Summary
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Driven by the clinical dilemma of the large symptomatic overlap of bvFTD and psychiatric disorders, the general aim of this thesis was to define clinical hallmarks able to discern a psychiatric origin from behavioral variant frontotemporal dementia in the late onset frontal lobe syndrome. We described our research on different aspects of the clinical overlap and differentiation of bvFTD, other neurodegenerative diseases and psychiatric disorders. In this section, the results of these research projects, implications for clinical practice and future perspectives are discussed.

Section 1. Behavioral variant frontotemporal dementia and psychiatric disorders

The starting point of **section 1** was to describe main aspects of clinical similarities between bvFTD and psychiatric disorders. In **chapter 2** we investigated the frequency and character of DSM-IV psychiatric disorders in patients with probable and definite bvFTD compared to patients with possible bvFTD, other neurodegenerative diseases, and patients diagnosed with a psychiatric disorder, using MINI-International Neuropsychiatric Interview. The MINI-International Neuropsychiatric Interview was based on DSM-IV and ICD-10 criteria for a psychiatric disorder.[1] We additionally compared psychiatric prodromes between these diagnostic groups. In this research 23 patients with probable and definite bvFTD, 3 patients with possible bvFTD, 25 with a non bvFTD neurodegenerative disease and 40 patients with a clinical psychiatric diagnosis were studied. Overall frequency of formal current and past psychiatric disorders in patients with probable and definite bvFTD (21.7% current, 8.7% past) did not differ from other neurodegenerative diseases (12.0% current, 16.0% past) or possible bvFTD (66.7% current, 66.7% past), but was less than in patients with a clinical psychiatric diagnosis (57.5% current, 62.5% past) ($P<0.01$). In patients with probable and definite bvFTD unipolar mood disorders were most common. Contrary to our expectations we concluded that formally diagnosed psychiatric disorders are not overrepresented in probable bvFTD. This conclusion is remarkable in the context of previous literature reporting that 50.7% of bvFTD patients receive a prior psychiatric diagnosis, found by retrospective chart review.[2] Our longitudinal study showed that correctly applying DSMIV and ICD-10 criteria in bvFTD gives a lower rate of formal psychiatric disorders in bvFTD (23.3%), and we suggested that psychiatric misdiagnosis in bvFTD might be reduced by strictly applying diagnostic criteria.
Further we found that in probable bvFTD patients unipolar mood disorders were the most common psychiatric disorders (13.9%). Previous literature has already shown the relative high prevalence of mood disturbances in bvFTD. A recent meta-analysis including 29 studies showed that depressive mood and its manifestations are recognized in approximately one third (33%) of patients with bvFTD.[3] Striking, the majority of these studies about the prevalence of (comorbid) depression in bvFTD were based upon reports of depressed mood only while studies into the prevalence of mood disorders based on formal criteria for depression are scarce.[3 4 5] The discrepancy between the prevalence of depressive mood in bvFTD and the prevalence of depressive and dysthymic disorder according to DSMIV and ICD-10 criteria as found in our study, highlights the symptomatic overlap of bvFTD and psychiatric disorders. More importantly, this research suggested that the use of formal criteria, not only for bvFTD but also for psychiatric disorders, might act as one of the clinical hallmarks helpful to distinguish psychiatric disorders from bvFTD in an early stage.
Chapter 3 was an overview of the prevalence of the broad spectrum of psychotic symptoms in bvFTD. This was the first study which was focused at psychosis in bvFTD beyond the well-known positive psychotic symptoms (hallucinations, delusions and suspiciousness/ paranoia). Besides positive psychotic symptoms we also studied negative psychotic symptoms (a diminution or loss of normal

functions, e.g. reduced motivation or reduced emotion) and formal thought disorders (a disorganization of thought). We prospectively employed a commonly used and validated clinical scale which quantifies the broad spectrum of psychotic symptoms (Positive and Negative Symptom Scale, PANSS) in patients with probable and definite bvFTD (n=22) and patients with a primary psychiatric disorder (n=35). Despite frequent misdiagnosis with schizophrenia, we found that bvFTD patients are not mainly characterized by positive psychotic symptoms (22.7% of bvFTD patients) while negative psychotic symptoms such as social and emotional withdrawal and blunted affect (95.5%) and formal thought disorders (81.8%) were frequent. It is remarkable that the prevalence of positive psychotic symptoms in bvFTD differed in several studies.[6 7 8] The frequency of positive psychotic symptoms we found might be associated with the amount of genetic mutations in the sample size, as positive psychotic symptoms have recently repeatedly been described in progranulin and C9ORF72 mutation carriers.[9 10 11 12] As our study contained only three patients with a genetic mutation (13.6% of bvFTD patients), the percentage of known genetic variants was lower compared to other studies (percentages of approximately 20-50% of hereditary etiologies found in other studies).[13 14] However, besides the discrepancies in frequency of positive psychotic symptoms, this first study into the broad spectrum of psychotic symptoms in bvFTD showed that negative psychotic symptoms and formal thought disorders are the main overlapping psychotic symptoms of bvFTD and psychiatric disorders. This was highlighted by the fact that our bvFTD patients tended to have a lower total score at the positive subscale of the PANSS than found in studies into schizophrenia (respectively 9.5 in our bvFTD patients versus 18.2 in schizophrenia patients) but similar scores at the negative subscale. [15] This paragraph also showed that difficulty in abstract thinking and stereotypical thinking (formal thought disorders) differentiated bvFTD from psychiatric disorders. The combined predictors "difficulty in abstract thinking", "stereotypical thinking", "anxiety", "guilt feelings," and "tension" explained 75% of variance in the diagnosis of bvFTD versus psychiatric disorders. Besides the use of formal diagnostic criteria, exploring the broad spectrum of psychotic symptoms in patients suspected of bvFTD can therefore be valuable in the differentiation of bvFTD and psychiatric disorders in clinical practice.

Section 2. Differentiating behavioral variant frontotemporal dementia from other neurodegenerative diseases and psychiatric disorders

In the **second section** we further elaborated on the clinical distinction of behavioral variant frontotemporal dementia from psychiatric disorders and other neurodegenerative diseases. Whereas deficits in social cognition have repeatedly been found in bvFTD, in **chapter 4** we studied whether social cognition distinguishes bvFTD from other neurodegenerative diseases and psychiatric disorders in patients presenting with the late onset frontal lobe syndrome. Social cognition was determined by the *Ekman 60 Faces test* and *Faux Pas test*.[16 17] We also set out to determine *executive functioning, memory, attention/concentration/mental speed* and *visuospatial functioning* in the diagnostic groups. Several previous studies already suggested that social cognition is markedly impaired in bvFTD when compared to healthy controls [18 19 20], AD patients and patients with a psychiatric disorder but the comparison was never completed within the symptom profile of the frontal lobe syndrome. We found that besides bvFTD, also patients with other neurodegenerative diseases and psychiatric disorders presenting with frontal symptoms had impaired social cognition, but even with overlapping symptomatology, total scores at *Ekman 60 Faces test* were significantly lower in bvFTD than in other neurodegenerative diseases and psychiatric disorders. We found that *Faux Pas* did not discriminate between the diagnostic groups. It is conceivable that *Faux Pas* is a more sensitive method for measuring social cognition while *Ekman 60 Faces test* is a more specific method.[21 22] *Ekman 60 Faces test* explained 91.2% of the variance

of psychiatric disorders and other neurodegenerative diseases versus bvFTD. We therefore suggested *Ekman 60 Faces test* as a valuable test to endorse clinical differentiation of bvFTD from other neurodegenerative diseases and psychiatric disorders.

One of the most striking results of this research was the finding that despite the association of social cognition with all other cognitive domains (*executive functioning, memory, attention/concentration/tempo and visuospatial functioning*), the other cognitive domains except *visuospatial functioning* did not differentiate between diagnostic groups. The current bvFTD criteria emphasize the impairment of executive functioning in neuropsychological tests in bvFTD[23], whereas the results we found suggest that social cognition measured by *Ekman 60 Faces test* might even be more useful.

The research described in **section 2, chapter 5,** focused at the diagnostic value of clinical variables and additional investigations to distinguish between psychiatric disorders and bvFTD. We found that the variables male gender, absence of stereotypy based on a low score on the *Stereotype Rating Inventory* (SRI), and the presence of depressive symptoms with high scores on the *Montgommery Asperg Depression Rating Scale* (MADRS) had good discriminating abilities for psychiatric disorders versus bvFTD (86%). We found that normal neuroimaging only slightly increased the diagnostic value for a psychiatric disorder versus bvFTD to 88.4%. Although depression and apathy are overlapping concepts, the MADRS focuses on symptoms specific for depression and may therefore be useful especially in diagnosing depression as comorbidity in bvFTD or as an alternative diagnosis of depression. Apathy is considered a bvFTD symptom, and may be misdiagnosed as major depression, as also discussed in **chapter 3** While MADRS may point to a psychiatric diagnosis in patients suspected of bvFTD, it is conceivable that a measuring instrument only focused at apathy would be indicative for a bvFTD diagnosis but this has not been studied so far. This chapter suggested that in patients with a late-onset frontal lobe syndrome psychiatric diagnoses can be established at a high accuracy based on clinical phenotyping and that the presence of stereotypy might be seen as another hallmark to differentiate bvFTD from psychiatric disorders.

Section 3. Disease course in late onset frontal lobe syndrome

In **section 3** we studied different aspects of disease course in the late onset frontal lobe syndrome. Patients with the benign bvFTD phenocopy syndrome were a first focus of interest, because of their remarkable disease course, as described in **chapter 6.**

As previously mentioned, in 2011, the International bvFTD Criteria Consortium established new diagnostic criteria whereby a degree of probability was assigned to the clinical diagnosis.[23] Some patients with a diagnosis of possible bvFTD develop changes on neuroimaging or will be found to have a genetic mutation and will therefore 'progress' into probable or definite bvFTD. Nevertheless, a significant number of possible patients with bvFTD do not convert clinically to probable or definite bvFTD and their neuroimaging results remain unchanged over time. In this study, we included 33 of these bvFTD phenocopy patients, while 19 patients with probable bvFTD served as a control group. We saw that according to previous research on the bvFTD phenocopy syndrome, most of our included bvFTD phenocopy cases were men and they were younger than patients with probable bvFTD.[24 25 26]

In patients with the bvFTD phenocopy syndrome the frequency of recent life events, relationship problems and cluster C personality traits was higher than in the probable bvFTD group and in most cases multiple factors played a contributory role. In accordance with previous hypotheses, mood disorders had a relatively large share in patients with benign bvFTD phenocopy syndrome (both major depressive disorder as well as bipolar disorder).[27] A bipolar disorder seemed to be more often present in patients

with phenocopy than in patients with probable bvFTD. However, the relative frequency of a depression among patients with the phenocopy syndrome was not higher than among patients with probable bvFTD, but exceeded the community prevalence of depression in late life.[28] As previously discussed, previous studies suggested depressive traits in neurodegenerative bvFTD (with percentages around 33% of cases), which might explain why the phenocopy group and probable bvFTD group showed approaching frequencies of depression.[29] [3] Relative frequencies of alcohol abuse among patients with the benign phenocopy syndrome and patients with probable bvFTD were also approaching possibly due to comorbidity in probable bvFTD, as studies reported compulsive consummatory behaviors in bvFTD including alcohol abuse. [30] It was remarkable that among patients with the benign bvFTD phenocopy syndrome, 85.2% of patients had psychiatric or psychological conditions that mainly consisted of recent life events, relationship problems and cluster C personality traits. By a focus at this aspect of disease course, treatment of reversible conditions is to be gained.

Chapter 7 was focused at the role of clinical and demographical variables in predicting progression in patients with a late onset frontal lobe syndrome. In this research progression was defined as institutionalisation, progression of frontal or temporal atrophy at Magnetic Resonance Imaging (MRI) or death after two years of follow up. Non-progression was defined as the absence of progression at MRI in addition to stable or improved *Mini Mental State Examination (MMSE)* and *Frontal Assessment Battery (FAB)* scores. As hypothesized we found that *progressors* in LOF were mainly patients with a neurodegenerative disease (82.9%), while *non-progressors* were mostly affected by psychiatric disorders (53.6%). Tools to predict progression in LOF were stereotypy and a neuropsychological profile with primarily executive deficits and relative sparing of episodic memory and visuospatial functions. Stereotypy as a predictor for progression in LOF was a new finding but joins in with previous studies into progression in bvFTD and has also been described as a hallmark in **chapter 5.**[31] It is remarkable that although more than half of the *progressors* had another disease than bvFTD in our cohort, a neuropsychological profile with mainly executive deficits, as described in Rascovsky criteria, still had value in the differentiation of *progression* versus *non-progression* in LOF.[23] A patients history and a family history with psychiatric disorders were found to be predictors for non-progression. Stereotypy and a neuropsychological profile with primarily executive deficits and relative sparing of episodic memory and visuospatial functions together with the absence of a psychiatric history or family history with psychiatric disorders were considerable capable to distinguish a *progressive* from a *non-progressive* discourse.

Section 4. Care and interventions in the late onset frontal lobe syndrome and bvFTD

After we cast light on disease course, we studied possible options for care and treatment in bvFTD and the late onset frontal lobe syndrome in **section 4**. In **chapter 8** we performed a systematic review on pharmacological treatment in patients with bvFTD.

All literature between 1970 and 2016 was searched systematically for reports on pharmacological interventions for bvFTD. A total number of 23 studies were included with 12 randomized controlled trials, 8 open-label studies and 3 case series reporting on 583 patients. We described the efficacy of pharmacological interventions by symptom profiles according to the FTDC-criteria: apathy, disinhibition, lack of empathy or sympathy, hyperorality, stereotypical behavior and executive dysfunction. This was the first systematic review based on symptom profile in bvFTD and not limited to randomized controlled trials but also including open label studies and case series. We found that, based on the *NeuroPsychiatric Inventory* (NPI), Trazodone had the greatest effect on the general

symptoms of bvFTD followed by Rivastigmine and Citalopram. As one of the limitations it needs to be noted that most studies were sponsored by pharmaceutical companies.[32] [33] [34] Besides, outcome measurements of changes in symptoms of bvFTD differed between studies. This needs attention in future research. However, this systematic research was an up to date clinical guidance in symptomatic pharmacological therapy for bvFTD. Highlighted by the lack of a disease modifying therapy in bvFTD so far, symptom management for this devastating disease may be of importance.

In **chapter 9** we discussed care in bvFTD by focusing on the caregiver. We described an explorative pilot study in caregivers of early onset dementia patients with behavioral problems. As frontal symptoms affect the personal identity of a patient, several studies have shown that burden and stress are higher in caregivers of dementia patients with predominantly frontal symptoms as compared to caregiver's burden in dementia patients with mainly memory problems.[35] We performed a tailored intervention including psychoeducation, social support and behavioral cognitive therapy for caregivers of dementia patients affected by apathy, disinhibition and/or stereotypical behavior. The intervention was given during 6 months and quantitative and qualitative data were collected at baseline and after the intervention. We found an increased sense of competence in the intervention group. Burden, perceived stress and depressive symptoms decreased, although not significantly different from the control group. The improvement in the caregiver's sense of competence in the intervention group is an interesting result that confirms some previous studies about support programs for caregivers of dementia patients who were not specifically selected on the base of dealing with behavioral problems.[36] [37] It is interesting that an absence of any significant group effect on the other indicators of feelings of burden (caregiver burden, perceived stress and depressive symptoms) was a result that was also found in previous research into the effectiveness of caregiver support programs.[38] Although caregivers who participated in these programs were satisfied with the support and managed to go on caring longer than caregivers who did not receive this support, a reduction of levels of burden could hardly be proven scientifically.[36] In the study of Mioshi with an intervention program performed in caregivers of patients with bvFTD, significant results on levels of burden were measured.[39] However, due to practical constraints, the participants in that study were not randomized, and the burden scores between the intervention group and control group differed at baseline. This lack of randomisation may have limited the results of their study, but these positive effects are hopeful. Another important aim of our study was the qualitative assessment of the intervention and to summarize recommendations for future caregiver interventions. After the intervention, caregivers turned out to have high levels of satisfaction and they reported various positive benefits in daily life. The three elements of this intervention, psychoeducation, cognitive behavioral therapy and social support, were equally appreciated and are recommended in future studies. Further research, on a larger scale, should conclude on the effectiveness of this support program for caregivers of early onset dementia patients with frontal behavioral changes.

Towards an early discrimination between bvFTD and psychiatric disorders in clinical practice

The distinction between bvFTD and other neurodegenerative diseases has become easier by the use of biomarkers, but differentiating bvFTD from psychiatric disorders remains difficult. The FTDC consensus criteria have clearly improved diagnostics but clinical practice still urges for hallmarks that can distinguish bvFTD from psychiatric disorders in an early stage.[23] This is notably of importance since the current clinical criteria require that "if behavioral disturbance is better accounted for by a psychiatric diagnosis, a diagnosis of bvFTD has to be excluded". To date, scientific research has no answer yet on how we should include or exclude bvFTD in case of a difficult differential diagnosis of bvFTD versus a psychiatric disorder.

Above all, this thesis revealed hallmarks helpful in the clinical differentiation of bvFTD and psychiatric disorders. In case of 'suspicion of bvFTD' 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 informant-based history with preferably multiple informants. Our data suggest that besides FTDC consensus criteria, formal criteria for a psychiatric disorder can be of value. In our cohort of patients with the late onset frontal lobe syndrome, DSM criteria were able to distinguish patients with a psychiatric disorder from patients with bvFTD. However, diagnostic interviews designed to establish psychiatric diagnosis according to DSM criteria are time-consuming as it takes at least 60 minutes for each interview, and they can only be performed by well-trained clinicians.[1] These types of interview do not seem suitable for screening. A face to face examination by a psychiatrist appears to be more appropriate, especially when the psychiatrist is aware that bvFTD can mimic a psychiatric disorder but rarely meets formal criteria for a psychiatric disorder.

Regarding hallmarks for the early differentiation between bvFTD and psychiatric disorders we also saw the importance of detecting stereotypy in an early stage. Both in our research primarily focused at the discrimination between bvFTD and psychiatric disorders as well as in our research aimed at distinguishing *progressors* from *non-progressors* in the late onset frontal lobe syndrome, we saw the predictive value of stereotypy, both for bvFTD and 'progression'. Amidst a difficult differential diagnosis of bvFTD versus psychiatric disorders the presence of stereotypy seems to be an early warning sign and a high risk of impending dementia. Since the *Stereotypy Rating Inventory* includes both severity as well as frequency of stereotypical behavior, it appears to be a suitable method to gather information about the prevalence of stereotypy in daily life of patients.

To distinguish primary psychiatric disorders from bvFTD, we also found discriminating abilities in the *Montgomery Asberg Depression Rating Scale (MADRS)*, which is an applicable patient-based measuring instrument.[40] The good diagnostic value for psychiatric disorders versus bvFTD of this instrument was revealed while neuroimaging only slightly increased this value. This emphasizes the importance to distinguish bvFTD from psychiatric disorders as far as possible already in the clinical phase.

To exclude a psychiatric disorder in an early stage, use of the *Positive and Negative Symptoms Scale (PANSS*) could be considered. [41] In three-quarter of our patients with the late onset frontal lobe syndrome, the variance of psychiatric disorders versus bvFTD could be explained by items of the *PANSS.* Above all, our implementation of the *PANSS* in patients with the late onset frontal lobe syndrome, provided insight in the high prevalence of formal thought disorders and negative psychotic symptoms in patients with bvFTD and the relatively small prevalence of positive psychotic symptoms such as hallucinations and paranoia. The pitfall of misdiagnosis with a psychotic disorder in patients with bvFTD seems to be largely caused by the presence of negative psychotic symptoms such as emotional withdrawal and reduced affect. However, performance of the PANSS is reserved for well-trained clinicians and the hazard of inter-person variability is clearly present. Besides, implementation of the PANSS amidst a difficult diagnosis of bvFTD versus psychiatric disorders is time-consuming and does not seem advisable. Instead, it underlines the need for a close collaboration between the neurologist and psychiatrist in diagnostics of bvFTD and both should stay aware that especially negative psychotic symptoms can mimic bvFTD. Besides, in case of a difficult differential diagnosis of bvFTD versus a psychotic disorder, specific items from the *PANSS*, especially formal thought disorders such as "difficulty in abstract thinking" and "stereotypical thinking" can help to differentiate as these items pointed to bvFTD.

Other hallmarks to distinguish bvFTD from psychiatric disorders and vice versa were found by studying disease course in the late onset frontal lobe syndrome. A subset of bvFTD patients appear to show a

benign course and do not deteriorate at the same speed as other bvFTD patients, despite meeting clinical diagnostic criteria for possible bvFTD at presentation. Our study into these patients taught us that calling them 'phenocopy cases' does not cover the full load. In most of these patients a combination of psychiatric and psychological conditions was present among which recent life events, relationship problems and mood disorders were the most common. Being aware of these conditions, the ability to discern psychiatric conditions from bvFTD in an early stage can increase. Noteworthy, in 9% of our bvFTD phenocopy patients an intellectual disability was present which leads to the recommendation to test intelligence in case of diagnostic doubt, especially in case of a non-progressive disease course with a lack of a genetic mutation. The high prevalence of relationship problems (30.3%) in this bvFTD phenocopy group emphasized the importance of a history from a second and sometimes even third independent informant.

By studying disease course in the late onset frontal lobe syndrome, besides stereotypy we also found executive dysfunction to be a predictor for progression. In the current criteria for bvFTD a neuropsychological profile with mainly executive deficits with relative sparing of memory and visuospatial functions is supportive for a bvFTD diagnosis. As we found this neuropsychological profile to be a predictor for progression (in terms of a neurodegenerative disease), in case of late onset behavioral changes, this neuropsychological profile might gingerly act as an early warning sign to discern frank incapacitating dementia in general from psychiatric disorders. However, this outcome needs to be take with caution as it has not been replicated so far and another recent study shows less differences in neuropsychological profile between bvFTD and psychiatric disorders. [Vijverberg et al., submitted]

Last but not least, a promising hallmark to differentiate bvFTD from psychiatric disorders seemed to be social cognition as measured with the *Ekman 60 Faces Test.* While deficits in social cognition can also be found in neurodegenerative diseases and psychiatric disorders such as autism spectrum disorders, total scores at the *Ekman 60 Faces Test* were significantly lower in bvFTD than in these other diagnostic groups. It is promising that this test appeared to have a good diagnostic accuracy in precisely the most difficult differential diagnosis. Previous research was also focused at discriminating abilities of this test but was never performed in a group of patients included on the base of symptom profile instead of diagnoses. The maximum test score indicating best performance for all six tested emotions of the *Ekman Faces Test* is 60. While none of the patients with another neurodegenerative disease or a psychiatric disorder scored below 20, several bvFTD patients did. The discriminating ability of the *Ekman 60 Faces Test* in the difficult differential diagnosis of bvFTD versus psychiatric disorders in the late onset frontal lobe syndrome suits in with previous literature and seems meaningful for clinical practice. Social cognition is recommended as a convincing hallmark for clinical practice and our study even provided arguments for incorporation of social cognition in future diagnostic guidelines for bvFTD.

Table 4 presents hallmarks useful in the early differentiation between bvFTD and psychiatric disorders.

Presenting symptoms	**Supporting probable or definite bvFTD**	**Supporting a psychiatric disorder**
Mood and apathy	· Low score at the *Montgomery Asperg Depression Rating Scale(MADRS)*	· High score at *Montgomery Asperg Depression Rating Scale(MADRS)* · High score at PANSS items *Tension, Anxiety* and *Guilt feelings*
Stereotypy	· High score at the *Stereotypical Rating Inventory*	· Low score at the *Stereotypical Rating Inventory* · Being male
Disinhibition	· Not fulfilling DSM criteria for Bipolar Disorder	· Fulfilling criteria for Bipolar Disorder
Loss of empathy	· Low score at *Ekman 60 Faces test* (preferably score <20)	· High score at *Ekman 60 Faces test* (preferably score >46)
Psychotic symptoms	· High score at PANSS items *Stereotypical thinking* and *Difficulty in abstract thinking*	· Low total score at the *Negative subscale* of PANSS
Indistinct behavior	· Not fulfilling formal *DSM criteria* for a psychiatric disorder	· Fulfilling *DSM criteria* for a psychiatric disorder
Symptom duration		
Long symptom duration without conversion from possible to probable bvFTD, lacking a genetic mutation	· Being female and absence of most of the following conditions, or being male and absence of all of the following conditions: recent life events, mood problems, cluster C personality traits, relationship problems, low intelligence	· Being male and one of the following conditions, or being female and at least 3 of the following conditions: recent life events, mood problems, cluster C personality traits, relationship problems, low intelligence

Table 4. Clinical hallmarks useful for the differentiation of bvFTD from psychiatric disorders and vice versa in patients presenting with the late onset frontal lobe syndrome

Care and symptom relief in the late onset frontal lobe syndrome

Besides hallmarks for differentiation between bvFTD and psychiatric disorders, this thesis highlighted the importance of care and symptom relief in clinical practice. In the first place, the focus at an early differentiation between bvFTD and psychiatric disorders had an important aim: psychiatric disorders are treatable and with therapy, symptom relief in patients with a psychiatric disorder is to be gained. Second, whereas the aim of our systematic review in chapter 8 was to study the effect of medication on the specific symptoms of bvFTD based on the FTDC criteria[23], guidance for symptom relief in bvFTD was given. Based on NPI scores, Trazodone followed by Rivastigmine and Citalopram was recommended to relief the general symptoms of bvFTD. [42] [43] [44] [45] Besides these medications, Memantine

can be considered in case of apathy as it has been found in multiple studies to slightly relief this symptom[46 47], while Dexamphetamin, Methylphenidate and Paroxetin can be taken into account in case of disinhibition.[48 49 50]Paroxetin might be prescribed to increase empathy in bvFTD patients.[50] In case of hyperorality Trazodone is suggested.[43] Recommendations regarding stereotypical behavior in bvFTD are still pending as only limited research on stereotypical behavior in bvFTD is carried out until this moment.

While there is still no cure for bvFTD and other neurodegenerative diseases, some improvement of quality of life of patients and their loved ones might be achieved by support for the caregivers. As caregivers of dementia patients with predominantly behavioral problems experience high levels of burden, support for these caregivers is indispensable. The support program we invented for these caregivers was a group wise intervention given on a regular base during 6 months. Although it was an explorative pilot study and further research on a larger scale is needed to conclude on the effectiveness of this support program, it is a hopeful result that the sense of competence of the caregivers significantly increased in the intervention group. The three components of the intervention (psychoeducation, social support and cognitive behavioral therapy) were highly rated and an implementation of these three components in future support groups seems valuable. This focus at support for caregivers might not only be favorable for the quality of life of caregivers, in accordance with previous research, it could contribute to extended possibilities for patients to live at home, with beneficial consequences for the patient as well as for society. [51 52]

Future recommendations

A longer prospective follow-up of a cohort of patients with a late onset frontal lobe syndrome is warranted to confirm our results. In our cohort of patients with a late onset frontal lobe syndrome, we currently use a gold standard of two years follow-up but it has not been confirmed yet if this follow up duration is indeed long enough for the best diagnostic certainty that is possible during patient' life or if a longer follow up duration is needed.

We would also recommend to develop clinical instruments to investigate the course of frontal behavioral symptoms during progression of disease. This may include electronic equipment or gadgets able to measure behavioral changes over time. Clinical practice urges for measuring instruments able to measure the progression of late onset behavioral problems to surpass the subjective character of current notifications of progression as done by caregivers. In patients with the benign bvFTD phenocopy syndrome caregivers often report a progression of symptoms while impending dementia is lacking. Furthermore, predicting progression is demanded by patients and family when the diagnosis is told.

Next, we would also recommend to study whether neuropsychological profiles change over time in bvFTD as well as in psychiatric disorders. In the current consensus criteria for bvFTD, besides supporting imaging results, functional decline is needed to meet criteria for probable bvFTD. As it has not been investigated so far, it needs to be examined whether bvFTD patients indeed show progression at neuropsychological tests during time and if this discriminates them from patients with a psychiatric disorder presenting with a late onset frontal lobe syndrome.

We recommend adjustment of the criteria for bvFTD. The FTDC criteria from 2011 are more sensitive for bvFTD compared to the older criteria, but also less restrictive. In patients with late onset behavioral changes, the diagnostic certainty of bvFTD increases when frontotemporal abnormalities are found on structural neuroimaging.[53 54] However, both the clinical symptoms as well as the functional imaging findings in psychiatric patients may mimic bvFTD. These psychiatric 'bvFTD mimics' lower the specificity of the FTDC criteria and will cloud the outcomes of trials in bvFTD. It is warranted to

examine whether frontal and/or anterior temporal hypoperfusion or hypometabolism on PET or SPECT is indeed indicative of a bvFTD diagnosis in patients presenting with late onset behavioral problems, as abnormal frontal and/or temporal lobe function at neuroimaging may also point to psychiatric disorders.[55] [56] [57] [58] Psychiatric 'bvFTD mimics' who exhibit similar FDG-PET results need to be recognized in an early stage and excluded from a bvFTD diagnosis. Careful multidisciplinary follow-up by a neurologist and a psychiatrist, especially in this group of bvFTD mimics, seems to improve the reliability of the diagnosis in the long run.

Following our own hopeful results concerning the discriminating abilities of social cognition in patients presenting with a late onset frontal lobe syndrome, it is recommended to replicate studies into social cognition in bvFTD and patients with a psychiatric disorder wherein these patients are not included on the base of their diagnosis but based on symptom profile resembling clinical practice. This would strengthen our results and is needed to eventually incorporate social cognition in future diagnostic guidelines for bvFTD.

Last but not least, genetic screening, especially for the C9orf72 repeat mutation, contributes to the diagnostic work-up. Accumulating research exists into traits of symptom duration and psychotic phenomena in patients with C9ORF72 repeat mutation, but other characteristics of this subgroup of patients have not been described so far. Clinical practice urges to study whether patients with bvFTD due to the C9ORF72 repeat expansion can be characterized by a profile of typical neuropsychiatric symptoms (during disease course or even before onset of bvFTD symptoms) which discerns them from other bvFTD patients or patients with a psychiatric disorder. Clinical practice seems to reveal that especially this subgroup of patients has a diagnostic delay due to medical referral from neurologist to psychiatrist and vice versa during the disease course. This obliges early recognition of the symptom profile or course of life of these patients which can ensure straight profit for clinical practice. As for daily clinical practice, patient care for suspected bvFTD cases is improved by a multidisciplinary approach, reuniting neurology with psychiatry.

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