In this final chapter the main findings of this thesis are summarized, integrated and placed in the context of existing literature, followed by methodological considerations. Finally, the clinical implications and future directions for research in the field of neuropsychiatry are discussed.

In this thesis the following research questions were studied:

1. Which of the neuropsychiatric symptoms or signs in the late-onset frontal lobe syndrome can distinguish between bvFTD and primary psychiatric disorders and what are their diagnostic accuracies?
2. What is the diagnostic accuracy of current biomarkers (notably CSF) in the late-onset frontal lobe syndrome, in particular for bvFTD versus primary psychiatric disorders?
3. Which of the neuropsychiatric symptoms or signs in the late-onset frontal lobe syndrome can distinguish betweenbvFTD and primary psychiatric disorders and are they suitable as a diagnostic tool?

5.1 Summary

In paragraph 2.1, we prospectively assessed the diagnostic accuracy of the revised diagnostic criteria for bvFTD (FTDC) among subjects presenting with a frontal lobe syndrome in middle-late adulthood. The FTDC criteria constitute a classification based on the certainty of the bvFTD diagnosis. While possible bvFTD contains a number of required clinical hallmarks found in bvFTD, a diagnosis of probable bvFTD is based on the clinical symptoms in the presence of functional decline plus frontotemporal changes on neuroimaging. In this clinically relevant cohort we used the 2-year-follow-up clinical diagnosis as gold standard, whereas definite bvFTD had been diagnosed in some cases via genetic screening or neuropathological examination. We found a sensitivity of 85% and a specificity of only 27% for the FTDC criteria for possible bvFTD. This indicates that on a purely clinical basis, many other conditions mimic bvFTD. Among these similar clinical conditions, 38.6% received a primary psychiatric diagnosis, such as major/minor depression, bipolar disorder, schizophrenia or personality disorders. These disorders have previously been described as the most common primary psychiatric misdiagnoses for bvFTD(1-3). When adding neuroimaging evidence of frontotemporal changes, the specificity increased to 82% for bvFTD, thereby stressing the great relevance of frontotemporal changes on neuroimaging for a diagnosis of bvFTD in patients that present with behavioural changes. Furthermore, we did not find a sensitivity of 100% for possible and probable bvFTD, because three cases meeting definite bvFTD did not even
fullfil criteria for possible bvFTD. Overall, we found a good diagnostic accuracy for FTDC probable bvFTD.

In paragraph 2.2 we set out to compare the neuropsychological profiles in bvFTD with its most common primary psychiatric differential diagnoses, major depression, bipolar disorder and schizophrenia. The included psychiatric cohorts where all older patients (> 65 years) with active psychiatric symptoms. In this way, we approached the clinical challenges of the bvFTD differential diagnosis when using a neuropsychological battery as a diagnostic tool. By investigating cognitive deficits in these disorders, we also explored the diagnostic relevance of the sixth clinical criterion of possible bvFTD: presence of a neuropsychological profile with executive/generation deficits with relative sparing of memory and visuospatial functions. Firstly, we found that all patient groups had significantly lower scores on the cognitive tests compared to healthy controls, as expected. Secondly, bvFTD patients showed less severe deficits on executive functions and verbal memory tests compared to all three primary psychiatric disorders. On the other hand, bvFTD patients had more difficulties with tests of verbal fluency, more specifically on animal naming. Attention/working memory was most impaired in major depression compared to bipolar disorder, schizophrenia and bvFTD patients. In conclusion, these results are in line with our findings regarding the non-specific behavioural features of bvFTD found in paragraph 2.1 and indicate that in the differential diagnosis of bvFTD, cognitive impairment does not rule out the presence of a primary psychiatric diagnosis.

In paragraph 2.3 we prospectively investigated the broad spectrum of psychotic symptoms in bvFTD versus primary psychiatric disorders. We found that 76.9% of bvFTD patients showed any psychotic symptom, although not the typical positive psychotic symptoms (delusions, hallucinations and paranoia) but rather the negative psychotic symptoms (apathy or inertia) and formal thought disorders. Difficulty in abstract thinking and stereotypical thinking clinically differentiated bvFTD from patients with a primary psychiatric disorder. In contrast, primary psychiatric disorders were characterized by the presence of anxiety, guilt feelings and tension (general subscale), which distinguished them from bvFTD patients. These findings indicate that positive psychotic symptoms are infrequently present in bvFTD. However, negative psychotic symptoms and formal thought disorders are frequently present, indicating that negative psychotic symptoms have an significant contribution to the pitfall of misdiagnosis in bvFTD.

In paragraph 3.1 we aimed to determine the diagnostic accuracy of MRI and \([^{18}\text{F}]\text{FDG-PET}\) scan, separately and in combination, to diagnose bvFTD among subjects with late onset behavioural changes. Like we described in paragraph 2.1, when using these conventional biomarkers, bvFTD can be diagnosed at a much higher accuracy. However,
the question remains which of these 2 biomarkers is more accurate for bvFTD. We found that the sensitivity of frontotemporal changes on MRI for bvFTD is 70% with a specificity of 93%. The additional [18F] FDG-PET, if the MRI was inconclusive, had a sensitivity of 90% at the cost of a lower specificity of 68%. The combination of MRI and [18F] FDG-PET-scan had a sensitivity of 96% and a specificity of 73%. The relatively low sensitivity of the MRI was partly caused by atypical MRI atrophy patterns of genetic cases of bvFTD, indicating that these MRI patterns should not prevent genetic testing in case of suspected bvFTD. On the other hand, the low specificity of [18F]FDG-PET-scan is due to false positive scans in the primary psychiatric cases and cases with various other types of dementia. Moreover, 60% of the false positive rated scans were in patients with primary psychiatric disorders such as major/minor depressive disorder, bipolar disorder, schizophrenia, personality disorders and relational problems. The other 40% were patients diagnosed with dementia other than bvFTD, including patients with Alzheimer’s disease, semantic dementia (SD), progressive supranuclear palsy (PSP) and cortical basal syndrome (CBS). Our results show that an abnormal [18F] FDG-PET-scan does not exclude a primary psychiatric disorder and should not be considered to be pathognomic for bvFTD. Conclusively, these results support the notion for clinical practice to perform MRI investigation first in patients with behavioural changes and clinically bvFTD, and if inconclusive for bvFTD, to perform an additional [18F]FDG-PET-scan.

In paragraph 3.2 we investigated the diagnostic value of CSF tau/Aβ1-42 ratio, p-tau/tau ratio, light chain neurofilaments (NfL) and YKL40 to differentiate between bvFTD and primary psychiatric disorders. We found that the CSF NfL levels (Area under the curve (AUC) 0.93, p<0.001, 95% CI 0.85-1.00) and the CSF p-tau/tau ratio (AUC 0.87, p<0.001, 95% CI 0.77-0.97) are accurate biomarkers for the separation between bvFTD and primary psychiatric disorders. Likewise, the levels of CSF YKL40 (AUC 0.82, p=0.001, 95% CI 0.68-0.97) were increased in probable/definite bvFTD and showed a relative good diagnostic accuracy. The combination of these three biomarkers had a sensitivity of 91% (95% CI 66-100%) at a specificity of 83% (95% CI 65%-95%) with a AUC of 0.94 (p< 0.001, 95% CI 0.87-1.00) for bvFTD. The value of CSF tau/Aβ1-42 ratio in distinguishing between these illnesses was less accurate (AUC of 0.74 (p=0.006, 95% CI 0.54-0.84)), although there was a higher ratio in the group of probable/definite bvFTD. Furthermore, there were increased values of CSF tau in probable/definite bvFTD. In general, this study strengthens the idea that the use of CSF as a potential additional biomarker to neuroimaging in distinguishing bvFTD from primary psychiatric disorders is of diagnostic relevance and might be incorporated in future diagnostic guidelines for bvFTD.

In paragraph 3.3 and 3.4 we explored a ‘novel’ method that measures brain connectivity with inter-regional grey matter covariance that provides a quantified structural network in
which each cortical area represents a network node and the edge is defined as statistical
covariance in morphometrically between nodes. We first explored the difference for
bvFTD versus AD (paragraph 3.3). We found that grey matter networks of AD patients
showed lower connectivity density and global clustering values compared to bvFTD
patients, which is suggestive of a less ordered, or more random network organisation in
AD. Furthermore, we found that disruptions of grey matter volume together with network
properties degree and clustering coefficient values of specific anatomical areas could
differentiate between these two neurodegenerative disorders. In addition, we were able
to show that grey matter volume and grey matter network properties in specific
anatomical areas were specifically associated with cognitive disturbances measured with
a neuropsychological assessment covering memory, language, visuospatial, attention an
effective function. This suggests that grey matter networks may have use for clinical
practice, helping to distinguish between neurodegenerative disorders.

We studied the dissimilarity and similarity in grey matter networks between bvFTD and
MDD in paragraph 3.4, subjects with subjective cognitive decline were used as
reference. The main finding of this study was that MDD and bvFTD showed disease
specific network alterations. Moreover, these alterations affected specific anatomical
areas: MDD patients showed a reduced degree in frontal, temporal and posterior brain
regions and bvFTD showed an anatomically widespread decrease in clustering values.
Compared to controls, MDD and bvFTD both showed lower clustering values in the right
fusiform gyrus and a lower betweenness centrality values in the left supplementary motor
area. Directly comparing MDD and bvFTD showed that the networks of MDD patients
were more randomly organised as indicated by lower values for path length, gamma,
lambda and the small world coefficient. MDD subjects showed, compared to bvFTD
subjects, lower degree values in brain areas that often are associated with the
functionally defined ‘Default Mode Network’ (DMN) and ‘Salience Network’ (SN) regions.
Together our findings indicate that network organisation is disorganised in MDD and
bvFTD in a disease-specific way and suggests that grey matter network properties could
be a biomarker in the future for distinguishing between these clinical overlapping brain
disorders.

In paragraph 4.1 we investigated which combination of clinical characteristics could
distinguish between primary psychiatric disorders and probable/definite bvFTD. We
found that male gender (OR 5.9 CI 95%:1.3-26.0), less stereotypy symptoms (OR 0.08
CI 95%:0.02-0.34), and more depressive symptoms (OR 1.13 CI 95%:1.04-1.24) were
associated with primary psychiatric disorders, and less likely with probable/definite
bvFTD. Furthermore, we found that neuroimaging with absence of frontotemporal
abnormalities (OR 0.02 95%:0.002-0.123) predicted a primary psychiatric disorder
versus probable/definite bvFTD with a relatively good accuracy. In conclusion, primary
psychiatric disorders can be distinguished from probable/definite bvFTD with a clinical evaluation by a psychiatrist and neurologist in addition to validated questionnaires for depression and stereotypy, and even more when combined with neuroimaging.

5.2 General discussion

The differential diagnosis of the late-onset frontal lobe syndrome is challenging, especially when discriminating bvFTD from primary psychiatric disorders such as major depression, bipolar disorder and schizophrenia. Therefore, the Late Onset Frontal Lobe Syndrome study (LOF) was designed to develop a ‘new’ paradigm to tackle this clinical challenge. Patients were included between the age of 45-75 years with a frontal behavioural change consisting of apathy, disinhibition, or compulsive/stereotypical behaviour. In the current thesis, we investigate the prospective data of the LOF by using the two-year-follow-up final diagnosis as gold standard to investigate the baseline data for bvFTD and primary psychiatric disorders. The following discussion will focus on these two disorders.

A proportion, however, of subjects that were included in the LOF study based on their behavioural characteristics turned out to have other neurological disorders such as Alzheimer's disease (AD), dementia with Lewy bodies (DLB), vascular dementia (VaD), multiple sclerosis (MS) etc. In general, these disorders already have good accurate biomarkers to discriminate between bvFTD or primary psychiatric disorders. For example, the frontal variant of AD can be distinguished from bvFTD by showing more brain atrophy in temporoparietal cortex, presence of APOE e4 allele, more executive dysfunction that behavioural changes or with a CSF AD profile or positive amyloid PET(4,5). In the case of MS, it is well known that during the disease course MS patients develop behavioural and/or cognitive deficits without a history of a clinical isolated syndrome or other physical impairments(6). Using a MRI with gadolinium and CSF markers (elevated immunoglobulin G index or oligoclonal bands)(7), MS can be distinguished from bvFTD or primary psychiatric disorders. Our finding that neurological disorders can present with an atypical presentation of behavioural changes, underscores that clinicians should look beyond the borders of clinical guidelines and must consider atypical presentations of otherwise clearly described neurological disorders. Furthermore, it strongly supports the use of current diagnostic tools.

5.2.1 Clinical similarities and dissimilarities between bvFTD and primary psychiatric disorders

In this section of the thesis we attempt to indicate which neuropsychiatric symptoms or signs in the late-onset frontal lobe syndrome show similarity or dissimilarity between
bvFTD and primary psychiatric disorders. In general, we found that patients that clinically present with perseverative, stereotyped or compulsive behaviour are more likely to have bvFTD, while primary psychiatric disorders have more symptoms of anxiety, guilt feelings, tension and depression. In a heterogeneous group of patients with a frontal lobe syndrome, a profile of executive dysfunction with relative sparing of memory and visuospatial skills is specific for bvFTD, while compared to non-euthymic or remitted psychiatric patients, bvFTD patients perform better on every cognitive domain, apart from verbal fluency.

For probable/definite bvFTD, the most accurately distinguishing clinical symptom is perseverative, stereotypical or compulsive behaviour with the highest sensitivity (89%, 95% CI (0.73-0.97)), and a relatively high specificity (62%, 95% CI (0.52-0.72)) in a cohort of patients that present with a late-onset frontal lobe syndrome. Accordingly, we found that higher scores on the validated questionnaire Stereotypy Rating Inventory (SRI) as well as stereotypical thinking measured with the Positive and Negative Syndrome Scale (PANNS) predicted probable/definite bvFTD versus primary psychiatric disorders. In previous studies stereotypical behaviour has been found to be a marked symptom in bvFTD(8,9) and is a reliable and good discriminator between other neurodegenerative disorders(10-13). For example, in the autopsy-confirmed FTDC cohort the sensitivity of stereotypical behaviour was nearly 70%(14). This lower sensitivity compared to our study, could be caused by the retrospective design of that study, in which stereotypical behaviour was not systematically rated. Moreover, our finding seems quite novel because stereotypy also discriminated bvFTD from primary psychiatric disorders. Of note, it might be a less specific discriminator from psychiatric illnesses such as obsessive-compulsive disorder (OCD) or OCD-related disorders (isolated hoarding), where the key clinical features are compulsive/ritualistic behaviours(15). Dissimilarity between patients with OCD and bvFTD must be then found in the lack of insight of the obsession and that these stereotypical symptoms are not accompanied by anxiety in bvFTD(16).

The presence of anxiety, guilt feelings, tension and more depressive symptoms predicts a primary psychiatric disorder compared to a bvFTD diagnosis. Probably these symptoms are more specific for psychiatric diagnoses because these clinical concepts reflect insight or awareness of ‘distress’, which is most prevalent in primary psychiatric diagnoses and widely used in the DSM system(15). In contrast, bvFTD patients are more characterized by the absence or the lack of insight of these symptoms. In addition, an early sign in bvFTD is the lack of recognition of any disease-specific acquired symptom (anosognosia)(17) or a lack of concern of the condition (anosodiaphoria). This former sign is probably more a result of apathy and caused by lesions in the right frontal cortex(18), whereas anosognosia is more associated with lesions in the parietotemporal...
areas(19). In our study, we did not directly assess self-awareness, however, it has previously been described that patients with bvFTD fail to report ‘psychiatric’ complains on self-report items, which is then in contrast to the reports by their care-givers(16,20,21). Nevertheless, in some cases of bvFTD behavioural or psychiatric symptoms are reported by the patients themselves(22). In general, regardless the cause of lower scores on self-report items, we may conclude that higher scores on self-report items on behavioural or psychiatric symptoms in validated questionnaires are more predictive for a psychiatric diagnosis than bvFTD.

The most common clinical feature that shows similarity between bvFTD and primary psychiatric disorder is apathy/inertia. We found that apathy/inertia rated with behavioural questionnaires and clinical observations was the most frequent (79%) and had the lowest sensitivity and specificity for bvFTD (sensitivity =0.65, 95% CI (0.46-0.82), specificity = 0.17, 95% CI (0.10-0.25)) in patients with behavioural changes. These findings are in line with the view in the DSM-5 where apathy is merely a non-specific symptom with an extensive differential diagnosis(15). Also, in the autopsy-confirmed FTDC cohort the sensitivity of apathy was above 80%(14). Consequently, apathy/inertia contributes to the misdiagnosis of bvFTD or primary psychiatric disorders in a daily clinical practice(1). Furthermore, the symptoms of apathy are relatively often interpreted as symptoms of depression(23). Although the clinical concepts apathy and depression include both diminished interest, fatigue or hypersomnia(23) and relate to the involvement of frontal subcortical circuits(24), they differ significantly on other symptoms. For example, symptoms that are more related to depression are dysphoria, self-criticism, feelings of guilt, hopelessness or suicidal thoughts(23,25), whereas apathy is more related to blurred emotional response, indifference, diminished initiation and poor persistence. Moreover, we show that it is clinically relevant that these concepts are correctly used and rated, because differences between these concepts help to discriminate between primary psychiatric disorders and bvFTD. We illustrate that the balance between symptoms of apathy and depression leans towards symptoms of apathy in bvFTD and towards depression in primary psychiatric disorders. This result is consistent with previous studies where the rate of symptoms of depression are found to be lower in bvFTD(22) than the rates of symptoms of apathy(24). Overall, when symptoms of apathy or depression are the major complaint or sign in a patient with behavioural changes, additional awareness/attention is required about the final diagnosis.

Another clinical hallmark in bvFTD is the early loss of inhibition. The behavioural concept of disinhibition consists of inappropriate social behaviour, loss of decorum or impulsive and careless actions(14). This may mimic a manic episode as seen in bipolar disorder(15,26). Furthermore, reported neurological causes of disinhibition or mania include AD, MS, Huntington’s disease or vascular disorders. It is not surprising, then,
that in our LOF cohort disinhibition had a sensitivity of 73% (95% CI 0.54-0.87) at a specificity of 26% (95% CI 0.17-0.35) for bvFTD and was present in 74% of the included patients. This finding underscores that symptoms of disinhibition are not specific for bvFTD. However, older patients with a new-onset mania are more than twice as likely to suffer from a neurological disorder than a primary psychiatric disorder(27). From a psychiatric point of view, it is then encouraged to consult a neurologist when an older patient presents with disinhibition or a mania. On the other hand, for a neurologist when an older patient presents with disinhibition and it is not accompanied with euphoric or elevated mood, an increase of energy or decreased need for sleep it is more likely to have bvFTD than a manic episode in the presence of a bipolar disorder(28).

The above described similarity and dissimilarity in behavioural features between bvFTD and primary psychiatric disorders are mostly accompanied with some degree of cognitive impairment. Therefore, we also investigated the neuropsychological profiles between bvFTD, primary psychiatric disorders and other types of neuropsychiatric disorders. A neuropsychological profile of executive deficits with relative sparing of memory and visuospatial skills had a relative low sensitivity with a high specificity (sensitivity = 0.40 (95% CI 0.23–0.60), specificity = 0.79 (95% CI 0.70–0.86)) for bvFTD. Moreover, in this cohort only 25% of the patients had another type of dementia which is in line with previous research that show that a neuropsychological profile with mainly executive deficits are helpful in discerning bvFTD from other types of dementia. A novel finding, however, is that this profile also discriminates between bvFTD and primary psychiatric disorders (38.6% of the cohort). This is probably explained by the fact that the largest differential diagnoses were mood disorders where attention and memory are more impaired than executive functions(29,30), while the smallest group was schizophrenia that shows mainly executive dysfunction(31). Also, relatively few patients with bvFTD had this specific neuropsychological profile (25% of the bvFTD patients), indicating that bvFTD is still a brain disorder that presents with predominately behavioural features and it denotes that a different neuropsychological profile does not rule out a bvFTD diagnosis. Altogether, we found evidence that executive dysfunction points towards a bvFTD diagnosis in a cohort of different neuropsychiatric disorders. However, a detailed neuropsychological profile of bvFTD versus primary psychiatric disorders is still lacking.

In paragraph 2.2, we studied the differences in neuropsychological profiles between bvFTD and its most common primary psychiatric misdiagnoses; major depression, bipolar disorder and schizophrenia in older aged patients with active psychiatric symptoms. By selecting these illnesses in their active state, our study resembled a clinical practice where patients present with behavioural and mood symptoms and neuropsychological assessment is used as a diagnostic tool. In comparison with health controls, we showed that there was a significant difference in cognitive functioning in
patients with bvFTD and primary psychiatric disorders. The cognitive impairment in these primary psychiatric disorders were consistent with other neuropsychological studies that also found substantial evidence of cognitive impairment in the same cognitive domains(29,32,33). For bvFTD, however, we deviate from the neuropsychological profile as described in the FTDC criteria(14) by finding relative more memory impairment than executive dysfunction. Moreover, memory impairment has long been regarded as a feature pleading against bvFTD(34). However, in clinical and autopsy-confirmed bvFTD cases, loss of memory is proven to be commoner than previously thought(35,36).

Contrary to expectations, when we compared bvFTD with primary psychiatric disorders, bvFTD patients performed the best on executive function compared to the primary psychiatric disorders. BvFTD patients also showed a better performance on attention, working and verbal memory. In previous research, neuropsychological profiles were compared between schizophrenia and bvFTD and showed a relative similar profile between these illnesses(37,38). A possible explanation for the contrasting findings could be that they included less patients with an active symptomatic-state of schizophrenia than our study. For MD and BD, a detailed comparison with bvFTD was never conducted before.

The large difference between these disorders on cognitive functioning and the contrasting finding of a high specificity for executive dysfunction in bvFTD could be explained by the fact that these cognitive domains strongly correlate with severity of behavioural changes(39,40), since these symptoms derive from the same fronto-subcortical neural circuits(41,42). By selecting patients with active psychiatric symptomatology and comparing them with bvFTD patients with a relative short disease duration (3.3 years), we might conclude that more cognitive impairment in these primary psychiatric disorders are related to more severe behavioural disturbances in these disorders. Nevertheless, our findings in paragraph 2.1 and 2.2 denote a relevant and important message for the clinician that in the differential diagnosis of bvFTD, cognitive impairment measured with neuropsychological tests does not rule out primary psychiatric diagnoses, nor does it exclude a bvFTD diagnosis. It is possible that by using a larger dataset in combination with an accurate severity scale for behavioural disturbances, we might find more discriminating factors in neuropsychological profiles.

Overall, we found substantial evidence that a phenotype of cognitive impairment and behavioural disturbances is not fully specific for bvFTD or a primary psychiatric disorder, especially in comparison with major depression, bipolar disorder and schizophrenia. In patients with a late-onset frontal lobe syndrome we reported a sensitivity of 85% and a specificity of only 27% for the FTDC criteria for possible bvFTD and showed that 76% (88 out of the 116 cases) met 3 or more of the core criteria for possible bvFTD, rendering
the concept ‘possible’ not suitable for clinical use. Clinicians must not confuse psychological certainty with epistemic certainty, and be cautious in communicating this concept to patients. We could conclude that ‘possible’ bvFTD is just a clinical starting point from where to use additional investigations in both a neurological or psychiatric department.

The fact that these illnesses that are etiologically or pathology different show identical clinical symptoms, emphasizes that clinical symptoms of bvFTD and several primary psychiatric disorders arise from a complex framework of different explanatory levels. Moreover, building a conceptual framework of the frontal lobe syndrome requires also knowledge about environmental and biological determinants of these disorders. Biologically, brain connectivity or the function of the synapses might point out where these disorders separate each other on their common pathway. Furthermore, when unravelling the different explanatory levels, it reveals the gap between a neurologist and a psychiatrist and so underscores the relevance of a close collaboration between them.

5.2.2 Biomarkers in the separation of bvFTD and primary psychiatric disorders

In this second section, we discuss the accuracy of the conventional biomarkers and we explore novel biomarkers in distinguishing bvFTD from primary psychiatric disorders. Overall, we found that the combination of neuroimaging and some specific CSF biomarkers (p/t-tau, NfL and YKL40) showed a high diagnostic accuracy for bvFTD. Furthermore, we illustrated that the architecture of structural network in bvFTD, AD and MDD were altered disease-specifically.

Prior evidence strongly suggested that in patients with bvFTD frontotemporal atrophy on MRI or frontotemporal hypometabolism on [18F]FDG-PET is present and that these biomarkers have a good diagnostic accuracy in a cohort of other neurodegenerative disorders (43-47). However, these studies did not include primary psychiatric disorders that may have similar changes on functional neuroimaging (e.g. [18F]FDG-PET), and to a lesser extent on structural imaging (e.g. MRI) (43-45,47-49). In our heterogeneous cohort that includes bvFTD and primary psychiatric disorders, we found that frontotemporal changes on structural imaging (MRI had a sensitivity of 70% (95% CI 52-85%) with a specificity of 93% (95% CI 86-97%)) are more specific for bvFTD than for primary psychiatric disorders or other disorders with behavioural changes. This emphasizes that bvFTD is a neurodegenerative disorder. [18F]FDG-PET had a sensitivity of 90% (95% CI 66-100%) with a specificity of 68% (95% CI 56-79%) in the same cohort. This result is probably because these brain diseases share the same topographic distribution of neural dysfunction with a possible common pathway of synaptic dysfunction, measured with the [18F]FDG-PET scan(50). Moreover, synaptic loss is
prominently found in the prefrontal cortex due to neurodegeneration in bvFTD patients, and correlates with the behavioural and cognitive deficits found in these patients(51). In primary psychiatric disorders, the synaptic dysfunction depends on the morphology and microanatomy of dendritic spines which vary among primary psychiatric disorders(52). For example, in schizophrenia reduced dendritic spines are found in the dorsolateral prefrontal cortex(53). A hypothetical difference between bvFTD and primary psychiatric disorders could be that psychiatric disorders have reversible frontotemporal hypometabolism on the $^{[18]}$FDG-PET after proper treatment, whereas bvFTD does not. This possible difference is an important issue for future research. Overall, we encourage the use of both neuroimaging techniques as stated in diagnostic criteria of bvFTD, however, considerable caution is advised when using the $^{[18]}$FDG-PET scan as only abnormal investigations. In contrast, a normal $^{[18]}$FDG-PET scan has a negative predictive value of 98% (95% CI 90-100%), underscoring the value of a normal finding.

Three CSF biomarkers (p-tau/tau ratio, NfL and YKL40) showed similar or higher diagnostic accuracies for bvFTD versus primary psychiatric disorders compared to the currently used neuroimaging biomarkers(44,46). A combination of these CSF biomarkers showed a sensitivity of 91% with a specificity of 83% for bvFTD, while in the same cohort the combination of MRI/$^{[18]}$FDG-PET had a sensitivity of 96% at a specificity of 73%. Therefore, we advocate that these CSF biomarkers are also included in the diagnostic guidelines of bvFTD. This statement is not solely based on our study, but is supported by previous studies that found that a decreased p-tau/tau ratio and increased CSF NfL is a marker of a underlying TDP43 pathology(54,55) and tau pathology(56) in FTD. Furthermore, there is also evidence that the CSF marker YKL40 is a good diagnostic marker for bvFTD patients compared with other neurodegenerative disorders(57).

Another intriguing finding was that primary psychiatric disorders with a similar phenotype as bvFTD had increased CSF levels of YKL40(57) and NfL(58-60), compared with levels previously found in healthy controls. This finding supports the presence of neuro-inflammation and synaptic dysfunction in primary psychiatric disorders. YKL40 is a glycoprotein that is produced by activated microglia and higher levels reflect increased inflammatory processes that may contribute to the neural or synaptic dysfunction(59,61,62). NfL is a protein of the neural cytoskeleton that has a role in axonal and dendritic branching and growth(63). Increased NfL levels reflect axonal dysfunction. The hypothesis of neuro-inflammation in psychiatric disorders is mostly applied to mood disorders (BD and MD)(64,65). A potential pathophysiological mechanism is the over-activation of microglia, leading to neuro-apoptosis and inappropriate synaptic pruning (destroying of unused synapses) (66). This pathological process eventually leads to neural circuit dysfunction which is associated with neuropsychiatric symptoms(65,67).
Furthermore, we illustrated that structural network properties contribute meaningful knowledge above volumetric values in neuropsychiatric disorders. It increases the accuracy to differentiate between these disorders and correlates with cognitive symptoms. We also found that bvFTD had a more ordered network compared to AD and MDD patients. Generally, network architectures are optimal when there is a high clustering and small path length(68). In the case of bvFTD, larger path length with relative high clustering were found, while in AD and MDD shorter path length and clustering was found. Our finding of a shift toward a more ordered network architecture in bvFTD is in line with structural and functional networks studies(69-73). A possible explanation for this phenomenon has previously been argued: Normally, in human functional brain networks the frontal module has extensive connections with other brain areas (74). The pathological changes in these frontal areas in bvFTD might cause altered long-distance connections from the frontal regions to other parts of the brain, thereby causing the pathologically ordered architecture, as reflected in larger path length in bvFTD(73). It is conceivable that this process of altered long-distance connections contribute to clinical symptoms of abnormal behaviour and cognitive deficits. Overall, we found significant differences between network properties in bvFTD and other neuropsychiatric disorders (AD and MDD). Nevertheless, it is too early to use structural grey matter networks as a diagnostic tool, further research is needed that shows a good longitudinal correlation with neuropsychiatric symptoms or a pathological correlation.

5.2.3 Methodological considerations

The LOF study has several unique strengths: first, the participants were recruited based on their symptoms. This created a clinically relevant cohort and reduced the selection bias. Second, it is a relatively large neuropsychiatric cohort compared to other studies. Third, the close monitoring and extensive investigations of participants during follow-up resulted in a nearly complete follow-up after two years. Specific methodological issues are discussed in the relevant chapters; I will only discuss potential sources of error and bias due to our gold standard that was used in many studies and the use of visual rating scales in neuroimaging.

5.2.3.1 Gold standard

For the gold standard definition, we had to rely on the clinical consensus diagnosis and additional investigations at two-year-follow-up. As a consequence of the two-year-follow-up, we were unable to rule out a neurodegenerative disease in the patients in the primary psychiatric group. However, the absence of clinical decline or changes on neuroimaging in two years made a neurodegenerative cause of the frontal symptoms less likely. Furthermore, recent cases reported in the literature support the idea that slowly
progressive cases of bvFTD that mimic psychiatric disorders and show no changes on neuro-imaging can be due to C9orf72 repeat expansion (75-79). Because of this, we screened all patients that were included in the LOF cohort (n=137) on C9orf72 repeat expansion and only found two cases. Our cohort does represent the heterogeneous group of bvFTD and primary psychiatric patients seen in daily clinical practice, increasing the generalizability of our findings.

5.2.3.2 Visual rating scales in neuroimaging

An alternative explanation for the false negative and/or false positive results of the neuroimaging in our studies that measured the diagnostic accuracy of the FTDC criteria (paragraph 2.1) and neuroimaging (paragraph 3.1) can be the relative unreliability of the visual rating scales used on the MRI and \(^{18}\text{F}\)FDG-PET-scan. In previous studies, it has been illustrated that using visual rating scales to distinguish between different causes of the frontal syndrome on MRI is proven to be highly susceptible to interpretation errors (80,81). They concluded that without further knowledge of the clinical symptoms and when visual rating scores are in the lower range (rated 0-1), a neuro-radiologist is prone to making diagnostic errors. In general, this limits the accuracy of our results to a certain degree. Furthermore, it gives a possible explanation of our finding in paragraph 3.1 (table 3) that the correctly assessed scans in our study were with high visual rating scores and that the false positive scans were with more lower visual rating scores. However, there is also strong evidence that 75% of the cases of bvFTD could be detected by visual rating and that interrater reliability is proven to be substantial in bvFTD (45,82).

\(^{18}\text{F}\)FDG-PET-scan has been proven to be an independent, objective, and quantitative biomarker for identifying different types of dementia (83,84). The majority of these studies found that visual rating on \(^{18}\text{F}\)FDG-PET-scan correlates strongly with atrophy of the dementia pathology (85). However, visual rating for bvFTD may also produce interpretation errors (86,87). Providing no differential diagnosis to the nuclear medicine physician in combination with frontotemporal abnormalities on \(^{18}\text{F}\)FDG-PET-scan might produce a high false positive rate.

Notwithstanding these limitations of visual rating scales, our studies resemble common practice of scoring neuroimaging in a daily clinic, making our results directly generalizable. Furthermore, we had very experienced neuro-radiologists for assessing the MRI-scans and an very experienced nuclear medicine physician that assessed and interpreted \(^{18}\text{F}\)FDG-PET-scan (all unblinded for the study design and age, blinded to the patients’ symptoms, complaints and medical history), rendering a high accuracy of the rating.
5.2.4 Implications and future directions

5.2.4.1 Clinical implications

The general aim of this thesis was to prospectively investigate the diagnostic accuracy of neuropsychiatric symptoms of the frontal lobe syndrome and biomarkers in distinguishing bvFTD from primary psychiatric disorders. By answering this aim, we automatically generate clinical relevant data that can be used in daily practice by a neurologist and psychiatrist. Our data is mainly focused and useful for the neuropsychiatric patients in whom the question arises ‘Are these behavioural or cognitive changes caused by bvFTD or a primary psychiatric disorder?’. Of course, our findings are also useful in other neurological disorders that present with a late-onset frontal lobe syndrome. However, as mentioned previously, most neurodegenerative disorders have already good accurate biomarkers. We propose a flow-chart for the clinical approach of patients presenting with LOF based on our findings described in this thesis (figure 1). Applying this flow-chart, we might tackle the diagnostic challenge to separate bvFTD from primary psychiatric disorders and make it simpler to organize clinical information about these patients.

We advocate the use of validated questionnaires for behavioural symptoms to assess stereotypical behaviour and to discriminate between symptoms of depression and apathy. Most of all, we emphasize the use of neuroimaging in patients with behavioural changes. In specific cases where the neuroimaging is not conclusive (no frontotemporal changes on MRI and [18F] FDG-PET or only a positive [18F] FDG-PET scan) and the differential diagnosis is still between bvFTD and primary psychiatric disorders, we advocate genetic testing (C9orf72) and the use of CSF biomarkers (p-tau / tau ratio, NfL and YKL40) which can help to minimalize the diagnostic challenge. Overall, we must conclude that clinically bvFTD and primary primary disorders show more similarities than dissimilarities, and that the balance for additional investigations leads to more dissimilarities than similarities. Thoughtfulness is still highly recommended in these neuropsychiatric patients in combination with a multidisciplinary approach and an appropriate duration of follow-up.

5.2.4.2 Future research implications

Although we illustrated some clinical dissimilarities between bvFTD and primary psychiatric disorders, in future clinical research features such as self-awareness, knowledge of other people state of mind and other social cognitive tests must be better investigated, because there is evidence that these clinical features are altered differentially between bvFTD and primary psychiatric disorders (88-90). Both from a...
clinical and pharmacological point of view there is a growing demand for accurate clinical markers that measure behavioural decline in bvFTD. Therefore, future neuropsychiatric cohorts should include an extensive battery that longitudinally measures all aspects of social cognition.

Furthermore, due to the strong evidence of a non-specific clinical spectrum in these brain disorders, a pathophysiological direction for future research is strongly needed. For example, in this current thesis we found some evidence that there is a synaptic dysfunction in neuropsychiatric patients with different types of aetiologies. Previously, measuring in vivo the density or function of synapses was difficult, however, a recent new PET-tracer makes this more conceivable. The new \[^{11}\text{C}]\) UCB-J PET tracer (91) measures synaptic density and might provide a specific way to identify different topographical distributions in neuropsychiatric disorders including primary psychiatric disorders. Moreover, the status of synapses can also be assessed using CSF markers, for example with neuromodulin (GAP43), neurogranin (NRGN) or synaptophysin. GAP43 is a synaptic protein in the presynaptic terminals and is associated with neuronal development and axonal growth(92). It is found that GAP43 is decreased in the frontal cortex and hippocampus of neuropsychiatric patients (AD, schizophrenia and mood disorders) and increased in their CSF, however, in bvFTD patients less elevated(93-95). NRGN is a postsynaptic protein that is involved in synaptic plasticity(96). A previous study illustrated a increase of CSF NRGN in AD patients, which could also be the case in other disorders(97). Overall, there is evidence that synaptic markers in CSF or with a PET-tracer are potential markers to discriminate bvFTD from mood disorders or schizophrenia and should be further investigated.

Related to the previous section on synaptic function, studying brain connectivity in these disorders should be encouraged. Changes in structural networks might lead to loss of functional properties of the brain such as the reduced adaptive ability due to the loss of synaptic plasticity, which is then reflected in alterations of the functional connectivity architecture(98,99). In addition, we need to measure these structural and functional properties longitudinally in larger groups. Also, we must correlate these properties to more neuropsychiatric symptoms besides cognition. Our findings that grey matter networks are changed in specific areas between disorders further raises the important question if these altered grey matter network properties also correlate with the neuropathology of neurodegenerative disorders.

Also, fundamental research in primary psychiatric disorders such as major depression, bipolar disorder, schizophrenia or obsessive-compulsive disorder is required to better understand the underlying aetiology and pathophysiology of these
disorders. By conducting more pathological studies in primary psychiatric disorders, we could develop theories about the molecular and cellular basis (100,101). The Netherlands Brain Bank for Psychiatry is currently collecting brain tissue of post-mortem brains of psychiatric donors and is available for research. Nevertheless, more psychiatric donors are needed.

**Figure 1.** Proposed flow-chart for the clinical approach in patients with behavioural changes and/or cognitive changes.

Abbreviations: 1. Based on the findings found in paragraph 3.2, if possible include CSF NfL and YKL40 measurements. 2. If deemed appropriate, genetic screening included the MAPT, GRN, PSEN1, APP genes, C9orf72 hexanucleotide repeat expansion.
5.2.4.3 Future directions for Neuropsychiatry

Based on the research conducted in this thesis and current literature about neuropsychiatry, I will discuss some points that in my opinion should be changed or created to support and accelerate the development of neuropsychiatry.

One of the requirements for a good clinical practice is a correct diagnosis which is based on the clinician’s expertise and knowledge. To accomplish this, further development of the medical discipline neuropsychiatry is probably needed. Not by integrating neurology and psychiatry, but to create a new medical subspecialisation that serves as a diagnostic specialist for neuropsychiatric patients and so gain highly focused expertise, knowledge and skills obtained by additional training and certification beyond a general neurologist or psychiatrist. Currently, neuropsychiatry is mostly covered by a specialised psychiatrist. However, we advocate a more cross-disciplinary subspecialty by emphasizing a good collaboration between a specialised neurologist and psychiatrist. In our studies, we have shown that a close collaboration has direct benefits for clinical practice and eventually it could improve the education of doctor’s in training that become a neuropsychiatrist, recruited from either a psychiatric or a neurologic training.

Another point that needs to be changed is the dichotomous view and the use of the concepts ‘functional’ versus ‘structural’ disorders. This view works counterproductive in the development of neuropsychiatry and thus not illustrate the complex causal network of neuropsychiatric disorders, as described in the brain-body-environment organization. Most mental symptoms are still viewed as functional properties, thereby suggesting that they are non-bound to their biological structure. In contrast to this traditional dichotomous view, this thesis and current literature contain supportive evidence that neuropsychiatric symptoms may have a biological basis. Of course many mental disorders and their symptoms still show no clear biological feature with the applied investigations, however, it is suggested that these tools are not yet sensitive enough to unravel the complexity of the brain. Nevertheless, the trend is set to increase the use and development of biomarkers and create molecular and cellular hypotheses for mental disorders.

Furthermore, to accomplish this monistic biological view of a separated neuropsychiatric discipline, a more suitable vocabulary and an adequate explanatory framework must be created that reflects much more the actual state of the brain and that can embrace the psychological, sociological and anthropological features of behavioural, affective, motivational and cognitive symptoms. Since neuropsychiatry will be a rapid changing discipline, it is important to discuss how to merge or bridge/link these two different theoretical well-developed disciplines (neurology and psychiatry) to one framework of neuropsychiatry, especially when conducting science in this field. For example, the most
dominant approach in medical and neuroscience to integrate different theories is reductionism(102). It commonly refers to a reduction of a phenomenon of interest (behavioural properties; psychological) to other lower levels (neuroanatomy or molecular pathways; neurological)(103). Epistemologically, ‘mechanistic reduction’ is now considered the most elegant way, which claims to understand the mechanism responsible for the phenomenon of interest, the researcher must identify the various parts of that mechanism (decomposition) and determine how they are organized to realize (localisation) the phenomenon of interest(104). At this moment, a more suitable model for neuropsychiatry is a liberal view of the ‘mechanistic reduction’ that considers also anti-reductive features, such composition and contextualization issues(105). Thereby allowing more features to be embraced such as spatial, temporal, causal, hierarchical and organizational features. A big challenge, however, are two main issues that arise using this liberal approach(106); (1) When a component of the mechanistic structure cannot be decomposed, you can only discuss this component on a organizational level as seen in many essential psychiatric features such as psychological, sociological and anthropological concepts. (2) When the relation between components are non-linear. How we decompose and localize these parts?

In conclusion, the gap between neurology and psychiatry is rapidly disappearing and requires some old paradigms to be replaced by new paradigms that aim to achieve one common goal: to understand the neuropsychiatric symptoms from a brain, body and environmental point of view.
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