Published in final edited form as:

J Clin Psychiatry. 2011 February ; 72(2): 126–133. doi:10.4088/JCP.10m06382oli.

The diagnostic challenge of psychiatric symptoms in neurodegenerative disease; rates of and risk factors for prior psychiatric diagnosis in patients with early neurodegenerative disease

Josh D. Woolley, MD, PhD,

University of California San Francisco, Langley Porter, Department of Psychiatry, 401 Parnassus Avenue, Room 159, San Francisco, CA 94143

Baber K. Khan, B.A.,

University of California San Francisco, Memory and Aging Center, Department of Neurology, 350 Parnassus Avenue, San Francisco, CA 94143

Nikhil K. Murthy, B.A.,

University of California San Francisco, Memory and Aging Center, Department of Neurology, 350 Parnassus Avenue, San Francisco, CA 94143

Bruce L. Miller, MD, and

University of California San Francisco, Memory and Aging Center, Department of Neurology, 350 Parnassus Avenue, San Francisco, CA 94143

Katherine P. Rankin, PhD

University of California San Francisco, Memory and Aging Center, Department of Neurology, 350 Parnassus Avenue, San Francisco, CA 94143

Abstract

Objective—To identify rates of and risk factors for psychiatric diagnosis preceding the diagnosis of neurodegenerative disease (ND).

Method—Systematic, retrospective, blinded chart review of patients with a ND diagnosis [behavioral variant frontotemporal dementia (bvFTD n=69); Alzheimer's disease (AD n=65); semantic dementia (SemD n=41); progressive non-fluent aphasia (PNFA n=17); corticobasal degeneration (n=25); progressive supranuclear palsy (n=15); and amyotrophic lateral sclerosis (ALS n=20)].

Results—28.2% of patients with a ND received a prior psychiatric diagnosis. Depression was the most common psychiatric diagnosis in all groups. BvFTD patients received a prior psychiatric diagnosis significantly more often (52.2%) than patients with AD (23.1%), SemD (24.4%), or PNFA (11.8%), and were more likely to receive diagnoses of bipolar affective disorder or schizophrenia than patients with other NDs ($p<0.001$). Younger age, higher education and a family history of psychiatric illness increased the rate of prior psychiatric diagnosis in patients

Corresponding Author: Josh Woolley, 401 Parnassus Avenue, Room 159, San Francisco, CA 94143. Phone: 415-476-7463
Josh.Woolley@ucsf.edu.

Declaration of interest for all authors: All authors report no competing interests.

Location: University of California San Francisco Memory and Aging Center, Department of Neurology, 350 Parnassus Avenue, San Francisco, CA 94143.

with bvFTD ($p < 0.05$). Cognitive, behavioral and emotional characteristics did not distinguish patients who did and did not receive a prior psychiatric diagnosis.

Conclusion—ND is often mistaken for psychiatric disease with bvFTD patients at highest risk for misdiagnosis. Because psychiatric misdiagnosis can lead to delayed and inappropriate treatment, and family and patient distress, physicians should consider referring mid- to late-life patients with new onset neuropsychiatric symptoms for ND evaluation.

Keywords

neurodegenerative disease; misdiagnosis; frontotemporal dementia; neuropsychiatric; diagnostic confusion

Introduction

Patients with a neurodegenerative disease (ND) often receive psychiatric diagnoses either because their ND has a psychiatric prodrome or because neuropsychiatric symptoms of the ND are mistaken for those of a primary psychiatric disorder. Both patterns are seen in Alzheimer's disease (AD), which has a poorly understood relationship with depression¹, but psychiatric misdiagnosis appears to be particularly common in frontotemporal dementia (FTD). This non-Alzheimer type ND consists of several clinical syndromes including behavioral (frontal-variant) frontotemporal dementia (bvFTD), semantic dementia (temporal-variant FTD; SemD) and progressive non-fluent aphasia (PNFA)². BvFTD is characterized by progressive changes in behavior, mood and personality¹. Behavioral changes may include disinhibition, compulsions, loss of insight, social inappropriateness, excessive jocularity, and gluttonous overeating^{2, 3}. Patients make impaired moral decisions⁴ and often exhibit antisocial behaviors such as indecent exposure, erratic driving and petty theft⁵. Mood disturbances including apathy, euphoria, and irritability are common², while personality changes include loss of interpersonal warmth, empathy, assertiveness and extraversion². Due to these symptoms, patients with bvFTD often initially receive diagnoses of major depressive disorder (MDD), bipolar affective disorder (BAD) or schizophrenia^{6–17}. SemD is characterized by loss of semantic elements of language with preserved grammar and motor speech². Little is known about the psychiatric misdiagnosis of patients with SemD; however, these patients exhibit social and behavioral symptoms that overlap with those of psychiatric disorders¹⁸. Patients with PNFA, who demonstrate agrammatism and motor speech impairment with spared semantic knowledge and single word memory², do not develop a significant behavioral syndrome.

Previous case series have lacked adequate power to investigate the extent to which patients receive psychiatric diagnoses prior to a final ND diagnosis. Furthermore, risk factors for prior psychiatric diagnosis in ND remain poorly understood. To quantify and characterize rates of psychiatric diagnosis in patients with various forms of ND, we performed a systematic, retrospective, chart review of a large sample of patients at a tertiary memory disorders clinic.

Methods

Subjects

We analyzed charts of 252 consecutive patients seen at our specialty clinic over the last decade: 69 with bvFTD, 41 with SemD, 17 with PNFA (meeting Neary research criteria¹⁹); 65 with AD (meeting National Institute of Neurologic and Communicative Disorders and Stroke- Alzheimer's Disease and Related Disorders Association research criteria²⁰); 25 with corticobasal degeneration (CBD), 15 with progressive supranuclear palsy (PSP) (meeting

Litvan research criteria^{21, 22}); and 20 with amyotrophic lateral sclerosis (ALS). We reviewed clinical histories of patients diagnosed with both ALS and another ND to determine which symptoms developed first. If the earliest symptoms were motor deficits, the patient was placed in the ALS group for analysis; otherwise, they were placed in the respective ND group (usually bvFTD) for analysis. Reviewers remained blinded to each patient's final ND diagnosis while reviewing charts. At our clinic, patients were evaluated by a multidisciplinary team who performed behavioral, neurological, and neuropsychological assessments. Extensive caregiver interviews were conducted to ensure accurate and reliable diagnostic histories. All patients signed an institutional review board-approved research consent form.

Assessment of Psychiatric and Neurologic History

For each patient, we recorded history of psychiatric diagnosis, family psychiatric and neurological history, age of symptom onset, and demographic information. A psychiatric diagnosis was recorded if: (1) a psychiatric diagnosis was found in the chart; and (2) the psychiatric diagnosis was within ten years of the eventual ND diagnosis. Charts, which typically included past medical records, were reviewed to qualitatively determine which symptoms led to the psychiatric diagnosis.

The time interval between psychiatric diagnosis and ND diagnosis in our clinic was determined. Age of ND onset was calculated as the age of first verified symptoms attributable to a ND. One patient was excluded because her psychiatric diagnosis was attributable to a situational factor (MDD diagnosed one week after death of a family member). A new team of blinded evaluators reviewed six chart passages deemed ambiguous by initial evaluators. Genetic counselors prospectively determined family history information. A family history of psychiatric or neurological illness was recorded if the patient had at least one affected blood relative.

During their evaluation, patients underwent a series of cognitive, neuropsychiatric, and functional evaluations including Mini Mental Status Examination (MMSE), Clinical Dementia Rating scale (CDR), Neuropsychiatric Inventory (NPI) and Geriatric Depression Scale (GDS). The MMSE measures cognitive decline, the CDR measures ND severity and the NPI is a caregiver interview that measures neuropsychiatric and behavioral disturbances. The GDS is a 30-item self-report questionnaire that screens for depression.

Statistics

Chi-square analyses were conducted to determine differences in rates and types of psychiatric diagnoses across ND groups, and to determine differences in family history of psychiatric and neurological illnesses across ND groups. General linear models (SAS Proc GLM) were used to test differences in age of onset between patients who received a psychiatric diagnosis and patients who did not, as well as to compare cognitive testing scores within ND groups, using gender and age as covariates in all analyses. Main findings for the general linear model tests are presented as means (standard deviation).

Results

Demographic data

There were more men than women with bvFTD (2:1 (male:female)), AD (1.4:1), SemD (1.3:1), ALS (3:1) and PSP (1.5:1) but not PNFA (0.3:1) and CBD (0.8:1). Patients were predominantly Caucasian (>95%).

Psychiatric diagnosis, age, gender and education

71 of 252 (28.2%) patients had a prior psychiatric diagnosis of which MDD and BAD were the most frequent (Table 1). No patients were diagnosed with personality or obsessive-compulsive disorders, although some patients did demonstrate obsessive-compulsive behaviors. Significantly more patients with bvFTD had a prior psychiatric diagnosis than other groups ($\chi^2=18.9$, $p<0.001$; Table 1). Patients with bvFTD who received a psychiatric diagnosis were younger (50.8 years (10.2) versus 57.2 years (6.9); $F=8.84$, $p<0.001$, $df=2$) and more educated ($p<0.05$) than those who did not receive a psychiatric diagnosis (Table 2). Women with bvFTD received a psychiatric diagnosis more often than men with bvFTD ($p<0.05$; Fig. 1).

Neuropsychiatric Symptoms

Patients with bvFTD given a prior psychiatric diagnosis scored lower on the NPI Delusions subscale when compared to bvFTD patients who were not given a psychiatric diagnosis ($p<0.05$; Table 3). Patients with SemD given a prior psychiatric diagnosis scored lower on the Irritability subscale than patients with SemD who were not given a psychiatric diagnosis ($p<0.05$). There were no differences in other NPI subscales or in MMSE, GDS or CDR scores in patients with and without psychiatric diagnoses across ND groups (Table 3). Initial symptoms leading to prior psychiatric diagnoses are documented in Table 4.

Family history

Patients with bvFTD were more likely to have a family history of psychiatric illness compared to those with other NDs ($\chi^2=22.3$, $p<0.001$), and patients with ND who were given a psychiatric diagnosis had higher rates of family history of psychiatric illness than ND patients who had not received a psychiatric diagnosis ($\chi^2=5.1$, $p<0.05$, Table 2).

Referral Period

The mean delay between receiving psychiatric and ND diagnoses was 33.3 (3.4) months. For patients previously diagnosed with MDD, the delay was 33.9 (4.6) months, while with BAD there was a delay of 32.2 (7.9) months. One bvFTD patient diagnosed with schizophrenia had a delay of 81 months and the other a delay of 2 months.

Discussion

In 252 patients with various forms of ND, 28.2% received a psychiatric diagnosis prior to ND diagnosis. Rates of prior psychiatric diagnosis ranged from <12% in patients with PNFA, CBD, or ALS (disorders with prominent speech, language or motor impairments) to 24.3% in SemD, 23.1% in AD and 50.7% in bvFTD (disorders with predominantly cognitive or behavioral symptoms). Across groups, the most commonly observed prior psychiatric diagnosis was MDD, but diagnoses of BAD and schizophrenia also occurred. While symptom type and severity upon our evaluation were unrelated to psychiatric diagnosis, younger age of symptom onset was associated with increased rates of prior psychiatric diagnosis in bvFTD. Most (58.6%) patients were diagnosed with a psychiatric disorder within three years of ND diagnosis, but one patient waited 81 months before her diagnosis was revised from schizophrenia to bvFTD. These high rates of psychiatric diagnosis were driven by several factors including significant symptom overlap between psychiatric disorders and ND, particularly with bvFTD.

Overlap in Symptoms

Early ND symptoms may mimic psychiatric symptoms, leading to psychiatric misdiagnosis. Apathetic symptoms such as low social engagement, fatigue and lack of initiation are

common in both ND² and MDD, and lead to diagnostic confusion⁸. Loss of empathy and emotional blunting are common in bvFTD and SemD² and may be mistaken for MDD symptoms of social withdrawal or anhedonia. Importantly, bvFTD patients rarely complain of subjective sadness²³, a hallmark symptom of MDD. Furthermore, the profound loss of empathy that characterizes bvFTD and some SemD patients is unusual with late-life psychiatric disorders. In fact, geriatric patients diagnosed with a psychiatric disorder show increased social anxiety and are more attentive to clinician expectations than either healthy older adults or ND patients²³. Patients with bvFTD and SemD often display dramatic dietary changes including ritualistic food selection or compulsive overeating, which sometimes results in weight gain³, whereas decreased appetite and weight loss are common in AD²⁴. While these dietary changes overlap with symptoms of MDD, compulsive or ritualistic eating and either dramatic weight gain or loss (seen with bvFTD with comorbid ALS) is more typical of bvFTD. Variations on these emotional and eating symptoms were frequently cited as reasons for MDD diagnosis in our sample suggesting that ND symptoms were confused with symptoms of primary psychiatric disorders.

Patients with AD have high levels of subjective sadness²⁵, which may lead to high rates of MDD diagnosis; however, in our study, subjective sadness was not often cited as a symptom that led to prior diagnosis of MDD in patients with AD. In contrast, memory loss was a common reason for patients with AD or SemD to receive a diagnosis of MDD. Although late-life depression may cause some cognitive impairment (i.e. “pseudodementia”), up to 70% of patients with pseudodementia will eventually develop ND leading to doubts regarding the diagnostic utility of pseudodementia²⁶. Personality changes are typical in early AD, particularly loss of extraversion and social assertiveness²⁷, which may be mistaken for MDD-related social withdrawal. Given the high symptom overlap between ND and MDD, physicians should have a high index of suspicion for ND in middle- to late-age patients with new onset depressive or cognitive symptoms, and should refer such patients for specialist consultation to rule out ND. This has been emphasized by others⁸.

BAD was the second most common psychiatric diagnosis and usually occurred in bvFTD. Patients ranged in age between 27 and 61 when diagnosed with BAD and appear to have been erroneously diagnosed with BAD due to symptom overlap. Epidemiologic studies suggest that over 8% of new BAD cases occur in geriatric patients²⁸, though even these studies may have inadvertently included patients who had bipolar symptoms due to a ND. Symptoms of bvFTD such as euphoria, disinhibition, impulsivity, poor decision-making, and compulsive behaviors² are similar to those seen in primary mania, which may lead to diagnostic confusion. In bvFTD, euphoria presents as inappropriate childlike jocularity (e.g. repetitive phrases and jokes) rather than pressured speech and sustained emotional intensity. Disinhibition in bvFTD presents as undue familiarity, carelessly voicing insulting observations, petty theft, sexual acting out, or poor financial decisions. However, unlike BAD patients, bvFTD patients are unlikely to demonstrate remorse, even when confronted with the consequences of their behavior. Complex stereotyped movements, vocalizations, and other compulsions are frequent in bvFTD and may resemble agitation seen in patients with BAD². In bvFTD patients, however, these typically have the appearance of mindless habits that are invariant for months, rather than occurring as variable, impulsive expressions of intense emotion, as seen in true mania. Useful symptoms to distinguish bvFTD from BAD include insidious onset and progressive nature, stereotyped movement and speech, prominent disinhibition without remorse, profound loss of empathy and social sensitivity, overeating or compulsive eating fads, lack of insight and concern (i.e. “*la belle indifférence*”), and absence of symptom periodicity.

In our sample, two patients later found to have bvFTD were diagnosed with schizophrenia at ages 33 and 34, late but not unprecedented ages for schizophrenia onset. Neither had

psychotic symptoms, but both had behavioral disturbances such as social withdrawal, sexual disinhibition, impulsivity, stealing, hoarding, repetitive speech and compulsive behaviors, which may have led to misdiagnosis. Both exhibited symptom progression typical of bvFTD. Psychotic symptoms occur in approximately 10% of patients with FTD²⁹, thus this symptom is not diagnostically definitive. Misdiagnosis of bvFTD patients with schizophrenia is documented, and meta-analysis indicates that younger age of bvFTD onset is associated with increased risk for schizophrenia diagnosis³⁰. While some have argued that this may be due to an interaction between brain development and neuropathology leading to psychotic symptoms³⁰, it is more likely due to misdiagnosis of young patients presenting with personality change, amotivation and bizarre behavior. It is unusual but not unheard of for patients in their thirties to develop ND. Up to 50% of patients with FTD have a family history of ND, often through an autosomal dominant pattern of inheritance³¹, which is rarely observed in schizophrenia. Thus, development of symptoms in the third decade of life or a family history of a highly penetrant illness should raise concern for an underlying ND.

Shared Etiology versus Independent Risk Factor

Psychiatric symptoms in patients who go on to develop ND may represent a prodrome to the ND or an independent risk factor for developing ND. These two hypotheses are difficult to differentiate and are not mutually exclusive. For example, MDD occurs in up to 30% of patients with AD¹, although the causal direction remains unclear¹. Depressed patients with AD have greater reductions in catecholamines, hormones implicated in affective disorders, than non-depressed AD patients³². Also, MDD is associated with hypofunctioning frontostriatal and limbic circuits³³, areas damaged in NDs such as bvFTD and SemD³⁴ suggesting that MDD may be a consequence of injury to the same regions affected in ND. Similarly, more severe vascular damage to these circuits causes increasingly worse depressive symptoms in a dose-response relationship³⁵. Alternatively, depression may increase the risk for developing AD and cognitive impairment¹, possibly through glucocorticoid-induced hippocampal damage in MDD¹. Patients with AD in our sample typically received an MDD diagnosis (often for memory loss) within 3 years of being diagnosed with AD. While not conclusive, this tight timeframe and symptom overlap suggest that MDD can represent either a prodrome to AD or early AD may be mistaken for MDD, but that MDD is unlikely to play a causative role AD development.

Age and Family History

FTD typically occurs in the fifth or sixth decade of life at which time it is equally prevalent with AD (FTD: 3.5–4.8 and AD: 4.2 per 100,000 people aged 45–64^{36, 37}). These rates are roughly 40 times smaller than new onset MDD (190 per 100,000 people)³⁸, but similar to rates of new-onset BAD in this age group (11.3 per 100,000 people)³⁹. Thus, MDD may be frequently diagnosed in patients with ND because MDD is more common in this age group.

Measures of depression, cognition, functional status, and neuropsychiatric symptoms did not distinguish ND patients who received a psychiatric diagnosis, suggesting that no specific symptom clusters were associated with prior psychiatric diagnosis. Patients with bvFTD who received a psychiatric diagnosis were significantly younger and more educated than their counterparts who had not received such a diagnosis, which may indicate that more educated individuals are held to different standards during initial evaluation. Patients with ND who previously received a psychiatric diagnosis had higher rates of family history of psychiatric disorders, which may have biased physicians toward psychiatric etiologies rather than NDs. Five out of eight bvFTD patients diagnosed with BAD had family histories of BAD. 35% to 50% of patients with an FTD syndrome show a pattern of genetic inheritance¹³, thus these patients' family history of BAD may actually represent a history of familial FTD that was repeatedly misdiagnosed. Taken together, these data suggest that

youth, education and a family history of psychiatric diagnosis predispose patients with a ND to receive psychiatric diagnoses.

Limitations

Because all ND groups were age-matched to patients with FTD, our sample includes many patients with atypical, early-onset NDs. Such patients may be especially diagnostically challenging, possibly skewing our data towards higher rates of psychiatric diagnosis. Furthermore, our retrospective study design is susceptible to recall and selection biases. To mitigate against this, we included consecutive patients from our center, and reviewers remained blinded to ND diagnoses. However, our data depend on the quality of physician notes, and we cannot exclude the possibility of systematic bias in documentation. Furthermore, only a subset (63 of 252) of patients had autopsy confirmed ND diagnosis, although all 63 autopsied patients were correctly diagnosed by our clinic pre-mortem testifying to our diagnostic accuracy.

Implications

Up to 18.5 million individuals worldwide will develop a neurodegenerative disease by 2050⁴⁰. Patients with ND are frequently misdiagnosed as having a psychiatric disorder, often causing them to lose precious time during the initial phase of their disease. Accurate diagnosis of bvFTD appears to present a particular diagnostic challenge. Misdiagnosis of ND leads to ineffective and potentially harmful treatments, delays in organizing proper support, and increased family stress⁴¹. Accurate diagnosis allows families to begin to cope with their loved one's altered behavior and impaired cognition, and allows time to plan for future care, receive counseling and resolve legal matters. Furthermore, disease-modifying treatments for AD and FTD are currently in clinical trials, underscoring the importance of early and accurate diagnosis. Physicians must be cognizant that there is significant symptom overlap between ND and primary psychiatric disorders, NDs affecting social and emotional behaviors can begin in the third decade of life, and new-onset psychiatric symptoms may actually be prodromal to ND. A detailed history, paying particular attention to evidence of insidious onset and progression or focal cognitive impairments, and a sophisticated clinical understanding of how ND symptoms differ from those of psychiatric disorders are critical. Physicians should consider referral to a specialist to rule out ND in patients who present with new-onset behavioral, emotional, or cognitive changes after age 40.

Acknowledgments

Funding Support: This research was supported in part by the National Institute on Aging (NIA) grants 5-P01 AG19724 and P50 AG023501, the State of California, Alzheimer's Disease Research Center of California (ARCC) grant 03-7527.

Alexander Dao B.A. UC Berkeley

References

1. Jorm A. History of depression as a risk factor for dementia: an updated review. *Aust N Z J Psychiatry*. 2001; 35:776–81. [PubMed: 11990888]
2. Weder ND, Aziz R, Wilkins K, et al. Frontotemporal dementias: a review. *Ann Gen Psychiatry*. Jan 1; 2007 6(15):1–10. [PubMed: 17204160]
3. Woolley J, Gorno-Tempini M, Seeley W, et al. Binge eating is associated with right orbitofrontal-insular-striatal atrophy in frontotemporal dementia. *Neurology*. 2007; 69(14):1423–33.
4. Mendez M, Shapira J. Altered emotional morality in frontotemporal dementia. *Cogn Neuropsychiatry*. 2009; 14(3):165–79. [PubMed: 19499384]

5. Miller B, Darby A, Benson D, et al. Aggressive, socially disruptive and antisocial behaviour fronto-temporal dementia. *Br J Psychiatry*. 1997; 170:150–4. [PubMed: 9093504]
6. Appleby B, Rosenberg P. Mania as a Possible Prodrome to Dementia. *J Neuropsychiatry Clin Neuroscience*. 2007; 19(2):194.
7. Bernardo N, Camacho A, Lara D, et al. A case series on the hypothesized connection between dementia and bipolar spectrum disorders: Bipolar type VI? *J Affect Disord*. 2008; 107:307–15. [PubMed: 17889374]
8. Blass DM, Rabins PV. Depression in frontotemporal dementia. *Psychosomatics*. Jan 1; 2009 50(3): 239–47. [PubMed: 19567763]
9. Brooks JO, Hoblyn JC. Secondary mania in older adults. *Am J Psychiatry*. Nov 1; 2005 162(11): 2033–8. [PubMed: 16263839]
10. Gálvez-Andres A, Hilario B-F, MDP, et al. Secondary Bipolar Disorder and Diogenes Syndrome in Frontotemporal Dementia. *Journal of Clinical Psychopharmacology*. 2007; 27:722–3. [PubMed: 18004150]
11. Gafoor R, O'Keane V. Three case reports of secondary mania: evidence supporting a right frontotemporal locus. *European Psychiatry*. 2002; 18:32–3. [PubMed: 12648894]
12. Gigi A, Pirrotta R, Kelley-Puskas M, et al. Behavior disturbances in emergency psychiatry or fronto-temporal dementia diagnosis? A challenge for psychiatrists. *Encephale*. 2006; 32:775–780. [PubMed: 17099602]
13. Hallam BJ, Silverberg ND, Lamarre AK, et al. Clinical presentation of prodromal frontotemporal dementia. *Am J Alzheimers Dis Other Demen*. Jan 1; 2007 22(6):456–67. [PubMed: 18166605]
14. Mendez M. Mania in neurologic disorders. *Curr Psychiatry Rep*. 2000; 4(5):440–5. [PubMed: 11122994]
15. Vanderzypen F, Bier J, Genevrois C, et al. Frontal dementia or dementia praecox? A case report of a psychotic disorder with a severe decline. *Encephale*. 2003; 29:172–80. [PubMed: 14567169]
16. Velakoulis D, Walterfang M, Mocellin R, et al. Frontotemporal dementia presenting as schizophrenia-like psychosis in young people: clinicopathological series and review of cases. *The British journal of psychiatry : the journal of mental science*. Apr 1; 2009 194(4):298–305. [PubMed: 19336778]
17. Woolley JD, Wilson MR, Hung E, et al. Frontotemporal dementia and mania. *Am J Psychiatry*. Dec 1; 2007 164(12):1811–6. [PubMed: 18056235]
18. Seeley W, Bauer A, Miller B, et al. The natural history of temporal variant frontotemporal dementia. *Neurology*. 2005; 64(8):1384–90. [PubMed: 15851728]
19. Neary D, Snowden JS, Gustafson L, et al. Frontotemporal Lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology*. 1998; 51:1546–54. [PubMed: 9855500]
20. McKhann G, Drachman D, Folstein M, et al. Clinical Diagnosis of Alzheimer's Disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*. 1984; 34:939–44. [PubMed: 6610841]
21. Litvan I, Agid Y, Calne D, et al. Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP international workshop. *Neurology*. 1996; 47:1–9. [PubMed: 8710059]
22. Litvan I, Bhatia K, Burn D, et al. Movement Disorders Society Scientific Issues Committee report: SIC Task Force appraisal of clinical diagnostic criteria for Parkinsonian disorders. *Mov Disord*. 2003; 18:467–86. [PubMed: 12722160]
23. Rankin K, Santos-Modesitt W, Kramer J, et al. Spontaneous social behaviors discriminate behavioral dementias from psychiatric disorders and other dementias. *J Clin Psychiatry*. Jan 1; 2008 69(1):60–73. [PubMed: 18312039]
24. Wang P, Yang C, Lin C, et al. Weight loss, nutritional status and physical activity in patients with Alzheimer's Disease. A controlled study. *J neurol*. 2004; 251:314–20. [PubMed: 15015012]
25. Cummings JL, Miller B, Hill M, et al. Neuropsychiatric Aspects of Multi-infarct Dementia and Dementia of the Alzheimer Type. *Arch Neurol*. 1987; 44(4):389–93. [PubMed: 3827694]
26. Sáez-Fonseca J, Lee L, Walker Z. Long-term outcome of depressive pseudodementia in the elderly. *J Affect Disord*. 2007; 101:123–9. E-Pub(1–3). [PubMed: 17184844]

27. Rankin K, Kramer J, Mychack P, et al. Double dissociation of social functioning in frontotemporal dementia. *Neurology*. 2003; 60(2):266–71. [PubMed: 12552042]
28. Almeida O, Fenner S. Bipolar disorder: similarities and differences between patients with illness onset before and after 65 years of age. *Int Psychogeriatrics*. 2002; 14(3):311–22.
29. Swartz JR, Miller BL, Lesser IM, et al. Frontotemporal dementia: treatment response to serotonin selective reuptake inhibitors. *J Clin Psychiatry*. May 1; 1997 58(5):212–6. [PubMed: 9184615]
30. Velakoulis D, Mark W, Ramon M, et al. Abnormal hippocampal distribution of TDP-43 in patients with-late onset psychosis. *Aust N Z J Psychiatry*. 2009; 43:739–45. [PubMed: 19629795]
31. Chow TW, Miller BL, Hayashi VN, et al. Inheritance of frontotemporal dementia. *Arch Neurol*. Jul 1; 1999 56(7):817–22. [PubMed: 10404983]
32. Zubenko G, Moossy J, Kopp U. Neurochemical correlates of major depression in primary dementia. *Arch Neurol*. 1990; 47(2):209–14. [PubMed: 1689144]
33. Gunning F, Cheng J, Murphy C, et al. Anterior cingulate cortical volumes and treatment remission of geriatric depression. *Int J Geriatr Psychiatry*. 2009; 24(8):829–36. [PubMed: 19551696]
34. Rosen H, Allison S, Schauer G, et al. Neuroanatomical correlates of behavioural disorders in dementia. *Brain*. 2005; 128:2612–25. E-pub. [PubMed: 16195246]
35. Wright SL, Persad C. Distinguishing between depression and dementia in older persons: neuropsychological and neuropathological correlates. *J Geriatr Psychiatry Neurol*. Dec 1; 2007 20(4):189–98. [PubMed: 18004006]
36. Knopman DS, Petersen RC, Edland SD, et al. The incidence of frontotemporal lobar degeneration in Rochester, Minnesota, 1990 through 1994. *Neurology*. Feb 10; 2004 62(3):506–8. [PubMed: 14872045]
37. Mercy L, Hodges JR, Dawson K, et al. Incidence of early-onset dementias in Cambridgeshire, United Kingdom. *Neurology*. Nov 4; 2008 71(19):1496–9. [PubMed: 18981371]
38. Eaton WW, Kalaydjian A, Scharfstein DO, et al. Prevalence and incidence of depressive disorder: the Baltimore ECA follow-up, 1981–2004. *Acta Psychiatr Scand*. Sep 1; 2007 116(3):182–8. [PubMed: 17655559]
39. Kennedy N, Boydell J, Kalidindi S, et al. Gender differences in incidence and age at onset of mania and bipolar disorder over a 35-year period in Camberwell, England. *Am J Psychiatry*. Feb 1; 2005 162(2):257–62. [PubMed: 15677588]
40. Sloane PD, Zimmerman S, Suchindran C, et al. The public health impact of Alzheimer's disease, 2000–2050: potential implication of treatment advances. *Annu Rev Public Health*. Jan 1.2002 23:213–31. [PubMed: 11910061]
41. Passant U, Elfgrén C, Englund E, et al. Psychiatric symptoms and their psychosocial consequences in frontotemporal dementia. *Alzheimer Dis Assoc Disord*. Jan 1; 2005 19 (Suppl 1):S15–8. [PubMed: 16317252]

Figure 1. Rates of Psychiatric Diagnosis within each Neurodegenerative Disease
Percentage of patients given a psychiatric diagnosis for symptoms that eventually led to a ND diagnosis separated by gender. ♂ denotes male while ♀ denotes female patients.
(*= $p < 0.01$; †= $p < 0.05$)

Table 1
Characterization of the Psychiatric Diagnoses within each Neurodegenerative Disease

Frequency of psychiatric diagnoses separated by the eventual ND diagnosis and gender. The category of 'Other' includes conversion disorder, normal aging, inattention, and pseudodementia.

Average (SD)	BvFTD		AD		SemD		PA		ALS		CBD		PSP	
	w/oΨ 38.9 (22.6)	w/oΨ 35.7 (21.6)	w/oΨ 17.5 (10.7)	w/oΨ 15.0 (19.0)	w/oΨ 30.9 (26.9)	w/oΨ 22.6 (17.1)	w/oΨ 9.0 (0.0)	w/oΨ 10.1 (10.0)	w/oΨ 30.5 (13.4)	w/oΨ 21.4 (17.8)	w/oΨ 21.0 (4.2)	w/oΨ 14.4 (14.0)	w/oΨ 23.2 (13.3)	w/oΨ 16.4 (18.7)
Subscores														
Delusion	0.4 [†] (1.5)	1.2 (2.2)	0.3 (0.6)	0.1 (0.6)	0.1 (0.3)	0.3 (1.1)	0.0 (0.0)	0.0 (0.0)	1.0 (1.4)	0.3 (1.0)	0.0 (0.0)	0.5 (1.7)	0.6 (1.3)	0.0 (0.0)
Hallucination	0.1 (0.2)	0.2 (0.8)	0.2 (0.6)	0.2 (0.9)	0.0 (0.0)	0.4 (1.1)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.1 (0.5)	0.0 (0.0)	0.3 (0.9)	0.0 (0.0)	0.0 (0.0)
Agitation	2.5 (3.4)	2.7 (3.6)	1.0 (1.9)	1.6 (3.1)	3.3 (4.4)	2.1 (2.8)	0.0 (0.0)	1.2 (2.1)	1.0 (1.4)	2.6 (3.9)	1.5 (2.1)	1.0 (1.7)	1.0 (1.7)	2.7 (4.3)
Depression	1.7 (3.1)	1.9 (3.4)	2.8 (2.9)	1.7 (2.7)	1.8 (3.8)	1.5 (2.7)	6.0 (0.0)	1.6 (3.2)	3.0 (4.2)	1.6 (2.5)	1.0 (1.4)	1.8 (2.6)	2.8 (3.1)	3.0 (2.4)
Anxiety	2.9 (3.3)	2.6 (3.9)	2.2 (3.1)	1.0 (2.2)	2.8 (5.0)	1.8 (2.7)	2.0 (0.0)	1.7 (2.7)	5.0 (1.4)	1.5 (2.7)	1.5 (2.1)	1.1 (1.9)	2.2 (2.7)	1.6 (2.9)
Euphoria	1.9 (3.3)	2.0 (2.7)	0.1 (0.4)	0.3 (1.0)	1.6 (3.0)	1.2 (2.9)	0.0 (0.0)	0.2 (0.6)	1.0 (1.4)	1.1 (1.4)	1.0 (1.4)	0.0 (0.0)	1.4 (1.9)	0.0 (0.0)
Apathy	8.1 (4.0)	7.2 (3.8)	3.6 (3.4)	2.8 (3.3)	5.6 (5.1)	2.5 (3.8)	1.0 (0.0)	1.5 (3.0)	8.0 (0.0)	4.3 (3.7)	5.0 (4.2)	2.3 (3.5)	5.0 (2.8)	2.0 (3.1)
Disinhibition	5.6 (4.4)	5.2 (4.2)	1.2 (2.0)	1.3 (3.1)	5.1 (5.3)	3.5 (3.8)	0.0 (0.0)	0.0 (0.0)	4.0 (2.8)	0.6 (1.1)	2.5 (0.7)	0.6 (1.1)	3.2 (3.0)	0.6 (1.1)
Irritability	2.1 (3.2)	1.9 (2.6)	1.4 (2.4)	1.4 (2.4)	0.3 [†] (0.7)	2.0 (3.3)	0.0 (0.0)	1.0 (2.0)	3.0 (4.2)	1.9 (3.6)	2.0 (2.8)	1.6 (2.9)	2.0 (2.5)	2.6 (4.3)
Motor	5.8 (4.8)	4.3 (4.1)	1.6 (2.4)	1.3 (2.8)	5.2 (4.9)	2.3 (3.5)	0.0 (0.0)	0.9 (2.3)	0.0 (0.0)	2.4 (4.3)	2.0 (2.8)	2.5 (3.9)	1.4 (1.3)	0.6 (1.5)
Eat	6.5 (4.2)	4.6 (3.1)	2.3 (3.2)	2.0 (3.0)	2.8 (3.8)	3.6 (3.7)	0.0 (0.0)	1.9 (2.4)	4.5 (4.9)	3.3 (4.3)	3.0 (4.2)	1.1 (1.5)	3.6 (3.6)	1.7 (3.1)
Sleep	6.5 (4.2)	4.6 (3.4)	2.3 (3.2)	2.0 (3.0)	2.8 (3.8)	3.4 (4.0)	0.0 (0.0)	1.9 (2.4)	4.5 (4.9)	3.3 (4.3)	3.0 (4.2)	1.1 (1.5)	3.6 (3.6)	1.7 (3.1)
Distress	16.1 (9.8)	15.7 (10.5)	10.0 (6.6)	8.2 (9.9)	12.6 (12.1)	13.0 (9.9)	8.0 (0.0)	5.1 (6.0)	18.5 (4.9)	8.8 (7.8)	15.0 (2.8)	9.0 (7.8)	17.2 (13.9)	6.2 (6.4)

* p<0.01;

(-) denotes a value of zero; percent listed is in comparison to ND group

Table 2
Demographics, Family History and Cognitive Test Scores

Numbers represent mean (standard deviation) in all categories except for family history where the numbers represent numerical count (percent).

	Ψ Dx	Initial Symptoms leading to Ψ Dx	Ψ Dx	Initial Symptoms leading to Ψ Dx
BvFTD	BAD	social withdrawal and lack of empathy	MDD	apathy and lack of empathy
	BAD	euphoria, alternating mood, dietary changes, lack of judgment	MDD	apathy and social withdrawal
	BAD	euphoria, disinhibition, impulsivity, alternating mood, compulsive behaviors	MDD	lack of empathy and apathy
	BAD	lack of judgment, disinhibition, compulsive behaviors, euphoria	MDD	lack of empathy and lack of insight
	BAD	euphoria and hobby changes	MDD	profound apathy
	BAD	disinhibition, impulsivity, mental rigidity	MDD	apathy, anhedonia and social withdrawal
	Schizophrenia	sexual disinhibition, impulsivity, stealing, repetitive speech	MDD	lack of empathy, dietary changes, anhedonia, poor hygiene
	Schizophrenia	apathy, social withdrawal, poor hygiene, compulsive behaviors	MDD	apathy, social withdrawal and anhedonia
	MDD	heavy drinking	MDD	lack of judgment and compulsive behaviors
	MDD	profound apathy	MDD	cognitive problems
SemD	MDD	no empathy for wife's breast cancer		
	BAD	disinhibition, compulsive behaviors, impulsivity	MDD	severe lack of empathy
	MDD	apathy, emotional distance, loss of sexual interest	MDD	memory deficits
AD	MDD	memory deficits, dietary changes, insomnia		
	BAD	slight disinhibition and anxiety	MDD	memory difficulties and mood disturbance
	MDD	memory difficulties and mood disturbance	MDD	memory deficits and stealing
	MDD	reduced speech and movement	MDD	memory deficits and disorientation

* significant difference compared to patients without a psychiatric diagnosis in same ND group ($p < 0.01$);

[†] significant difference compared to patients who were not bvFTD and received a psychiatric diagnosis ($p < 0.01$);

[‡] significant difference compared to patients without a psychiatric diagnosis in same ND group ($p < 0.05$).

Table 3

Neuropsychiatric Inventory Scores

NPI scores categorized by patients' eventual ND diagnosis and whether or not a psychiatric diagnosis was given.

	BvFTD		AD		SemD		PA		Totals
	♂	♀	♂	♀	♂	♀	♂	♀	
Depression	13 (65%)*	8 (50%)*	4 (40%)	4 (80%)	3 (60%)	3 (60%)	1 (100%)	1 (100%)	37 (60%)
BAD	4 (20%)*	4 (25%)*	-	1 (20%)	-	2 (40%)	-	-	-11 (18%)
Schizophrenia	1 (5%)	1 (6%)	-	-	-	-	-	-	-2 (3%)
Anxiety	-	1 (6%)	1 (10%)	-	1 (20%)	-	-	-	-3 (5%)
Adj. Disorder	-	-	3 (30%)	-	-	-	-	-	-3 (5%)
Other	2 (10%)	2 (13%)	2 (20%)	-	1 (20%)	-	-	-	-6 (9%)

* significant difference compared to patients without psychiatric diagnosis in same ND group ($p < 0.05$).

Table 4

Initial Symptoms Leading to Preliminary Psychiatric Diagnosis

Categorization of initial symptoms leading to a preliminary psychiatric diagnosis for the patients whose medical charts contained appropriate documentation.

		N (# missing family histories)	Gender Ratio (M/F)	Age of symptom onset	Education	# of patients with family histories (%)		MMSE	CDR	GDS
						ND History	Ψ History			
BvFTD	w/Ψ Dx	36(1)	0.57	51.1 (10.0) *	16.1 (3.1) [‡]	12(33.3)	17(47.2) [‡]	22.2 (8.8)	1.4 (0.8)	9.3 (6.2)
	w/o Ψ Dx	33(4)	0.76	56.8 (7.1)	14.9 (3.1)	13(39.4)	6(18.2)	23.1 (6.7)	1.2 (0.7)	5.8 (6.6)
AD	w/Ψ Dx	15(0)	0.67	55.1 (7.9)	14.7 (2.7)	5(33.3)	4(26.7)	18.7 (7.0)	0.9 (0.6)	5.8 (4.2)
	w/o Ψ Dx	50(1)	0.56	57.5 (9.0)	15.8 (3.2)	25(50.0)	11(22.0)	21.6 (6.6)	0.9 (0.5)	7.7 (5.1)
SemD	w/Ψ Dx	10(2)	0.5	54.6 (5.3)	16.4 (2.4)	4(40.0)	1(10.0)	20.9 (10.1)	1.1 (0.9)	7.7 (7.2)
	w/o Ψ Dx	31(1)	0.58	59.7 (7.4)	15.7 (3.1)	9(29.0)	6(19.4)	21.4 (7.2)	0.8 (0.5)	6.9 (3.7)
PNFA	w/Ψ Dx	2(0)	0.5	55.0 (7.1)	18.0 (0.0)	0(0)	0(0)	17 (0.0)	0.5 (0.0)	2 (0.0)
	w/o Ψ Dx	15(1)	0.2	62.8 (8.6)	15.1 (3.3)	5(33.3)	4(26.7)	25.4 (3.9)	0.4 (0.3)	7.8 (5.9)
ALS	w/Ψ Dx	2(2)	1	55.5 (0.7)	15.0 (0.0)	--	--	28.0 (1.4)	1.5 (0.7)	11.5 (7.8)
	w/o Ψ Dx	18(0)	0.72	55.4 (10.2)	16.1 (2.2)	11(61.1)	5(27.8)	24.9 (7.6)	0.9 (0.7)	8.5 (4.6)
CBD	w/Ψ Dx	2(2)	1	62.0 (12.7)	19.0 (0.0)	--	--	27.0 (1.4)	0.8 (0.4)	2.5 (0.7)
	w/o Ψ Dx	23(0)	0.39	59.4 (8.0)	15.1 (2.3)	7(30.4)	4(17.4)	20.7 (6.9)	0.9 (0.7)	8.5 (5.7)
PSP	w/Ψ Dx	4(4)	0.5	59.0 (6.7)	17.5 (5.0)	--	--	27.4 (2.9)	0.8 (0.3)	11.2 (3.4)
	w/o Ψ Dx	11(2)	0.64	63.4 (7.0)	16.7 (3.4)	7(63.6)	0(0)	27.3 (2.1)	0.6 (0.3)	12.5 (7.6)