Summary

Frontotemporal dementia (FTD) is a neurodegenerative disorder predominantly affecting the frontal and / or temporal lobes. Clinically it presents with behavioural, personality and emotional features. Cognitive features consist of executive and language dysfunction with memory disturbances to a lesser extent. The clinical syndrome is often unrecognised. Standard diagnostic tests have a relatively low sensitivity. In the first part of this thesis the clinical recognition of FTD was investigated. In the second part new diagnostic tools were explored.

In Chapter 1 a historic overview of FTD since the first description by Arnold Pick in 1892 is given. Frontotemporal lobar degeneration (FTLD), besides FTD encompasses the clinical syndromes of semantic dementia and progressive non-fluent aphasia, that both present with language features. The FTLD clinical syndromes are described at the background of pathologic, epidemiologic and genetic findings. An illustration of current diagnostic difficulties is given.

Chapter 2.1 presents a retrospective case note study in patients with the three prototypical FTLD syndromes. Presenting complaints were most misleading in FTD, with none of the patients and less than 50% of their caregivers reporting behavioural change. Both FTD patients and their partners relatively often reported memory complaints. Misinterpretation of first symptoms resulted in diagnostic delay in 62% of the FTD patients.

In chapter 2.2 the value of the clinical diagnostic criteria for FTD is evaluated in a memory clinic cohort. A written caregiver questionnaire was designed, containing the five core clinical hallmarks of FTD, according to international consensus. The questionnaire was applied at first memory clinic presentation. The caregiver answers were evaluated in relation to the clinical diagnosis, made by the multidisciplinary team that was blinded to the caregiver answers. A consistent clinical diagnosis over at least one year was regarded as the gold standard. After exclusion of obvious, non-neurodegenerative causes of cognitive and behavioural decline, the questionnaire had a specificity of 90% and sensitivity of 73% for a diagnosis of FTD. These figures remained essentially the same when the FTD study population was enlarged by adding patients from two other memory clinics.
In chapter 2.3 the diagnostic dilemma of FTD versus late-onset schizophrenia (LOS) is illustrated by the case descriptions of 4 patients who were clinically diagnosed with either FTD or schizophrenia. The four patients shared a considerable number of clinical and neuropsychological features. As the underlying pathophysiology of LOS is unknown, there is still a lack of a gold standard to resolve this dilemma. A multidisciplinary approach in the evaluation of patients presenting with behavioural change and or psychosis is advocated.

In Chapter 3.1 the role of the routine CSF biomarkers, tau and amyloid beta (1-42) (Aβ42), in the diagnosis of FTLD is investigated. CSF levels of both biomarkers were highly variable in FTLD, as opposed to patients with Alzheimer’s disease (AD) and cognitively healthy control subjects. Based on the pattern of CSF tau and Aβ42, the identification of FTLD subjects was not satisfactory. Subsequently (Chapter 3.2), relationships between CSF protein levels and clinical characteristics, neuroimaging characteristics and Apolipoprotein E (ApoE) genotype were looked for. For CSF Aβ42 no relationships with the above factors were found. For CSF tau, there was an influence of predominant localisation (frontal or temporal). Furthermore, in the temporal subgroup CSF tau levels were related to CSF Aβ42 levels, age, disease duration and disease severity. In the frontal subgroup there was an effect of ApoE genotype.

In Chapter 3.3 a possible role for CSF neurofilaments in the diagnosis of FTD is explored. CSF levels of light and heavy chain neurofilaments as well as the hyperphosphorylated heavy chain neurofilament were compared between patients with FTD, early-onset Alzheimer’s disease (EOAD) and cognitively healthy controls. The EOAD patient group had higher median CSF levels of the light chain neurofilament than control subjects. A subgroup of FTD patients had very high levels of both types of neurofilaments. The degree of neurofilament phosphorylation, as computed by the ratio hyperphosphorylated / total heavy chain neurofilament was higher in FTD than in the other groups.

In Chapter 3.4 concentrations of CSF Aβ40 and Aβ42 were measured in CSF of patients with FTLD, AD and cognitively healthy controls. Aβ40 levels were lower and Aβ42/40 ratios higher in FTLD than in AD patients and controls.
In chapter 3.5 the role of the visually rated EEG in the diagnosis of FTLD was reevaluated and the potential of EEG functional connectivity measures was explored. In our group of FTD patients the visually rated EEG was as normal as in the control group, in contrast with the AD patients, using the Grand Total EEG score. Exploring differences in resting-state EEG functional connectivity, however, we found that the synchronization likelihood was higher in FTLD compared to AD in the lower alpha frequency band, particularly over the frontal electrodes.

Based on this thesis the following conclusions can be drawn:
The clinical recognition of FTD may be influenced by the presentation of complaints. In particular when complaints are lacking or have a cognitive nature, there is a risk of diagnostic delay. For an accurate recognition of FTLD, in particular the behavioural variant FTD, an informant based structured behavioural interview is essential.
The currently used clinical diagnostic criteria for FTD, when applied as a questionnaire in a memory clinic setting, have a good specificity for a diagnosis of FTD, whereas sensitivity is relatively lower. Clinical and neuropsychological findings in FTD and late onset schizophrenia refer to involvement of the frontal and temporal lobes. A gold standard to distinguish the two disorders is lacking and long term follow-up seems to be indicated. The routinely used CSF biomarkers tau and Aβ42 are not useful in the diagnosis of FTD. We found preliminary evidence for a role of neurofilaments and amyloid beta in the pathophysiology of FTLD. The diagnostic usefulness of CSF neurofilaments, Aβ40 and Aβ42/40 ratio needs to be investigated further.
The visually rated EEG is normal in FTLD; thus an abnormal EEG in patients with presenile dementia is in favour of a diagnosis of AD. Measures of functional connectivity might offer a better opportunity to distinguish FTD from AD and persons with subjective memory complaints.