Part 4

GENERAL DISCUSSION
Chapter 9
SUMMARIES AND GENERAL DISCUSSION
SUMMARY PART 1 – THE FRONTAL LOBE SYNDROME

Since the frontal lobe syndrome was the starting point of this thesis, in chapter 2 we investigated how the function of the frontal lobe was described and how the term ‘frontal lobe syndrome’ has been defined over the centuries as well as in the more recent literature. Compared to other brain dysfunctions associated with an anatomical localization, the frontal lobe syndrome was only described relatively late in medical history. By means of detailed observations of patients with acquired brain damage in conjunction with animal studies, the clinical effects of frontal dysfunction became apparent, in neurologic as well as in psychiatric conditions, mainly in the course of the 19th and early 20th century [1-4]. The rise of the implementation of psychosurgery like lobotomies in patients with severe psychiatric disorders provided increased insight into the anatomical substrates of the astounding behavioral changes observed [5-8]. At first, localized cortical areas were identified as the anatomical substrates for certain cognitive functions. In the mid and later 20th century it gradually became clear that several cortical, but also a number of deeper brain structures are anatomically closely linked [3;4;9;10]. Three anatomically distinct circuits, reaching from frontal cortical areas (dorsolateral prefrontal, orbitofrontal and mediofrontal / anterior cingulate) through the white matter to deep grey matter structures and back to the cortex, were described. Dysfunction within these circuits have repeatedly been shown to correlate with clinical syndromes: a stereotypical syndrome with mental rigidity, executive disturbances and perseveration, a disinhibited syndrome with loss of decorum, aggression and hyperorality, and an apathetic syndrome with loss of empathy and an absence of disease insight and awareness [4;9;11-13]. These networks may exhibit dysfunction when local damage (e.g. by tumor growth or vascular damage) occurs anywhere within the circuit, but a more diffuse process of altered activity may also arise. These diffuse changes are mainly seen in psychiatric disorders and in (the early stages of) neurodegenerative disorders. More recent developments in neuroscience gradually provided evidence that these frontal-subcortical networks, initially only anatomically defined, are also functionally related and are essential for the level of stressor associated anticipatory anxiety and homeostasis in mood and behavior in response to internal and external stimuli [12;14].

Summarizing the findings from the historical and recent literature, impairments in a frontal lobe syndrome may be described as deficits in the contextual integration of multiple (social) internal and external cues, deficits in the homeostasis of mood, affect or anxiety, and problems with initiating or suppressing intrinsically or environmentally driven actions or reactions.

In chapter 3 the distribution of neuropathological findings in patients with frontal lobe syndrome symptoms is described. For this study, brain tissue from patients, who had donated their brain to the Dutch Brain Bank, was used. Of the total number of 2814 Dutch
Brain Bank donors 262 patients who showed frontal behavioral disorders according to their medical records, were selected. This selection was carried out, independent of the underlying disease causing these behavioral disorders. The distribution of neuropathological abnormalities in the three anatomically defined frontal-subcortical circuits as described in chapter 2 was examined, by selecting the available brain tissue areas within these circuits. In 93% of the patients, pathological abnormalities were present somewhere within the specified frontal-subcortical circuits. In 34% the pathology was apparent only within the examined frontal cortical areas (the medial frontal gyrus and the anterior cingulate), and in 7% only in the examined frontal subcortical areas (the caudate nucleus, thalamus and the substantia nigra). 52% showed to have both cortical and subcortical pathological abnormalities. In the remaining 7% no pathology was found in the examined frontal regions. Next, the specific diagnoses causing these frontal pathological abnormalities were examined in retrospect. In the latter group of 7% in which no pathology was found, the diagnosis explained the absence of pathological abnormalities. In multiple sclerosis, it is likely that white matter abnormalities were present and the white matter was not included in our study. Moreover, there was a proportion of patients with a psychiatric diagnosis, in which no specific abnormalities were expected to be found on neuropathological examination. The proportion of patients in whom a frontal behavior disorder was reported was greatest within FTLD, followed by progressive supranuclear palsy and vascular dementia.

**SUMMARY PART 2 - WHERE NEUROLOGY MEETS PSYCHIATRY: CASES**

Chapter 4 illustrates relevant clinical dilemmas by means of a number of interesting cases. Four patients are presented with bipolar disorder who developed new behavioral disorders later in life. Both clinically and according to the Frontotemporal dementia consortium (FTDC) criteria they fulfilled the definition of possible behavioral variant frontotemporal dementia (bvFTD). However, after 3 to 7 years of follow-up, no clinical progression or deterioration on imaging was demonstrated and a neurodegenerative origin of the syndrome was found to be unlikely. The fifth patient described, fulfilled both the FTDC criteria for bvFTD as well as the DSM-IV criteria for late onset schizophrenia. This patient presented with psychosis and subsequently progressive behavioral problems with apathy, compulsions and executive dysfunction arose. An $^{18}$F-FDG-PET scan revealed bifrontal hypometabolism, therefore the patient did not only meet possible bvFTD diagnosis, but also probable bvFTD diagnosis. Given this increased level of confidence, this probable bvFTD diagnosis was made elsewhere and also at second opinion the neurologist tended towards this diagnosis. However, the conducted psychiatric evaluation revealed that the symptoms could also be explained by late onset schizophrenia. Some level of doubt remained, but the patient was treated according to the schizophrenia guidelines. Post-mortem examination
showed no abnormalities at autopsy. In retrospect, the diagnosis of schizophrenia was made and bvFTD was rejected.

SUMMARY PART 3 – THE LATE ONSET FRONTAL LOBE SYNDROME STUDY

In chapter 5 the design of our naturalistic cohort study, the late onset Frontal lobe syndrome study (LOF study), is described. 'LOF' is defined as a newly developed frontal lobe syndrome after the age of 40, as reported by a close and reliable informant. To fulfill the definition of a behavioral disturbance, patients had to present with either an apathetic syndrome, a disinhibited syndrome or a stereotypical/compulsive syndrome. The purpose of this behavior-based inclusion procedure is to obtain a realistic representation of the actual neuropsychiatric differential diagnosis of behavioral variant bvFTD. Within this clinically relevant differential diagnosis we attempted to diagnose bvFTD at an early stage. Within the LOF-study the neurologist and psychiatrist independently diagnosed each patient, before a meeting is held to make a consensus diagnosis. The study was designed so that the underlying etiologies (chapter 6), the role of MRI, [18F]FDG-PET and CSF biomarkers in this process (chapter 7), as well as the pitfalls in misdiagnosing early bvFTD in psychiatric or other neurological disorder (chapter 8) could be investigated. A total of 137 patients were included in the LOF-study, of which the cross-sectional data were used for the research described in chapter 6 and chapter 7. The final follow-up diagnosis is made after 2 years and is used as a gold standard for analyses in chapter 8 (Figure 1).

The research described in chapter 6 showed a broad clinical differential diagnosis underlying the frontal lobe symptoms within the LOF-study cohort. Cross-sectional multidisciplinary consensus diagnoses were made after clinical and neuropsychological examination, and neuroimaging and cerebral spinal fluid results were taken into account. Fifty-five (40%) of the patients received a bvFTD diagnosis (33% probable and 7% possible bvFTD). Twenty-one of the 45 patients with a probable bvFTD diagnosis showed frontal and/or temporal atrophy on the MRI and the remaining 24 patients (18%) showed frontal and/or temporal hypometabolism on the [18F]FDG-PET [15]. Fifty-one patients (37%) had a psychiatric disorder, including 20 with major depressive disorder. Only 7 patients with a major depressive disorder had had a psychiatric mood disorder at some time earlier in their medical history (range 6-40 years ago). Apart from the depressive disorder, a broad spectrum of psychiatric diagnosis (minor depression, bipolar disorder, schizophrenia, anxiety disorder) and a small minority of combined psychosociological conditions (such as personality traits, life events or marital problems) were found to be explanatory for the reported LOF. Thirty-one patients received an alternative neurological, including neurodegenerative, diagnosis. No
differences were found for age, gender, level of education and disease duration between the bvFTD and the non-bvFTD group. The scores on the MMSE and FAB were unspecific for a particular diagnostic group when comparing bvFTD with non-bvFTD. A score above 12 on the positive frontal behavioral inventory (FBI) subscale or a score above 5 and especially above 11 on the stereotypy rating inventory (SRI) were indicative of a bvFTD diagnosis.

The criteria for behavioral variant Frontotemporal dementia (bvFTD) incorporate MRI and $^{[18F]}$FDG-PET. CSF is merely advised to exclude Alzheimer’s disease. In chapter 7 the impact of biomarkers on diagnostic certainty and contingent changes of bvFTD diagnosis, within the clinically relevant neuropsychiatric differential diagnosis of subjects with a late onset frontal lobe syndrome (LOF), was examined. The diagnoses made by the neurologist, before and after the disclosure of biomarker results, were used (Figure 1). Also, a level of diagnostic certainty (‘a priori’, before biomarker result disclosure and ‘a posteriori’, after biomarker result disclosure) using a visual analogue scale from 0-100 was measured.

Patients were grouped into three major diagnostic groups for analyses (bvFTD, psychiatry, other neurological disorder (OND)). Biomarker disclosure was considered contributory after any substantial difference in diagnostic certainty or a diagnostic change. Biomarkers contributed in 53%, 60% and 41% of the LOF patients, for MRI, $^{[18F]}$FDG-PET and CSF respectively. Biomarkers changed the diagnosis in 14% of cases towards bvFTD and in 13% from bvFTD into an alternative. There were no significant differences between the diagnostic groups concerning the frequency in which the MRI and the $^{[18F]}$FDG-PET were rated as contributing. The absence or presence of abnormal CSF biomarkers, however, was considered contributing more often in subjects with a psychiatric diagnosis compared to the OND group.

The patient group with a diagnosis that changed had a lower a priori diagnostic certainty compared to the patient group with stable diagnoses. The chance of having a stable bvFTD diagnosis strongly increased per every 5-points increase of the a priori diagnostic certainty scale. The neurologist explicated that the MRI results increased diagnostic certainty in 49 cases, decreased certainty in 12 cases and changed the diagnosis in 11 cases. The neurologist explicated that the $^{[18F]}$FDG-PET results increased diagnostic certainty in 32 cases, decreased certainty in 17 cases and changed the diagnosis in 9 cases. The neurologist explicated that the CSF results increased diagnostic certainty in 29 cases, decreased certainty in 13 cases and changed the diagnosis in 2 cases. The group with a psychiatric diagnosis a posteriori contained a significantly higher number of male subjects.

Psychiatric misdiagnoses occur in up to 50% of bvFTD patients [16]. In chapter 8 we investigated the number of bvFTD misdiagnosis in psychiatric disorders, since numbers from this perspective were lacking so far. In 45.5% of the 35 patients with a (possible or probable) bvFTD diagnosis made by a specialized memory clinic neurologist at baseline, the diagnosis changed. In a few patients the diagnosis changed at baseline after consulting a psychiatrist. But the vast majority of these diagnoses was changed after multidisciplinary follow-up of two years by a neurologist and psychiatrist. Some received other neurological
Summaries and general discussion

Diagnoses, but most patients with a changed diagnosis were reclassified as having a psychiatric disorder. These patients, originally diagnosed with bvFTD, were reclassified as a depression, bipolar disorder, schizoaffective disorder or either a minor depression or an exacerbation of behavioral disturbances based on a personality disorder combined with severe relational problems. The results showed that especially a possible bvFTD diagnosis should be applied with caution and followed up carefully, since in our cohort all possible bvFTD baseline diagnoses were withdrawn during follow-up. That said, also a proportion of patients with a probable bvFTD diagnosis had the diagnosis withdrawn during follow-up. In one patient a C9orf72 repeat expansion was found to be explanatory for the behavioral changes. We found no differences for cognitive screening instruments and informant based behavioral questionnaires between patients with bvFTD at follow-up versus psychiatric diagnoses (originally thought to have bvFTD too). The results described in chapter 8 show that the clinical profiles and in some cases the neuroimaging findings of the psychiatric patients in which a bvFTD misdiagnosis was made, markedly mimicked a bvFTD profile.

DISCUSSION

Discussion part 1- The frontal lobe syndrome

In chapter 2 the evolution of the term frontal lobe syndrome is described. Naturally, no absolute borderline between normal and abnormal behavior exists and therefore this grey area remains subject of debate, but international research and literature will benefit from consistency in the terminology used. It will remain necessary to take the social and cultural setting into account, when defining abnormal behavior.
In chapter 3 the distribution of neuropathology in subjects with frontal lobe syndrome symptoms during life is described. Within this group, subgroups were found with mere cortical or mere subcortical pathology, supporting the theory that the frontal lobe syndrome might be the result of a lesion anywhere within the frontal subcortical circuits. Disorders like frontotemporal lobar degeneration (FTLD), previously mainly considered a focal cortical dementia, show subcortical involvement [17;18]. Other recent studies also support the involvement of subcortical areas in this disorder, including the white matter [19-21]. These findings may have consequences for future studies investigating the differentiating quality of for instance neuroimaging between dementia subgroups.

The proportion of patients in which a frontal behavior disorder was reported was greatest within FTLD, followed by progressive supranuclear palsy and vascular dementia. Nevertheless, a brain bank donation selection bias is likely, with underreporting of frontal lobe syndrome symptoms in the charts and a low ‘behavioral’ proportion in our study as a result. Since behavioral and psychological symptoms generally occur more often in dementia subtypes than our numbers indicate, some degree of underreporting is likely [22;23]. This seems to be even more applicable in psychiatric disorders. It seems plausible that physicians point out the possibility of brain donation more often to patients with suspected neurodegenerative diseases. Apparently, physicians do not always need to examine behavioral abnormalities in depth in order to correctly diagnose a disorder. Nevertheless, doing so and implementing management options could decrease caregiver burden, since this is clearly associated with abnormal behavior, psychosis and mood disturbances [24;25].

For many diagnostic studies on neurodegenerative diseases, prospectively obtained data with neuropathological confirmation constitute the ideal gold standard. Unfortunately, these data are hard to collect, considering the long follow-up duration and the fact that in a prospective study design not all patients will donate to a brain bank. Nevertheless, it would be very valuable if an increasing number of subjects were to donate, especially when yearly assessments have taken place. In our retrospective data collection, without the possibility of examining the time of onset of symptoms to the actual pathological examination, pathology has probably spread further since symptom onset. This results in more diffuse pathological findings than the actual pathology localization at the time of the first symptoms. In line with this, the majority of subjects already showed pathological abnormalities in multiple areas within the circuits, making it difficult to relate specific abnormalities directly to clinical symptoms. Furthermore, symptoms may result from direct neuropathological abnormalities in frontal areas, but possibly indirect effects due to severe dysfunction in highly connected more distant areas could also be explanatory. For research relating specific areas to clinical symptoms, functional imaging might be more suitable than neuropathological data. This said, as long as in vivo imaging techniques (alike amyloid-imaging using PET for AD) for all other pathology forms are lacking, neuropathological data are the most reliable diagnostic source of information at the time, when examining disease specific correlations.
Previously described anatomical circuits were confirmed using functional network analyses and the ‘salience’ and the ‘executive control network’ are the main functional connectivity networks thought to be involved in frontal-subcortical function. Most of the main grey matter areas within these networks were included in the study, but these networks also include the parietal cortex and fronto-insular to temporal areas [12;14]. These parts of the circuits were missing in the brain bank data and pathological abnormalities there could theoretically underlie frontal lobe symptoms without the anatomical etiology being included in our study. The same holds true for the orbital frontal cortex, which was not part of the brain bank protocol. A study design combining prospectively obtained clinical data with functional neuroimaging and eventual neuropathological confirmation would be very valuable for future insights.

**DISCUSSION PART 2 – WHERE NEUROLOGY MEETS PSYCHIATRY: CASES**

In chapter 4 four patients are described with bipolar disorder who developed a phenotype closely resembling possible bvFTD, but without progression over time. Although bipolar disorder has been classically considered a cyclic disease with full recovery between mood episodes, in the last decade evidence has accumulated supporting the notion that bipolar disorder is a progressive condition with functional decline over time. In older patients with bipolar disorder several studies have confirmed a significant cognitive dysfunction, that was not associated with mood or a prodromal phase of dementia [26-31]. It was hypothesized that this phenotype, resembling bvFTD, may be a possible manifestation of a long-standing bipolar disorder, resulting in relative dysfunction of the same anatomical areas affected in definite bvFTD syndromes.

The fifth patient described, fulfilled both the FTDC criteria for probable bvFTD as well as the DSM-IV criteria for late onset schizophrenia. Post-mortem examination showed no abnormalities fitting bvFTD. In retrospect, the diagnosis of schizophrenia was made. The sensitivity and specificity of the FTDC criteria for bvFTD have only been investigated within dementia cohorts, but not in neuropsychiatric cohorts. For this reason, well-considered application of the clinical diagnostic criteria is important, particularly in case of a psychiatric differential diagnosis, since the specificity of the FTDC criteria might be limited in such cases.
DISCUSSION PART 3 – THE LATE ONSET FRONTAL LOBE SYNDROME STUDY

Methodological issues
Several methodological issues have to be considered when interpreting the results presented in part 3 of this thesis.

The LOF-cohort
Inclusion and exclusion
A few choices were made in the study design concerning inclusion and exclusion. Most differentiating qualities of neuropsychological tests, imaging modalities or clinical features for bvFTD have been researched using a control group consisting of either healthy controls or other dementia subtypes, mainly Alzheimer’s disease, while the psychiatric disorders form the main differential diagnosis causing doubt and clinical dilemma’s in practice [32]. Since the main interest of the study was to detect early behavioral variant frontotemporal dementia within this clinically relevant neuropsychiatric differential diagnosis, inclusion was symptom-based, defined as an FBI score of \( \geq 11 \) and an SRI score of \( \geq 10 \), ensuring clinical relevance. Relatively low cut-offs have been chosen, since some degree of over-inclusiveness fits the studies’ aim of early detection of subtle changes in behavior.

The approach to diagnosing patients with behavioral changes is often monodisciplinary (either neurological or psychiatric). This cohort is the first study to prospectively include patients with a frontal lobe syndrome with a late-onset with neurological as well as psychiatric origins within the same multidisciplinary study.

A total of 234 patients with a LOF was screened for eligibility. Ninety-seven of these patients were excluded, of whom the vast majority had alcohol abuse (past or present) or incapability to complete baseline measurements (due to disease severity or logistics). The remaining 137 patients were included in the LOF-study. The reason for excluding subjects with chronic alcohol consumption is the evident influence on prefrontal functioning, making possible deficits more difficult to interpret and the brain volume reduction in various brain areas including the frontal lobe [33;34]. Nonetheless, bvFTD accompanied by disinhibition or hyperorality may in itself induce increased alcohol consumption, thereby possibly resulting in an inclusion bias. Precise numbers on alcohol abuse in bvFTD and other frontal lobe syndrome causes are lacking [35]. Another limitation of the present study is that patients in our tertiary referral center are relatively young and are likely to have relatively complex clinical features or atypical presentations. The results therefore cannot be easily generalized to any memory or psychiatric clinic. Possibly, the number of misdiagnoses described in chapter 8 is an underestimation of that in a general memory clinic in view of the expertise available. On the other hand, the earlier described complexity of cases in a tertiary center may increase the number of misdiagnoses. The diagnostic certainties as
reported by the specialists, the availability of the biomarkers and the contributing values attributed to these ancillary investigations (chapter 7) may be different in general clinics. A strength of the current approach is the recruitment of patients from a memory clinic as well as an old age psychiatry department, thereby avoiding referral bias.

**Diagnostic process and follow-up**

It strengthens our study that it has a standardized work-up and that we blinded both the neurologist and the psychiatrist in the diagnostic process for each other’s interpretations and results. Because both specialists are affiliated with a tertiary center, they are probably more familiar with the disorders of the ‘other’ specialization than an average neurologist or psychiatrist. This may have resulted in a lower number of patients in whom diagnostic discrepancy between the two specialists occurred. This may explain the low number of diagnostic changes from bvFTD into another diagnosis at baseline described in chapter 8 after psychiatric consultation by the neurologist.

Unfortunately, for the studies described in chapter 6 and 7 only cross-sectional data were available. Longitudinal follow-up would significantly strengthen the study design and increase the value of the results. Furthermore, the quality of studies greatly depends on the quality of the used gold standard. The gold standard of two years follow-up (chapter 8) may have been too short in some patients. It is hard to come by large numbers of suspected bvFTD subjects for prospective research, but we recommend longer follow-up duration and future repetition of the study in a larger cohort, ideally with a full genetic screening or neuropathological confirmation to increase diagnostic certainty. For the longitudinal data, the observational design may have resulted in non-random loss to follow-up, even though the total number of drop-outs was low and most severely affected individuals completed the study.

**Clinical implications**

The research in this thesis has several clinical implications, which will be outlined in the section below.

**Differential diagnosis to consider**

The results presented in chapter 6 show that in our multicenter cohort of middle-aged to old patients about one third was diagnosed with bvFTD, about one third with a psychiatric disorder and the remaining third with another neurologic disorder. Even though chapter 8 shows that during follow-up a significant number of diagnoses changed, this major subdivision will probably hold true, since diagnostic changes were made to and from bvFTD in about the same percentage. The clinical impact on subjects that received another neurodegenerative disorders than bvFTD, was considered less since these patients are receiving proper and adequate memory clinic care from baseline on. However, patients
with a psychiatric disorder included via the memory clinic would have missed adequate referral and treatment and their prognosis might have worsened by diagnostic delay, had they not received clinical evaluation and follow-up by a psychiatrist. The most prevalent psychiatric disorder was a major depressive disorder, although a minor depressive disorder was also quite prevalent. These subthreshold mood disorders are considerably common in this ‘younger elderly’ age group and have great impact on functioning, use of health care and quality of life, so their recognition has great clinical value [36-39]. A depression at an older age is known to present ‘atypical’ more often increasing the risk of being misdiagnosed as bvFTD [40;41]. Furthermore, a group of subjects who do not officially fulfill the criteria for a psychiatric disorder, but display a collection of symptoms caused by personality traits, life events, subthreshold psychiatric complaints and severe relational problems, markedly mimicking bvFTD is described. This part of our cohort shows clinical similarities with patients labeled by others as the ‘benign bvFTD-phenocopy syndrome’ [42;43].

The ‘bvFTD phenocopy syndrome’
The phenocopy-syndrome concerns patients, in whom clinical characteristics indistinguishable from possible bvFTD are noted, but no functional decline or neuroimaging abnormalities have been found. More evidence starts to emerge that atypical psychiatric disorders might be causing this so-called phenocopy syndrome and that psychiatric consultation might reveal treatable symptoms and disorders, not always fitting the definition of a major psychiatric disease [32;43]. Furthermore, our study shows another significant group of patients that clinically fits the phenocopy profile, but these patients do not fulfill the phenocopy definition, since they do show hypometabolism on $[^{18}F]$FDG-PET. In patients of this specific subgroup, initially considered a probable bvFTD group at baseline, the diagnosis was changed into an typical or atypical psychiatric disorder after follow-up. Therefore, these patients are not expected to show any progression over time. This suggests that careful psychiatric evaluation of patients is indicated in a broader defined group of subjects, and not just in those fulfilling the ‘phenocopy’ definition.

Screening instruments
It enhances the clinical workup carried out in each patient that cognitive as well as behavioral screening instruments are used. The main implications regarding these screening instruments are discussed below.
**MMSE and FAB**

The Mini-Mental State Examination (MMSE) and the Frontal Assessment Battery (FAB) are among the most widely used short screening instruments in memory clinics worldwide. The MMSE was developed as a screening instrument, grading cognitive impairment and has been widely applied for differentiating dementia patients from controls [44]. Since the MMSE is insensitive for frontal-subcortical dysfunction, the differentiating quality within the LOF-cohort was expected to be low and therefore the FAB, specifically designed to detect these frontal-subcortical disturbances and proven to have good reliability and validity, was included in the design [45;46]. Others have shown a FAB cut-off of 12 to have a sensitivity of 77% and a specificity of 87% for bvFTD versus AD [45;47]. Our study results show no distinguishing qualities for the MMSE or the FAB when differentiating bvFTD from its frontal differential diagnoses, even though the FAB is advocated in the literature for screening for bvFTD [47-49]. Considering the LOF-cohort, a heterogeneous group of neurologically impaired patients and a heterogeneous groups of psychiatric disorders, it is not surprising that all patient groups are expected to show normal or mildly impaired scores on the MMSE and FAB [28;44;45;50-53]. This suggests that even though the MMSE and FAB might be useful in differentiating bvFTD from controls or from AD, they have no added value when trying to differentiate bvFTD from other frontal lobe syndrome causes [45-47].

**FBI and SRI**

The frontal behavioral inventory (FBI, see Appendix) and the stereotypy rating inventory (SRI, see Appendix) are informant based screening instruments, developed for bvFTD. Both instruments have shown to differentiate bvFTD patients from AD, VaD or healthy controls [54;55].

Informant information is essential in patients lacking disease insight. Especially when information can be emotional or embarrassing, as is often the case in behavioral disturbances of a loved one, a structured interview has a clear advantage, since it guides the informant as well as the interviewer in a challenging consultation where often non-behavioral symptoms like memory impairment or somatic complaints are mentioned first [56]. Both questionnaires were included in the LOF-study and cut-off scores of 11 for the FBI and 10 for the SRI were used for inclusion [54;57]. As a result, research on the diagnostic value of the FBI and SRI is compromised, especially concerning scores around this cut-off point of inclusion [58]. The found increased risk for a bvFTD diagnosis with an mid-range score of 11-15 on the FBI described in chapter 6 is therefore difficult to interpret, since higher values of the negative subscale of the FBI did not differentiate between bvFTD and non-bvFTD subjects. Possibly, a proportion of the psychiatric patients also scored relatively high on the negative subscale of the FBI score, because loss of initiative is commonly reported in late-life depressive disorder [59]. We are therefore reluctant to suggest using
the negative subscale of the FBI for discriminating bvFTD from psychiatric disorders. The positive subscale of the FBI on the other hand, showed a somewhat stronger relationship with a bvFTD diagnosis. This might be related to the fact that our cohort included few patients with differential diagnosis with clear ‘positive symptoms’ at the time, e.g. manic episodes or psychosis.

**Chapter 6** showed that the total FBI score had a poor discriminating quality, even though the FBI is also advocated in the literature for identifying bvFTD [57;60]. We could not reproduce the findings of one study promoting the FBI in differentiating between bvFTD and depressive disorder [57]. The difference cannot be explained by difference in disease duration, since the mentioned study reports a mean bvFTD disease duration of two and a half years and in our cohort the mean was 3 years [57].

A high total SRI score showed to be most indicative of a bvFTD diagnosis in the study described in **chapter 6**. The SRI seems to be a quite specific measure since stereotypy is typically absent in other common frontal behavior causes like AD, DLB or depression. The number of patients with psychiatric diagnoses with clear stereotypical behavior, as theoretically could be seen in autism or obsessive compulsive disorder for example, was low in our cohort, as was the case with disorders exhibiting ‘positive’ frontal symptoms. The results indicate that particularly the highest scores on the SRI, which were far from the inclusion cut-offs, are indicative of a bvFTD diagnosis.

**Biomarkers**

Current imaging and CSF biomarkers when used separately are insensitive to a substantial part of the bvFTD patients. Imaging results show overlap with imaging abnormalities in psychiatric disorders, reducing the imaging specificity [61-72]. The sensitivity of neuroimaging for bvFTD is about 50-63.5% for MRI and about 81-90% for $[^{18}\text{F}]$FDG-PET within a memory clinic cohort [70;71;73;74]. But when the added value of $[^{18}\text{F}]$FDG-PET was examined in clinical bvFTD patients with a normal structural MRI, the sensitivity was only 47% with a relatively high specificity of 92% [75]. Our data do suggest an added value of $[^{18}\text{F}]$FDG-PET, but the specificity might be lower than reported by others in neuropsychiatric cohorts. In our study the patients with a clear atrophy pattern on MRI, fitting a bvFTD diagnosis, did not undergo an $[^{18}\text{F}]$FDG-PET-scan. This may have resulted in a selection bias concerning $[^{18}\text{F}]$FDG-PET and may underestimate the added value of $[^{18}\text{F}]$FDG-PET in our cohort. However, since the same selection takes place in clinical practice, we did follow the approach of the memory clinic routine. The measurement of CSF biomarkers (amyloid-beta, total-tau and phospho-tau (p-tau)) is mainly considered helpful to distinguish FTD from AD. No specific CSF biomarker pattern has been identified for FTD [66-69].

**Chapter 7** shows that MRI, $[^{18}\text{F}]$FDG-PET and CSF biomarkers each play a contributory role in the clinical differential diagnostic process of bvFTD, both by providing biomarker
evidence for this diagnosis as well as evidence for excluding the diagnosis. Particularly in those patients in whom there was a low level of certainty due to ambiguity about a differential diagnostic option, the imaging and CSF examinations had an added value. The most striking increase in certainty was seen in the patients with an a priori bvFTD diagnosis with a low level of certainty in which the diagnosis was changed towards a non-bvFTD diagnosis, based on the biomarker results.

The lack of specificity of the imaging is emphasized by the considerable group of subjects in our cohort described in chapter 8 with initially a probable bvFTD diagnosis, based on clinical features and hypofrontality on [18F]FDG-PET, in which the diagnosis was changed into a psychiatric disorder. The diagnostic change after follow-up was based upon clinical findings, increasingly suggesting a psychiatric origin of the complaints, as well as upon the absence of progression on the follow-up MRI. The reported percentage of ‘contributing’ [18F]FDG-PET-scans in chapter 7 might well be an overestimation, taking into account the results of chapter 8. The limited specificity of hypofrontality on [18F]FDG-PET for bvFTD within a cohort including psychiatric disorders, should be prospectively studied in more detail, preferably with considerable follow-up or neuropathological confirmation.

Recently, a higher total-tau level has been associated with a subgroup of FTD patients without pathogenic mutations with a relative fast rate of progression [76]. Also, a decreased phospho-tau-181/total-tau ratio differentiated FTD with underlying TDP-43 pathology from FTD with underlying tau-pathology [77;78]. These findings still concern a subgroup of bvFTD patients and need to be confirmed, but indicate an increasing potential future use for CSF biomarkers in bvFTD diagnosis. In psychiatric disorders like depression and schizophrenia CSF total-tau and p-tau levels vary between normal to slightly elevated compared to healthy controls, but are overall significantly lower than seen in AD [79-81]. Older schizophrenia subjects displayed lowered amyloid-beta levels compared to healthy controls, but higher than seen in AD patients and in this particular study group tau-levels were normal [82].

Misdiagnosis of bvFTD in psychiatry or vice versa: why do discriminating tests seem so scarce?

Correctly diagnosing or excluding bvFTD is of paramount importance for patients and caregivers, considering the caregiver burden involved, the different prognosis and considering the different treatment options in bvFTD versus its treatable psychiatric differential diagnosis [51;83-85]. The results described in chapter 8 show that not only the risk of making a psychiatric misdiagnosis in case of bvFTD is a pitfall to recognize, but also, a bvFTD misdiagnosis in case of a psychiatric disorder is an increasingly common scenario [16]. Further follow up of the complete LOF cohort is indicated to obtain more reliable data on misdiagnoses both ways.
The etiology of the great overlap in clinical presentation between bvFTD and psychiatric disorders is probably the fact that in both disease groups dysfunction in the same brain networks occurs [11;14;32;51;61;65;74;86-96]. This overlap with bvFTD, is seen mainly in psychosis, schizophrenia, compulsive behavior and unipolar or bipolar mood disorders, but also obsessive compulsive disorder or personality disorders combined with life events have been found in our results and by others [97-103]. The hallucinations and delusions, common in psychosis and schizophrenia, occur especially in FTD patients with progranulin or C9orf72 mutations [97;104-109]. Also, the ‘typical bvFTD’ neuropsychological profile of executive dysfunction, impaired social cognition with relatively intact visuospatial skills has been described in schizophrenia and in bipolar disorder [97;110-113]. Patients with a depressive disorder at an older age present with more bvFTD-like features, such as loss of interest, withdrawal, self-neglect and even reduced insight more often compared to younger patients, who report a sad mood or suicidal thoughts more [97;114;115]. These overlapping phenotypes compromise an early and correct diagnosis and challenge the development of differentiating instruments.

These findings and our results in chapter 8 underline that we must take into account that a percentage of our diagnoses will change during further follow-up. It has even been suggested that dementia releases latent psychiatric disorders in individuals who may possess certain predispositions, further complicating the differential diagnosis [51;97;116].

Psychiatric features as symptoms of the bvFTD itself, a comorbid psychiatric disorder or psychiatric symptoms in bvFTD as a prodromal phase of the already apparent FTLD pathology, have all been reported and must be considered [32;119].

In Alzheimer’s disease a comorbid depression has been found in up to 50% [117]. The comorbidity of psychiatric disorders in patients with bvFTD was not a primary subject of study in this thesis, but such a co-occurrence may have influenced the results. Depressive symptoms have been reported in 33% of bvFTD patients, but most data came from caregiver-based instruments in observational studies without consulting the patient on depressive symptoms [101]. No consensus on what constitutes a depressive syndrome in bvFTD is reached yet and further research is needed to investigate the co-occurrence of psychiatric disorders in bvFTD and the effect of treatment in such a comorbidity.

Chapter 6 illustrates the broad differential diagnoses to be considered, chapter 7 shows that many markers may assist a little, but none is very specific or sensitive for bvFTD and chapter 8 emphasizes the risk of misdiagnosis. The percentage of misdiagnosis in our tertiary centers was not as high as found in a study where 60% of bvFTD diagnoses made by community clinicians was withdrawn by specialists, but was still extensive [118].

Some authors suggest a shared causation underlies the concurrence of bvFTD and psychiatric symptoms, illustrated by the higher occurrence of psychosis in FTD in patients with relatives suffering from schizophrenia or schizoaffective disorder [51]. Furthermore, significantly more relatives of FTD than of AD patients were found to have schizophrenia.
Summaries and general discussion

However, this higher prevalence rate is almost the same as documented in the general population, so these numbers could also indicate a protective mechanism in AD [106]. Some polymorphisms of the progranulin gene may be involved in schizophrenia and bipolar disorder and hyperphosphorylation of tau may play a role in schizophrenia as well as FTD, suggesting the possibility of shared pathophysiological mechanisms [32;51;106;121;122]. It has been stated that C9orf72 mutations are not only a major cause of FTD, but also of late onset psychosis and bipolar affective disorder [51;123;124]. The question whether two such diagnoses should be made separately or should be seen as a spectrum of symptoms due to one underlying etiology has not been clearly answered yet. Considering the fact that many of the disorders examined in our study concern classifications or phenotypic syndromes and not nosologic entities makes further research of possible common etiologies necessary before conclusions can be drawn.

Using the FTDC criteria with care and caution

The recently developed FTDC criteria represent a great step forward, incorporating neuroimaging to determine the level of diagnostic certainty and increasing sensitivity for bvFTD diagnosis [15;125]. The need for cautious use of these new criteria with an increased sensitivity but also less restrictive exclusion features, especially in the psychiatric differential diagnosis, has been stressed by others as well, but the LOF-study is the first to prospectively examine this [126;127]. The criteria, especially for diagnosing probable bvFTD, has been described by many as robust [128]. Within a dementia cohort a sensitivity of 95% and a specificity of 82% have been described [129].

The sensitivity and specificity of the FTDC criteria in the LOF cohort could not be calculated yet, but will follow shortly when all follow-up data of the cohort become available. Nonetheless, the clinical impression of this group and results of the subgroup described in chapter 8 clearly suggest a limited specificity of the criteria within such a neuropsychiatric frontal cohort, especially for possible bvFTD, since meeting the inclusion criteria on the behavioral inventories does imply meeting the criteria for possible bvFTD in many cases. In a symptom based neuropsychiatric cohort the criteria therefore seem to be somewhat ‘overinclusive’. On the other hand, some degree of ‘overexclusiveness’ takes place when patients exposing psychiatric features fulfill a psychiatric diagnosis, although this is known to appear in FTD, are therefore excluded by the criteria for fulfilling a bvFTD diagnosis [15;99;100;104;130].

The DSM-5 criteria for ‘cognitive disorders’ have been adapted in order to include neurodegenerative disorders not presenting with memory decline as a first symptom, making them more fitting for bvFTD, compared to the DSM-IV [32;131;132]. But still, cognitive impairments are required and are not always present in (early) bvFTD and if the cognitive deficits may be primarily attributable to another mental disorder no neurocognitive disorder may be diagnosed.
Since we failed to identify strong clinically distinguishing features in the cognitive and behavioral screening instruments (chapter 6 and chapter 8) to aid the clinician in discerning bvFTD from its psychiatric differential diagnosis, we cannot identify a small subgroup that would benefit from psychiatric consultation. Therefore we would suggest applying the FTDC criteria and consulting a psychiatrist in all possible and probable bvFTD cases in the early diagnostic phase and during early follow-up.

Towards a diagnostic paradigm for bvFTD

Early onset bvFTD can resemble, mimic, co-occur with or be misdiagnosed as different psychiatric disorders. Even though we were not as yet able to identify tests or markers with ideal discriminating characteristics, some clinical impressions and consideration may be of value.

Above all, this thesis points out that an early and accurate bvFTD diagnosis within a neuropsychiatric cohort is challenging and has many pitfalls. This is illustrated by the fact that in current clinical practice bvFTD has the longest diagnostic delay compared to other dementia subtypes [133]. As long as strong diagnostic in vivo biomarkers are not available, careful and accurate weighing of the clinical and neuro-imaging findings should take place, considering the specific differential diagnosis in each patient individually in order to make a certain diagnosis as soon as possible [134]. This will help to achieve the most adequate clinical pharmacological and non-pharmacological care [134-137].

The first step is to identify those patients with a ‘suspicion of bvFTD’, but with a possible psychiatric differential diagnosis. A multidisciplinary diagnostic process in which the neurologist and psychiatrist carefully discuss the patients’ clinical symptoms in a cooperative manor is vital. Another approach would be to ‘flag’ early warning signs as a clinical prodrome without being able to pinpoint the underlying etiology yet, as is done in ‘mild cognitive impairments’ (MCI) [138]. An interesting study reintroduced the term MBI, mild behavioral impairment, and found neuropsychiatric symptoms, especially when not accompanied by cognitive impairments, to be a prodromal phase of dementia, especially of FTD, in up to half the cohort [139]. A label of MBI even conferred a higher risk of dementia conversion than mild cognitive impairment (MCI) [139]. This approach may lead to less referral bias towards this multidisciplinary diagnostic trajectory.

The clinical workup should at least include an interview and medical history of the patient, a family history, a mental state examination, a neurological examination and an interview in which all information from (preferably multiple) informants is of importance. Based on the detailed clinical syndrome found combined with demographic information of the patient, certain individualized choices can be made, but neuroimaging seems to be indicated in all of these patients. MRI as well as [18F]FDG-PET has diagnostic value and should be performed. If the MRI shows clear and typical atrophy patterns fitting bvFTD no functional imaging is indicated, as is also stated in the FTDC criteria. When (a dysexecutive
subtype of) Alzheimer’s disease is one of the differential diagnostic considerations, CSF collection or amyloid PET imaging would be indicated, but with increasing age of the patient, physicians should be aware of increasing numbers of false-positive findings, considering the higher number of patients with (asymptomatic) neuropathological amyloid deposition with inclining age [140].

Many clinical impressions were obtained during conduction of the LOF-study, not all studied quantitatively yet, of which some correspond with results found by others. For example, the finding that early compulsive-like behavior as a presenting symptom is suggestive of bvFTD was confirmed [119]. Nonetheless, it is important to consider what the most likely differential diagnosis is. In for instance a major depression these compulsive behaviors are rare, but when considering bvFTD versus an OCD the compulsions will not help much in differentiating. This suggests that even though the diagnostic criteria have improved, as long as there is no specific biomarker available, the ‘personalized medicine’ approach is necessary: depending on the specific clinical differential diagnosis in a patient some symptoms will be considered of great diagnostic weight, while in another patients the symptom might not be useful in the diagnostic process. The consequences of this approach are illustrated by the fact that in our LOF-cohort not many patients with OCD, autism or Tic-syndromes where present and therefore stereotypical measurements like the SRI where relatively discriminating. These diagnostic properties will differ in another patient group and the clinician should carefully weigh the instruments and the specific differential diagnosis. This ‘personalized medicine’ approach is necessary in other differential diagnoses as well and clinical expertise is the driving force behind an accurate and complete diagnosis. It has been suggested that a subacute onset, a positive family history or a previous medical history positive for psychiatric disorders, an atypical psychiatric disease course, insidious worsening during treatment or suicidal thoughts are all suggestive of a psychiatric origin, even though suicide attempts have been reported in bvFTD [102;141;142]. During follow-up, suspicion of a psychiatric origin should also arise when patients maintain a reasonable ADL function and do not develop language impairment, Parkinsonism or motor neuron disease [124].

Our data suggests that especially in male patients, in patients with low stereotypy rates, without structural imaging abnormalities, in those with multiple psychiatric of psychological disorder traits and in patients merely fulfilling possible bvFTD, the FTCD criteria must be applied with much caution and alternative diagnoses should be considered repeatedly during follow-up. Also in the bvFTD phenocopy syndrome in previous research male gender predominated [42]. Further research should clarify if indeed males with psychiatric disorders are more prone to be misdiagnosed as bvFTD. This would be an interesting topic to study, as in women the opposite seems to hold: women proved to receive a psychiatric misdiagnosis in actual bvFTD more often compared to men [16]. In our cohort depressive disorders were the most common psychiatric diagnosis. The lack of a positive family history
for mood disorders, a family history with dementia, Parkinsonism or motor neuron disease speaks in favor of an organic etiology in the differential diagnosis between bvFTD and a depression, although many of our psychiatric patients and their family members had no previous psychiatric medical history [97].

Psychosis-like episodes seem to be rare in bvFTD compared to psychiatric patients [119]. But a C9orf72 mutation is notorious for causing a very slowly progressive bvFTD, commonly accompanied by symptoms typically considered to be psychiatric [108;143-145]. Patients with a C9orf72 repeat expansion fit the FTDC criteria less and present with atypical clinical profiles more often [145;146]. So even though in our cohort only 2 patients (1.5%) had a C9orf72 repeat expansion, we do advise genetic screening for this gene in patients with a late onset frontal lobe syndrome, since it has great consequences for prognosis, management and family members. When a patient with bvFTD symptoms has a positive family history for at least one first-degree relative with early-onset dementia or motor neuron disease, genetic testing for MAPT and progranulin is indicated as well [103;147]. Genetic testing may be considered in patients with a positive family history for late onset schizophrenia, late onset bipolar disorder or late onset depression or in patients with only second-degree family members with early onset dementia or motor neuron disease. It is to be expected that in the near future the availability of genetic screening will increase as the costs decrease. This could facilitate screening for all other known single gene genetic causes of bvFTD more easily. Genetic counseling is always advised, since presymptomatic pathological mutations might be found.

**Future recommendations**

Longer prospective follow-up of cohorts with patients with a late onset frontal lobe syndrome or ‘mild behavioral impairment’ (MBI) is indicated, preferably including genetic and neuropathological data. The finding that MBI conferred a higher risk of dementia conversion than MCI, should be replicated. If this higher risk holds true, it is important that all memory clinics become aware of the need for follow-up in subjects with dysfunction in the behavioral domain only [139]. Because bvFTD is a relatively rare disease, pooling of data would be of great value, but it would demand some level of uniformity in the terms and instruments used.

More prospective research is needed to further characterize the group in which psychiatric screening is beneficial, since it should be a broader defined group, and not just those fulfilling the ‘phenocopy’ definition.

In the recent literature a number of discerning factors for bvFTD have been mentioned as promising by others, like tests specifically focusing on social cognition or theory of mind, on decision making, on humor and sarcasm, on olfactory dysfunction or decreased sensitivity to pain in FTD [111;112;148-155]. Also, detailed behavioral observation may be of more value than counting scores on screening instruments [156]. It would be possible
though, that certain psychiatric disorders exhibit the same abnormalities on these tests due to involvement of the same brain areas, so this should be further evaluated in studies with a neuropsychiatric control group [51;87;89;91;94;97;157-160].

A profound loss of empathy is sometimes seen in schizophrenia or severe depression, but seems to be more common in bvFTD [106]. Also hyperorality or compulsive eating, items within the SRI, are a more common feature in bvFTD, as is a profound lack of distress [134]. Since hyperorality, compulsive eating and a lack of distress were more commonly seen in bvFTD by others and a high score on the total SRI was suggestive for bvFTD in our cohort, it would be interesting to investigate which SRI items could discriminate bvFTD from psychiatric disorders [134].

Furthermore, a systematic analysis of specific signs suggestive of frontal neuronal damage, like an abnormal gait or frontal release signs, should take place in a neuropsychiatric cohort, even though the prevalence of these symptoms might be low [161;162].

Further studies are indicated for the risk of misdiagnosis by gender: in bvFTD misdiagnosis, male gender predominated and in psychiatric misdiagnosis in actual bvFTD female gender predominated [16;42]. At the time, much research is done to develop an in vivo biomarker for bvFTD or FTLD subtypes, for example tau binding ligands or computational analyses of functional imaging markers [85;163-165]. This has not lead to useful applications in clinical practice as yet, but could become of major importance.

All the possible differentiating instruments above and genetic screening will become of paramount importance once therapeutic options become available [166].

**Concluding remarks**

The classification of normal and abnormal behavior is situational and subject to social and cultural changes, so there will always be borderline cases, bound to cause debate. Nonetheless, the medical and research fields benefit from the consistent use of terms and from research on deviant behavior. The frontal lobe syndrome has a heterogeneous etiology and identifying bvFTD within this group is of great clinical importance.

The LOF-study described in this thesis is the first prospective study on early diagnosis of bvFTD within a neuropsychiatric cohort. A little bit over one third of the patient received a bvFTD diagnosis, about one third received a psychiatric diagnosis and the remaining patients received an other neurological diagnosis.

The biomarkers used, MRI, [18F]FDG-PET and CSF, all contributed to the diagnostic process at inclusion. The neuroimaging, and especially the [18F]FDG-PET, was rated as most contributing. Demographic characteristics and frequently used screening instruments like the MMSE did not differentiate between bvFTD and the other diagnostic groups. A high level of stereotypy on the other hand turned out to be suggestive for bvFTD, as might be the case with high ratings on disinhibition.

The FTDC criteria from 2011 are more sensitive for bvFTD compared to the older
criteria, but also less restrictive. Both the clinical symptoms as well as the functional imaging findings in psychiatric patients may mimic bvFTD. This results in diagnostic doubt in the clinical setting and was illustrated by the study results described in this thesis. These psychiatric ‘bvFTD mimics’ lower the specificity of the FTDC criteria. Careful multidisciplinary follow-up by a neurologist and a psychiatrist seems to improve the reliability of the diagnosis on the long run.

This follow-up procedure in the LOF-cohort resulted in a significant number of changed diagnoses over time. This finding suggests that the multidisciplinary follow-up is of even more importance than the multidisciplinary assessment at inclusion. Furthermore, the results indicate a necessity to be very reserved in making a possible bvFTD diagnosis, since all possible bvFTD diagnoses in the LOF-cohort were changed in non-bvFTD diagnoses after two years of follow-up. These same results indicate an initial overestimation of the value of the ‘typical bvFTD’ findings on $[^{18}\text{F}]$FDG-PET.

Future imaging techniques, the differentiating qualities of tests on social cognition, quantification of disease insight or quantification of the level of suffering or distress might be promising in identifying bvFTD from psychiatric disorders, but more prospective research is needed within neuropsychiatric cohorts.

It seems there is convincing evidence to systematically examine and follow patients with subtle behavioral disturbances for a number of years. Neuroimaging is indicated in this patient group and genetic screening, especially for the C9orf72 repeat mutation, contributes to the diagnostic work-up. Since these patient may display a prodrome of bvFTD or a prodrome of a late onset psychiatric disorder, a more neutral term like *mild behavioral impairments* seems to be more fitting than the frequently used term *bvFTD phenocopy syndrome*.
REFERENCE LIST


Summaries and general discussion


83. Pressman PS, Miller BL. Diagnosis and management of behavioral variant frontotemporal dementia. *Biol Psychiatry* 2014;75:574-81.


89. Kanahara N, Sekine Y, Haraguchi T, Uchida Y, Hashimoto K, Shimizu E, Iyo M. Orbitofrontal
cortex abnormality and deficit schizophrenia. *Schizophr Res* 2013;143:246-52.
91. Olabi B, Ellison-Wright I, Bullmore E, Lawrie SM. Structural brain changes in First Episode
Schizophrenia compared with Fronto-Temporal Lobar Degeneration: a meta-analysis. *BMC
Psychiatry* 2012;12:104.
93. Shenton ME, Dickey CC, Frumin M, McCarley RW. A review of MRI findings in schizophrenia.
*Schizophr Res* 2001;49:1-52.
94. Tekin S, Cummings JL. Frontal-subcortical neuronal circuits and clinical neuropsychiatry: an
95. Wolf DH, Satterthwaite TD, Calkins ME, Ruparel K, Elliott MA, Hopson RD, Jackson CT,
Prabhakaran K, Bilker WB, Hakonarson H, Gur RC, Gur RE. Functional neuroimaging
96. Zamboni G, Huey ED, Krueger F, Nichelli PF, Grafman J. Apathy and disinhibition in
97. Pose M, Cetkovich M, Gleichgerrcht E, Ibanez A, Torralva T, Manes F. The overlap of
symptomatic dimensions between frontotemporal dementia and several psychiatric disorders
98. Passant U, Elfgren C, Englund E, Gustafson L. Psychiatric symptoms and their psychosocial
99. Mendez MF, Perryman KM, Miller BL, Swartz JR, Cummings JL. Compulsive behaviors as
100. Mendez MF, Shapiro JS, Woods RJ, Licht EA, Saul RE. Psychotic symptoms in frontotemporal
101. Chakrabarty T, Sepehry AA, Jacova C, Hsiung GY. The prevalence of depressive symptoms in
102. Galimberti D, Dell’Osso B, Altamura A, Scarpini E. Psychiatric Symptoms in Frontotemporal
103. Ducharme S, Price BH, Larvie M, Dougherty DD, Dickerson BC. Clinical Approach to the
Differential Diagnosis Between Behavioral Variant Frontotemporal Dementia and Primary
der ZJ, Clot F, Bakchine S, Puel M, Ghanim M, Lacomblez L, Mikol J, Deramecourt V, Lejeune
D, Habert MO, Dubois B, Brice A. Phenotype variability in progranulin mutation carriers: a
105. Snowden JS, Rollinson S, Thompson JC, Harris JM, Stopford CL, Richardson AM, Jones M,
Gerhard A, Davidson YS, Robinson A, Gibbons L, Hu Q, DuPlessis D, Neary D, Mann DM,
Pickering-Brown SM. Distinct clinical and pathological characteristics of frontotemporal
106. Cooper JJ, Osvie F. The Relationship Between Schizophrenia and Frontotemporal Dementia. *J
Geriatr Psychiatry Neurol* 2013.


