Part 2: Molecular Imaging biomarkers in dementia

Chapter 5: Nuclear imaging in Frontotemporal dementia

F.E.Reesink, G.N. Stormezand, R.A.Dierckx, P.P De Deyn

PET and SPECT in Neurology, 339

DOI 10.1007/978-3-642-54307-4_15, © Springer-Verlag Berlin Heidelberg 2014
Abstract

Frontotemporal dementia (FTD) is a heterogeneous neurodegenerative syndrome, predominantly affecting the frontal and temporal lobes. Most patients present with behavioral deficits, executive dysfunction and language difficulties. FTD presents as two clinically recognized subtypes; the behavioral manifestation (FTD-b) and primary progressive aphasia (PPA), which can be divided into semantic dementia (SD) and progressive non fluent aphasia (PNFA). FTD is second to Alzheimer's disease (AD) as the major cause of young onset dementia. Neuropathological characteristics of FTD roughly can be divided in tauopathy (FTD-TAU) and ubiquitin pathology (FTD-U). Almost half of FTD occurs familial and genetic heterogeneity is reflected by the identification of mutations in causative genes. Diagnostic criteria have modest sensitivity and it may be challenging to differentiate FTD from other types of dementia, especially AD. Functional imaging, especially FDG-PET improves early diagnosis and frontotemporal hypometabolism correlates with clinical symptoms. Besides functional markers, nuclear imaging techniques may be helpful to detect specific markers of pathology or deficits of different neurotransmitter systems, depending on degeneration of subcortical nuclei and may provide valuable insight in the pathophysiology of FTD. Although currently no effective treatment is available for FTD, early and correct diagnosis is necessary for adequate clinical management, because of prognostic implications and for genetic counselling.

Introduction:

Frontotemporal dementia (FTD) after Alzheimer's disease (AD) constitutes the major cause of young onset dementia. The prevalence of FTD accounts up to 22% of dementia, starting before the age of 65 years. FTD is a heterogeneous neurodegenerative syndrome, predominantly affecting the frontal and temporal lobes. The clinical spectrum of FTD comprises an insidious onset and a progressive course, but with variable decline. FTD may manifest as two clinically recognized subtypes, based on the predominant features; behavioral and personality changes on the one hand, on the other hand language disturbances. The behavioral presentation (FTD-b) is characterized by severe changes in behavior and personality, such as disinhibition, apathy, loss of empathy, stereotypic behavior, dietary changes and executive cognitive deficits (table 1: 'Diagnostic criteria FTD-b'). FTD -b consensus criteria were recently revised, differentiating possible, probable and definite FTD-b with a higher sensitivity (76-86%). Predominant language difficulties are classified as primary progressive aphasia (PPA) and may be divided into semantic dementia (SD) and progressive non fluent aphasia (PNFA). SD presents with impaired comprehension and concomitant development of anomia, while speech production is spared. PNFA is characterized by effortful speech and grammatical errors, with sparing of language comprehension. Recently a third presentation was described, the logopenic progressive aphasia (LPA),
associated with a neuropathological diagnosis of Alzheimer’s disease (table 2: ‘Diagnostic criteria PPA’). In the heterogeneous spectrum of FTD there is also overlap with motor neuron disease (FTD-MND or FTD-ALS), as well as with Parkinsonian syndromes such as progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD).

Neurodegenerative changes in the brain are characterized by various patterns of atrophy of frontal and temporal lobes. Clinical phenotypes have a strong correlation with anatomic pathology. FTD-b is associated with symmetric atrophy of the frontal lobes, insula, anterior cingulate and anterior lobes. SD is associated with asymmetric atrophy of the left/ linguistic dominant anterior inferior temporal lobe. In patients with PNFA an asymmetric atrophy involving the anterior perisylvian cortex, mainly of the dominant hemisphere is seen.

The first patient with progressive aphasia and lobar atrophy was described by Arnold Pick in 1892. In 1911 Alois Alzheimer reported the presence of argyrophilic neuronal inclusions at neuropathological examination, later known as ‘Pick bodies’. Nowadays the neuropathology of FTD roughly can be divided in tauopathy (FTD-TAU) and ubiquitin pathology (FTD-U). Ubiquitin pathology is frequently combined with TAR DNA-binding protein (TDP-43) inclusions (FTD-TDP). A considerable number of TDP-43-negative FTD-U cases has inclusions of fused-in-sarcoma protein (FUS), referred to as FTD-FUS (Mackenzie 2010). Positive family history is observed in 40% of the FTD patients, most prominent in FTD-b (45%), and especially when concomitant symptoms of MND are present (60%) 14. Genetic heterogeneity of FTD is reflected by the identification of mutations in the MAPT and GRN genes, both linked at chromosome 17, in approximately 50% of familial cases. Mutations in the valosin containing protein (VCP), charged multivesicular body protein (CHMP2B), TAR-DNA binding protein (TAR-DP) and fused in sarcoma (FUS) genes are found in less than 5%. Mutations in progranulin (PGRN) gene are associated with ubiquitin pathology and TDP-43-positive inclusions15. Tauopathy is mostly caused by mutations in the microtubule-associated protein tau (MAPT) gene, but also presenelin 1 mutations are reported16. Recently mutations were identificated on 9p21, C9orf72 gene, associated also with ubiquitin pathology and TDP-43-positive inclusions17,18,19.

Neuro-imaging is useful in the diagnostic work up, especially MRI scans, but have a modest sensitivity of 50-64% and specificity around 70%, depending on the stage of neurodegeneration.

**Nuclear imaging**

**Regional cerebral blood flow and glucose metabolism**

Nuclear imaging techniques using Positron Emission Tomography (PET) or Single Photon Emission Computed Tomography (SPECT) tracers may visualize blood flow and
oxygen and glucose consumption. Several SPECT and PET studies have detected functional deficits in FTD patients in comparison to controls. In addition, perfusion or metabolic deficits may exist in a structurally normal brain. In 1977 Sokoloff et al. were the first to report that under physiological steady-state conditions, cerebral blood flow is coupled to the level of cerebral oxygen and glucose consumption. Cerebral glucose metabolic activity is an index of synaptic function and density and a characteristic feature of neurodegeneration. Stimulation of functional activity increases the local rate of glucose utilization while reduced functional activity lowers it. The PET tracer \(^{18}\)F- fluorodeoxyglucose (FDG) allows the measurement of the cerebral metabolic rate of glucose (CMRglc). Reivich et al. in 1979 were the first to study FDG-PET in man. The clinical test involves the qualitative visual interpretation of the scan images, on which metabolically active areas are indicated by greater degrees of FDG activity. FDG-PET imaging has been used extensively to identify characteristic disease-related patterns of regional glucose metabolism in patients with different variants of FTD. Although SPECT has been more broadly available, studies show PET has a higher diagnostic accuracy, suggesting that PET is superior to SPECT in its ability to separate healthy controls from patients with true dementing illnesses.

**Brain perfusion**

SPECT studies usually have been performed using \(^{99}\)Tc-HMPAO, providing measurements of cerebral blood flow (CBF). According the European Association of Nuclear Medicine Neuroimaging Committee (ENC) guidelines, brain perfusion SPECT can be used for early detection of various forms of dementia, including FTD. Early behavioural symptoms can precede the onset of dementia in FTD and SPECT can predict diagnosis. SPECT in addition to clinical evaluation increases the diagnostic accuracy for neurodegenerative diseases increase. FTD has typically been linked to a pattern of reduced cerebral blood flow (CBF) of symptomatic frontotemporal cortices. Using voxel-based statistical methods more specifically significant areas of hypoperfusion were detected, affecting association cortices, including hippocampus and amygdala, cingular and insular. SPECT provides useful information in differentiation of FTD subtypes; in Semantic Dementia (SD) shows hypoperfusion of the left temporal lobe is most prominent. SPECT imaging also aids in the differential diagnosis of patients with dementia. Numerous studies have been performed in patients with various forms of dementia, including AD, frontotemporal dementia, and vascular dementia, with demonstration of unique uptake patterns. The presence of a frontal or anterior perfusion deficit has been associated with frontotemporal dementia and not with AD, which is associated with a pattern of bitemporoparietal hypoperfusion. In one study in which a simple decision rule based on discriminant analysis of SPECT data was applied, 20 patients with probable AD and 20 with probable frontotemporal dementia were evaluated; hundred percent of patients with frontotemporal dementia and 90% of patients with AD were correctly classified. In a study of Pickut et al, using a
model, 81% of the FTD and 74% of the AD were correctly classified; bifrontal hypoperfusion was found to be the most powerful predictor of clinical classification. Patients showing bilateral anterior hypoperfusion are approximately 16 times more likely to suffer FTD than AD and are also considerably more likely to have FTD than vascular dementia or DLB. In another study with 16 patients with frontotemporal dementia, 71 patients with other forms of dementia, 28 control subjects, an anterior-to-posterior ratio was successfully used to classify patients with frontotemporal dementia from those with other forms of dementia and from control subjects with a sensitivity of 87.5% and a specificity of 78.6%.

The effect of different SPECT uptake patterns at baseline on modification of the differential diagnosis was evaluated in a study with 363 patients followed up for a median of 3 years. Patients were classified into disease groups on the basis of clinical criteria. A bilateral posterior perfusion abnormality was associated with AD, whereas a bilateral anterior abnormality was associated with frontotemporal dementia.

**Brain glucose metabolism**

Using the PET tracer $^{18}$F-fluorodeoxyglucose (FDG) in FTD a frontotemporal pattern of hypometabolism is found. Using voxel-based statistical methods a more widespread pattern has been reported with involvement of tempo-parietal association cortex, basal ganglia and thalamus and marginally in the primary sensorimotor cortex and cerebellum. Particularly, the ventromedial frontopolar cortex is known to be involved; this region is clinically related to decision making, feelings of rightness and social knowledge. The behavioral variant type FTD-b has been specifically related to hypometabolism of the right inferior frontal lobe (figure 1). Three different clinical presentations of primary progressive aphasia (PPA) are associated with signature patterns of glucose metabolism (figure 2). Progressive nonfluent aphasia (PNFA) shows (sometimes subtle) asymmetric left frontal hypo metabolism, semantic dementia (SD) prominent anterior temporal hypo metabolism, left greater than right, whereas logopenic aphasia (LPA) shows metabolic lesions in the left parietal and posterolateral temporal lobes. In order to distinguish FTD from AD, detection of hippocampal hypometabolism may be particularly useful. Hippocampal hypometabolism is present in almost all AD cases, but only in a minority of FTD patients. Other regions which have specifically impaired glucose metabolism in FTD in comparison to AD include the (bi) lateral ventromedial frontal area, the left anterior insula and the inferior frontal cortex. CBD, which shares clinical and pathologic features with FTD, has been associated with reduced metabolism of the primary sensorimotor region and/or basal ganglia and with asymmetric metabolic deficits in the hemispheres. Specific glucose metabolic patterns can differentiate FTD from other neurodegenerative brain diseases, like AD and DLB (figure 3, Teune 2013).
In addition to FTD, metabolic or inflammatory diseases, such as brain iron accumulation (NBIA) related neurodegeneration and voltage-gated potassium channel encephalitis may resemble FTD both clinically or using PET or SPECT.

FDG PET has been demonstrated to have higher sensitivity and specificity for the early detection of FTD when compared to perfusion SPECT. In a community-based prospective study of patients suspected of early-onset dementia, sensitivity of PET to detect FTD was 53%, whereas specificity was 95%. An FDG PET study of 45 patients with pathologically confirmed dementia showed that adding FDG PET, accuracy increased 11% compared to diagnoses based on clinical criteria alone. The sensitivities and specificities for the diagnosis of FTD were 36.5% and 100.0% for consensus criteria, 63.5% and 70.4% for magnetic resonance images, and 90.5% and 74.6% for SPECT/PET scans, respectively. With a previous prevalence of nearly 50% for FTD, the positive predictive value was greatest for consensus criteria (100.0%), and the negative predictive value was greatest for SPECT/PET (89.8%). The initial neuropsychological results did not distinguish FTD, but the pattern of progression (worse naming and executive functions and preserved constructional ability) helped establish the diagnosis after 2 years. Right frontal lobe hypometabolism seems to have the highest predictive value for developing FTD. After 2 years of follow up, patients showing hypoperfusion of this region at baseline were most likely to reach consensus criteria for FTD.

**Environmental factors**

Using PET a strong negative correlation has been found between the level of education and CMRglc, independent of demographics and the scores of the patients on cognitive testing. This finding suggests the presence of a cognitive reserve in highly educated FTD patients. A SPECT study showed a significant correlation between occupational attainments and hypoperfusion. In addition, Spreng et al. assessed 161 occupational variables and found a predominantly verbal occupation to be associated with hypometabolism of the left-hemispheric pars triangularis of the inferior frontal gyrus, whereas a physical occupation was inversely correlated with CMRglc in the right-sided supplementary motor cortex. These findings suggest that the translation of neuropathology into clinical symptoms may be influenced by environmental factors.

**Pharmacological treatments**

FDG PET also has been used to assess pharmacological treatment of FTD in small groups. Within a group treated with memantine, a noncompetitive N-methyl-D-aspartate and serotonin-3 receptor antagonist, an increase in glucose metabolism from baseline was observed, mainly in SD patients. However, this beneficial effect could not be correlated with an improvement in clinical symptoms. Other possible treatments have not been assessed using either PET or SPECT.
Longitudinal studies

In the early stage of FTD, hypometabolism may be evident in the frontal lobes, mainly on the right, with sparing of the motor cortex, while in the course of the disease hypometabolism tends to progress more symmetrical and cross lobar borders. Worsening of metabolic deficits has been reported specifically in the orbitofrontal parts of the frontal lobe as well as in subcortical structures. Another longitudinal study reported worsening of all hypometabolic structures at baseline and additional hypometabolism of the inferior frontal cortex, the inferior parietal lobe, left precuneus and the inferior and middle temporal lobes. These regions may secondarily be affected as a consequence of impaired input from frontal areas via the superior longitudinal fasciculus, the uncinate fasciculus and the cingulum bundle. Involvement of more posterior regions has been described to occur after disease duration of more than 5 years.

Correlation with behaviour

Initially, studies made use of a region-of-interest (ROI) analysis in which certain regions which are expected to be involved in the disease are investigated. More recently, voxel-based methods are used which allow detection of significantly altered brain regions without a-priori hypothesis. These methods seem particularly useful in relating clinical symptoms to specific brain regions. Table 3 shows the relationship studies between clinical symptoms of FTD and functional imaging.

Pathologic markers

Besides functional markers, specific markers of pathology are of interest in the evaluation of dementia. Recent advances in in vivo β-amyloid detection of AD allow further differentiation between FTD and AD. In the pathogenesis of AD, the depositions of amyloid-β are an early event in an amyloid cascade hypothesis. The first tracer to selectively visualizing amyloid-β in vivo is the Pittsburgh compound B ([11C]PiB). Nearly all AD patients show high retention of the [11C] PIB tracer, whereas retention in FTD is low or mild. Significant differences in retention of [11C]-PIB between AD and FTD patients have been shown in frontal, parietal, temporal, and occipital regions, as well as in the putamina. Correspondingly, inter-rater reliability is high, reflecting an on/off phenomenon for [11C]-PIB retention. Positive [11C]-PIB scans in FTD are quite common, but [11C]-PIB retention in supposedly FTD patients might also be reflective of concomitant AD pathology. With the introduction of fluorine-18 labelled amyloid tracers, such as [18F]-Florbetaben, distribution may be facilitated to medical centres without cyclotron. It has been shown in vitro that [18F]-Florbetaben does not bind to tau–protein, associated with FTD, or to α-synuclein, associated with DLB. A recent in vivo study, using [18F]-florbetaben, showed widespread cortical uptake in AD patients, and only mild binding in 1 out of 5 FTLD patients. Another study in a larger group showed a similar pattern of increased uptake in nearly all AD patients, and mild or low uptake in FTD patients. However, a majority of MCI subjects also demonstrated...
increased uptake. Further research is needed to investigate whether this finding reflects a prodromal state of AD or represents a feature of normal aging.

Another area of interest in neurodegenerative diseases is a process often referred to as ‘Glial activity’ was significantly increased in the frontal cortex of one PGC patient, in the occipital cortex of two PGCs patients and in the posterior cingulate of 1 PGC patient compared with healthy controls. Neuro-inflammation may be a marker of tau pathology in a pre-symptomatic state. However, radio-ligands specifically binding to FTD pathology, such as tau-proteins, are lacking.

Neurotransmitter systems

The involvement of different neurotransmitter systems varies between types of dementia, offering another possibility to differentiate FTD from other dementias. In this paragraph, findings in the serotonergic, dopaminergic and cholinergic system in FTD will be summarized.

Serotonergic system

Behavioral and psychological disorders are frequent in FTD and many of them are related to serotonergic dysfunction. A study using \([1^1C]\)WAY-100635 showed that FTD patients had significantly decreased serotonin (5-HT\(_{1A}\) ) binding potential (BP) compared with controls in all 10 brain regions examined, but most pronounced in frontal and temporal regions. The extent of BP reduction suggested that the potential of treatment with pharmacological agents, such as 5-HT\(_{1A}\) receptor blockers and serotonin reuptake inhibitors may be limited. However, this study was limited by small group size (n=4) and further research is warranted.

Dopaminergic system

The prevalence of extrapyramidal symptoms in FTD is between 23% and 83%. Akinesia, rigidity, and a shuffling with a short stride are typical findings. Neuropathologic mechanisms responsible for these symptoms have been evaluated in FTD using radiotracers which bind to pre- or postsynaptic dopaminergic receptors. Using \([1^{23}I]-FP-CIT\) SPECT (DAT-scan), the presynaptic dopamine transporter has been assessed in FTD patients. Significantly reduced uptake was noted in both the right and left striatum. In addition, there was a negative correlation between motor UPDRS scores in the right striatum and in the left striatum. These findings indicate functional loss of presynaptic dopamine transporters in FTD and underline the need for evaluation of dopamine drug treatment. Although reduced uptake of \([1^{23}I]-FP-CIT\) SPECT is considered characteristic for DLB and is rare in AD, reduced striatal uptake does not rule out FTD. Impaired function of the dopamine transporter in FTD has also been demonstrated using \([1^1C]-CFT\) PET, both in the nucleus caudate and in the putamen when compared to controls. This pattern of impaired nigrostriatal dopamine function is different from idiopathic Parkinson patients, in whom reduced uptake is usually more pronounced in the putamen, but may be similar to that observed in AD. Another PET
ligand, $[^{11}\text{C}]-\text{DTBZ}$, can be used to visualize the distribution volume of the vesicular monoamine transporter type 2 (VMAT2) and has been demonstrated to provide additional information to $[^{18}\text{F}]-\text{FDG}$ to facilitate differentiation between dementias, particularly between AD and DLB\textsuperscript{75}.

**Cholinergic system**

The cholinergic system has recently been investigated in FTD, CBD and PSP patients using the radiotracer $[^{11}\text{C}]-\text{MP4A}$. A distinct pattern of K3 values, reflecting acetylcholinesterase activity, was observed in each of these diseases. FTD patients did not show significant differences in K3 values compared to controls. In PSP, reduction of acetylcholinesterase activity was mild in the cortex, but pronounced in the thalamus, whereas in CBD acetylcholinesterase activity reduction was moderate in the cortex, but absent in the thalamus\textsuperscript{76}. However, in advanced stage FTD patients reduced acetylcholinesterase activity has been shown, indicating the above patterns may not be disease specific\textsuperscript{77}. Furthermore, both decreased and increased acetylcholinesterase activities have been reported in presymptomatic FTD-17 gene carriers\textsuperscript{68}.

**Conclusions**

Neuro-imaging, particularly functional brain studies, greatly increased the sensitivity of detecting FTD. Clinical diagnosis of FTD (consensus criteria) and neuropsychological and neuropsychiatric features combined with SPECT or PET findings increases accuracy of the diagnosis FTD. Frontotemporal hypometabolism is an early and specific sign and helps to differentiate from other forms of dementia, especially AD. FDG PET has been demonstrated to have higher sensitivity and specificity for the early detection of FTD when compared to perfusion SPECT. In addition to metabolic markers, nuclear imaging techniques may be helpful to detect specific markers of pathology or deficits of different neurotransmitter systems, depending on degeneration of subcortical nuclei and provide valuable insight in the pathophysiology of FTD.
Table 1: Diagnostic criteria FTD-b

<table>
<thead>
<tr>
<th>Behavioral variant (FTD-b)</th>
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<tbody>
<tr>
<td>Inclusionary criteria: progressive deterioration of behavior and/or cognition and <em>at least three</em> of the following symptoms (A-F):</td>
</tr>
<tr>
<td>A. Early (within the first 3 years) behavioral disinhibition (socially inappropriate behavior, loss of decorum/impulsive or careless actions)</td>
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<tr>
<td>B. Early apathy or inertia</td>
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<tr>
<td>C. Early loss of sympathy or empathy (diminished response or interest to other people's needs and feelings)</td>
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<tr>
<td>D. Early perseverative, stereotyped or compulsive/ritualistic behaviors</td>
</tr>
<tr>
<td>E. Hyperorality and dietary changes</td>
</tr>
<tr>
<td>F. Neuropsychological profile: executive deficits with relative sparing of memory and visuospatial functions</td>
</tr>
</tbody>
</table>

| Exclusionary criteria: A and B *must* be answered negatively for diagnosis. Criteria C *can* be positive for possible-, but *must* be negative for probable FTLD-b. |
| A. Pattern of deficits is better accounted for by other non-degenerative nervous system or medical disorder |
| B. Behavioral disturbance is better accounted for by a psychiatric diagnosis |
| C. Biomarkers strongly indicative of Alzheimer's disease or other neurodegenerative process |
Table 2: Diagnostic criteria PPA and variants\textsuperscript{3,78,43,79}

<table>
<thead>
<tr>
<th>Inclusionary criteria: 1-3 must be present:</th>
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<tbody>
<tr>
<td>1. Most prominent clinical feature is difficulty with language</td>
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<tr>
<td>2. These deficits are the principal cause of impaired daily living activity</td>
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<tr>
<td>3. Aphasia should be the most prominent deficit at symptom onset and for the initial phases of the disease</td>
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<table>
<thead>
<tr>
<th>Exclusionary criteria: 1- 4 must be answered negatively:</th>
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<tbody>
<tr>
<td>1. Pattern of deficits is better accounted for by other non-degenerative nervous system or medical disorders</td>
</tr>
<tr>
<td>2. Cognitive disturbance is better accounted for by a psychiatric diagnosis</td>
</tr>
<tr>
<td>3. Prominent initial episodic memory, visual memory and visuoperceptual impairments</td>
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<tr>
<td>4. Prominent initial behavioral disturbance</td>
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<tr>
<th>SD core features:</th>
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<tbody>
<tr>
<td>Impaired confrontation naming and single-word comprehension.</td>
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</table>

Other features: impaired object knowledge, surface dyslexia or dysgraphia, spared repetition, spared speech production.

<table>
<thead>
<tr>
<th>PNFA core features:</th>
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<tbody>
<tr>
<td>Agrammatism in language production and apraxia of speech.</td>
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</table>

At least 2 of 3 other features:
- Impaired comprehension of syntactically complex sentences, spared single-word comprehension, spared object knowledge.

<table>
<thead>
<tr>
<th>LPA core features:</th>
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<tbody>
<tr>
<td>Impaired single-word retrieval in spontaneous speech and repetition of sentences and phrases.</td>
</tr>
</tbody>
</table>

At least 3 other features:
- Phonologic errors in spontaneous speech and naming, spared single-word comprehension spared motor speech, absence of frank agrammatism.

<table>
<thead>
<tr>
<th>Imaging-supported:</th>
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<tr>
<td>Predominant anterior temporal lobe atrophy, left greater than right, on MRI or hypoperfusion or hypometabolism on SPECT or PET</td>
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<table>
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<tr>
<th>Imaging-supported:</th>
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<tr>
<td>Predominant left frontoinsular atrophy on MRI or hypoperfusion or hypometabolism on SPECT or PET</td>
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</table>

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<tr>
<th>Imaging-supported:</th>
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<tbody>
<tr>
<td>Predominant left parietal and posterolateral temporal lobe atrophy on MRI or hypoperfusion or hypometabolism on SPECT or PET</td>
</tr>
</tbody>
</table>

Definite pathology: clinical diagnosis and either criterion 1 or 2 must be present:
- 1. Histopathologic evidence of specific neurodegenerative pathology |
- 2. Presence of known pathogenic mutation

**PPA**= Primair Progressive Aphasia, **SD**= Semantic Dementia, **PNFA**= Progressive Non-Fluent Aphasia, **LPA**= Logopenic Progressive Aphasia
Table 3: Correlations between functional imaging and behavioural aspects of FTD

<table>
<thead>
<tr>
<th>Author</th>
<th>Groups</th>
<th>Tracer</th>
<th>Statistics</th>
<th>Main results of hypometabolism or reduced blood flow</th>
</tr>
</thead>
</table>
| Mendez et al.   | FTD (n=74)                      | [99Tc]-HMPAO SPECT | Visual assessment                | - Dysthymia and anxiety: R temporal lobe  
- Frivolous behaviour: temporal lobes, particularly R  
- Alterations in non-verbal behaviour: R frontal lobe. |
| et al. 2006(79) |                                 |            |                                   |                                                                                                                      |
| Le Ber et al.   | FTD-b (n=68: 25% inert, 19% disinhibit, 56% mixed) Age-matched Controls (n=28) | [99Tc]-HMPAO SPECT | Multicenter, Voxel-based, p<0.05, corrected | - Inertia: medial frontal cingulate gyrus  
- Disinhibition: predominant ventromedial prefrontal and temporal |
| 2006(32)        |                                 |            |                                   |                                                                                                                      |
| Raczka et al.   | FTD (n=17) Age-sex-matched Controls (n=9) | [18F]-FDG PET | Voxel-based, p<0.001, uncorrected  | - Executive dysfunction: anterior-mid cingulated gyrus, anterior medial frontal, L frontopolar and inferior/ middle/ superior frontal gyri, anterior and inferior part insula, globus pallidus, caudatum, thalamus  
- Behavioural impairment: L frontomedial inferior temporal gyrus and anterior/ superior part of the insula. |
| 2010(80)        |                                 |            |                                   |                                                                                                                      |
| Bastin et al.   | FTD-b (n=11) Controls (n=26)    | [18F]-FDG PET | Voxel based, p<0.05, corrected     | - Severe loss of autonoetic consciousness*:  
L anterior medial frontal, L middle frontal cortex- near the superior frontal sulcus, L inferior parietal cortex and the posterior cingulate cortex, R postcentral sulcus |
| 2012(81)        |                                 |            |                                   |                                                                                                                      |
| Borroni et al.  | FTD-b (n=207)                   | [99Tc]-ECD SPECT | Confirmatory factor analysis, p<0.005, uncorrected, minimum voxel size 25 | - Disinhibition: anterior cingulate, bilateral anterior temporal cortex hypoperfusion (R>L)  
- Apathy: L dorsolateral frontal cortex  
- Aggression: no region associated  
- Language deficits: L frontotemporal lobes |
| 2012(42)        |                                 |            |                                   |                                                                                                                      |

R=rightside, L=leftside

* autonoetic consciousness: ability to retrieve memories accompanied by recollection of encoding context
Figure 1: Single-headed HMPAO SPECT study of a patient suffering from frontotemporal dementia. Transaxial slices from bottom to top. Moderate to severe cortical hypoperfusion of the frontal lobes, especially on the left, and slight hypoperfusion of the temporal poles.

Figure 2: [$^{18}$F]-FDG PET in FTD-b, Behaviour Variant: right fronto(temporal) hypometabolism.
Figure 3: $[^{18}\text{F}]-\text{FDG PET in different types FDG patterns. Axial (z = 9, z = 27) and coronal (y = 64) slices of mean atrophy-corrected FDG images from (top to bottom) normal controls (N = 12). PNFA (N = 5), SD (N = 5), LPA (N = 4) and AD (N = 10). PNFA is characterized by left frontal hypometabolism (red arrow), SD by left greater than right anterior temporal hypometabolism (yellow arrows), and LPA by asymmetric left temporoparietal hypometabolism (light blue arrows).}
Figure 4: $[^{18}F]$- FDG PET in different types of dementia; DLB, AD, FTD (Teune 2013).

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