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# Disease trajectories in behavioural variant frontotemporal dementia, primary psychiatric and other neurodegenerative disorders presenting with behavioural change

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ABSTRACT

Behavioural variant frontotemporal dementia (bvFTD) is characterized by behavioural and social cognitive disturbances, while various psychiatric and neurodegenerative disorders may have similar clinical symptoms. Since neurodegenerative disorders are eventually progressive, whereas primary psychiatric disorders are not, this study aimed to investigate whether the change in clinical symptoms over time differed between groups and which biomarkers predicted rate of decline.

Disease trajectories (median follow-up = 3 years) of frontal and stereotyped behaviour, general and frontal cognitive functioning, and social cognition were examined in bvFTD (n = 34), other neurodegenerative (n = 28) and primary psychiatric disorders (n = 43), all presenting with late-onset frontal lobe syndrome (45–75 years), using linear mixed models. To gain more insight in underlying pathological processes driving disease progression, we studied the association of baseline cerebrospinal fluid (CSF) (neurofilament light (NfL) and YKL-40 levels, phosphotau$_{181}$ to total tau ratio) and neuroimaging markers with disease trajectories.

Frontal behavioural symptoms (e.g., disinhibition, apathy) worsened over time in bvFTD, whereas they improved in psychiatric disorders and remained stable in other neurodegenerative disorders. General and frontal cognitive decline was observed in bvFTD and other neurodegenerative disorders, but not in psychiatric disorders. None of the groups showed change in stereotypy and social cognition. For all diagnostic groups, higher CSF NfL levels were associated with faster frontal cognitive decline. A modest association was observed between caudate volume and stereotyped behaviour.

Tracking frontal behavioural symptoms and cognition has potential to distinguish bvFTD from other disorders. CSF NfL levels seem to be associated with decline in frontal cognitive functioning.

## 1. Introduction

Behavioural variant frontotemporal dementia (bvFTD) is a neurodegenerative disorder presenting with behavioural changes and deterioration of social cognition (Rascovsky et al., 2011). However, these symptoms can also be observed in various psychiatric and other neurodegenerative disorders, such as major depressive disorder and Alzheimer's disease (AD), (Pose et al., 2013; Woolley et al., 2011). It is important to differentiate between these disorders as clinical management will be different.

We have set up the late-onset frontal lobe syndrome (LOF) study, including individuals who presented with behavioural changes during

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middle to late adulthood at a memory clinic setting (Krudop et al., 2014). In earlier studies using baseline data from this cohort we have shown that impaired emotion recognition and the presence of stereotypy are suggestive of a diagnosis of bvFTD, while theory of mind and cognitive performances did not discriminate bvFTD from other disorders presenting with late-onset behavioural change, (Dols et al., 2016; Gossink et al., 2017; Krudop et al., 2015; Vijverberg et al., 2017a,b).

The present study aimed to investigate whether the change in behavioural, cognitive and social cognitive symptoms over time differed between diagnostic groups, and which biomarkers predicted rate of decline. Most prospective studies in bvFTD examined cognitive decline, (Boutoleau-Bretonniere et al., 2012; O'Connor et al., 2016; Smits et al., 2015; Tan et al., 2013), but not the progression of behavioural and social cognitive symptoms (Kumfor et al., 2014). The only study so far focussing on these measures has shown that bvFTD patients decline more rapidly on emotion recognition compared to AD patients (Kumfor et al., 2014). We hypothesize that disease progression is faster in bvFTD compared to primary psychiatric disorders, as neurodegenerative disorders are progressive and eventually terminal, whereas psychiatric disorders overall are not. Although other neurodegenerative disorders than bvFTD lack the specific frontotemporal distribution of pathology, in some cases clinical dysfunction related to frontotemporal areas may be predominant. The rate of change of clinical measures will mostly depend on the rate of neurodegeneration. To date too little information is available about the rate of decline in these atypical variants. It would therefore be difficult to hypothesize about the potential differences between bvFTD and other neurodegenerative diseases.

In order to better understand the underlying pathology driving disease progression, we tested which biomarkers could predict rate of decline. We selected subcortical volumes, frontal and temporal brain atrophy, as estimated by cortical thickness measurements, and decreased cerebrospinal (CSF) phosphorylated $tau_{181}$ to total tau (p/t-tau) ratio and increased CSF neurofilament light (NfL) and YKL-40 protein levels, biomarkers which all have been associated with bvFTD in previous studies, (Dolan, 1999; Meeter et al., 2016; Pijnenburg et al., 2015; Teunissen et al., 2016; Vijverberg et al., 2017a,b). CSF NfL and p/t-tau ratio reflect axonal degeneration and CSF YKL-40 is an inflammatory marker, (Meeter et al., 2016; Pijnenburg et al., 2015; Teunissen et al., 2016; Vijverberg et al., 2017a,b). Higher levels of brain atrophy in bvFTD have been associated with faster decline on emotion recognition and cognitive function, (Borroni et al., 2012; Josephs et al., 2011; Kumfor et al., 2014; Ranasinghe et al., 2016). Decreased CSF p/t-tau ratio and increased NfL levels have been associated with poorer prognosis across FTD subtypes (Pijnenburg et al., 2015). Therefore, we hypothesize that more abnormal biological values would predict faster decline.

## 2. Methods

### 2.1. Patients

137 patients ($n_{male}/n_{female}$ = 98/39, mean ± SD age = 62 ± 7) participated in the late-onset frontal lobe syndrome (LOF) study, which is a multi-centre observational and prospective follow-up study designed to examine the discrimination of bvFTD from other disorders presenting with similar clinical presentations, such as apathy, disinhibition, and/or compulsive stereotypical behaviour (Krudop et al., 2014). The LOF study is a naturalistic follow-up cohort study, thereby not preventing treatment (e.g., medication or cognitive therapy in the psychiatric group). Patients with a late onset (45–75 years) frontal lobe syndrome, defined as a clinical syndrome associated with functional or structural changes in the prefrontal cortex, leading to personality, affective or behavioural changes (Krudop and Pijnenburg, 2015), were recruited from the memory clinic of the Alzheimer Centre VUmc and the Old Age Psychiatry Department of GGZ inGeest, Amsterdam, The Netherlands, between April 2011 and June 2013. Inclusion and exclusion criteria of the LOF study have been described elsewhere in detail (Krudop et al., 2014). In short, patients were included when behavioural symptoms dominated the clinical presentation, the score on the Frontal Behavioural Inventory (FBI) was ≥11 or the Stereotypy Rating Inventory (SRI) score was ≥10, and the Mini-Mental State Examination (MMSE)-score was ≥18.

At baseline and after two years, a consensus diagnosis was made by a specialized neurologist and psychiatrist during a multidisciplinary meeting (Vijverberg et al., 2017a,b). Two-year follow-up diagnoses were used as gold standard. As the present study aimed to compare disease trajectories across probable/definite bvFTD, primary psychiatric and other neurodegenerative disorders, patients with an unknown diagnosis after two years of follow-up (n = 1) or other diagnoses, such as subjective complaints (n = 5), psychological problems (n = 1), relational/marital problems (n = 6), possible bvFTD (n = 5), other neurological or general diseases (e.g., multiple sclerosis, n = 10) or vascular mild cognitive impairment (n = 4), were excluded.

The analysis was conducted in 105 patients ($n_{bvFTD}$ = 34, $n_{psychiatric\ diagnosis}$ = 43, $n_{neurodegenerative\ diagnosis}$ = 28). At 2-year follow-up, 30 patients were diagnosed as having probable bvFTD and four as definite bvFTD (i.e., two C9orf72 expansion hexanucleotide repeat, one progranulin mutation and one histopathologically-confirmed tauopathy). In the primary psychiatric disorder group, 15 patients were diagnosed with major depressive disorder, 7 with bipolar disorder, 8 with personality disorder, 6 with minor depressive disorder, 3 with autism spectrum disorder, 1 with schizoaffective disorder, 1 with schizophrenia, 1 with obsessive compulsive disorder and 1 patient with anxiety disorder. The neurodegenerative diagnosis group consisted of 8 patients with Alzheimer's disease, 4 with vascular dementia, 4 with dementia with Lewy bodies, 5 with progressive supranuclear palsy, 3 with semantic dementia, 2 with neurodegenerative syndrome not otherwise specified, 1 with Huntington's disease, and 1 patient with corticobasal syndrome. The number of measurements was different between diagnostic groups for the majority of cognitive measures (Table 1), whereas follow-up duration did not differ across diagnostic groups (Table S1).

Informed consent, either from the patient or from the legal representative, was obtained from all participants. This study was approved by the Medical Ethics Committee of the VU University Medical Centre, Amsterdam.

### 2.2. Diagnostic work-up

At baseline, all patients received a standardized multidisciplinary assessment, consisting of medical history, informant-based history, neurological and medical examination, neuropsychological investigation, brain magnetic resonance imaging (MRI), standard laboratory work-up and lumbar puncture (Van der Flier et al., 2014). Diagnoses were based upon the psychiatric (American Psychiatric Association, 2000) and neurodegenerative disease guidelines, (McKeith et al., 2005; McKhann et al., 2011; Rascovsky et al., 2011; Roman et al., 1993). After 2-year follow-up, neurological and medical examination, neuropsychological investigation and brain MRI were repeated. After two years of follow-up, the presence of a hexanucleotide repeat expansion in C9orf72 was examined for n = 97 participants (Galimberti et al., 2013). In case of a positive family history, patients were referred to the clinical genetics department, where screening for other genetic mutations (MAPT, Progranulin, Presenilin 1) was offered.

### 2.3. Clinical and neuropsychiatric assessment

Clinical assessments were assessed at baseline and at 1-year and 2-year follow-up. Severity of frontal behavioural symptoms was rated using the informant-based FBI, which consists of negative (e.g., apathy, indifference, loss of insight) and positive (e.g., inappropriateness,