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Performance on Neuropsychological Tests Related to Single Photon Emission Computerised Tomography Findings in Frontotemporal Dementia

CHRISTINA I. ELFGREN, ERIK RYDING and ULLA PASSANT

Background. This study examines relations between regional cerebral blood flow (rCBF) and neuropsychological test results, age at onset and duration of disease in patients with frontotemporal-type dementia (FTD).

Method. Sixteen patients with a diagnosis of probable FTD were examined using single photon emission computerised tomography (SPECT) with ^{99m}Tc-HMPAO as the tracer. The rCBF of 14 regions of interest relative to cerebellar blood flow was calculated. Psychological tests assessing language, verbal fluency, memory and visuospatial constructive ability were given.

Results. Correlations were demonstrated between a global impairment score and relative blood flow in lateral frontal, medial frontal and left orbital frontal areas. Verbal fluency scores correlated with left lateral frontal, medial frontal and left anterior inferior temporal blood flow. No relationships between decrease in CBF and age at onset or duration of disease, or between impaired cognitive function and age at onset or duration of disease, were found.

Conclusions. The present study demonstrates a close coupling between reduced rCBF and specific neuropsychological deficits in FTD.

Frontotemporal dementia (FTD) has been distinguished from Alzheimer's disease in several studies (Jagust *et al*, 1989; Knopman *et al*, 1990; Miller *et al*, 1991; Brun, 1993; Gustafson, 1993; Neary *et al*, 1993). Frontotemporal dementia is a clinical syndrome characterised by slowly progressive social breakdown, changes of personality and cognitive dysfunction. Behaviour becomes disinhibited, socially inappropriate and inflexible. Psychotic symptoms such as hallucinations and delusions have been described. Changes in language function are a prominent feature. Speech becomes restricted and increasingly perseverative and stereotypic, in the advanced stage leading to mutism. Spatial orientation and praxis are usually preserved. Frontotemporal dementia might be caused by a number of disorders involving frontal and anterior temporal structures. The underlying histopathology is heterogeneous (Brun, 1993). Frontotemporal dementia has recently been described in a consensus (Table 1) by two research centres, Lund, Sweden, and Manchester, UK (Brun *et al*, 1994).

Neuropsychological investigations have revealed cognitive deficits implicating disordered function of the anterior cortex (Neary *et al*, 1988; Elfgren *et al*, 1993; Frisoni *et al*, 1995). A specific cognitive

Table 1
Clinical diagnostic features of FTD (selected items from the Lund and Manchester consensus statement; Brun *et al*, 1994)

Area of disorder	Signs of FTD
Behavioural disorder	Insidious onset and slow progression
	Early decline of personal and social awareness
	Early signs of disinhibition
	Early decline of insight
	Mental rigidity and inflexibility
	Stereotyped and perseverative behaviour
	Distractibility, impulsivity, and impersistence
	Hyperorality and utilisation behaviour
Affective symptoms	Emotional unconcern, depression, and hypochondriasis
Speech disorder	Progressive reduction and stereotypy of speech
	Late mutism
Spatial orientation and praxis	Comparatively preserved
Investigations	Normal electroencephalogram despite clinically evident dementia
	Predominant frontal or frontotemporal abnormality on brain imaging
	Profound failure on 'frontal lobe' neuropsychological tests in the absence of severe amnesia, aphasia, or perceptual spatial disorder

profile has been delineated, with better performance on visuospatial than verbal tasks (Johanson & Hagberg, 1989; Elfgren *et al*, 1994).

Findings from functional imaging in FTD have been consistent across a variety of techniques (Chase *et al*, 1987; Neary *et al*, 1987; Risberg, 1987; Miller *et al*, 1991; Risberg *et al*, 1993; Frisoni *et al*, 1995; Pasquier *et al*, 1995). Patients with FTD show bilateral reductions in frontal and anterior temporal flow in contrast to the characteristic findings in patients with dementia of Alzheimer type (DAT), in which flow reductions are mainly in postcentral areas (Gustafson *et al*, 1977; Minoshima *et al*, 1994). Various studies have addressed the relationships between neuropsychological test performance and regional cerebral blood flow (rCBF) in DAT using single photon emission computerised tomography (SPECT) (O'Brien *et al*, 1992). However, few studies have examined how the cognitive state of the patients might parallel SPECT findings in FTD (Jagust *et al*, 1989; Miller *et al*, 1991; Pasquier *et al*, 1995).

The main purpose of this study was to investigate the relation between specific neuropsychological test results and rCBF in patients with a clinical diagnosis of probable FTD. A second aim was to examine the correlations between global neuropsychological impairment, rCBF and age at onset and duration of disease.

Method

Patient selection

Sixteen patients (6 men, 10 women) with probable FTD were included in the study. They were selected from a group of 30 consecutive patients with frontal lobe symptoms referred to our psychogeriatric clinic. All 30 patients were given a thorough examination, which included somatic and neuropsychiatric investigations, routine laboratory tests, interview of relatives, neuropsychological assessment, cerebral blood flow, computerised tomography or magnetic resonance imaging (or both), and electroencephalography (EEG) investigations. Out of this larger patient group, 16 patients fulfilled the specific criteria from the consensus statement on "Clinical and neuropathological criteria for frontotemporal dementia" (Brun *et al*, 1994). Rigorous inclusion and exclusion criteria were followed to exclude cases with any other disorder that might be associated with dementia. Table 2 gives subject characteristics. The mean age at examination was 62.6 years (range 41–77 years). The mean duration of illness at examination was 4.9 years (range 2–9 years). Twelve of the patients had an educational level between 7 and 9 years, three of the patients between 10 and 12 years, and one of the patients had a higher educational level (university degree). Nine of the 16 patients had a certain family history of a similar disorder in a first-degree relative. Eleven of the patients had disease onset before 65 years. Seven of the patients were in need of permanent observation and care.

Clinical follow-up in all cases has further supported the diagnoses of FTD. Two of the patients are deceased. Neuropathological findings have verified the diagnosis in one of the deceased patients; in the other case no autopsy was performed.

Neuropsychological assessment

All 16 patients were examined with a selection of tests from Luria's neuropsychological investigation (Christensen, 1974). The tasks were chosen to assess: motor functions of the hand, verbal memory, receptive and expressive speech, basic ability to write and read, and basic arithmetic skills. The different tasks were evaluated on a three-point scale (0 = normal, 1 = slight/moderate impairment,

Table 2
Subject characteristics

Cases	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Sex	M	F	F	F	M	M	F	F	F	F	F	F	M	M	F	M
Years of education[1]	1	1	1	2	2	3	1	1	1	1	1	1	1	2	1	1
Family history[2]	N	Y	N	Y	?	Y	N	N	N	Y	Y	Y	Y	Y	Y	?
Age at onset: years	60	56	65	75	56	71	46	48	37	61	70	60	50	61	65	41
Duration of illness at examination: year	5	3	7	2	5	3	7	5	4	4	5	5	9	5	5	5
Need of permanent care	N	N	N	N	N	N	N	N	N	Y	Y	Y	Y	Y	Y	Y
Impairment score (0–52)	3	5	6	6	9	12	15	18	18	19	26	37	42	42	45	47

1. 1=7–9 years; 2=10–12 years; 3=> 12 years of education.
2. History of a similar disorder to FTD in a first-degree relative (N, no; Y, yes).

2 = severe impairment) and summed to give a total impairment score.

In addition, 12 patients who were able to complete further cognitive testing were examined with a neuropsychological test battery including: (1) verbal fluency, measured by the Controlled Oral Word Association Test, in which subjects were instructed to say as many words they could think of beginning with a specified target letter (e.g. F, A, S; Benton & Hamsher, 1976); (2) verbal memory, measured by the Paired Associates Test, in which 3 lists of 10 word pairs each were read aloud by the examiner and immediate associate recall was recorded (Cronholm & Molander, 1965); (3) verbal ability, measured by the Vocabulary Test, a word definition test (Husén, 1956); (4) visuospatial constructive ability, as measured by the Block Design Test (Wechsler, 1958). The first three tests were chosen because they have been proven to examine functions subserved by frontotemporal areas. The Block Design Test was selected as a comparison, as this test to a greater extent assesses postcentral functions. The last three tests have been used in other investigations as discriminators between DAT and FTD (Johanson & Hagberg, 1989; Elfgren *et al*, 1994).

Measurements of rCBF

The rCBF measurements were made after intravenous administration of technetium-99m hexamethylpropyleneamine-oxime (^{99m}Tc-HMPAO). This substance, in its initial lipophilic state, is delivered into the brain in proportion to the rCBF. Inside the brain cells it is converted within a few minutes to its hydrophilic form, which cannot easily leave the brain cells (Holmes *et al*, 1985). The ^{99m}Tc-HMPAO distribution in the brain thus remains unchanged for several hours.

At the time of the ^{99m}Tc-HMPAO administration the patients were resting supine with eyes open and instructed to remain so during the next five minutes. There was only some ambient noise. About 10 minutes later the intracerebral distribution of ^{99m}Tc-HMPAO was recorded by a Tomomatic 564 SPECT camera.

The rCBF distribution was recorded in 10 contiguous slices 1 cm thick from 1 cm below the orbitomeatal (OM) line and upwards. The intraslice resolution was about 1 cm (full width half-maximum). The recorded rCBF distribution was quantified by the use of a standardised set of three-dimensional regions of interest (ROI) based on an anatomical atlas (Kretschmann & Weirinch, 1986). The ROI set was positioned and scaled to the recorded SPECT slices based on the external borders of each slice (Fig. 1). The measured value in each ROI was quantified as a percentage of the mean cerebellar ^{99m}Tc-HMPAO concentration. No linearisation of the SPECT data was made.

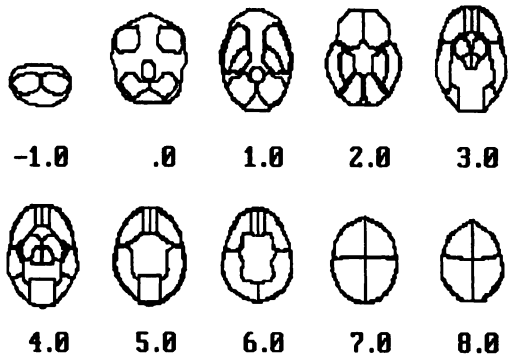

Fig. 1 The ROIs used in the analysis of the SPECT pictures. Each of the contiguous 10 slices has a corresponding ROI set which is scaled to its external borders. The figures denote the slice position relative to the OM line.

Non-linearised data of the ^{99m}Tc-HMPAO rCBF distribution in normal subjects (aged 61–80 years; Waldemar *et al*, 1991) were used as a normal reference.

Statistical analysis

Spearman's correlation coefficients were calculated between rCBF in the ROIs and the neuropsychological performance and selected clinical variables. Five cortical and one subcortical ROI per hemisphere, and two midline ROIs (frontal and occipital) representing areas of grey matter in the brain, were chosen for this purpose. Subjects generally had SPECT imaging performed within one month of neuropsychological testing. Since a large number of correlations were calculated only coefficients with a significance level of $P<0.001$ were considered.

Results

Neuropsychological findings

The 16 patients varied in the severity of dementia as measured by the global impairment scale, scores ranging from 3 to 47 (Table 2). A high total score indicates more severe impairment. The raw scores of the tests of verbal ability, verbal memory and visuospatial constructive ability were transformed to a stanine scale (scores 1–9, mean 5, s.d. 2) with

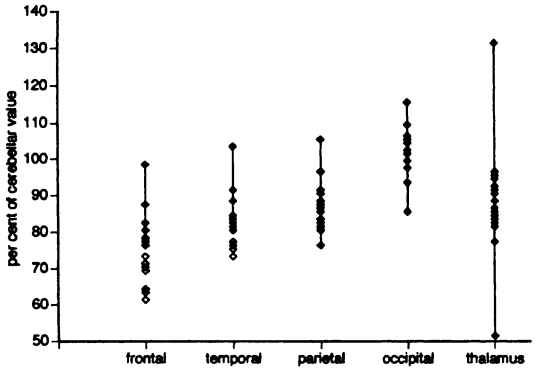

Fig. 2 The rCBF distribution of the FTD patients in relation to the age-matched normal range, which is denoted by filled squares (mean ± 2 s.d.; data from Waldemar *et al*, 1991). In the frontal regions about half the patients, and in the temporal regions about a third, have rCBF below the normal range. In contrast, the remaining regions all have normal rCBF values. Note that data points for some patients overlie each other.

reference to normative data given in the manual of each test. This transformation yielded a mean stanine of 2 (s.d. 1.2) for the verbal ability test, 1 (s.d. 1.6) for the verbal memory test, and 3 (s.d. 2.2) for the visuospatial constructive test. There is no published Swedish normative data for the verbal fluency test.

The SPECT results

The mean rCBF distribution in the FTD patients is illustrated in Figs 2 and 3. Compared with the mean rCBF in normal subjects, the FTD patients showed a moderate to severe decrease in the frontal regions, with 10 of the 16 patients (right, 11/16; left 9/16) having rCBF levels more than 2 s.d. below normal. The corresponding values for the temporal lobes were 8 of the 16 (right 11/16; left, 5/16) and for the parietal lobes 1 of the 16. There were no other regions in the FTD patients with SPECT rCBF outside normal limits (mean ± 2 s.d.).

Correlations between rCBF and the global impairment score

Significant negative correlations were found between the overall impairment score and the right frontal lateral, left frontal lateral, frontal medial and left frontal orbital ROIs ($P < 0.001$), meaning that a high impairment score is associated with a low rCBF (Table 3).

Correlations between rCBF and the results of the specific neuropsychological tests

Correlations were calculated between the raw scores of the four neuropsychological tests and the relative

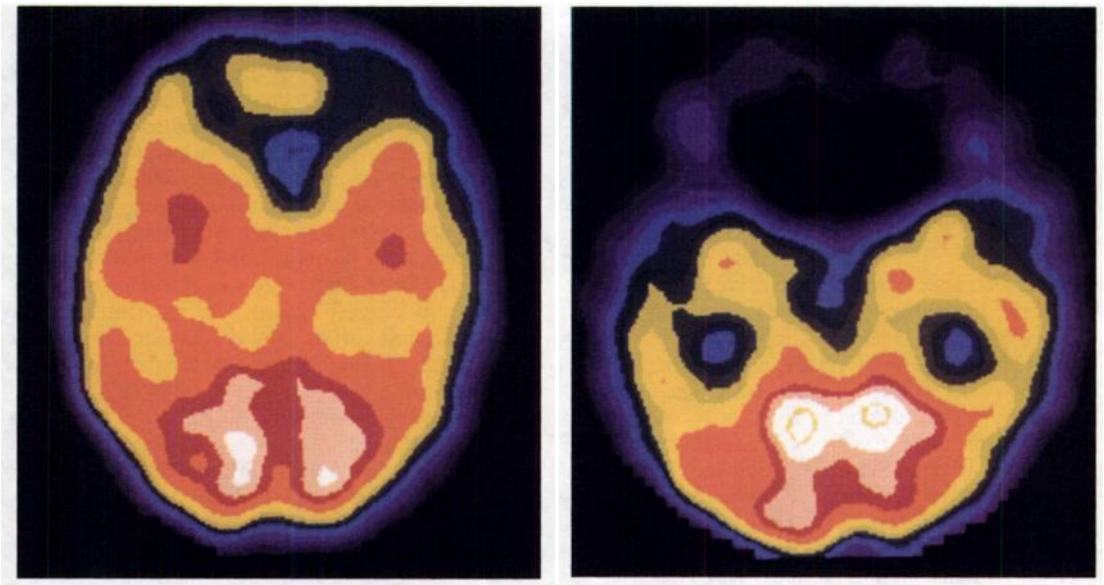

Fig. 3 The SPECT rCBF measurements at rest from two FTD patients: (a) the almost normal finding at an early stage with low grade of disability (case 2); (b) the profoundly decreased rCBF in the frontal regions at an advanced stage of dementia (case 16). Higher rCBF levels are shown by red and yellow, and lower levels by dark green and blue colours.

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Table 3
Correlations between impairment scores, neuropsychological tests and rCBF

Regions of interest	Impairment score (n=16)	Verbal fluency (n=12)	Verbal memory (n=12)	Verbal ability (n=12)	Visuospatial ability (n=12)
Right frontal lateral	−0.75*	0.67	0.57	0.42	0.25
Left frontal lateral	−0.88*	0.79*	0.62	0.50	0.13
Frontal medial	−0.80*	0.80*	0.77	0.60	−0.02
Right frontal orbital	−0.68	0.50	0.31	0.28	0.18
Left frontal orbital	−0.87*	0.70	0.37	0.52	0.13
Right temporal anterior inferior	−0.27	0.38	0.07	0.08	0.08
Left temporal anterior inferior	−0.50	0.85*	0.34	0.56	−0.00
Right temporal posterior superior	−0.30	0.20	0.30	0.11	−0.10
Left temporal posterior superior	−0.59	0.50	0.28	0.38	−0.31
Right parietal	−0.38	0.50	0.46	0.25	0.02
Left parietal	−0.54	0.49	0.30	0.23	−0.07
Occipital	−0.13	0.26	−0.10	0.03	0.10
Right thalamus	−0.47	0.36	0.20	0.24	−0.34
Left thalamus	−0.64	0.54	0.31	0.58	−0.50

*P<0.001.

blood flow of the ROIs. Significant positive correlations were found between verbal fluency and left frontal lateral, frontal medial and left temporal anterior inferior ROIs (P<0.001). Thus, poor performance on this cognitive test was related to lower rCBF (Table 3).

Relationship to age at onset and duration of disease

There were no significant correlations between level of impairment, as measured by the total impairment score, and age at onset or duration of disease. There were no significant correlations between rCBF and age at onset or duration of disease.

Discussion

Comparison with previous studies

Previous studies have shown that FTD patients have a distinct cognitive profile, with impairment on tests measuring executive functions, verbal fluency and vocabulary, while visuospatial ability is relatively preserved (Johanson & Hagberg, 1989; Miller *et al*, 1991; Elfgren *et al*, 1993). The results of the present study of patients with a clinical diagnosis of FTD have confirmed these findings and have also demonstrated significant correlations between level of performance on neuropsychological tests and rCBF measured with SPECT and ^{99m}Tc-HMPAO.

The patients demonstrated hypoperfusion in frontal and anterior temporal areas especially, and relative sparing of the flow of more posterior parts of the brain. The same pattern of cortical blood flow has been demonstrated in previous studies using the ^{133}Xe inhalation technique (Risberg, 1987; Risberg *et al*, 1993), positron emission tomography (Chase *et al*, 1987) and SPECT (Neary *et al*, 1987; Jagust *et al*, 1989; Miller *et al*, 1991; Pasquier *et al*, 1995; Frisoni *et al*, 1995).

Correlation between rCBF and global measures of cognitive impairment

Some tasks were selected from Luria's neuropsychological investigation for the evaluation of cognitive impairment (Christensen, 1974). The results of the different tasks were summed into a total impairment score. The selected tasks were elementary, all within the scope of the ability of any normal subject, covering motor functions of the hand, verbal memory, receptive and expressive speech, basic ability to write and read, and basic arithmetic skills. The variation of the impairment scores was large in the group. There was a close relationship between the overall impairment score and the frontal cortical blood flow, illustrating the importance of frontal regions for the functions assessed.

Several global dementia rating scales to assess mental status have been developed. One of the most commonly used is the Mini-Mental State Examination (MMSE; Folstein *et al*, 1975). Two studies exploring relations between cortical blood flow and cognitive performance in FTD patients have (among other tests) used the MMSE as a measure of cognitive impairment (Jagust *et al*, 1989; Miller *et al*, 1991). Miller *et al* (1991) studied eight patients with frontal lobe dementia using ^{133}Xe and

HMPAO SPECT. Performance on the MMSE was correlated with the SPECT findings, with a significant relationship found in posterior parietal but not in frontal areas. In a study of five patients with frontal lobe dementia, significant correlations were reported between MMSE performance and SPECT findings in the inferior frontal and parietal cortex (Jagust *et al*, 1989). However, the correlations found in these two studies can be questioned with regard to the limited number of FTD patients examined. Jagust *et al* (1989) have underlined the limitations of brief cognitive rating scales such as the MMSE, since they tend to underestimate the severity of frontal lobe dysfunction, and emphasise cognition more than behaviour. The items of the present impairment scale were selected to provide a global cognitive assessment. Since in the present study impairment scores were associated with a decrease of rCBF in frontal regions, the selected items appear to be more related to frontal than to postcentral functions. Nevertheless, no definite conclusion about any difference between our global impairment scale and the MMSE can be drawn since the MMSE was not administered in the present study.

Correlations between rCBF and specific neuropsychological tests

The FTD patients showed varying ability to perform the four more specific neuropsychological tests. A floor effect was apparent, since 4 of the 16 patients were not able to complete any of the specific neuropsychological tests. High correlations were found between the verbal fluency test and left frontal lateral, frontal medial and left temporal anterior inferior ROIs.

In the study by Miller *et al* (1991), six patients able to complete more specific neuropsychological tests performed badly on three of four frontal lobe tests, among them a verbal fluency test. In addition, four patients in the study of frontal lobe dementia by Jagust *et al* (1989) were tested with the MMSE; these FTD patients performed more poorly than DAT patients on tests of verbal fluency but had better memory. Similarly, Frisoni *et al* (1995), in an investigation of 16 FTD and 10 DAT patients, demonstrated poorer verbal fluency in FTD than in DAT patients. Furthermore, frontal hypoperfusion was more prominent in the FTD than in the DAT patients. However, in a study of 10 FTD and 10 DAT patients by Pasquier *et al* (1995), FTD patients did not differ from DAT patients in a verbal letter fluency test or in a verbal category fluency test. All patients with FTD had frontal hypoperfusion on SPECT, but no correlation between frontal index, frontal/parietal index, and fluency was found. Thus the results of these studies disagree.

In the present study there was no association between performance on the visuospatial test (Block Design) and rCBF in any region. However, in DAT patients examined by O'Brien *et al* (1992) a correlation between Block Design scores and right parietal blood flow was found. Visuospatial constructional ability depends mainly on the integrity of the parietal cortex, which in our group of FTD patients appeared to be intact, as indicated by the SPECT findings. There were no significant correlations between performance on the verbal ability test or the verbal memory test and rCBF in any region (Table 3).

Conclusions

In the current study no relationship between decrease in rCBF and age at onset or duration of disease or between impaired cognitive function and age at onset or duration of disease could be revealed. This might be explained by the high variability of duration of illness and rate of progression in FTD (Neary *et al*, 1988; Gustafson, 1992).

The results show strong relationships between verbal fluency and relative blood flow in the frontal and left temporal anterior inferior areas. Nevertheless, because of floor effects, the use of verbal

Clinical implications

- The results show a close coupling between reduced rCBF and specific neuropsychological deficits in FTD.
- The present global impairment scale might be useful for following the progress of even severely impaired FTD patients.
- No relationship between decrease in CBF or impaired cognitive function and age at onset or duration of disease could be demonstrated.

Limitations

- Autopsy-verified diagnosis was available for only one of the patients.
- The impairment scale has not been compared with other brief cognitive rating scales (e.g. the MMSE).
- No comparison with other dementia groups was made.

fluency tests is limited in late-stage FTD. However, the present global impairment scale is applicable for more impaired patients. The relative absence of a floor effect makes this scale useful in detecting and following the progress of frontal deficiencies in FTD patients.

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Christina I. Elfgren, MSc, Department of Psychogeriatrics; **Erik Ryding**, MD, Department of Clinical Neurophysiology; **Ulla Passant**, MD, Department of Psychogeriatrics, University Hospital, Lund, Sweden

Correspondence: Christina I. Elfgren, MSc, Clinical Neuropsychologist, Department of Psychogeriatrics, University Hospital, PO Box 638, S-22009 Lund, Sweden

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