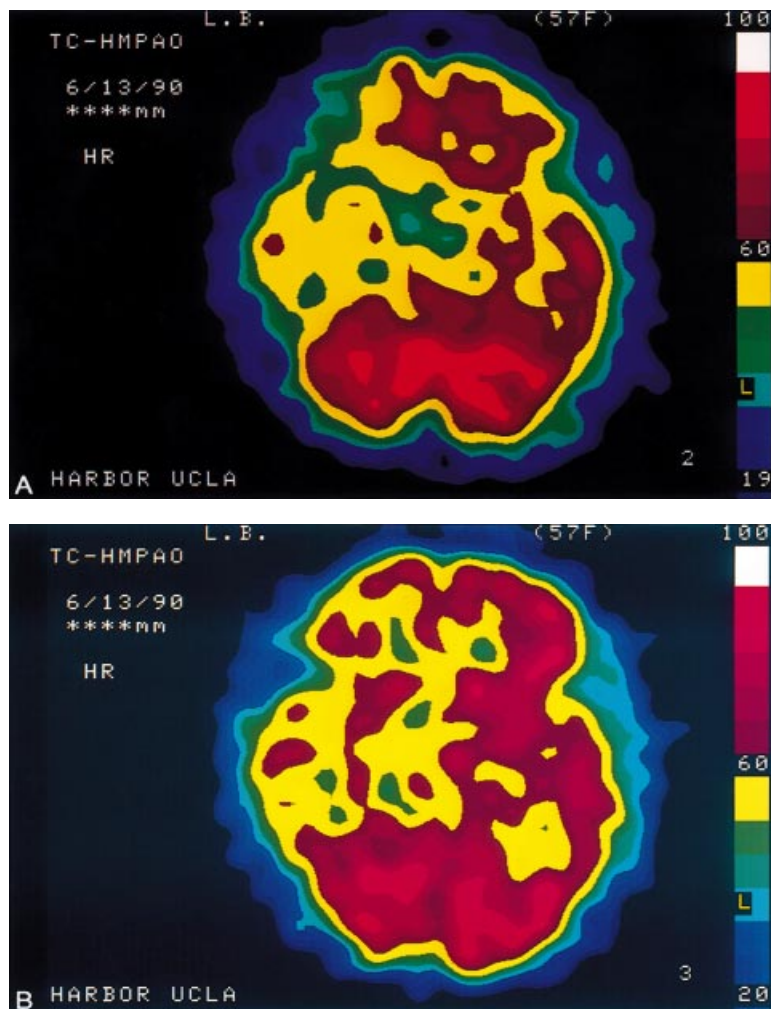


Fig. 1 (A) A transaxial HMPAO SPECT from Patient RTL2 which demonstrates cerebral perfusion in the low temporal/basal frontal areas. The SPECT shows marked right anterior temporal hypoperfusion and mild left anterior temporal hypoperfusion. The colour scale is set so that red changes to yellow at 60% maximum cerebral uptake. (B) A slightly higher HMPAO SPECT from Patient RTL2 which goes through the high temporal lobes and dorsolateral frontal cortex and mid-parietal cortex. It shows marked right anterior temporal hypoperfusion with sparing of the frontal lobes.

Rey–Osterrieth 3-min delayed recall <1st%), and executive skills were impaired (FAS = 25, 1st%; WCST = 1st%; Stroop C = 1st%; Trails B <1st%).

MRI showed right temporal lobe atrophy. HMPAO SPECT showed right anterior temporal lobe hypoperfusion, mild involvement of adjacent parietal lobe and mildly decreased left temporal lobe perfusion (Fig. 1). She eventually entered a nursing-home with advanced dementia.

Patient RTL3

A 66-year-old right-handed female had 2 years of behavioural and cognitive change. Previously social, she withdrew and her religious beliefs heightened. She could not recognize her son's voice on the telephone and developed word-finding

trouble. Driving competency remained normal and she continued to manage family finances and housework.

On examination she was irritable, remote and easily upset. MMSE score was 23. She had mild anomia and a mild decrease in language comprehension. Memory was impaired but drawings and calculations were normal. She did not cooperate for PIQ but VIQ (78) was in the borderline range. Basic attention (Digit Span = 37%) was normal, but learning and memory ranged from low average to borderline (shopping list Trial 5 = 7; , delayed recall = 5; Rey–Osterrieth delay = 14, 25th%). In contrast, information processing speed (Trails A <1st%; Stroop A and B <1st%), word-retrieval (Boston Naming Test = 10, <1st%), and executive skills were severely impaired (FAS <1st%; Stroop C = 200 seconds, 2nd %).

MRI was normal, but SPECT revealed bitemporal

hypoperfusion, worse on the right than the left. Over the next 2 years she became increasingly irritable and remote. Although too uncooperative for testing, she continued to run her household.

Patient RTLV 4

A 68-year-old right-handed retired stock broker was seen for a dementing illness. Thirteen years earlier he became depressed following the death of his wife. He started low protein diets and began seeing a psychologist. He was briefly treated with the drug MDMA (3,4-methylenedioxymethamphetamine) and changes in his language, clothes and behaviour were noted. He described himself as having 'open' or 'closed' periods, wore only lavender clothes, and began pastel painting. During closed periods sounds and colours reverberated painfully in his head. Over the next 10 years his painting skills steadily improved. He continued to manage his stocks successfully.

He became verbally repetitive and had difficulty understanding words. There was mild disinhibition and he changed clothes in public parking lots. Subsequently, he began shoplifting and his family found hoards of pens that he did not purchase. He searched the city for coins, intentionally passing telephone booths, laundromats, cash registers and banks. He took tips from tables in restaurants and was caught stealing from women's purses. He swam nude in public swimming pools and made lewd comments to women. He bumped and berated people on streets and kicked the family dog. He stopped bathing or changing clothes and adhered to faddish diets.

On examination he was remote and uncooperative, but showed heightened interest in his environment commenting extensively on the colours of objects or sounds. MMSE was 15. He had fluent language with mild comprehension difficulty. There was an anomia and he could not recognize animal sounds. Verbal memory was poor on formal tests, although he correctly remembered the day's stock prices. He performed complex additions and drew well. Formal neuropsychological tests revealed overall intellectual level within the mentally retarded range (FSIQ = 69) with PIQ (74) higher than VIQ (67). Information processing speed was normal (Digit Symbol = 37%) while constructional skills were low average (Rey-Osterrieth copy = 31, 16th%). In contrast, executive skills (FAS = 5; Stroop C and Trails B could not be performed), memory (Rey-Osterrieth = 5, 1st%), and word-retrieval (Boston Naming Test = 32, <1st%) were markedly impaired.

MRI showed generalized atrophy with more severe changes in the temporal and parietal lobes. SPECT had bilateral temporal hypoperfusion, worse on the right than the left.

Patient RTLV 5

A 66-year-old right-handed woman was seen for changes in behaviour. At the age of 55 years she unexpectedly divorced

her husband and began a homosexual liaison. By the age of 64 years she had become forgetful and bizarre. She repetitively played solitaire and a game which required finding and circling hidden words. She could not recognize familiar faces or places. At the age of 67 years, while looking in the mirror, she complained of seeing another person and started to think that her son was her husband. By the age of 68 years personal hygiene had deteriorated, she talked to photographs and repeatedly copied simple phrases from books.

On examination she was bizarre and robot-like and talked to herself. She attempted to hit the neurologist and stole the neuropsychologist's pen. She had heightened interest in words and read incessantly. MMSE score was 16. By the age of 70 years she had stopped all word games but continued copying words from books. She was bizarre and robot-like and made a sexual advance to a woman physician. She had a fluent aphasia and followed simple commands but showed no interest in communication. Neuropsychological testing and revealed a VIQ within the mentally retarded range (69) with markedly impaired performances (<1st%) on all other neuropsychological measures attempted. SPECT showed bitemporal hypoperfusion, right greater than left and mild right frontal involvement.

Patient histories: predominantly left temporal TLV

Patient LTLV 1 (left-handed)

A 56-year-old left-handed woman was seen after 9 years of progressive dementia. At the age of 46 years she was demoted from administrative secretary to account clerk. She deposited money incorrectly and forgot co-workers' names. She was irritable, threw bills at employees, shoplifted and embarrassed her family in public. At 51 years a psychologist noted that she had trouble understanding simple words and that her behaviour was 'bizarre and inappropriate.' At the age of 53 rapid, empty paraphasic speech was present. Intellectual testing revealed overall IQ within the borderline range (FSIQ = 75) with PIQ (85) substantially higher than VIQ (67). Basic attention (Digit Span = 37%) and constructional skills (Rey-Osterrieth copy = 63rd%) were normal, while information processing speed (Digit Symbol = 16%; Trails A = 10%; Stroop A and B <1st%) and nonverbal memory (Rey-Osterrieth delayed recall = 18th%). In contrast, executive skills (FAS was <1st%; Stroop C <1st%; Trails B = 7th%), word-retrieval, and verbal learning memory (Shopping List <1st%) were markedly impaired.

By the age of 56 years she initiated incoherent conversation with strangers, lifted her shirt in public and touched strangers' buttocks. Previously vegetarian, she now ate meat. She spent the day copying verbatim from the Bible and successfully played the search and circle word game (Fig. 2) similarly to Patient RTLV 5. Previously learned piano playing was largely preserved.

On examination she was disinhibited, touching the

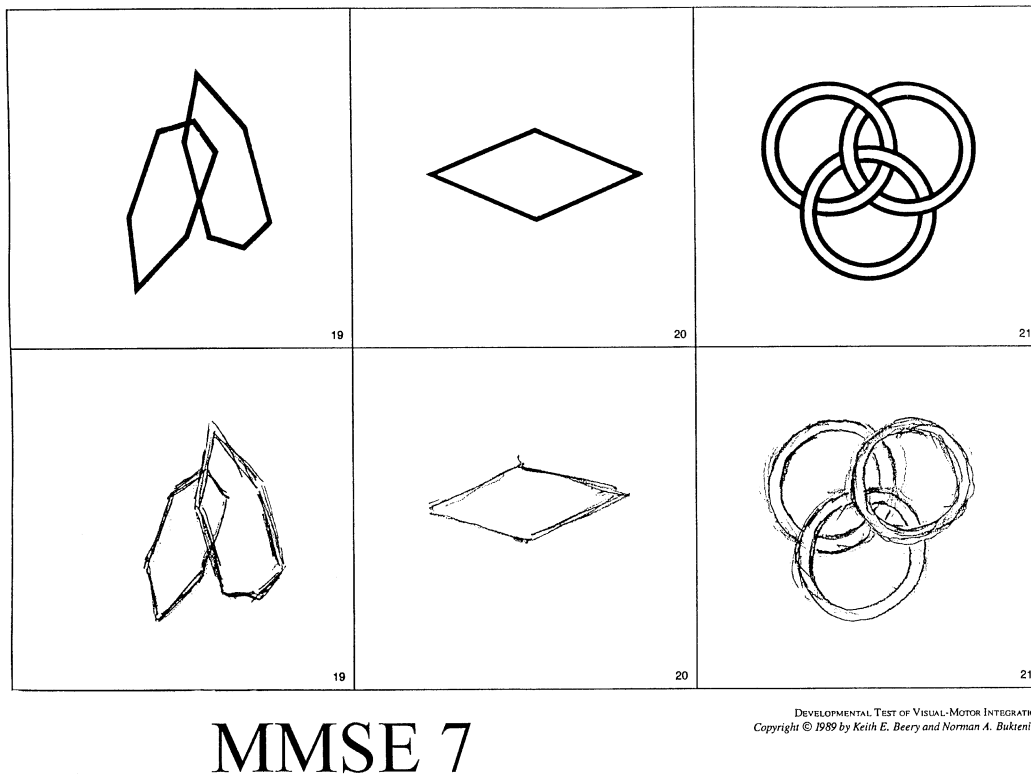


Fig. 3 The copy of a three-dimensional drawing from Patient LTLV 2 at a time when his MMSE was 7.

Patient LTLV 3

A 69-year-old right-handed woman developed progressive aphasia. Employed as a teacher's aide, she first became aware of a problem when she recognized faces of the children in her class but could not recall their names. She developed word-finding trouble and forgot telephone numbers. Arranging her finances became difficult, although she successfully performed this task, lived alone without help and continued teaching. She admitted to mild depression. A sister had similar language problems.

Examination revealed a socially appropriate depressed female. MMSE score was 26. Language output was slow but fluent and she had difficulty finding nouns during conversation. Nonverbal learning was impaired but copying was intact. MRI showed left temporal lobe atrophy and SPECT showed left temporal hypoperfusion (*see* Fig. 4).

Patient LTLV 4

A 71-year-old right-handed woman was evaluated for a 6-year history of progressive language disturbance. Her husband first noticed that she was having problems recalling people's names and, later, that she substituted one word for another. The year prior to evaluation, she had difficulty understanding what others said and stopped reading newspapers or writing letters. Surprisingly, she managed the family stocks and bonds, filed their taxes and maintained cooking, cleaning, and shopping. She cried daily and had suicidal ideation, and

a sleep disturbance. Shortly prior to evaluation she was arrested at a store for placing an item in her pocket. Her husband felt that the theft was an accident and denied any other evidence of disinhibition.

Examination showed a dysphoric socially appropriate woman with suicidal thoughts. MMSE score was 14. She had fluent aphasia with paraphasias and followed only two-step commands. Visual spatial skills and mathematical abilities were spared. MRI showed marked atrophy of the anterior left temporal lobe. SPECT revealed extensive left and mild right temporal hypoperfusion.

Patient LTLV 5

A 68-year-old right-handed woman was evaluated for word-finding difficulty 9 years after she had retired due to this problem. Despite language changes, she lived alone, cooked, cleaned, paid her mother's bills, and volunteered in the hospital making patient mail deliveries. She exercised regularly and dieted vigorously. Relatives noted a change in personality. They described progressive mellowing in a woman who was previously angry.

On examination she was pleasant and cooperative with poor eye contact. At the end of her interview, she made a sexual proposition to the examiner but was otherwise behaviourally appropriate. She followed one-step commands. She was anomic and had paraphasic errors in spontaneous speech. Verbal and nonverbal memory were diminished.



Fig. 4 An anterior coronal SPECT from Patient LTLV 3 which shows marked hypoperfusion in the left anterior temporal lobe. The colour scale is set so that red changes to yellow at 60% maximum cerebral uptake.

Visuoconstructive skills were normal. MRI showed small clinically insignificant white matter lesions. SPECT revealed bitemporal and orbital-frontal hypoperfusion slightly worse on the left.

At the age of 69 years her behaviour worsened. She piled food onto her plate and stole salt and pepper shakers. She started an affair with a married neighbour. Her MMSE score was now 15. She could still draw overlapping pentagons. At the age of 71 years, she lived alone, and successfully cooked and cleaned. She showed increased irritability and insulted customers in restaurants. Her MMSE score dropped to nine but she could still draw the pentagons and perform calculations. Six months later she developed incontinence but still cooked, cleaned and volunteered in the hospital. On examination, she was remote, flat and bizarre. She was severely aphasic, following only simple commands. Her drawing and complex arithmetic skills remained intact as did facial recognition. A repeat SPECT showed worsening of the bitemporal hypoperfusion.

Summary of clinical features

Seven women and three men are reported in this study. Results are reported as mean \pm SD. Mean age was 66.1 ± 7.2 years, duration of illness was 6.4 ± 3.8 years suggesting a mean age at onset of 59.7 years. Patients were all of European heritage. Table 1 summarizes demographic features of the TLV population. Due to a profound behavioural alteration, the RTLTV patients required more attention from their caregivers than the LTLV group.

Summary of neuropsychological features

The main findings are noted in Table 2. RTLTV and LTLV subjects had good to outstanding copying skills, even those with low MMSE scores. Subjects with MMSEs of 14 and 7

(Patients RTLTV 4 and Patient LTLV 2) were competent at drawing and painting, three (Patients LTLV 3, 4 and 5) managed their own finances despite a severe aphasia, while Patient LTLV 1 played the piano and could knit with an MMSE of 1. Two patients spent hours playing the identical word game which required finding and circling hidden words. Also, both repetitively copied words.

Neuropsychological testing tended to show profound deficits in all cognitive spheres. In part, this failure reflected severe aphasia or an inability to attend to the tests. In the few in whom formal neuropsychological testing was performed earlier in the course of the illness, there was relative sparing of digit span, block design, and the Rey-Osterrieth copy. Semantic anomia was present in eight of 10 subjects.

Summary of neuropsychiatric symptoms

Table 3 shows the significant neuropsychiatric features of TLV. Apathy was present in all patients; irritability and disinhibition in eight; depression, agitation and anxiety in five; aberrant motor activity in four; delusions in two; and euphoria in two. One had hallucinations. Three of the five RTLTV subjects had increased religious ideas or heightened philosophical thinking and four adopted eccentric modes of dress. Six stole small objects, three with RTLTV (Patients RTLTV 2, 4 and 5) and three with LTLV (Patients LTLV 1, 4 and 5).

In contrast, Table 4 shows neuropsychiatric symptoms from another group of 10 patients with selective frontal dysfunction in whom the temporal lobes appeared spared with SPECT. The patients with frontal dysfunction were more apathetic than the TLV group while the TLV group showed more disinhibition, irritability, sociopathy and bizarre affect, and like the TLV subjects, the patients with right-

Table 1 Summary of demographics

Patient	Sex	Family history	Age years	Duration of illness (years)	MMSE
RTLTV 1	Male	No	59	3	22
RTLTV 2	Female	No	56	10	24
RTLTV 3	Female	No	67	2	23
RTLTV 4	Male	No	68	12	14
RTLTV 5	Female	No	66	11	16
LTLTV 1	Female	No	56	10	1
LTLTV 2	Male	No	81	6	7
LTLTV 3	Female	Yes	69	2	26
LTLTV 4	Female	No	71	2	14
LTLTV 5	Female	No	68	9	15

Table 2 Summary of neuropsychological features

Patient	Semantic anomia	Memory	MMSE drawing
RTLTV 1	Present	Impaired	Normal
RTLTV 2	Absent	Impaired	Impaired
RTLTV 3	Present	Impaired	Normal
RTLTV 4	Present	Impaired	Normal
RTLTV 5	Present	Impaired	Impaired
LTLTV 1	Present	Impaired	Normal
LTLTV 2	Absent	Impaired	Normal
LTLTV 3	Present	Impaired	Normal
LTLTV 4	Present	Impaired	Normal
LTLTV 5	Present	Impaired	Normal

Table 3 Summary of neuropsychiatric symptoms

Patient	Affect	Depression	Psychosis	Sociopathy [†]	Irritability	Disinhibition
RTLTV 1	Remote	Atypical	No	Unknown	Severe	Moderate
RTLTV 2	Bizarre	Atypical	Yes	Violence	Severe	Severe
RTLTV 3	Remote	No	No	No	Severe	Mild
RTLTV 4	Remote	No	No	Theft/assault	Mild	Severe
RTLTV 5	Remote	No	No	Theft	Severe	Severe
LTLTV 1*	Bizarre	Atypical	No	Theft/assault	Moderate	Severe
LTLTV 2	Flat	No	No	No	Mild	Mild
LTLTV 3	Flat	Typical	No	No	Mild	None
LTLTV 4	Flat	Typical	No	Theft	Mild	None
LTLTV 5	Flat	No	No	No	No	Mild

*Left-handed. [†]Crime, violence or violent gestures.

Table 4 Summary of neuropsychiatric symptoms

Patient	Affect	Depression	Psychosis	Sociopathy	Irritability	Disinhibition
RFL 1	Childish, overly friendly	Atypical	No	No	Mild	Mild
RFL 2	Flat	No	No	No	None	No
RFL 3	Flat and remote	No	No	No	None	No
RFL 4	Childish, overly friendly	Atypical	No	No	Moderate	Mild
RFL 5	Remote, overly friendly	Atypical	No	Theft	Moderate	Severe
LFL 1	Normal	No	No	No	No	No
LFL 2	Normal	Yes	No	No	Mild	No
LFL 3	Flat	No	No	No	No	No
LFL 4	Flat	No	No	No	No	No
LFL 5	Flat	Atypical	No	No	Mild	Mild

sided frontal dysfunction were more behaviourally disturbed than the group with left-sided frontal dysfunction.

Summary of MRI

Table 5 summarizes the results of structural brain scans. In all of the subjects the MRI or CT (one case) showed temporal lobe atrophy. In only one subject, Patient RTL V 3, were the frontal lobes considered atrophic. Yet, all subjects showed bitemporal lobe atrophy ranging from mild to severe. Hence, the MRIs support the designation of these subjects as a predominantly temporal variant of frontotemporal dementia. Also, in nine out of the 10 patients, the side suggested as more affected on visual inspection of SPECT was indeed more atrophic on MRI. Only Patient RTL V 4, in whom the MRI was rated as slightly more atrophic on the left, were MRI and SPECT not congruent. In the group with frontal lobe involvement, six MRI scans were available and all showed more atrophy in frontal than in temporal regions, supporting the rCBF data described below.

Summary of rCBF

Table 6 summarizes rCBF measured with ^{133}Xe -SPECT. The rCBF of the frontal lobes was compared with that of the

Table 5 Summary of MRI atrophy

Patient	Left temporal lobe	Right temporal lobe
RTL V 1*	Mild	Moderate
RTL V 2	Mild	Moderate
RTL V 3 [†]	Mild	Moderate
RTL V 4	Severe/moderate	Moderate/mild
RTL V 5	Mild	Moderate
LTL V 1 [‡]	Severe	Moderate
LTL V 2	Severe	Moderate
LTL V 3	Moderate	Moderate/mild
LTL V 4	Severe	Moderate
LTL V 5	Moderate	Mild

*Based on reports from CT and neuropathology. [†]This patient also had mild right frontal atrophy. [‡]Patient is left-handed

Table 6 Regional cerebral blood flow (rCBF)

Patient	Left frontal region	Right frontal region	Degenerated temporal lobe	Spared region	Occipital region
RTL V 1	37.0	36.5	27.0	35.0	43.0
RTL V 2	51.0	49.0	29.0	35.0	35.0
RTL V 3	24.5	20.5	19.0	29.0	41.0
RTL V 4	37.5	41.5	10.0	17.0	35.0
RTL V 5	27.5	32.5	20.0	24.0	31.0
LTL V 1*	34.5	38.0	23.0	29.0	48.0
LTL V 2	28.5	27.5	22.5	21.5	23.0
LTL V 3	32.0	29.5	26.0	37.0	38.0
LTL V 4	40.0	44.5	26.0	28.0	40.0
LTL V 5	40.0	38.0	25.0	31.0	46.0
Mean \pm SD	35.0 \pm 5.0	35.5 \pm 7.0	24.5 \pm 1.7	29.3 \pm 5.9	39.0 \pm 9.8

*Left-handed.

occipital lobes using a *t* test. No significant difference was present ($P = 0.475$). Table 6 allows comparison of average rCBF values in both frontal lobes with those in the temporal lobe with most degeneration. The highly significant difference ($P = 0.005$) confirms that frontal lobes were spared in relation to the degenerated temporal areas. When the more severely affected temporal lobe was compared with the less affected one, the difference was significant ($P = 0.039$), confirming the asymmetrical dysfunction of the temporal lobes.

In the patients with predominantly frontal dysfunction the mean frontal rCBF was 30.7 ± 8.9 , and temporal rCBF was 38.2 ± 7.3 . This difference was statistically significant ($P = 0.028$). Hence, rCBF data supports two different frontotemporal dementia subgroups, one with predominantly temporal, and the other with predominantly frontal, dysfunction.

Discussion

The TLV patients described here represent a subgroup of frontotemporal dementia with selective bilateral dysfunction of the anterior temporal and basal-frontal areas. They constitute ~20% of the frontotemporal dementia cohort presenting to our institution. SPECT showed asymmetrical hypoperfusion in the temporal and basal-frontal regions in all TLV subjects. Unlike patients with more classical frontotemporal dementia, in whom both the frontal and temporal lobes are dysfunctional, perfusion in the TLV patients was relatively spared in the frontal lobes, except for the basal-frontal region. Although all patients had bilateral temporal hypoperfusion on SPECT, five had more left-sided involvement, while in five it was worse on the right. In one subject (Patient RTL V 4), although SPECT suggested that the right temporal lobe was more severely affected, MRI showed worse problems on the left. Therefore, this subject was more difficult to classify and could be considered a subject with bilateral dysfunction. These patients offer a potential model for the study of clinical symptoms in patients with

asymmetrical anterior temporal and inferior frontal lobe dysfunction.

Clinical and cognitive findings

In all but one patient the disorder began in the pre-senium. Typically, symptoms were present for many years prior to evaluation. In at least five patients, symptoms started more than 10 years prior to referral for our clinical assessment. A family history suggesting a dominantly inherited disorder was obtained in two out of the 10 subjects. We cannot be certain that these TLV patients represent a single pathological disorder, but the one subject who came to a post-mortem had the typical findings of frontotemporal dementia: gliosis, anterior temporal neuronal loss and tissue spongiosis; in this case the temporal and right-sided temporal predominance observed clinically was confirmed by the pathologist. Because pathological confirmation is still lacking in the other cases, it is possible that some will eventually be demonstrated to non-frontotemporal dementia pathology. However, the clinical features of the TLV group were distinctive and offered insights into the functions of the anterior temporal lobes.

Certain neuropsychological abnormalities were present in all subjects, but others were more typical of either RTLTV or LTLV. Although all of the TLV subjects had an abnormal performance on neuropsychological tests, many functioned well in their daily activities. The TLV group continued to drive, cook, clean and even repair household items despite low MMSE scores. Patient LTLV 5 lived alone, did voluntary work at a hospital, managed her own finances, cooked and cleaned despite a MMSE score of 9. Patient LTLV 4 successfully managed a financial portfolio with a MMSE score of 14. Patients LTLV 2 and 3 continued to work despite severe aphasia. A severe behavioural disturbance found in the RTLTV patients, often made them socially dependent upon their families, despite intact language and visuo-spatial skills.

The aphasia in LTLV was severe, but several of the patients with bilateral, but more severe involvement of the right temporal lobe, had language impairment. Semantic anomia, a disorder in which the meaning of the word was lost, although it could be read aloud, repeated and even spelled aloud, was present in three RTLTV subjects (including Patient RTLTV 4 in whom MRI showed abnormalities in both temporal lobes) and four LTLV patients. These subjects had difficulty with confrontation naming which did not improve when they were given semantic or phonological clues for the words. Progressive semantic anomia has been called 'semantic dementia' (Hodges *et al.*, 1992) and is considered to be a left temporal lobe language abnormality. It is unusual with vascular disease or tumour where the injury to the temporal lobe is more likely to be unilateral. However, semantic anomia is common in TLV, even those patients with predominantly right-sided involvement, which suggests that the right anterior temporal lobe may participate in name recognition to a greater degree than was previously

appreciated. Additionally, the finding of this unusual aphasia syndrome in the majority of our TLV subjects supports the importance of left anterior temporal dysfunction for this syndrome.

Formal testing of both verbal and nonverbal memory showed impairment in all subjects. However, this may indicate difficulty getting the subjects into proper mood for memory testing, or a confounding language disturbance. Despite this difficulty on formal tests of visual memory, visuoconstructive skills were relatively intact. Eight of 10 subjects drew the pentagons on the MMSE, even those with scores as low as 1, 5 or 14. One scored at or above the 75th percentile on block design despite low scores on most other tests.

An interesting feature of TLV was preservation of previously artistic skills in Patient LTLV 3 and musical ability in Patient LTLV 1. Even more remarkable was the new development of outstanding artistic ability in Patient RTLTV 4 (Miller *et al.*, 1996). The mechanism for the maintenance of artistic and musical abilities is unknown, although preservation of frontal and parietal cortex undoubtedly plays an important role in the preservation of behaviours that are usually lost early in Alzheimer's disease.

Neuropsychiatry

Psychiatric symptoms were noted in all TLV patients but the character of symptoms differed considerably depending upon the predominant side of involvement. RTLTV patients were socially inept, agitated and profoundly irritable. Verbal and physical threats were common. Patient RTLTV 2 hit her husband when angry, Patient RTLTV 4 made violent gestures at clerks and berated and bumped strangers on the street, and Patient RTLTV 5 hit an examiner during testing. Patients RTLTV 1 and 3 were impatient, irritable and argumentative without violent gestures. In no circumstance did the violent acts or gestures result in serious harm to others.

In contrast, LTLV patients were pleasant and socially appropriate except for Patient LTLV 1 who behaved in a manner similar to patients with RTLTV. However, because Patient LTLV 1 was left-handed, her hemispheric dominance is unknown for these potentially lateralized functions. At the first interview, Patients LTLV 2, 3, 4 and 5 were pleasant and had no significant problems with interpersonal relations. Patient LTLV 5 initially showed a mellowing of her personality, although late in the illness she became irritable (coincident with more severe right temporal lobe involvement).

Depression was present in both subgroups, but had different features depending upon the predominant side of degeneration in each patient. All RTLTV patients had remote/bizarre affect, and several developed an atypical depression with lack of insight and denial of illness. The LTLV subjects were more likely to show a classical major depressive episode with anhedonia, feelings of worthlessness and crying.

Eccentricity was prominent in RTLTV and odd or outlandish changes in dress were seen in four of the five RTLTV subjects

(Patients RTLV 1, 2, 4 and 5). Patient RTLV 1 wore mismatched socks and shoes, buttoned shirts backwards, and he tucked his jacket into his trousers. Patient RTLV 4 wore only lavender clothes, while Patients RTLV 2 and 3 were slovenly and indifferent to their appearance. The RTLV patients demonstrated poor personal hygiene early in the disease. Patients with LTLV maintained their grooming and dressing habits. Three patients with RTLV (1, 3 and 4) had increased religious or philosophical concerns. Patient RTLV 1 developed greater interest in church activities, Patient RTLV 3 professed new religious beliefs and Patient RTLV 4 became more involved in alternate lifestyles and philosophies.

Finally, obsessive visual attention, originally called hypermetamorphosis (Kluver, 1951) was present in nearly every subject. This led to 'shoplifting' in six subjects, repetitive playing of search and circle games in two, and intensive successful artistic activity in one (Miller *et al.*, 1996). In the six who shoplifted, this appeared to reflect a visual preoccupation with small objects as much as disinhibition. For example, in Patient LTLV 4, there was no behavioural disinhibition, but she was unexpectedly caught stealing a small object from a store. Patient RTLV 4 became obsessed with coins and walked daily intentionally passing phone booths, cash registers, busy city streets and restaurant tables, all places where he might find and pocket coins. This behaviour was associated with efforts to steal pens, wallets and tips from restaurant tables. In contrast, only one of the 10 subjects with predominantly frontal involvement shoplifted.

The group of patients used for comparison, those with predominantly frontal hypoperfusion and temporal sparing, showed less behavioural disturbance. Disinhibition and irritability were less common and less severe in the group with frontal dysfunction, while apathy was more prominent; only one subject (with right-sided involvement) exhibited antisocial behaviour. Similarly, there were fewer subjects with depression. Affect was blunted or over-modulated in the frontal group, but only one patient showed the bizarre remote affect that was common in the RTLV group. As with the TLV subjects, in the patients with frontal dysfunction, right-sided dysfunction was more likely to be associated with more severe psychiatric symptomatology.

Implications for behavioural correlates of the temporal lobe

The anterior temporal lobes are difficult to study in humans, and the functions of the right anterior temporal lobe remain poorly characterized. The right temporal lobe is important for visual perception (Meadows, 1974), facial recognition (Hecaen and Angelergues, 1962; Meadows, 1974; Evans *et al.*, 1995), recognition of facial emotion (Adolphs *et al.*, 1994) and nonverbal or emotional memory (Bechara *et al.*, 1995). Ross (1981) presented a theory regarding the right temporal lobe's role in encoding emotional elements of

communication, but did not address specific functions of the anterior temporal lobes.

Ablation studies in primates and temporal lobe epilepsy studies, with or without surgical treatment, offer insight into anterior temporal lobe function, yet neither are truly analogous to the TLV of frontotemporal dementia. Profound social alterations occur after bilateral lesions of the anterior temporal lobes, orbital-frontal cortex, and/or amygdala. Kluver and Bucy described behaviour in macaques after bilateral temporal lobectomy (Kluver, 1951). These monkeys showed hyperorality, psychic blindness, hypermetamorphosis, a blunted emotional response, hypersexuality, and dietary changes. The initial observations involved caged animals so that the behaviours observed in these animals did not occur in the usual social milieu.

Later studies were performed on social conduct in animals returned to their social environment after ablation studies (Franzen and Myers 1973; Kling and Steklis 1976). In Old World monkeys, Kling and Steklis (1976) found that bilateral anterior temporal lobectomy, selective bilateral amygdectomy or bilateral prefrontal lobectomy led to decreased social interaction and loss of social rank. The operated monkeys were withdrawn and fearful of other monkeys and some were attacked and even killed. In rhesus monkeys following either bilateral prefrontal or bilateral anterior temporal lobectomy (Franzen and Myers 1973) there were indiscriminate approaches toward others, irrespective of rank; loss of facial expression, postures, and gestures; and impaired mothering. Monkeys with prefrontal lesions were passive and showed decreased affiliative behaviour and absent sexual interaction. The temporal lobectomized group had decreased socially affiliative behaviour, aggression toward their own babies when they requested mothering, but preserved interest in sex. These studies did not focus upon unilateral ablations. However, injury to both anterior temporal lobes and/or to prefrontal cortex led to loss of effective social behaviour.

The behavioural patterns associated with temporal lobe epilepsy are relevant to the psychopathology associated with temporal lobe dysfunction. Several clinical studies have found a tendency for left temporal seizure foci to produce greater psychopathology than right temporal foci. Sherwin, in a literature review (1980) and his own studies (1982), found that aggressive behaviour in epileptics was more often associated with left temporal lobe foci. Bear and Fedio (1977) looking at a broad spectrum of behaviours, did not find a clear right-left distinction; instead, they showed that right seizure subjects ignored or downplayed their own behavioural problems (polishers), whereas left seizure subjects were highly honest (tarnishers). Thus, self-reports (the basis for most clinical studies) may tilt the prevalence of reported psychopathology toward left temporal subjects, even if the problem group was right-sided.

No report suggests that either right or left anterior temporal lobectomy is more effective in control of psychopathology, although surgical therapy for temporal lobe seizures, even the *en bloc* removal of either temporal lobe, is not truly

analogous to TLV. The brain restructures in association with congenital and early epileptic foci and following lobectomy decreased seizure frequency, less need for anti-convulsant medications, and the potential for recovery and remodelling of adjacent temporal lobes all help to ameliorate symptoms. Additionally, while some epileptics may have combined orbital and anterior temporal damage (particularly post-traumatic cases), most have pure temporal disorders (e.g. hamartoma, medial temporal sclerosis).

We found that social interactions were more severely disrupted in subjects with right-sided degeneration. LTLV subjects showed flat emotional expression, but relatively normal social skills and interaction. In contrast, RTLTV patients exhibited socially offensive behaviour, including sexual disinhibition, decreased personal hygiene, poor work habits, aggression, egocentric behaviour and abnormal facial expression and gestures. Social impropriety in RTLTV and preserved social functioning in LTLV suggests that the right hemisphere, at least the orbital frontal and anterior temporal aspects, may be necessary for mediation of socially appealing behaviour in humans, as previously suggested by Miller *et al.* (1993).

A central role of the right hemisphere in social skills is supported by the absence of behavioural disturbance in primary progressive aphasia, a degenerative dementia that involves predominantly the left hemisphere (Mesulam 1982; Chawluk *et al.*, 1986; Snowden *et al.*, 1992; Caselli *et al.*, 1993; Kertesz *et al.*, 1994; Scheltens *et al.*, 1994). However, the absence of severe behavioural disturbance in unilateral lobectomized patients suggests that the severe impairment of behaviour in the RTLTV group probably required bitemporal involvement.

The observations from this small study offer an opportunity for conjecture on the neurological basis of social behaviour. One implication of our data is that both anterior temporal lobes, particularly the right anterior temporal region, are important mediators for social behaviour. A second interpretation would invoke a greater role for the orbital-frontal cortex, quite possibly reciprocal with that of the anterior temporal structures. Anatomical relationships between the amygdala and surrounding anterior temporal limbic structures and the ipsilateral orbital-frontal cortex are well-known (Aggleton, 1992). In addition, each of these areas has connections with the hypothalamus and the putamen. The dearth of focal, unilateral orbital-frontal damage lesions is as great as it is for the anterior temporal lobe. However, patients with injury to the orbital-frontal area secondary to limited frontal leucotomy (Scoville, 1960) tend to become bland and apathetic; the behavioural eccentricities found in our group of TLV subjects were not described.

The exact anatomical localization of structures underlying the behaviours described is not yet possible. However, it is reasonable to assume that the TLV of frontotemporal dementia has unevenly influenced a complex network of interrelated social functions. It can be stated unequivocally that the TLV

of frontotemporal dementia provides a useful tool for probing the functions of the anterior temporal and basal-frontal lobes.

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