Chapter 1.0

Introduction
1.1 General background

A central and challenging topic in neuropsychiatry is how to discriminate behavioural variant frontotemporal dementia (bvFTD) from frequently occurring primary psychiatric disorders that can present with a late onset frontal lobe syndrome (age above >45 years). The lack of knowledge in the current literature about the diagnostic accuracy of behavioural and cognitive features or how accurate biomarkers are in differentiating bvFTD from primary psychiatric disorders increases the challenge of the diagnostic process. Therefore, in this thesis I attempt to gather more insight about the diagnostic accuracy and how to use these features to reduce the diagnostic difficulties. In the following I will discuss some conceptual issues on the subject neuropsychiatry and will introduce various brain regions, important for, and involved in, neuropsychiatric diseases. Furthermore, I will briefly describe epidemiological, clinical and diagnostic aspects for bvFTD and its most common primary psychiatric misdiagnosis (major depression, bipolar disorder and schizophrenia).

1.1.1 Neuropsychiatry

Defining the concept of ‘neuropsychiatry’ is challenging due to the continuously changing factors on which this concept depends such as developing and diverging ideas about mental and brain disorders(1). Nowadays, with modern neuroscience using neuroimaging and molecular biology the trend is set to fill the gap between brain (neurology) and mental (psychiatry) disorders. The findings that neurological and psychiatric disorders share clinical phenotypes and genetics(2-4), and the proof of neural plasticity due to growing knowledge on synaptic function in the brain, pushed the concepts of brain and mental disorders even more together. Due to this rapidly extending clinical and scientific field of mental and brain disorders, a new definition of neuropsychiatry as a discipline is essential. By defining a clear empirical and theoretical concept of neuropsychiatry, we can conduct better research and improve medical care for these patients.

However, merging the different views of the disciplines neurology and psychiatry towards a unifying and monistic concept of neuropsychiatry or the explanation of how mental processes derive from the brain, ensues several difficult issues which causes friction. For example, the dominant nosological view in psychiatry is the classification of mental disorders such as described in the Diagnostic and Statistical Manual (DSM) and International Classification of Diseases (ICD). Classifying disorders in psychiatry is the identification of the category or group (disorder) to which an individual belongs on the basis of its characteristics (symptoms)(5), not bound to aetiological or theories. In
contrast, the nosological view in neurology is based on the ‘diagnosis’ of disorders, which is the identification of a distinguishable disorder on the basis of known aetiology or a theory about pathophysiology and serves as a basis for treatment. Another example is the dissimilarity in conceptual frameworks between a neurologist and psychiatrist that defines ideas around behaviour, affective, motivational and cognitive symptoms like the concept apathy. Apathy is defined in the dictionary as a state of motivational impairments(6), however, for a neurologist probable less ascribed to emotional distress or contextual issues as mostly done by a psychiatrist. In other words, clinicians or scientists are using the same concept for a different brain state, resulting in miscommunication and so causing a counteractive effect for the understanding of both brain and behaviour aspects in neuropsychiatric disorders.

Acknowledging the conceptual and intellectual challenges associated with the concept of neuropsychiatry, a definition of neuropsychiatry is proposed by various people that serves as a fundamental view in this thesis(7,8):

**Neuropsychiatry is a medical subspecialisation of neurology or psychiatry, focussing on diagnosing a spectrum of brain disorders with predominately behavioural, affective, motivational and cognitive symptoms and its treatment. The scientific objective of modern neuropsychiatry is to understand the symptoms described above from a brain, body and environmental point of view. A better understanding of neuropsychiatric diseases will accelerate the development of new treatments.**

1.1.2 The frontal lobes

1.1.2.1 Anatomy of the frontal lobes

The frontal lobes are crucial in the understanding of the ‘brain’ pathophysiological point of view of neuropsychiatric symptoms. The human frontal lobes refer to an anatomical area of the brain which is associated with vital properties for normal human behaviour and executive functions(9,10). Through these properties humans acquire and display many social skills. One of the most relevant regions of the frontal lobe is the anterior part of the cingulate gyrus, which is associated with both motivational and movement disorders(11). Lesions of the anterior cingulate produce emotional blunting and decreased motivation which is found in mood disorders and neurodegenerative disorders(12). In addition to the cingulate gyrus, the medial orbitofrontal gyri are associated with the regulation of behaviour. Disruption in these orbitofrontal lobes, especially the right side, lead to social inappropriate behaviour(13,14). The dorsolateral-prefrontal cortex of the frontal lobes is more involved with executive functions such as...
planning and organization, flexibility, abstract thinking and making complex association. A lesion in this area may result in executive dysfunction and stereotypical behaviour(15).

The macro-structures described above are cortical areas, however, lesions of subcortical structures and the connections between them can also give rise to similar neuropsychiatric symptoms. In general, the frontal-subcortical circuits that are involved with neuropsychiatric features consist of connections between the frontal cortex with the caudate, putamen and the ventral striatum. From the striatum, a connection trough the globus pallidus and substantia nigra with the thalamus exists. Finally, the thalamus is again connected with the frontal cortical areas(15). Moreover, with modern neuroimaging methods we can measure in vivo structural and functional connectivity of large-scale networks in the brain that are altered in neuropsychiatric disorders(16,17). For example, in the ‘Salience Network’ (SN) and the ‘Executive Network’(18), which both include anatomic regions of the frontal lobe that are involved with social-emotional and executive functions.

1.1.2.2 Clinical aspects associated with the frontal lobes

Structural deterioration or dysfunction of brain networks that are involved with the frontal lobes lead to abnormal behaviour and executive dysfunction and changes in the regulation of social, interpersonal and personal conduct. The umbrella term for these symptoms is the frontal lobe syndrome(19,20) and is commonly used to describe symptoms in neuropsychiatric disorders which target the frontal lobes(3). In addition, the more posterior part of the frontal lobes are more associated with motor, speech and autonomic functions and when these areas are disturbed, gait disorders, disturbances of eye-movements, urine-incontinence and speech impairments arise. These symptoms can also be considered as part of the frontal lobe syndrome, but are outside the focus of this thesis, since the human behaviour and executive functions are major phenomena of interest in this thesis. A brief description of the concept behaviour and executive function follows:

Behaviour is the way in which someone acts or conducts oneself, towards others and to features of the surrounding environment. Every observable and non-observable activity, intentional or non-intentional, in a continuous flow of spatiotemporal features, can be considered as behaviour and is a product of a complex causal network of different aspects from different explanatory levels, simplistically described as brain-body-environment organization(See model 1).
Model 1. Brain-body-environment organization for behaviour.

To classify behaviour as either normal or abnormal is difficult, as the norm may vary in time, society and culture. However, for the definition of abnormal behaviour we use the most widely accepted definition as stated in the DSM-V for mental disorders which include a statement about abnormal behaviour(21):

A mental disorder is a syndrome characterized by clinically significant disturbance in an individual’s cognition, emotion regulation, or behaviour that reflects a dysfunction in the psychological, biological or developmental processes underlying mental functioning. Mental disorders are usually associated with significant distress or disability in social, occupational, or other important activities. An expectable or culturally approved response to a common stressor or loss, such as the death of a loved one, is not a mental disorder. Socially deviant behaviour (e.g. political, religious, or sexual) and conflicts that are primarily between the individual and society are not mental disorders unless the deviance or conflict results from dysfunction in the individual, as described above.

Executive functions are cognitive abilities that are major determinants for normal behaviour. It is the ability of planning, initiation, sequencing and monitoring of complex goal-directed behaviour. Executive function is also associated with insight, will, abstraction and judgment. Furthermore, it integrates the other cognitive domains such as memory, language, praxis and motor skills appropriately to internal and external stimuli. Impairment of executive functions can be due to its own dysfunction, dysfunction of the integrated domains(22) or due to behavioural or emotional disturbances(23,24).
1.1.3 Disorders associated with the frontal lobes

Several disorders can target the frontal lobes and thus present with neuropsychiatric symptoms. In this thesis, the behavioural variant frontotemporal dementia (bvFTD) and its most common primary psychiatric misdiagnosis that present with a late-onset frontal lobe syndrome, is the central topic.

1.1.3.1 Behavioural variant frontotemporal dementia

The neurodegenerative disorder bvFTD is part of a neuropathological spectrum called frontotemporal lobar degeneration (FTLD) defined by abnormal aggregation of proteins in the frontal and/or temporal lobes. FTLD accounts for 50% of the presenile cases of dementia and up to 20% of all dementias(25). The most common clinical phenotype of FTLD is bvFTD which is also the second most common early onset dementia (under the age of 65 years) after Alzheimer’s disease (AD)(26,27). The estimated incidence of bvFTD is 2.7-4.1 per 100,000 and the prevalence is 15-22 per 100,000(28). Some studies report an overrepresentation of male gender in bvFTD(26,29), but overall it is considered to have an equal gender incidence(27). Age of onset varies between 40 and 70(28), however, onset at the age 20 is also described.

Clinically, bvFTD is characterized by insidious changes in behaviour, personality, and cognition, causing loss of social skills(30). The clinical syndrome consist of behavioural changes which include the loss of inhibition or impulsive acts causing inappropriate behaviour that leads to violation of social norms(31,32), loss of manners or decorum. Furthermore, apathy (loss of motivation, drive or interest) and inertia (decreased initiation of behaviour) are very common clinical features in bvFTD(33). Severe apathy or inertia can even result in hypersomnia. The ability to gather knowledge of other people emotional state (‘Theory of mind’) is also impaired in bvFTD. These bvFTD patients will show loss of empathy and decline of social interaction(34). Other behavioural changes are perseverative, stereotyped or compulsive/ritualistic behaviour which clinically can be observed as simple repetitive movements such as tapping, clapping or throat clearing or complex stereotyped behaviour such as cleaning, counting, hoarding or walking fixed routes(35). In addition, symptoms in bvFTD can also be hyperorality or diet changes like more sweets or food fats(36), loss of self-awareness(37), prosopagnosia, hyperreligiosity, topographagnosia, hypochondria, speech and language impairments and utilization behaviour(38). Cognitive deficits in bvFTD mainly consist of executive dysfunctions with less prominent memory and language deficits and in end-stage of the diseases visuospatial impairment.
The histopathology of bvFTD has three main categories: Microtubule-associated protein (MAP) Tau (FTLD-Tau); TAR DNA-binding protein-43 (FTLD-TDP); and fused in sarcoma protein (FTLD-FUS)(39). FTLD-Tau is characterized by accumulation of tau in neurons, astrocytes and oligodendrocytes and is associated with MAPT gene(40). The hallmark of FTLD-TDP pathology is TDP-43, a ubiquitously expressed nuclear protein which becomes hyper-phosphorylated and accumulates in the neurons(41) and can be sporadic or familial involving progranulin (PGRN)(42), valosin-containing protein (VCP), C9ORF72 hexanucleotide repeats(43) and TARDBP mutations(44). The smallest pathological group is FTLD-FUS and is encoded by the FUS/TLS gene on chromosome 16(41).

The diagnosis of bvFTD is made on basis of clinical consensus criteria developed by an international expert group (FTDC)(29) that were published in 2011(table 1).

**1.1.3.2 Late onset primary psychiatric disorders**

Among the most prevalent primary psychiatric disorders that are included in the differential diagnosis of the late-onset frontal lobe syndrome are major depression (MD), bipolar disorder (BD) or schizophrenia. These illnesses share the same disturbance of macro-structures of the frontal cortex and the fronto-subcortical circuits(15,45). Moreover, in primary psychiatric disorders different hypotheses about the aetiology have been described such as changes in the morphology and microanatomy of dendritic spines in the region of the frontal lobes(46) or neuro-inflammation causing permanent changes in the fronto-subcortical circuits during mood episodes(47,48). Loss of a feature or aspects of ‘normal’ behaviour such as apathy or social withdrawal are associated with depression, schizophrenia and autism spectrum. An enhancement of a feature of behaviour such as behaviour caused by disinhibition and stereotypy are more associated with manic episodes, anxiety disorders or obsessive-compulsive disorder.

One of the most common primary psychiatric disorders in the differential diagnosis of the frontal lobe syndrome is MD. In older adults the rates of depression vary between 2% to about 10% of the general adult population(49). The prevalence of depression is higher in women than in men across all ages(50). Patients in a depressive state have different types of symptoms such as feelings of sadness, despair, anxiety, emptiness, loss of motivation or interest and vegetative changes such as sleep and diet changes(21). Furthermore, patients with a severe depressive state can have cognitive deficits such as impairment in attention, psychomotor speed, memory and executive dysfunction(51). The diagnose MD is based on syndromal criteria, and rests on clinical examinations with no biomarker or clear pathology known (See table 2). MD can be treated with psychotherapy, medication or electroconvulsive therapy(52).
The neuropsychiatric features that are described in the frontal lobe syndrome are also commonly found in patients with BD. BD is diagnosed on the basis of a clinical evaluation (See table 3). This psychiatric illness accounts for 5-19% of mood disorders in the elderly(53) and it prevalence for individuals aged 65 is 0.1 to 0.7 percent(54). Female is the predominant gender in older ages bipolar patients, whereas in younger BD the ratio between female and male is equal(55). BD is characterized by episodes of mania with symptoms such as disinhibition, irritability, distractibility, impaired of social judgment and episodes of major depression as seen in MD(21,56). Cognitive impairment can be
present with deficits in attention, psychomotor speed, memory and executive dysfunction(57). Treatment of BD is with mood stabilizers such as Lithium, anti-epileptics or antipsychotics.

Schizophrenia is clinically characterized by a spectrum of psychotic symptoms with behavioural features. The prevalence of schizophrenia is approximately 1% of general population and the incidence is about 15.2 per 100,000. Male is the predominately gender in schizophrenia(58). The positive symptoms in schizophrenia include hallucinations (sensory experiences that occur in absence of a stimulus), delusions (false beliefs) and thought disorders (dysfunctional thinking). Negative symptoms include apathy or/and inertia, reduced speaking and social withdrawal(59). Schizophrenia is diagnosed using the DSM classification scheme(21)(see table 4). Cognitive deficits in schizophrenia may precede psychotic symptoms and consist of memory and executive dysfunction, with impairment in social cognition(60,61). Patients are treated with antipsychotic medication.

Table 2. DSM-5 diagnostic criteria for a major depressive episode.

<table>
<thead>
<tr>
<th>A. Five (or more) of the following symptoms have been present during the same two-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. NOTE: Do not include symptoms that are clearly attributable to another medical condition.</th>
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<tr>
<td>A.1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observations made by others (e.g., appears tearful). (NOTE: In children and adolescents, can be irritable mood.)</td>
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<tr>
<td>A.2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation)</td>
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<td>A.3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5 percent of body weight in a month), or decrease or increase in appetite nearly every day. (NOTE: In children, consider failure to make expected weight gain.)</td>
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<td>A.4. Insomnia or hypersomnia nearly every day</td>
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<td>A.5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)</td>
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<td>A.6. Fatigue or loss of energy nearly every day</td>
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<td>A.7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)</td>
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<td>A.8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by their subjective account or as observed by others)</td>
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<td>A.9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide</td>
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| B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. |
| C. The episode is not attributable to the direct physiological effects of a substance or to another medical condition. NOTE: Criteria A through C represent a major depressive episode. |
| D. The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders. |
| E. There has never been a manic or hypomanic episode. NOTE: This exclusion does not apply if all of the manic-like or hypomanic-like episodes are substance-induced or are attributable to the physiological effects of another medical condition. |
The diagnostic challenge of the late-onset frontal lobe syndrome

One of the biggest challenges for clinicians in a neurology or psychiatry department is the differential diagnosis of the late-onset frontal lobe syndrome, especially distinguishing bvFTD from primary psychiatric disorders. In the following, I will discuss why separating bvFTD from primary psychiatric disorders is more difficult than separating bvFTD from other types of dementia and for what reasons this problem should be tackled.

1.2.1 The syndromic diagnose and the big pitfall

Making a diagnostic decision in a daily medical practice is a combination between an inductive process (symptoms to disease) and a deductive process (knowledge about aetiological or pathogenetically processes of disorders and the availability of diagnostic tools (e.g. imaging or CSF markers). Furthermore, the variation of the quality and quantity of these three properties causes the clinician to make different types of diagnoses (e.g. symptomatic, syndromic, anatomical or causal-related) that are associated with different degrees of certainty.

A late-onset frontal lobe syndrome has an extensive differential diagnosis of different types of neuropsychiatric disorders that vary from pure syndromic diagnosis with no diagnostic tool available up to clinical-pathological classified disorders with or without specific biomarkers. More specific for this thesis, the great clinical overlap and the absence of highly accurate biomarkers for bvFTD and primary psychiatric disorders in combination of the lack of knowledge about aetiological or pathogenetically processes in primary psychiatric disorders renders the diagnostic process of these illnesses, to be quite challenging (3,62).

In the case of bvFTD that has a clear pathology of a neurodegenerative origin and a relatively accurate diagnostic biomarker (frontotemporal abnormalities on neuroimaging), the clinical diagnosis is still subdivided according to the degree of the certainty (possible, probable or definite bvFTD). Where possible is pure a syndromic diagnose, probable an anatomical associated diagnosis and definite a pathological or mutation associated diagnosis. Furthermore, due to increase of the availability of specific biomarkers for other neurodegenerative disorders, bvFTD can be differentiated from these disorders with a relatively good accuracy (29,63-65). In contrast, however, psychiatric disorders remain syndromal in terms of diagnosis. Therefore, the differentiation between bvFTD and these

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**Table 3. DSM-5 diagnostic criteria for manic episode.**

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<th>Criteria</th>
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<td><strong>A.</strong> A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy, lasting at least one week and present most of the day, nearly every day (or any duration if hospitalization is necessary).</td>
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<tr>
<td><strong>B.</strong> During the period of mood disturbance and increased energy or activity, three (or more) of the following symptoms (four if the mood is only irritable) are present to a significant degree and represent a noticeable change from usual behaviour:</td>
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<td>B.1. Inflated self-esteem or grandiosity</td>
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<td>B.2. Decreased need for sleep (eg, feels rested after only three hours of sleep).</td>
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<tr>
<td>B.3. More talkative than usual or pressure to keep talking.</td>
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<td>B.4. Flight of ideas or subjective experience that thoughts are racing.</td>
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<td>B.5. Distractibility (attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed.</td>
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<tr>
<td>B.6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation (ie, purposeless non-goal-directed activity)</td>
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<td>B.7. Excessive involvement in activities that have a high potential for painful consequences (eg, engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).</td>
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| **C.** The mood disturbance is sufficiently severe to cause marked impairment in social or occupational functioning or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features. |

| **D.** The episode is not attributable to the physiological effects of a substance (eg, a drug of abuse, a medication, other treatment) or to another medical condition. **NOTE:** A full manic episode that emerges during antidepressant treatment (eg, medication, electroconvulsive therapy) but persists at a fully syndromal level beyond the physiological effect of that treatment is sufficient evidence for a manic episode and, therefore, a bipolar I diagnosis. |

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**Table 4. DSM-5 diagnostic criteria for schizophrenia.**

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<th>Criteria</th>
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<td><strong>A.</strong> Two (or more) of the following, each present for a significant portion of time during a one-month period (or less if successfully treated). At least one of these must be (A.1), (A.2), or (A.3):</td>
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<tr>
<td>A.1. Delusions</td>
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<td>A.2. Hallucinations</td>
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<td>A.3. Disorganized speech (eg, frequent derailment or incoherence).</td>
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<tr>
<td>A.4. Grossly disorganized or catatonic behavior</td>
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<tr>
<td>A.5. Negative symptoms (ie, diminished emotional expression or avolition).</td>
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| **B.** For a significant portion of the time since the onset of the disturbance, level of functioning in one or more major areas, such as work, interpersonal relations, or self-care, is markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, there is failure to achieve expected level of interpersonal, academic, or occupational functioning). |

| **C.** Continuous signs of the disturbance persist for at least 6 months. This six-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (ie, active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or by two or more symptoms listed in Criterion A present in an attenuated form (eg, odd beliefs, unusual perceptual experiences). |

| **D.** Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either 1) no major depressive or manic episodes have occurred concurrently with the active-phase symptoms, or 2) if mood episodes have occurred during active-phase symptoms, they have been present for a minority of the total duration of the active and residual periods of the illness. |

| **E.** The disturbance is not attributable to the direct physiological effects of a substance (eg, a drug of abuse, a medication) or another medical condition. |

| **F.** If there is a history of autism spectrum disorder or a communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations, in addition to the other required symptoms of schizophrenia, are also present for at least one month (or less if successfully treated). |
1.2 The diagnostic challenge of the late onset frontal lobe syndrome

One of the biggest challenges for clinicians in a neurology or psychiatry department is the differential diagnosis of the late-onset frontal lobe syndrome, especially distinguishing bvFTD from primary psychiatric disorders. In the following, I will discuss why separating bvFTD from primary psychiatric disorders is more difficult than separating bvFTD from other types of dementia and for what reasons this problem should be tackled.

1.2.1 The syndromic diagnose and the big pitfall

Making a diagnostic decision in a daily medical practice is a combination between an inductive process (symptoms to disease) and a deductive process (knowledge about disorders to symptoms). These processes are grounded on the expertise of the clinician, the variation of knowledge about aetiological or pathogenically processes of disorders and the availability of diagnostic tools (e.g. imaging or CSF-markers). Furthermore, the variation of the quality and quantity of these three properties causes the clinician to make different types of diagnoses (e.g. symptomatic, syndromic, anatomical or causal-related) that are associated with different degrees of certainty.

A late-onset frontal lobe syndrome has an extensive differential diagnosis of different types of neuropsychiatric disorders that vary from pure syndromic diagnosis with no diagnostic tool available up to clinical-pathological classified disorders with or without specific biomarkers. More specific for this thesis, the great clinical overlap and the absence of highly accurate biomarkers for bvFTD and primary psychiatric disorders in combination of the lack of knowledge about aetiological or pathogenically processes in primary psychiatric disorders renders the diagnostic process of these illnesses, to be quite challenging(3,62).

In the case of bvFTD that has a clear pathology of a neurodegenerative origin and a relative accurate diagnostic biomarker (frontotemporal abnormalities on neuroimaging), the clinical diagnosis is still subdivided according to the degree of the certainty (possible, probable or definite bvFTD). Where possible is pure a syndromic diagnose, probable an anatomical associated diagnosis and definite a pathological or mutation associated diagnosis. Furthermore, due to increase of the availability of specific biomarkers for other neurodegenerative disorders, bvFTD can be differentiated from these disorders with a relatively good accuracy(29,63-65). In contrast, however, psychiatric disorders remain syndromal in terms of diagnosis. Therefore, the differentiation between bvFTD and these
psychiatric illnesses with the same symptomatology is still predominately based on clinical judgment of the clinician.

Despite the clinical advantages of the current diagnostic criteria for bvFTD or primary psychiatric disorders, they involve a number of problems in clinical practice/use. For example, the FTDC criteria states that a diagnosis of bvFTD is excluded when ‘behavioral disturbance is better accounted for by a psychiatric diagnosis’, and before diagnosing a primary psychiatric disorder the DSM states that a psychiatric disorder is excluded when ‘the disturbance is attributable to another medical condition’. Using these guidelines in clinical practice results in a vicious circle and does not provide a solution how to solve this challenge.

Consequently, the big pitfall in the diagnostic process of bvFTD is the high rate of primary psychiatric misdiagnosis or that these neuropsychiatric syndromes are merely classified as ‘difficult’ or ‘odd’. Around 50% of bvFTD patients initially receive a psychiatric diagnosis(2). For primary psychiatric diseases the exact number of a dementia misdiagnosis is not known, however, studies indicate that it is not uncommon(66). The most common primary psychiatric misdiagnoses for bvFTD are mood disorders (MD and BD) and psychotic disorders (schizophrenia)(2). Other common bvFTD misdiagnoses are obsessive-compulsive disorders (OCD), neurodevelopmental disorders and personality disorders(3). The diagnostic delay in these disorders is several years(67) and the uncertainty about the correctness of these diagnoses are mostly caused by the nature and course of the symptoms over time. In bvFTD, there is a gradual functional decline over time, whereas in psychiatric disorders, fluctuation or improvement over time is present more often. Cases with a C9orf72 mutation which often present as a primary psychiatric disorders, make this diagnosis even more challenging(68,69).

1.2.2 How big is the challenge now?

In recent years, a few authors have started to emphasize the diagnostic challenge between bvFTD and primary psychiatric disorders and hypothesized how to approach this important issue(2,3,62). However, most of these studies were reviews or retrospective analyses. Therefore, we designed the Late Onset Frontal Lobe Syndrome study (LOF) that is a multicentre, cross-sectional, and prospective follow-up study that aims to evaluate the spectrum of aetiologies underlying the late-onset frontal lobe syndrome and to separate bvFTD from the widest clinically relevant differential diagnosis including primary psychiatric disorders(70). Krudop et al. studied the cross-sectional data of the LOF study and demonstrated the broad differential diagnoses to be considered in late-onset frontal lobe syndrome(71). They illustrated that many markers marginally assist in the diagnostic process which highlights the risk of a psychiatric
misdiagnosis(72). Although there is mounting evidence and knowledge among clinicians about the overlap between bvFTD and primary psychiatric disorders, the current literature still lacks knowledge about the diagnostic capabilities of the current clinical criteria of bvFTD and additional biomarkers in the context bvFTD versus primary psychiatric disorders. In general, studies on the current diagnostic criteria for bvFTD and biomarkers have measured the diagnostic accuracy of these features among cohorts of patients with neurodegenerative disorders.

In addition, based on autopsy verified bvFTD cases, the sensitivity of the revised criteria for FTDC probable bvFTD is 76% and for possible bvFTD 86%(29). The specificity of the revised criteria in this study could not be measured due to the absence of a control group. In a retrospective, autopsy-confirmed early-onset dementia cohort, sensitivity for probable bvFTD was found to be 85% and 95% for possible bvFTD. The specificity for probable bvFTD was 95% and 82% for possible bvFTD(63). However, in these studies less atypical presentations of bvFTD patients and very few patients with a primary psychiatric disorder, that can mimic bvFTD were included. The same problem arises for studies that investigated the accuracy of neuroimaging in bvFTD. Since these studies did not included primary psychiatric disorders that have evidence of changes in frontotemporal regions on MRI and $[^{18}\text{F}]$FDG-PET-scan(48,73-77).

To reduce the big challenge, several other biomarkers have been investigated in bvFTD and primary psychiatric disorders. For example, several studies investigated the utility of cerebrospinal fluid (CSF) since CSF biomarkers are considered to reflect pathological processes taking place in the brain. However, these studies are confronted with different types of problems such as the clinical phenotype bvFTD which has a heterogeneous pathology and most CSF studies in bvFTD had to rely on clinically diagnosed cases. As a consequence, various results have been found regarding the conventional biomarkers (total-tau (tau), phosphorylated-tau (p-tau), Amyloid-β1-42 (Aβ1-42)). More recently, however, a decreased p/t-tau ratio, increased CSF light chain neurofilaments (NfL), and YKL-40 have been identified as markers in bvFTD(78-80). The lack of strong neuropathological changes in primary psychiatric disorders resulted in some evidence of axonal dysfunction(81-83), however, it is unknown to what extent levels of CSF biomarkers are elevated or decreased compared to bvFTD patients.

Another way to differentiate bvFTD from primary psychiatric disorders could be by measuring the brain connectivity. Because a network description of the brain is likely to contribute explanations of the clinical symptoms across neuropsychiatric disorders(84). Moreover, in bvFTD a more ‘ordered’ network and less activity in the Salience Network has been found(16,85,86), while in primary psychiatric disorders such as MD(87) and schizophrenia(88) alterations are found in the Default Mode Network or other specific
network properties. So, in the future brain connectivity might be used as a diagnostic tool.

1.2.3 The importance of early diagnosis

Getting an accurate, early bvFTD or psychiatric diagnosis is especially critical since most primary psychiatric disorders are treatable. A misdiagnosis of bvFTD or primary psychiatric disorder might cause inappropriate or delayed treatment and an increase in the burden for patients and caregivers(2,89,90). Very often, the diagnosis of a frontal lobe syndrome is made before the age of 60 years. Many patients may then still have young children that need the support of their parents or patients provide the main income of the household. Also being unaware of the reason behind behavioural changes in patients, may cause couples to get a divorce, their children being emotionally harmed and patients losing their jobs, jeopardizing depriving them from income and other benefits. In addition, the first and crucial step for a clinical intervention trail for bvFTD or primary psychiatric disorders is the inclusion of highly accurate diagnosis.

1.3 Rationale of this thesis

As mentioned, the diagnostic challenge is currently acknowledged, nevertheless it is still big, and requires a good paradigm about how to approach patients with late-onset behavioural changes, especially for bvFTD versus primary psychiatric disorders. This may be achieved by investigating the longitudinal data of the LOF study. This cohort includes 137 patients with behavioural changes during middle to late adulthood consisting of apathy, disinhibition, and/or compulsive/stereotypical behaviour. All patients underwent full neurological and psychiatric examination with cognitive screening tests and neuropsychological test battery. Also, patients underwent a MRI scan of the brain, [18F] FDG-PET scan and CSF was obtained with a lumbar puncture. Thus we designed a clinical relevant cohort to prospectively measure the diagnostic accuracies of different features or new biomarkers such as brain connectivity for either bvFTD or primary psychiatric disorders. With our findings, we might reduce the diagnostic challenge of this differential diagnosis. Making it easier to organize clinical information about these patients, which may lead to better communication between professionals. Finally, it will lead to a more appropriate treatment including counselling about prognosis. In addition, these diagnostic markers might be useful in clinical trials for new medication and future research for both bvFTD and primary psychiatric disorders.
1.3.1 Aims of this thesis

The aim of the research described in this thesis is to gain more insight in the diagnostic accuracy of neuropsychiatric symptoms and biomarkers in differentiating bvFTD from primary psychiatric disorders. We address the following questions:

1. Which of the neuropsychiatric symptoms or signs in the late-onset frontal lobe syndrome can distinguish between bvFTD and primary psychiatric disorders and what are their diagnostic accuracies?
2. What is the diagnostic accuracy of brain imaging (notably MRI and $^{[18]}$F FDG-PET) for bvFTD in patients presenting with the late-onset frontal lobe syndrome?
3. What is the diagnostic accuracy of current biomarkers (notably CSF) in the late-onset frontal lobe syndrome, in particular for bvFTD versus primary psychiatric disorders?
4. Do grey matter network properties differ between neuropsychiatric disorders and are they suitable as a diagnostic tool?

1.3.2 Outline of this thesis

In this thesis I will systematically score and measure the diagnostic accuracy of the various behavioural (paragraph 2.1 and 2.3) and cognitive symptoms (paragraph 2.2) for bvFTD and primary psychiatric disorders. Also, measure the diagnostic accuracy of the ancillary investigations (MRI and $^{[18]}$F FDG-PET) (paragraph 3.1) that are included in the FTDC criteria for bvFTD, primary psychiatric disorders and other types of neuropsychiatric disorders. Furthermore, I explore new markers for bvFTD and primary psychiatric disorders such as cerebrospinal fluid (CSF) biomarkers (paragraph 3.2) and by measuring structural connectivity in bvFTD and other neuropsychiatric disorders (paragraph 3.3 and 3.4). Finally, I investigate which symptoms or findings of the ancillary investigations have a predictive value for bvFTD or psychiatric disorders (paragraph 4.1).
References


