

Demographic, neurological and behavioural characteristics and brain perfusion SPECT in frontal variant of frontotemporal dementia

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We conducted a French multicentric cross-sectional study to describe in detail the demographic, neurological and behavioural characteristics of the frontal variant of frontotemporal dementia (fvFTD) and to characterize the pattern of brain perfusion SPECT in comparison to a healthy control group. A total of 68 fvFTD patients had technetium-99m-ECD brain perfusion SPECT at inclusion, 61 of which also underwent an in-depth evaluation including 70 items assessing behaviour, language and affect/emotion at onset and at inclusion. The mean age-at-onset was 60.4 ± 7.8 years (35–75). Twenty-six per cent of the patients were older than 65 at onset. A positive familial history consistent with an autosomal dominant inheritance was found in 18% of the patients. At onset, the behavioural profile was predominantly inert in 25% of the patients, disinhibited in 18% and mixed in others. The behavioural features progressed to predominantly mixed or inert forms. Although, inertia was associated with predominant medial frontal and cingulate hypoperfusion, and patients with disinhibition exhibited predominant ventromedial prefrontal and temporal hypoperfusion, there were no major clinical differences between disinhibited and inert patients. Forty-five per cent of the deceased patients survived <6 years (short survival), and 34% of the patients survived >8 years (long survival). This shows that the final outcome of fvFTD is highly variable. No clinical factors predictive of short or long survival were identified. Unexpected,

however, was the finding that brainstem hypoperfusion distinguished patients with a short survival from patients with long survival. In conclusion, this study shows that fvFTD is clinically a rather homogeneous entity. It also provides evidence that different behavioural presentations at onset are related to different anatomical localizations of degenerative damage. Finally, it demonstrates the prognostic value of brainstem hypoperfusion in a subgroup of patients with a short survival.

Keywords: frontotemporal lobar degeneration; fvFTD; frontotemporal dementia; *MAPT* gene; SPECT; SPM

Abbreviations: FTLT = frontotemporal lobar degeneration; fvFTD = frontal variant of frontotemporal dementia; MND = motor neuron disease; PNFA = progressive non-fluent aphasia

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Introduction

Frontotemporal lobar degeneration (FTLD) accounts for up to 20% of dementias in the presenium (Brun, 1987; Ratnavalli *et al.*, 2002; Kertesz *et al.*, 2003; Hodges *et al.*, 2004). It is characterized by prominent and gradual behavioural and language disorders, whereas instrumental functions and memory are relatively preserved. The onset usually occurs before the age of 65. Diagnostic criteria were established in 1994 (The Lund and Manchester groups, 1994) and revised by Neary *et al.* (1998) and McKhann *et al.* (2001). Based on the clinical presentation, Neary *et al.* distinguished variants of FTLT with signature sets of presenting symptoms and regional patterns of atrophy (Neary *et al.*, 1998): semantic dementia and progressive non-fluent aphasia (PNFA), both characterized by prominent language disorders (Mesulam, 1982; Hodges *et al.*, 1992, 1999; Hodges and Patterson, 1996; Snowden *et al.*, 1996), and the frontal variant of frontotemporal dementia (fvFTD), with predominant behavioural dysfunction, dominated by either inertia or disinhibition. Disinhibition is associated with atrophy of the orbito-medial frontal lobes and temporal pole, whereas inertia is associated with widespread frontal lobe atrophy that extends to the dorsolateral frontal cortex (Snowden *et al.*, 2001; Kertesz *et al.*, 2003; Sarazin *et al.*, 2003; Rosen *et al.*, 2005).

Brain perfusion SPECT provides an independent diagnostic criterion for FTLT. Early perfusion anomalies suggesting degenerative changes can be detected routinely. This method of functional imaging shows that left temporopolar hypoperfusion is associated with semantic dementia, left perisylvian hypoperfusion with PNFA; in the frontal variant different patterns of hypoperfusion in frontal association, insular and anterior temporal cortices have been reported (Didic *et al.*, 1998; Hodges, 2001).

The definite diagnosis of FTLT is made by neuropathological examination. Most pathological studies included the whole spectrum of FTLT disorders (Hodges *et al.*, 2004; Johnson *et al.*, 2005; Kertesz *et al.*, 2005; Knopman *et al.*, 2005; Forman *et al.*, 2006; Josephs *et al.*, 2006). The major pathological subtypes are FTLT with tau-positive pathology, including FTDP-17, Pick's disease, corticobasal degeneration and supranuclear palsy and FTLT with tau-negative

ubiquitin-positive inclusions (FTLT-U). Recent neuropathological studies emphasized the importance of the FTLT-U subtype (Hodges *et al.*, 2004; Lipton *et al.*, 2004; Taniguchi *et al.*, 2004; Johnson *et al.*, 2005; Shi *et al.*, 2005; Forman *et al.*, 2006; Josephs *et al.*, 2006). Dementia lacking distinctive histological features, i.e. that are tau-negative and ubiquitin-negative, is very rare (Lipton *et al.*, 2004; Josephs *et al.*, 2006), as are dementias with neurofilament-positive inclusions (Cairns *et al.*, 2003, 2004).

A positive family history is present in 20–56% of the patients with FTLT (Stevens *et al.*, 1998; Chow *et al.*, 1999; Ratnavalli *et al.*, 2002; Hodges *et al.*, 2003; Sleegers *et al.*, 2004). The mode of inheritance is autosomal dominant in the majority of cases. Interest in FTLT has increased during the past decade, since hereditary fvFTD was found in some cases to be associated with mutations in the microtubule associated protein tau (*MAPT*) gene (Hutton *et al.*, 1998). Two other genes, *VCP* (Watts *et al.*, 2004) and *CHMP2B* (Skibinski *et al.*, 2005) are responsible for a minority of familial cases. Recently, mutations in the *PGRN* gene, coding for progranulin were found in FTLT-U families (Baker *et al.*, 2006; Cruts *et al.*, 2006). The frequency of *PGRN* mutations in FTD patients is 5% and reaches 10–20% in familial forms of the disease (Gass *et al.*, 2006).

Since the diagnostic criteria were established, several cohort studies have been performed on patients with FTLT, most of which included all three variants (PNFA, semantic dementia and frontal variant) with few distinctions. Although, fvFTD is the most frequent type, no large cohorts focusing specifically on fvFTD patients have been studied. We therefore undertook a French multicentric cross-sectional study of a large number of patients with fvFTD, in order to describe in detail the demographic, neurological and behavioural characteristics of this variant and to characterize the pattern of brain perfusion SPECT in fvFTD in comparison to a healthy control group. Particular attention was given to the potential effect of age-at-onset, behavioural presentation at onset (disinhibited/inert), family history and length of survival to evaluate whether these characteristics are associated with a particular form of the disease or specific brain perfusion patterns. We also studied

the progression of the disease, the factors predictive of long or short survival and the progression of hypoperfusion in the course of the disease.

Material and methods

Study design and diagnostic criteria

A large national multicentric cross-sectional open-cohort study of patients with fvFTD was performed between December 1996 and October 2005. Patients with the fvFTD were recruited by the French FTD research network, a group of 12 centres from 12 different university hospitals with expertise in the field of dementia. All centres applied standardized evaluations and diagnosis procedures. The patients had neurological examinations, behavioural evaluations, neuropsychological tests, brain MRI and brain perfusion ECD-SPECT studies. SPECT was performed in all patients within 3 months of their clinical inclusion.

The diagnosis of FTD was based on the revised Lund and Manchester criteria (The Lund and Manchester groups, 1994; Neary *et al.*, 1998). Additional criteria for the diagnosis were based on the SPECT and neuropsychological results. All patients with doubtful diagnosis or inconsistent brain perfusion SPECT or neuropsychological profiles were excluded.

Our study focused on patients who met the criteria for fvFTD. Patients with semantic dementia or PNFA were not included in this series. Other exclusion criteria were: acute onset, history of alcohol or drug abuse, endocrinal pathologies, vascular illness, lesions on brain imaging, severe psychiatric disease, early impairment of praxis and spatial skills, inflammatory, infectious or vascular diseases, Alzheimer's disease or other suspected neurodegenerative dementias (progressive supranuclear palsy, corticobasal degeneration and Lewy body dementia) according to the international consensus diagnosis criteria (Lang *et al.*, 1994; Litvan *et al.*, 1996; McKeith *et al.*, 1999). Patients with both FTD and motor neuron disease (FTD-MND), which were recruited massively for another study ($n = 140$), were also excluded to avoid a bias caused by their overrepresentation. All the patients who developed MND during the follow-up or who had relatives with FTD-MND or isolated MND were also excluded.

Standardized charts were used by all of the neurologists in the network to record all the demographic, neurological, behavioural and neuropsychological evaluations. At the end of the study, the clinical, behavioural, neurological, neuropsychological, brain imaging and brain perfusion SPECT data of all the patients were reevaluated independently by two experts (C.T.A. and B.D.) to ascertain the clinical diagnosis of fvFTD and validate their definite inclusion in the study. Sixty-eight patients were finally included, 61 of which underwent both behavioural and SPECT evaluations and seven additional patients fulfilling the same diagnostic criteria for fvFTD who had brain SPECT perfusion did not undergo the detailed behavioural evaluation. This study was approved by the Medical Research Ethics Committee of 'Assistance Publique-Hôpitaux de Paris' and the ethics committee of the Salpêtrière Hospital.

Demographic, neurological and behavioural evaluations

The patients and the principal informant were interviewed to obtain demographic data, and information concerning behavioural

and neurological changes in the patient. The age-at-onset was defined as the age when the first symptom appeared as reported by the principal informant. In almost all cases, a second informant was questioned independently to accurately determine the age-at-onset and signs at onset. Behavioural symptoms occurring during the two first years of the disease were considered present at disease onset. Age-at-onset of neurological signs was determined by follow-up examinations or in medical records when neurological signs occurred before inclusion.

Information concerning four generations, the patient, his/her parents and grandparents, their siblings and children, was also collected. The familial history was considered certain when three patients were affected with a history of a disease among the FTLD spectrum in at least two successive generations and probable when only two patients were affected in the same family. Cases were considered sporadic when there was no FTLD in the family over three generations. They were considered possibly sporadic when there was no other case in the family, but the family history was incomplete or censored—e.g. a parent died before the age of 70 years.

A detailed behavioural inventory was constructed to evaluate behavioural signs in a standardized manner at disease onset and at inclusion in the study. There were 70 items evaluating inertia, disinhibition, affect/emotion, eating/oral behaviours, stereotyped and ritualistic behaviours, attention/executive dysfunctions, speech disorders and others (delusions, hallucinations, delirium, escape, somatic complaint, tiredness, impatience and echopraxia). For each item, the informant was asked to recall the age-at-onset of the symptom and its progression between onset and inclusion in the study. To determine whether the patient was distressed or concerned when confronted with his/her functional disabilities, he was questioned about his awareness of his disease, his behavioural changes and his memory disorders. The informant was also questioned about the patient's awareness of the same signs. At the end of the behavioural interview, each referent neurologist was asked to determine the behavioural profile of the patient at onset as disinhibited, inert or mixed, based on this detailed interview.

Neuropsychological evaluation

The patients were evaluated with a standardized neuropsychological battery including the Mini Mental Status Examination (MMSE) (Folstein *et al.*, 1975), the MATTIS Dementia Rating Scale (MDRS) (Mattis, 1988), the Frontal Assessment Battery (Dubois *et al.*, 2000), the Wisconsin Card Sorting Test (WCST) (Nelson, 1976) and the Free and Cued Recall Test (Van der Linden *et al.*, 2004).

Behavioural categorization: inert/disinhibited/mixed

One aim of the study was to determine whether specific characteristics are associated with a predominantly disinhibited or inert behavioural presentation. The patients were separated into three groups according to the most prominent profile at onset: disinhibition (D), inertia (I) or mixed (M), according to the evaluation of the referent neurologist. To ensure the reliability of this classification, a second evaluation was performed by two experts (B.D. and C.T.A.) that independently reviewed the behavioural data and validated the final classification of all the patients.

Progression of the disease and analysis of factors predicting survival time

Little is known about the natural history of fvFTD. The progression of behavioural signs was evaluated between onset and inclusion. In addition, the informants were contacted at the end of the study to determine whether the patients were still alive or their age at death, as well as the disease duration when they became mute, bedridden or were institutionalized.

Another aim of the study was to evaluate survival and to determine the factors predictive of shorter or longer survival. The mean survival of FTD patients after onset is 6 (Hodges *et al.*, 2003) to 8 years (Neary *et al.*, 2005; Rascovsky *et al.*, 2005). Patients who died within 6 years were considered to have survival times shorter than the mean. Those who were still alive 8 years after onset of the disease were considered to have longer survival times than the mean. We have examined whether demographic, neurological or behavioural characteristics influence survival time. Particular attention was paid to age-at-onset, the presence of a parkinsonian syndrome, the loss of awareness of the disease, medication, mode of inheritance and genetic factors.

Brain perfusion SPECT

A total of 68 patients underwent brain SPECT perfusion. Twenty-eight neurologically healthy controls, matched for age, were also included in this study (65.6 ± 10.1 years). Brain perfusion SPECT was acquired in seven centres, with gamma-cameras that differed with respect to field of view, spatial resolution and collimators. Normal subjects data came from two of these centres. Acquisition was performed resting in quiet surroundings with the eyes closed after an intravenous injection of 740–925 MBq of ^{99m}Tc -ECD). A voxel-by-voxel intergroup study was performed with SPM2. We minimized the centre effect by filtering and masking as reported previously (Herholz *et al.*, 2002). Images were first converted from the DICOM to the Analyze format using MRIcro, then transferred to SPM2. The data were then standardized with respect to the Montreal Neurological Institute atlas with a 12-parameter affine transformation, followed by non-linear transformations and a trilinear interpolation. Dimensions of the resulting voxel were $2 \times 2 \times 2$ mm. Images were then smoothed by a Gaussian filter of 12 mm FWHM that was limited to measured brain tissue. A grey matter mask was defined by voxels that had an intensity above whole-brain average on low- and high-resolution scanner types (Herholz *et al.*, 2002). Non-measured voxels were excluded from analysis. Global normalization was performed using proportional scaling. The SPM {T} maps were obtained at a height threshold of $P = 0.05$, corrected for multiple comparisons for the cluster. At this corrected threshold, no differences in brain perfusion were observed in patients of different centres using non-parametric or parametric statistical analysis, when age, gender and disease duration were considered as nuisance variables, except for a small area including the bilateral primary visual cortex, which was thereafter excluded from group and subgroup analysis. Age, gender and disease duration were considered as nuisance variables, when they differed statistically among the subgroups studied.

Comparisons and statistical analyses

Statistical analyses were conducted using SAS software version 8.2. Centres were analysed as a covariate to evaluate if there was an effect on the demographic data, age-at-onset, disease duration at

inclusion, or neurological, behavioural and neuropsychological data. There were no statistical differences among the reference centres.

Clinical study

Each item of the behavioural interview, the neurological and the neuropsychological examinations was analysed individually. χ^2 and Student tests were used to compare the demographic data (age-at-onset, age at inclusion, disease duration at inclusion, gender and educational level), 70 behavioural items at onset and at inclusion, neurological signs at inclusion, mean scores of neuropsychological tests and proportion of disinhibited/inert patients in the following subgroups of patients: (1) hyphen; age-at-onset below 65 compared to age-at-onset >65 , (2) hyphen; familial compared to non-familial cases, (3) hyphen; disinhibited compared to inert presentation at onset, (4) hyphen; groups with slow (e.g. disease duration ≤ 6 years) or fast progression (≥ 8 years). Given the large number of comparisons, a threshold at 0.01 was considered to be significant. Fisher's exact test and Wilcoxon test were performed to compare groups of small size.

SPECT study

Comparisons of regional brain perfusion were performed in the same subgroups of patients defined by age-at-onset, familial history of FTLT, behavioural profile at onset and survival time. For analysis of the age-at-onset, the healthy control group was divided in two subgroups: controls younger than 65 years were compared to patients with onset before 65 years, and controls older than 65 years compared to patients with age-at-onset older than 65 years. We also evaluated the progression of the functional change with the course of the disease by comparing three subgroups of patients at different stages of the disease: group 1 with a disease duration <3 years (29%, 20/68), group 2 with a disease duration of 3–5 years (47%, 32/68) and group 3 with a disease duration >5 years (24%, 16/68). The χ^2 -test or ANOVA followed by the Tukey test were used to compare the three groups of patients at different stages of the disease.

Results

General characteristics of the patients

Demographic features

Almost all patients were French (59/61). One was North African and one Portuguese. The demographic characteristics of this population are detailed in Table 1. The mean age-at-onset was 60.4 ± 7.8 years (35–75) and the mean duration at inclusion 4.0 ± 3.5 years (1–10). The family history was censured in 18 patients, due to the advanced age of the patient at onset of the disease. Eleven patients had a positive familial history consistent with autosomal dominant inheritance; 32 had no family history of the disease. Therefore, the frequency of familial forms was 18% (11/61) in our population of patients using stringent criteria for the presence of a family history and 25% (11/43) in the population with documented family history.

Neurological signs (Table 2)

At the time of inclusion, a parkinsonian syndrome was present in 18% of the patients; it occurred 5.2 ± 2.4 years (1–9) after onset of the disease. An akinetorigid form (60%) was more frequent than rest tremor (40%). Other movement

Table 1 Demographic and behavioural characteristics and neuropsychological performances of patients with fvFTD included in the clinical and in the SPECT studies

	Clinical study	SPECT study ^a
Demographic characteristics		
Number of patients	<i>n</i> = 61	<i>n</i> = 68
Gender, male/female (number)	36/25	41/27
Inheritance, familial/non-familial (%)	18/82	18/82
Educational level (%)		
Primary	67	68
Secondary	24	23
High school	9	9
Mean age-at-onset, years \pm SD (range)	60.4 \pm 7.8 (35–75)	61.0 \pm 7.9 (35–75)
Age-at-onset older than 65 (number of patients)	26% (16)	27% (19)
Age-at-onset older than 70 (number of patients)	7% (4)	9% (6)
Mean age at inclusion, years \pm SD (range)	64.3 \pm 7.2 (43–79)	64.9 \pm 7.3 (41–79)
Mean disease duration at inclusion, years \pm SD (range)	4.0 \pm 3.5 (1–10)	3.9 \pm 2.3 (1–11)
Disease duration 1–2 years (%)	30	29
Disease duration 3–5 (%)	48	47
Disease duration >5 (%)	22	24
Behavioural forms ^b		
Inert (%)	25	25
Disinhibited (%)	18	19
Mixed (%)	57	56
Survival		
Survival \leq 6 years (number of patients)	9	9
Survival \geq 8 years (number of patients)	21	24
Neuropsychological characteristics		
MMS ^c (<i>n</i> = 45/52)		
Total score (range)	21.4 \pm 5.4 (2–29)	21.5 \pm 5.6 (2–29)
MDRS ^d (<i>n</i> = 44/48)		
Total score (range)	109.0 \pm 17.5 (70–141)	107 \pm 19 (55–141)
WCST ^e (<i>n</i> = 24/28)		
Number of categories	2.1 \pm 1.4 (1–6)	1.8 \pm 1.5 (0–6)
Number of perseverative errors	21.1 \pm 13.8 (2–42)	26.8 \pm 14.7 (2–55)
Number of maintaining errors	3.8 \pm 2.2 (1–6)	4.3 \pm 2.6 (1–8)
FAB ^f (<i>n</i> = 41/41)		
Total score	9.4 \pm 4.4 (1–17)	9.4 \pm 4.4 (1–17)
FCRT ^g (<i>n</i> = 36/39)		
Free recall	12.9 \pm 6.3 (1–28)	12.4 \pm 6.8 (0–28)
Total recall	34.8 \pm 10.1 (1–48)	35.1 \pm 9.9 (5–48)
Index sensitivity (%)	68.4 \pm 24.2 (25–100)	65.4 \pm 24.3 (25–100)

The number of patients evaluated is given in parenthesis (clinical study/SPECT study). SD: standard deviation.

^aIncluding 61 patients of the clinical study and 7 additional fvFTD patients.

^bSee Material and methods.

^cFolstein *et al.* (1975).

^dMattis (1988).

^eNelson (1976).

^fDubois *et al.* (2000).

^gVan der Linden *et al.* (2004).

Table 2 Clinical characteristics of 61 patients with fvFTD at inclusion (4.0 years of disease duration)

Neurological signs	
Primary reflexes	
Grasping	36%
Sucking	10%
Urinary incontinence	13%
Parkinsonian syndrome	18%
Pyramidal signs	13%
Postural tremor	3%
Oculomotor disorders	5%
Eyelid apraxia	2%

disorders were less common (8%). The most frequent was postural tremor, present in 3% of the patients. Oculomotor disturbances were noted in 5% of the patients and consisted mainly in slow saccades (4%) and up-gaze limitation (1%), after verification that none of these patients had parkinsonian syndrome or fulfilled the international consensus diagnosis criteria for progressive supranuclear palsy (Litvan *et al.*, 1996).

Behavioural symptoms at onset of disease

The present study evaluated 70 items characteristic of behavioural disorders. The frequency of each item present at

onset is indicated in Table 3 and their categories in Fig. 1. The most frequent signs were loss of awareness (65%), reduction in activities of daily living (54%), loss of interest (54%), loss of initiative (51%), lack of empathy/indifference to others (49%), apathy (43%), logopenia (42%), social withdrawal (41%), self-centredness (41%) and decreased attention (41%). Eighty-eight percent of the patients had at least one of the three most frequent behavioural items at onset (loss of awareness, reduction in activities of daily living and loss of interest). Five percent of the patients had delirium and 2% had hallucinations at the onset of the disease.

The 70 behavioural items reflect the major behavioural categories: inertia, disinhibition, affect/emotion disorders, eating/oral behaviours, stereotyped and ritualistic behaviours and speech disorders (Table 3) (Gustafson, 1993; Neary *et al.*, 1998; McKhann *et al.*, 2001; Snowden *et al.*, 2002). The frequency of the patients presenting at least one sign in each behavioural category at onset has also been evaluated (Fig. 1).

Neuropsychological evaluation

The neuropsychological profile was consistent with the diagnosis of FTD in all patients that could be tested. Some patients were not able to undergo the full battery of tests at inclusion, mainly because of the severity of the disease. The mean scores for each test are given in Table 1 and in the Supplementary Table 1.

Behavioural categorization: inert/disinhibited/mixed

At onset of the disease, the majority of the patients were mixed (57%, $n = 35/61$ patients). Twenty-five percent were inert ($n = 15/61$ patients) and 18% ($n = 11/61$) disinhibited. However, after a mean disease duration of 4 years, at the time they were included in the study, the behavioural disorders had progressed towards a mixed or inert profile: 100% of the disinhibited patients developed at least one sign of inertia and 55% of inert patients developed one sign of disinhibition (Fig. 1).

Comparisons of disinhibited and inert patients

The groups were similar in terms of gender, educational level, mode of inheritance, mean age-at-onset and mean disease duration at inclusion. All the characteristics were similar in inert and disinhibited patients, except for a few behavioural signs: as expected and inherent to the study, all behavioural signs related to inertia were more frequent in inert patients and those related to disinhibition were more frequent in disinhibited patients. All other items evaluating affect/emotion, eating/oral, stereotyped/ritualistic behaviours, attention/executive dysfunctions and speech disorders were similar in inert and in disinhibited patients. The frequency of neurological signs and the severity of

dementia, evaluated by the mean scores of neuropsychological tests, were similar at inclusion (data not shown).

Influence of various parameters on the general characteristics of the disease

There were only small effects of age-at-onset and mode of inheritance on the characteristics of fvFTD. Some behavioural items were significantly more frequent in patients with an older age-at-onset (excessive spending) or in non-familial forms (poor judgement). Otherwise the age-at-onset and the mode of inheritance had no effect on the demographic, behavioural, neurological characteristics, neuropsychological performance or survival (data not shown).

Progression and factors predictive of survival time

Progression of the disease

Thirty-two patients (52%) were still alive at the end of the study (October 2005). In these patients, the mean disease duration was 7.8 ± 3.7 years (1–14). Contact was lost with nine patients (15%) after a mean follow-up of 3.0 ± 0.9 years (2–5). Twenty patients (33%) died in the course of the study, after a mean disease duration of 6.9 ± 3.6 years (2–14). The mean age at death was 68.7 ± 9.3 years (49–84). All patients, except two, died of the disease. The causes of death were difficulty swallowing and aspiration pneumonia or complications because they were bedridden. The neuropathological diagnosis in one case that came to autopsy was a tau-negative ubiquitin-negative type of dementia.

Six percent of the patients were institutionalized at inclusion. The mean interval between onset of the disease and institutionalization was 6.2 ± 1.8 years (4–9). Sixteen patients were mute after mean disease duration of 6.4 ± 3.4 years (4–13). Between inclusion and the end of follow-up, 8% of patients became bedridden a mean of 6.0 ± 2.8 years (4–10) after onset of the disease.

Progression of behavioural symptoms

At inclusion, i.e. 4.0 ± 3.5 years after the onset of the disease, almost all behavioural disorders had progressed. The symptoms that progressed most were overeating/gluttony, bulimia, food fads, monosyllabic answers, logopenia, echolalia and obsessive/compulsive rituals. The categories or behavioural disorders that progressed most were the stereotyped/ritualistic behaviours, eating/oral and speech disorders (Fig. 1).

Survival and predictive factors

Nine patients had short survival times and died within 6 years of onset (45% of the deceased patients, 9/20; 15% among the overall population). In this group, the mean disease duration before death was 4.6 ± 1.7 years (1–6). All these patients were followed until their death, and none developed MND. Twenty-one patients survived 8 years or more (34%). In this group, the mean disease duration was

Table 3 Frequencies of behavioural symptoms at disease onset

Behavioural disorders	Very frequent signs ($\geq 25\%$)	Frequent signs (10–25%)	Rare signs ($\leq 10\%$)
Inertia	Reduction in activities (54%) Loss of interest (54%) Loss of initiative (51%) Apathy (43%) Social withdrawal (41%) Self-centredness (41%) Lack of projects (34%) Aspontaneity (33%)	Neglect of administrative tasks (21%) Neglect of clothing/hygiene (16%)	
Disinhibition	Impulsivity (28%)	Euphoria (23%) Excessive spending (21%) Inappropriate laughing (18%) Excessive familiarity (18%) Physical/clothing disinhibition (15%) Incessant wandering (12%) Aberrant behaviours (12%) No moral perception (12%) Verbal violence (12%)	Coarseness (10%) Verbal disinhibition (10%) Physical violence (10%) Sexual disinhibition (8%) Exhibitionism (7%) Offensive behaviours (2%)
Affect and emotion disorders	Loss of awareness (65%) Lack of empathy/Indifference to others (49%) Sadness (31%)	Emotional lability (18%) Anxiety (15%) Irritability/anger (33%)	Exaggerated emotional display (10%) Suicidal ideas (5%)
Eating and oral behaviours		Altered food preferences (20%) Bulimia (16%) Overeating/gluttony (11%)	Alcohol abuse (10%) Food fads (10%) Tobacco abuse (3%) Oral exploration of objects (2%)
Stereotyped and ritualistic behaviours		Ritualistic behaviours (13%) perseverative behaviours (13%) Inflexibility/rigid adherence (12%) Hoarding (12%)	Fixed ideas (8%) Cleaning rituals (6%) Obsessive/compulsive rituals (5%)
Speech disorders	Logopenia (42%)	Verbal preservations (15%) Verbal stereotypies (12%)	Monosyllabic answers (8%) Inappropriate discourse (5%) Humming (5%) Echolalia (3%) Pallilalia (2%) Vocalizations (1%)
Attention and executive disorders	Loss of attention (41%) Memory disorders (36%) Distractibility (30%) Poor judgement (28%)	Loss of perspicacity (15%)	
Others		Impatience (20%) Tiredness (16%)	Somatic complaints (7%) Escape (5%) Delusions (5%) Delirium (5%) Echopraxia (3%) Hallucinations (2%)

The percentage of patients having each sign is noted in parentheses.

10.9 \pm 2.1 (8–15). Short and long survival groups had similar ages at inclusion. Age-at-onset, gender, mode of inheritance, behavioural profile, associated neurological signs and neuropsychological performances had no effect on survival; nor did parkinsonian signs, loss of awareness of the disease or medication (neuroleptic or serotonergic re-uptake inhibitors) (data not shown).

Brain perfusion SPECT of fvFTD patients

The 61 patients who underwent detailed clinical and behavioural evaluations and seven additional patients were included in the SPECT study. This large population of patients ($n = 68$) had strictly similar disease duration at inclusion and demographic, behavioural, neuropsychological and survival characteristics to the clinical cohort (Table 1).

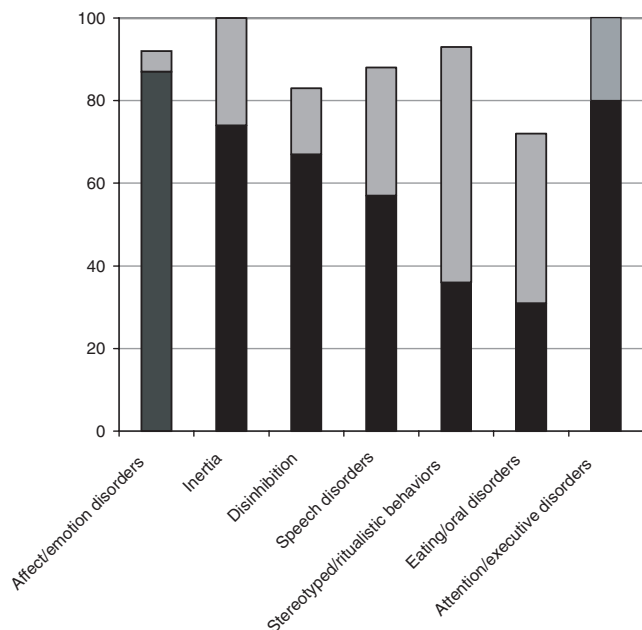


Fig. 1 Progression of behavioural categories between disease onset and the inclusion in the study (mean disease duration of 4.0 ± 3.5 years). The frequency of patients having at least one symptom of each behavioural categories was evaluated at onset (black bars) and at inclusion (grey bars).

The only difference was found in the comparison of the disease duration at inclusion in the groups of patients with ages at onset under or over 65. The disease duration was similar in the 2 groups in the clinical study ($n = 61$), but significantly different in the enlarged series of 68 patients because five of the seven additional patients that were included in the SPECT study had ages at onset over 65 (see below).

Brain perfusion in the overall population

In comparison to the healthy age-matched control group, fvFTD patients had bilateral anterior hypoperfusion, affecting association frontal, temporal, cingular and insular cortices. The region of temporal hypoperfusion included the amygdala and hippocampus. There was also bilateral hypoperfusion in the thalamus and striatum (Fig. 2, Supplementary Table 2).

Profiles of perfusion according to age-at-onset

Duration of the disease at the time of inclusion in the study was significantly different in the following two groups ($P = 0.004$): disease duration was 4.4 ± 2.4 years for patients with onset before the age of 65, and 2.7 ± 1.5 years for patients with onset after the age of 65. The cerebral perfusion patterns in these two subgroups were both evocative of fvFTD (Supplementary Fig. 1, Supplementary Table 3) because of predominant bilateral anterior predominant frontotemporal hypoperfusion. Consistent with the mean duration of the disease, age-at-onset before 65 years hypoperfusion was more severe and extensive in particular

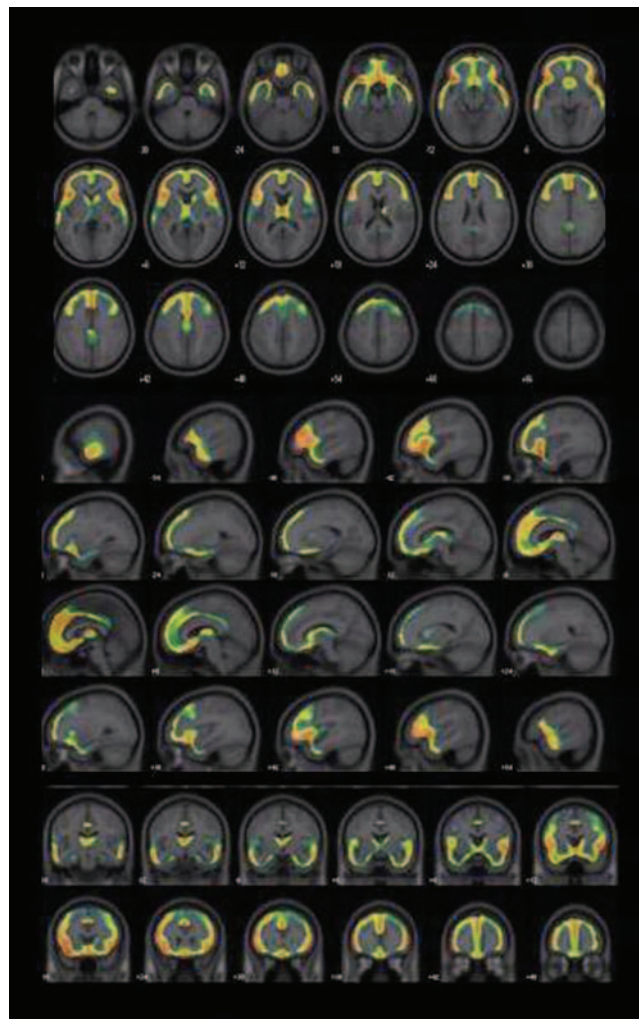


Fig. 2 Anatomical localization of peaks of hypoperfusions when comparing fvFTD patients to healthy subjects (pcluster-level < 0.05 ; corrected for multiple comparisons). fvFTD patients exhibited bilateral anterior hypoperfusion, including association frontal, temporal, cingular and insular cortices. Temporal hypoperfusion included amygdala and hippocampus. Thalami and striata were also hypoperfused (anatomical convention: right side = right hemisphere; left side = left hemisphere).

in the medial and dorsolateral frontal and cingular cortices. A much more severe hypoperfusion in mesiotemporal structures was noted for a subgroup of patients with onset after 65 despite shorter mean disease durations.

Perfusion patterns in patients with or without family histories

SPM analysis revealed no differences between familial and non-familial cases.

Perfusion pattern and behavioural profiles

Significant differences in cerebral perfusion developed in the course of the disease, however, in the three groups (disinhibition, inertia and mixed) (Fig. 3, Supplementary Table 4, Supplementary Figs 2 and 3).

Inert fvFTD subgroup vs healthy control group: in the course of the disease, the group of inert patients had preferential anterior bilateral frontal, cingular and insular hypoperfusion that was more prominent in the frontomesial and anterior cingulate cortices, and the dorsolateral prefrontal cortex. The ventromedial prefrontal and temporal cortices were relatively preserved.

Disinhibited fvFTD subgroup versus healthy control group: hypoperfusion in disinhibited patients was preferentially bilateral in the anterobasal frontotemporal region, predominating in the ventromedial prefrontal and anterior temporal cortex. Medial and dorsolateral prefrontal and anterior cingulate cortices were relatively preserved.

Mixed fvFTD subgroup versus healthy control group: patients with a mixed behavioural profile had perfusion characteristics that combined those of inert and disinhibited patients, with hypoperfusion bilaterally (i) in the anterior frontotemporal, cingular and insular regions, including the medial and dorsolateral prefrontal and anterior cingulate cortex and (ii) in the ventromedial prefrontal and anterior temporal cortex.

Progression of hypoperfusion in the course of the disease

The three subgroups of patients at different stages of the disease (group 1: disease duration <3 years, group 2:

3–5 years and group 3: >5 years) were similar in age, gender, age-at-onset, mode of inheritance and behavioural profile. Group 1 had hypoperfusion in the orbitoventral, temporo-occipital, mesiotemporal, cingular and insular cortex, but also in the thalami and striata. In group 2, frontal hypoperfusion was accompanied by frontomesial and dorsolateral hypoperfusion. Patients in group 3 also had a more posterior hypoperfusion, in the parieto-occipital cortex (Fig. 4, Supplementary Table 5).

Perfusion pattern in patients with short versus long survival times

Patients with longer survival times had severe and extensive cortical hypoperfusion, consistent with longer disease durations, whereas only patients with shorter survival exhibited hypoperfusion of the brainstem (Fig. 5, Supplementary Table 6).

Discussion

This study describes the demographic, neurological, behavioural, neuropsychological and SPECT characteristics of fvFTD. This study is the largest study specifically devoted to the frontal variant of FTD and provides further insight into brain perfusion SPECT characteristics of the fvFTD. The validity of this work is guaranteed by the expertise of the

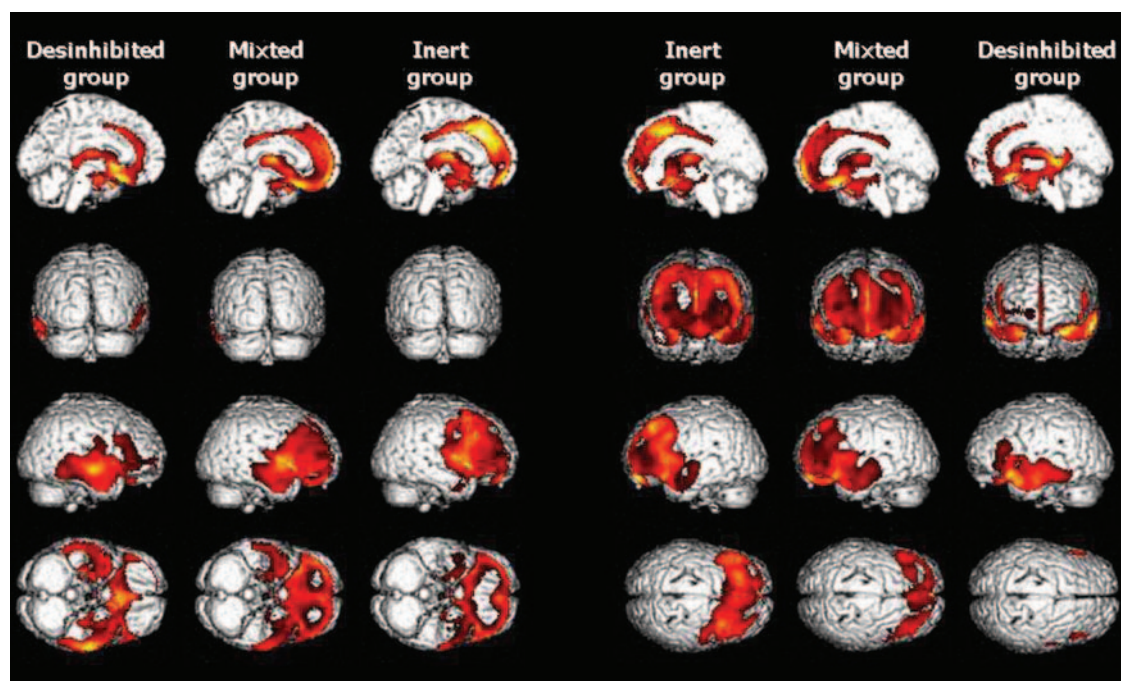


Fig. 3 Anatomical localization of peaks of hypoperfusions when comparing fvFTD clinical groups to healthy subjects (pcluster-level < 0.05; corrected for multiple comparisons): disinhibited group, inert group and mixed group. Inertia was associated with predominant medial frontal and cingular hypoperfusions, whereas patients with disinhibition exhibited predominant ventromedial prefrontal and temporal hypoperfusions. These findings were validated by the mixed group, which presented perfusion characteristics of both inert and disinhibited groups.

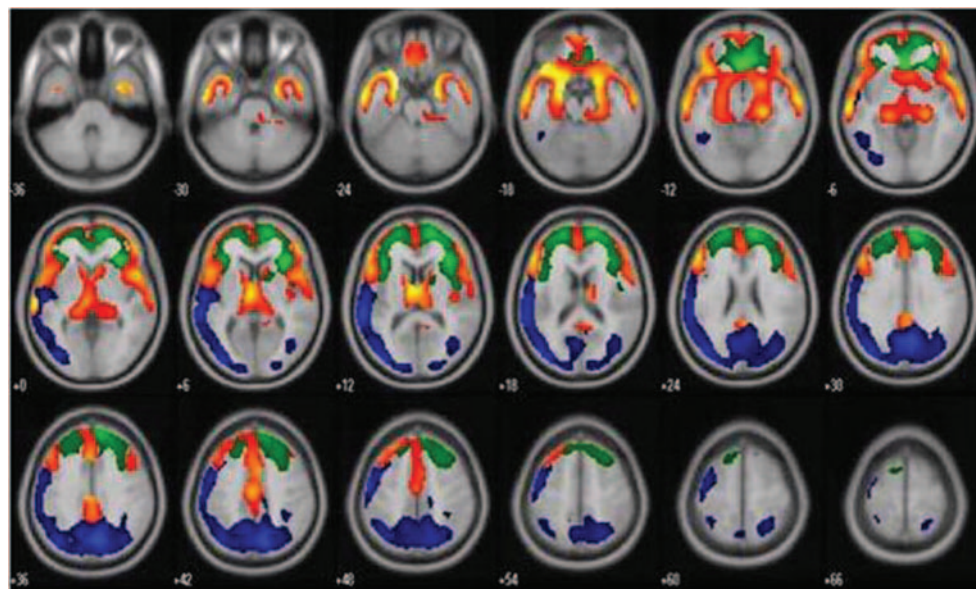


Fig. 4 Anatomical localization of peaks of hypoperfusions when comparing fvFTD subgroups to healthy subjects (pcluster-level < 0.05; corrected for multiple comparisons): patients subgroup with disease duration of 2 years or less (red), patient subgroup with a disease duration of 3 or 4 years (green), and patients subgroup with a disease duration of >4 years (blue). Early hypoperfusions involved orbitoventral, temporopolar, mesiotemporal, cingulate and insular cortices, but also thalami and striata. After 2 years of evolution, hypoperfusions were also found in medial and dorsolateral frontal areas. Patients with disease duration of >4 years showed in addition posterior hypoperfusion, involving the parieto-occipital cortex (anatomical convention: right side = right hemisphere; left side = left hemisphere).

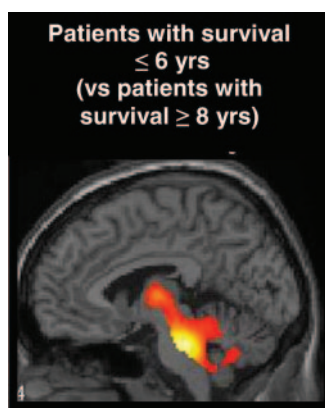


Fig. 5 Anatomical localization of peaks of hypoperfusions when comparing fvFTD patients whose survival is less than 6 years to patients whose survival is longer than 8 years (pcluster-level < 0.05; corrected for multiple comparisons). Patients with shorter survival had additional hypoperfusion of the brainstem.

referring neurologists, the double evaluation by independent experts, the SPECT methodology used to minimize the centre effect inherent in all multicentric neuroimaging studies and the comparison with a large healthy control group using voxel-based analysis. In addition, since most of the patients were evaluated at least twice and in most cases two informants were questioned about symptoms present at onset, recall bias has been minimized.

The proportion of patients with onset after 65 was high in our study (27%), but similar frequencies of fvFTD patients with onset after the age of 65 were found in other clinical (Rosso *et al.*, 2003; Borroni *et al.*, 2005; Rascovsky *et al.*, 2005) and pathological studies (Johnson *et al.*, 2005; Knopman *et al.*, 2005). Our study shows that clinical characteristics of patients with onset before or after the age of 65 years did not differ significantly in any respect. Moreover, the patterns of brain perfusion analysed by SPECT in these two subgroups were both evocative of fvFTD. Differences in perfusion in these two groups resulted from differences in disease duration, except for the more severe hypoperfusion of medial temporal structures in the older subgroup, despite a shorter mean disease duration. This pattern is probably not related to Alzheimer's disease, since this group of patients did not have parietal or retrosplenial hypoperfusion (Bonte *et al.*, 2004). These structures may therefore be more susceptible to ageing (Hsu *et al.*, 2002). These SPECT and clinical data demonstrate that these two populations are very similar and that there is only little effect of age-at-onset on the characteristics of fvFTD. The diagnosis of fvFTD should therefore be considered even in elderly patients.

There was also little effect of mode of inheritance on the characteristics of fvFTD. The clinical phenotype of familial cases of fvFTD was similar to that of sporadic cases. There was no major difference in the age-at-onset or the behavioural and neurological characteristics of patients

with family histories and those without. Brain perfusion patterns were also similar. This confirms previous results obtained in a smaller series of patients (Piguet *et al.*, 2004). This also reinforces the results of an autopsied-cases study, which showed similar behavioural features in familial and sporadic cases with ubiquitin-positive tau-negative inclusions (Godbolt *et al.*, 2005).

Early behavioural abnormalities are the hallmark of fvFTD (Neary *et al.*, 1998; Lindau *et al.*, 2000; McKhann *et al.*, 2001). The primary goal of this study was, therefore, to define the time of occurrence, the nature and the frequencies of the behavioural changes. The most frequent behavioural signs in the early stage of fvFTD in our series represent both affect/emotion disorders (loss of awareness and lack of empathy/indifference to others) and inertia (reduction in activities of daily living, loss of interest, loss of initiative and apathy). It is not surprising that affective and emotional disorders were the most frequent types of behavioural changes at onset, given the role of the orbital and ventromedial cortices in emotional control (Kertesz *et al.*, 2003; Sarazin *et al.*, 2003; Rankin *et al.*, 2004; Rosen *et al.*, 2005) and their early involvement in fvFTD (Broe *et al.*, 2003; Salmon *et al.*, 2003; Kril and Halliday, 2004).

Although they are usually considered essential for the diagnosis of fvFTD, no ritualistic/stereotyped behaviours or dietary changes were among the most frequent signs at onset (Bozeat *et al.*, 2000; Snowden *et al.*, 2001; Ikeda *et al.*, 2002; Shigenobu *et al.*, 2002; Nyatsanza *et al.*, 2003; Mendez *et al.*, 2005). This may be because the temporal variants of FTD, characterized by early speech disorders and more severe stereotyped behaviours (Seeley *et al.*, 2005), were excluded from our study. This may also be because we evaluated our patients at very early stages of the disease. Indeed, this study shows that these disorders became much more frequent with time. Interestingly overeating/gluttony were by far the symptoms that progressed most dramatically in the course of the disease in our study. Overeating is observed following bilateral lesion of the temporal cortex and amygdala in the Klüver-Bucy syndrome and therefore may result from the progression of degenerative brain damage to these structures in fvFTD (Cummings and Duchen, 1981). It may also be possibly related to the role of orbitofrontal cortex in the representation of gustatory sensorial information, the control of satiety and food preference (Rolls *et al.*, 1999; Rolls, 2005).

Similarly, the frequency of stereotyped behaviours reached 81% as the disease progressed. The most frequent behavioural stereotypes were fixed ideas, perseverative behaviours, hoarding and ritualistic behaviours. Verbal stereotypes were less frequent, even in a late stage of the disease. They did not discriminate between inert and disinhibited patients in our study, contrary to the observation of Snowden *et al.* (2001) who found verbal stereotypes significantly more frequently in disinhibited patients. The frequency of behavioural stereotypes was also

similar in all groups of patients, showing that these disorders are not associated with a particular form of fvFTD.

This prospective study on a large multicentric cohort provides further insight into brain perfusion SPECT characteristics of fvFTD. Our methodology aimed to minimize centre effects, and patients group comparison across centres did not yield significant differences, therefore a centre effect biasing our results seems unlikely. This SPECT study confirms that fvFTD patients have significant bilateral anterior hypoperfusion, affecting association areas in the frontal lobes and in the temporal, cingular and insular cortex, but also the thalamus and the striatum. Temporal hypoperfusion included the amygdala and the hippocampus. These findings confirm in a larger group of patients the results of previous imaging or pathological studies (Kamo *et al.*, 1987; Miller *et al.*, 1991; Hooten and Lyketsos, 1996; Santens *et al.*, 2001; Jeong *et al.*, 2005). In particular, hypoperfusion in subcortical regions does not seem to be due to artefacts of SPM spatial normalization, which can fail in periventricular structures where there is brain atrophy, since it was observed in our study even at the beginning of disease; these abnormalities have also been reported in studies using the region-of-interest method (Ishii *et al.*, 1998).

As the disease progressed, we found that hypoperfusion spread to the medial frontal and cingulate cortex, and later to the parieto-occipital cortex. Posterior progression of fvFTD was also reported in a recent longitudinal PET study (Diehl-Schmid *et al.*, 2006). Hypoperfusion in the parietal cortex that occurs late in fvFTD should not be confounded with the early involvement of posterior cortical regions in Alzheimer's disease (Bonte *et al.*, 2004). These results suggest the progression of neurodegenerative changes in these regions. Clinical progression towards a predominant mixed/inert behavioural profile may therefore be due to the spread of the disease to the medial frontal and cingulate cortex. Posterior hypoperfusion may either be related to the late diffusion of the disease to this structure (Broe *et al.*, 2003) or to a late posterior diaschisis resulting from massive damage of the frontal lobes (Nguyen and Botez, 1998; Zappoli, 2003).

To answer the question whether disinhibited and inert patients suffer from different diseases, we evaluated whether they were associated with specific demographic or clinical characteristics or brain perfusion patterns. The main demographic, neurological, neuropsychological characteristics were similar regardless of the initial behavioural presentation. Most of the behavioural items that differentiated the two groups were related to inertia in inert patients or to disinhibition in disinhibited patients. No other characteristic distinguished inert from disinhibited patients. We therefore conclude that inert and disinhibited forms of fvFTD are not dichotomized entities with specific characteristics.

Specific patterns of perfusion were associated, however, with the initial behavioural presentation. Inertia was associated with predominant medial frontal and cingulate

hypoperfusion, whereas patients with disinhibition had predominant ventromedial prefrontal and temporal hypoperfusion. These patterns of perfusion are coherent with data obtained in previous neuropathological studies (Tissot *et al.*, 1975) and SPECT imaging studies in patients with fvFTD performed on smaller groups of patients (Starkstein *et al.*, 1994; Didic *et al.*, 1998), as well as with findings from case studies of patients with focal lesions. The findings are validated by the existence of a mixed group, which had the perfusion characteristics of both the inert and disinhibited patients. Medial frontal hypometabolism (Craig *et al.*, 1996; Benoit *et al.*, 1999; Migneco *et al.*, 2001) and plaque burden in the anterior cingulate cortex at autopsy (Tekin *et al.*, 2001) have both been correlated with inertia in patients with Alzheimer's disease. The medial frontal cortex is involved in self-activation behaviours (Levy and Dubois, 2006). It is therefore not surprising that it is affected in patients with inertia (Rosen *et al.*, 2005; McMurtry *et al.*, 2006). Disinhibition has been reported following focal brain lesions in the ventromedial prefrontal cortex (Eslinger and Damasio, 1985; Tranel *et al.*, 2002; Hornak *et al.*, 2003), which also cause specific clinical disturbances including inappropriate affect and socially inappropriate behaviour (Barrash *et al.*, 2000). These results confirm that the disinhibited or inert presentations are associated with different perfusion patterns probably related to distinct anatomical localizations of the neurodegenerative lesions.

Little is known about the progression of the fvFTD. Survival in patients with FTLT is significantly shorter than in patients with Alzheimer's disease (Rascovsky *et al.*, 2005; Roberson *et al.*, 2005). The three FTLT variants progressed differently. Survival times, ~8 years, are similar in patients with fvFTD and PNFA but longer, close to 12 years, in semantic dementia (Hodges *et al.*, 2003; Le Rhun *et al.*, 2005; Roberson *et al.*, 2005; Seeley *et al.*, 2005). Our study shows that the final outcome of fvFTD is also variable. Forty-five percent of the deceased patients survived 6 years or less, whereas 34% of the patients survived >8 years. Neither age-at-onset, association with a parkinsonian syndrome, loss of awareness of the disease, medication or mode of inheritance affected survival. It was unexpected that brainstem hypoperfusion would distinguish patients with long survival times to patients with short survival times. The involvement of the brainstem in fvFTD has, however, been reported in neuropathological studies (Yang and Schmitt, 2001). It was suggested that the serotonergic raphe nuclei that project to the forebrain become directly or indirectly involved in FTLT both with and without MND, and might be related to causes of death in FTD, such as aspiration pneumonia or dysphagia. Our study suggests that brainstem hypoperfusion may be an important prognostic factor for a rapid progression of the disease. More research is needed to identify others factors that influence survival in fvFTD. This is of major importance for the counseling of patients and for the evaluation of therapeutic benefit.

In conclusion, this study shows that there were only small differences in the clinical phenotype of familial and sporadic cases or in patients with different age-at-onset. FvFTD is therefore a rather homogeneous clinically entity. The study provides evidence that different behavioural presentations at onset are related to differential anatomical localization of degenerative damage. Importantly, this work had demonstrated the prognostic value of brainstem hypoperfusion, which is probably related to the extension of the degenerative process in the course of the disease. Finally, this study has enhanced our knowledge of the characteristics and the natural history of fvFTD and should help avoid misdiagnosis and improve the accuracy of prognosis.

Supplementary material

Supplementary data are available at *Brain* Online.

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