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Trajectories of Behavioral Disturbance in Dementia

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Abstract

Predicting the progression of dementia is a challenge for clinicians yet this information is highly valued by patients' families. An informally observed 4-stage model of dementia can be helpful in educating caregivers and preparing them for what lies ahead. In the behavioral variant of frontotemporal dementia (bvFTD), this model describes the evolution of behavioral disturbances and is characterized by an inflection point between stage 2 (progressively severe behavioral aberration) and stage 3 (increasing apathy and remission of behavior problems). In this study we sought evidence for this model using a database of serial Neuropsychiatric Inventory (NPI) scores for 45 patients with FTD and 47 patients with Alzheimer's disease (AD). We transformed the NPI scores into a single variable for each participant that represented the rate of change in NPI score over time (NPI slope) and used this as the dependent variable in a multivariate linear regression. Age at onset of dementia, NPI score at initial visit, and duration of illness at first NPI all contributed significantly to the regression model for NPI slope in the bvFTD group. Participants with an initial NPI acquired before 6 years of disease duration tended to have a more positive NPI slope (representing worsening behavioral disturbances) than those with an initial NPI performed after 6 years. None of the aforementioned variables were significantly associated with NPI slope in the AD group. These results support a crescendo-decrescendo trajectory of behavioral symptoms in bvFTD but do not suggest that there is a similar pattern in AD, and further longitudinal data collection is necessary.

Keywords

Alzheimer's disease; agitation; apathy; behavioral symptoms; disease progression; frontotemporal dementia; longitudinal study; neurobehavioral manifestations

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Introduction

At the completion of a diagnostic evaluation for dementia, while families want to know "How long before he dies?" they also want to know what to expect over the next few years The literature gives median estimates of life expectancy for each diagnosis [1, 2, 3], and we know that early-onset Alzheimer's disease (AD) has a greater impact on survival than late-onset [4, 5] and patients with frontotemporal dementias (FTD) have a shorter life expectancy than those with Alzheimer's disease [6, 7]. However, each family will have a different experience based upon age at patient's onset of illness, co-morbidity, and consequences of the main features of the dementia. Clinicians have difficulty predicting exactly when a patient will die.

It is easier and perhaps more helpful to serve caregivers by turning their attention to operational concerns --- How will we manage as this goes on over the next year, the next 3 years? It has been useful to explain to caregivers 4 general stages of dementia:

1. **Early, inconsistent and mild changes:** In Alzheimer's disease, we call this mild cognitive impairment (MCI) [8]. In FTD, this may have been the rare episode of odd, unexpected behavior or nascent anomia and speech difficulties.
2. **Consistent, accelerating impairment:** During this stage of illness, symptomatic treatment with psychotropics is usually initiated and maintained. Nursing home placement for FTD is not uncommon at this stage.
3. **Withdrawal:** This stage seems to be a "slippery slope" into little or no goal-directed behavior, less communication of needs, progression of aphasia to mutism, and the start of dysphagia. Behavioral and psychiatric symptoms of dementia are generally slowing down, although some purposeless behaviors, such as bruxism may persist through this stage. Apathy dominates.
4. **Severe, advanced, bedridden:** There is little or no meaningful interpersonal communication; patients require full assistance for transfers and moderate assistance for feeding and/or anorexia; somnolence and incontinence are highly prevalent.

Whereas in AD the trajectory of memory loss is mainly downward, in our clinics, the prevalence and severity of the main feature of behavioral variant FTD (bvFTD), behavioral disturbances, have appeared to ramp up then decelerate over time (see Figure 1). An inflection point between stages 2 and 3 is an important milestone for both caregivers and clinicians, as it marks the transition between worsening behavioral disturbances and decline into apathy. Based on our clinical findings that most patients present at approximately 4 years post-onset of disease [9] and more informal observations that behavioral disturbances continue to progress and require pharmacologic intervention for at least 1–2 years after this, we hypothesized that this point of inflection should occur between 4 and 7 years in bvFTD. We explored a longitudinal dataset from the University of California at San Francisco to find behavioral inventory evidence to demonstrate a crescendo-decrescendo trajectory for bvFTD, as well as for AD, assuming that the two dementias progress differently. Behavioral disturbances in AD are common [9, 10, 11], and although the memory loss can decline fairly

regularly over time, patients with AD may follow the same crescendo-decrescendo pattern as in bvFTD.

Materials and Methods

Participants had been recruited and evaluated by the National Institute on Aging-funded Alzheimer's Disease Research Center at the University of California at San Francisco (UCSF). Procedures for obtaining the dataset were approved by the UCSF Institutional Review Board. Participants met criteria for bvFTD or progressive non-fluent aphasia (PNFA) or semantic dementia by Neary criteria [12] or probable AD by NINDS-ADRDA criteria [13]. Neuropathological confirmation of diagnosis was not required for inclusion in the study. Participants who met diagnostic criteria for additional, non-FTD diagnoses were excluded.

To answer our study question, further inclusion criteria for participants were: at least two complete Neuropsychiatric Inventory (NPI) scores separated by at least 11 months and initial NPI within 10 years of disease onset. Disease onset was defined as informant-reported year of earliest persistently abnormal clinical feature in the domain of language, behavioral comportment, memory, or executive functioning as elicited by staff during either research or clinic visit. Where date of onset data differed between these two sources, we selected the onset date that was reported at a research visit.

The NPI covers 12 neuropsychiatric symptom domains: delusions, hallucinations, agitation/aggression, dysphoria/depression, anxiety, euphoria/elation, apathy/indifference, disinhibition, irritability/emotional lability, aberrant motor behaviors, nighttime behavioral disturbances and appetite/eating disturbances. Clinical Nurse Specialists completed the NPIs via in-person semi-structured interviews with the participant's informant (typically a family member who was familiar with the patient's status). NPIs were collected at the annual research visits. If patients, due to advanced disease, were too impaired to complete the research visits in-person, the NPI was completed over the phone with the informant.

Statistical analysis

The data for this study were collected prospectively over annually repeated sessions, but since the starting point relative to onset of illness among participants differed, we calculated an annual rate of change in total NPI score for each participant. This was accomplished by performing separate linear regression analyses for each participant with total NPI score as the dependent variable and duration of illness at each time of testing as the independent variable. The majority of participants had either 2 (49% of bvFTD and 36% of AD participants) or 3 (27% of bvFTD and 40% of AD participants) complete NPI scores available for analysis. The resulting beta-coefficient gave us a measure of yearly change in total NPI score for each participant.

Next, we fit multivariable linear models to describe the estimate of yearly change in total NPI score within each dementia group (AD and bvFTD). This was accomplished by sequential multivariate linear regressions in which we systematically combined the following potential predictor variables: duration of illness at first available NPI, first NPI

total score, onset age, time elapsed from first to last NPI (NPI span), education level, sex, and relationship of informant to participant. In order to identify the hypothesized inflection point (the transition from increasing to decreasing NPI scores – presumably associated with the transition from stage 2 to stage 3 in the clinical model of dementia progression), we created five binary variables indicating whether duration of illness at first NPI assessment was greater or less than 3, 4, 5, 6, or 7 years.

We selected the combination of independent variables which resulted in the largest R^2 score as our model for yearly change in NPI. Our final step was to determine the relative contribution of each independent variable to the overall model. We accomplished this by post-hoc visual examination of scatter plots to explore the collinearity of these factors as well as by conducting separate bivariate regressions to determine the relationship of each independent variable with yearly change in total NPI. Analyses for bvFTD and AD were conducted separately, using IBM SPSS Statistics 20 (IBM Corporation, NY).

Results

Characterization of the sample: the database query revealed 45 participants with bvFTD (8 of whom also met Mesulam criteria for primary progressive aphasia [14]) and 47 with probable AD. The AD group in this sample has an atypically early mean age at onset. This is because the UCSF Memory Clinic database has been designed to age-match the AD participants with the FTD participants for comparative purposes. None of the bvFTD or AD cases have been confirmed by autopsy. Demographics of the sample are listed in Table 1. The results of genetic testing for the sample are summarized in Table 2. The bvFTD and AD groups did not reflect potential bias from known progranulin, microtubule associated protein tau, or presenilin mutations occurring more frequently than expected in the general population, but the AD group proportion of 1 or more apolipoprotein E epsilon 4 allele was greater than 50%, and this could have an effect on the group's decline over time.[JF, there are probably one or 2 refs that should be cited here re APOE4 effect on AD course (at the very least, there is old work on APOE4 converting MCI into AD faster)]

Behavioral variant FTD

Linear regression yielded a model for the yearly change in NPI total score consisting of (i) duration of illness at initial NPI coded as less than or greater than 6 years, (ii) initial total NPI score, and (iii) age at onset of illness (see Table 3). This multivariate linear regression model's R^2 value was 0.530. NPI span, education, sex, and caregiver relationship did not contribute to the model.

Separate bivariate regression analyses revealed that among the three predictor variables used in the model, initial NPI score was nominally the strongest followed by duration of illness and onset age (see Table 3). NPI span (R^2=0.006), education (R^2<0.001), sex (R^2=0.018) and caregiver relationship (R^2=0.001) were not significantly associated with yearly change in total NPI score in bivariate analysis.

One might expect the three identified factors to show collinearity. For example, a person presenting sooner in the course of illness might have severe behavioral disturbance (high

initial total NPI) as a motivation for seeking medical attention earlier. Or a person with very early onset age, even for early-onset bvFTD, might come to medical attention earlier in the course of illness than someone at age 70 with similar functional impairments. We visualized the data on scatter plots to explore the impact of those three variables on each other.

The longer the duration of illness at start of NPI tracking, the less was the increase seen in NPI scores over time. A clearer demonstration of the association between these two variables resulted when duration of illness was converted into a categorical variable reflecting whether duration was greater than or less than 6 years at the time of the initial NPI. Those with an initial NPI collected post-6 years of onset tended to have a more negative rate of change in NPI score over time (see Table 3 for beta coefficients and significance).

Yearly change in total NPI score correlated inversely with the initial total NPI score. That is, total NPI scores worsened over time if they started low at the initial evaluation. Conversely, cases entering with high total NPI scores (>25) did not exhibit worsening (see Figure 2).

Figure 2 also reflects how onset age had a more complex relationship with the yearly rate of change in total NPI score over time. Onset age was not a significant factor in the regression on its own. Instead, its relationship to initial NPI scores contributed to the model. Stratification of the sample into low (< 26), medium (26–53) and high (≥ 53) initial NPI scores revealed that later onset age within the bvFTD group accompanied a greater rate of decline in NPI score among those cases with high initial score. Although most participants with medium initial scores tended to show increases in NPI score over time, the rate of change in NPI score was negatively correlated with onset age to the point where participants with onset age greater than 60 tended to show a decrease in NPI score over time. The participants with low initial NPI score (including the three oldest bvFTD participants in the sample) did not show an association between onset age and yearly change in NPI total score. Those three older participants did not differ in demographics (education level, sex, primary language, primary caregiver, residence status) or diagnosis (2 bvFTD, 1 bvFTD and PPA) from the rest of the bvFTD sample. Their initial NPIs were performed early in the course of illness, at either 1 or 2 years' duration, reducing the likelihood that their data represent the late or end-stage of previously unrecognized dementia.

Alzheimer's disease

Linear regression for this diagnostic group yielded no associations between the yearly rate of change in total NPI scores over the evaluation period (in years) and duration of illness at initial NPI or age of disease onset. Omitting mild initial NPI score (total NPI < 12) revealed a strong negative correlation between rate of change and initial NPI score, which on visual inspection was almost entirely driven by the 2 outlying data points in the dataset (see Figure 3). The two extreme observations were greater than 3 standard deviations from the mean rate of change in total NPI score for AD and their initial NPI score was at the xxth percentile of patients with AD, but there were no demographic or diagnostic differences in these participants from the rest of the AD sample. The negative correlation was not apparent when the regression was repeated with these two observations removed.

Discussion

The purpose of this study was to make use of longitudinal NPI data to find evidence for hypotheses derived from our informal clinical observations. Different clinical patterns were observed in bvFTD and AD progression. Based on the change in course between stages 2 and 3 of the bvFTD progression model we expected to observe an initial acceleration phase, during which total NPI scores would be driven by increasingly abnormal behavior to a maximum sometime between 4 and 7 years post-onset of disease. After this point we expected to see a decline in total NPI scores as behavioral symptoms give way to immobility and apathy. Although there were few participants in this sample with NPIs timed to capture this crescendo-decrescendo progression for individuals, we did find some indicators for a 6-year inflection point in the behavioral trajectory using our regression model.

An observation that was consistent with the clinical progression model of bvFTD was that the rate of change in total NPI score was negatively correlated with duration of illness at the initial NPI. In other words, participants presenting sooner after disease onset tended to show large increases in total NPI score, whereas participants who presented later in disease were more likely to show a decline in total NPI score. However, there were some participants who presented late in the course of illness (after 6 years' duration) and showed unexpected increases in NPI total over time. All of these participants had low initial NPI scores, implying either a delayed trajectory of progression or an informant's overestimation of duration of illness.

Our finding that the age of onset had an impact on the change in NPI scores raises the possibility of distinct bvFTD progression trajectories based on onset age. This could suggest, for example, that participants with later-onset bvFTD reach the peak of behavioral disturbance sooner or decline faster with disease progression than those with earlier onset age. Further longitudinal data collection and analysis are necessary to clarify this observation.

There was a strong association between initial NPI score and change in NPI score over time. Participants who presented with low initial NPI scores (mild behavioral disturbance) tended to show continued upward progression of NPI scores. They may have represented participants at earlier stages of illness, although the duration of illness stated for this group was not necessarily short (range 1 to 5 years). "Initial" in this study refers to the first time an NPI was administered, which does not necessarily correlate with first medical evaluation for dementia or even the onset of symptoms. On the other end of the spectrum, participants who presented with high initial NPI scores (>53) tended to show subsequent decline in the NPI, which raises a question of whether behavioral disturbances peaked without being captured by the NPI (previous to its administration or between administration points) and then began to subside. There were few participants who did not change over the evaluation period. It is possible that the initial NPI score is telling us more about how participants presented for treatment at UCSF and responded to medication than it is about the course of FTD itself.

Participants with AD did not show any evidence of a crescendo-decrescendo pattern of behavioral symptoms and instead showed a mild increase in total NPI score over time. This

may be consistent with the emphasis on memory and cognitive loss instead of behavioral change in AD, even among participants with early-onset AD as in this sample or may simply be a reflection of the AD participants not being followed for a long enough period in order to see this pattern. Alternatively, this finding may lend support to observations that behavioral symptoms do not progress consistently in AD and fluctuate throughout the course of disease [15]. In fact, there seem to be groups of AD patients with different profiles of neuropsychiatric symptoms and these groups progress differently over time [15, 16]. One study identified 3 such groups of AD patients consisting of (1) a group with minimal behavioral or neuropsychiatric symptoms, (2) a group with mood disorder symptoms, and (3) a group with primarily psychotic symptoms [16].

Evidence from cross-sectional studies has shown that AD and bvFTD patients can be differentiated by behavioral inventory scores [11, 17, 18, 19]. Patients with bvFTD have greater total NPI scores as well as higher NPI subscale scores on apathy, disinhibition, euphoria, and aberrant motor behavior [11]. We do not know of any prior studies that have compared dementias longitudinally using a neuropsychiatric or behavioral symptom inventory. However, several studies have investigated the relationship between severity of disease (as measured by cognitive or global functioning scores) and NPI score. Not surprisingly, in FTD patients increasing severity of disease is associated with higher total NPI scores [20]. The picture is less clear in other dementia types. One study did not find a significant correlation between total NPI and degree of cognitive impairment [21]. Others suggest that total NPI score tends to increase with increasing severity of dementia [22, 23, 24]. Another study found that total NPI score increases over time in patients with mild disease severity and then decreases over time in severe dementia [25].

This study was restricted by the number of completed NPIs available for each participant. Most participants had two or three NPI assessments that did not cover the expected crescendo-decrescendo period of interest. There was also a great degree of variability in the duration of onset at first NPI. In addition, both the NPI score and the age of dementia onset are informant-dependent and thus prone to bias. Until a reliable biomarker to objectively indicate duration of illness is identified, the generalizability of our results is constrained by the accuracy of the information available from informants.

Establishing recognizable stages of dementia is an important service clinicians can provide to families and the rest of a multidisciplinary care team as they plan for short- and long-term goals to enhance the quality of life for patients with dementia. While we cannot predict with certainty the year of death, we can help the family recognize whether they are at the beginning of one of the four stages of dementia described here so that they can pace themselves for whatever remains of the course ahead. Continued data collection to observe individuals through the midpoint of illness may help clarify these observations.

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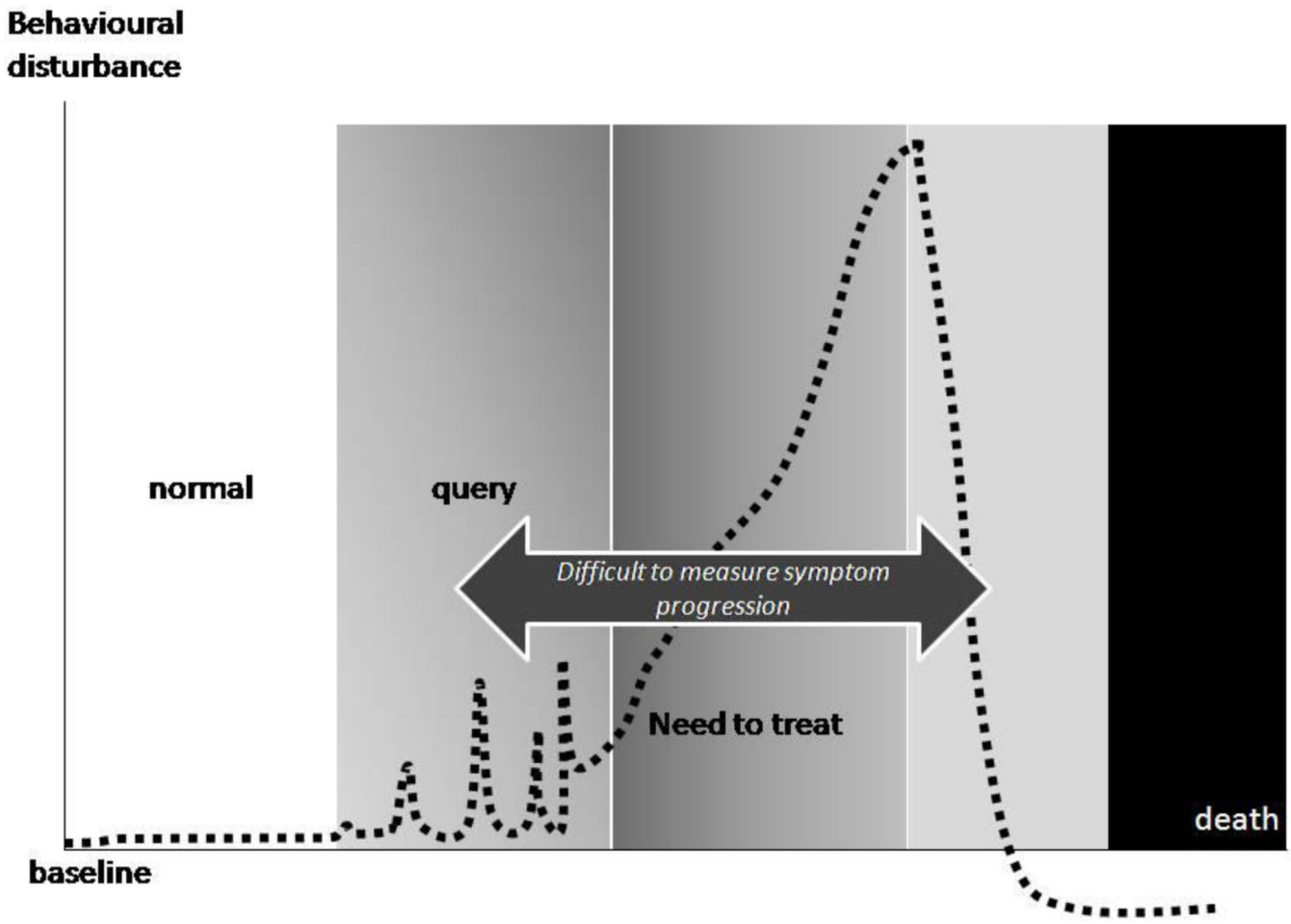

Figure 1.

Informally observed trajectory of behavioral disturbance in bvFTD. The amount of time spent in each stage can vary widely among individuals.

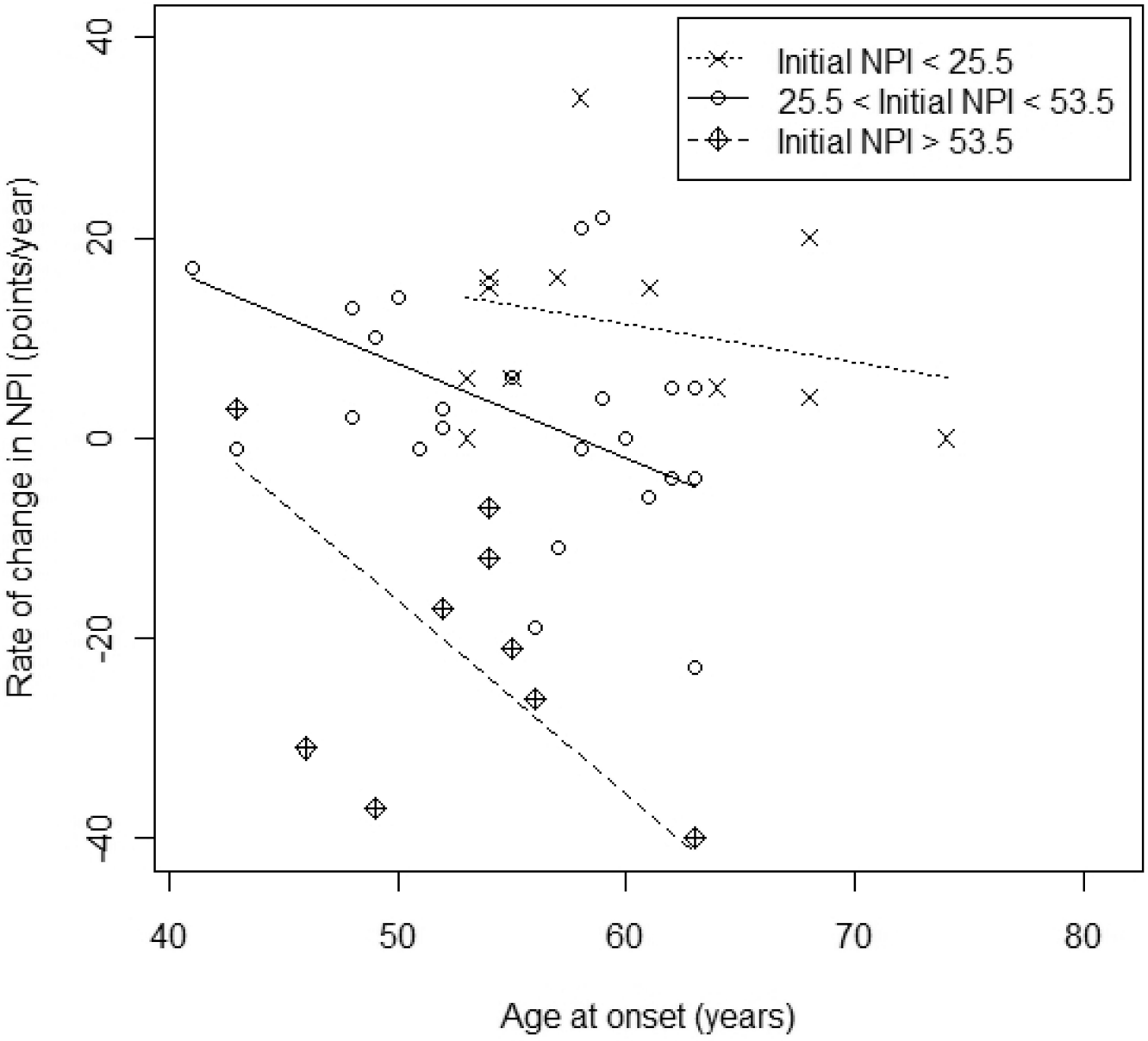

Figure 2.

The estimated yearly change in total NPI score versus age at onset of disease in the bvFTD group. Participants are classified based on initial NPI total score and reveal a negative correlation between rate of change and age at onset.

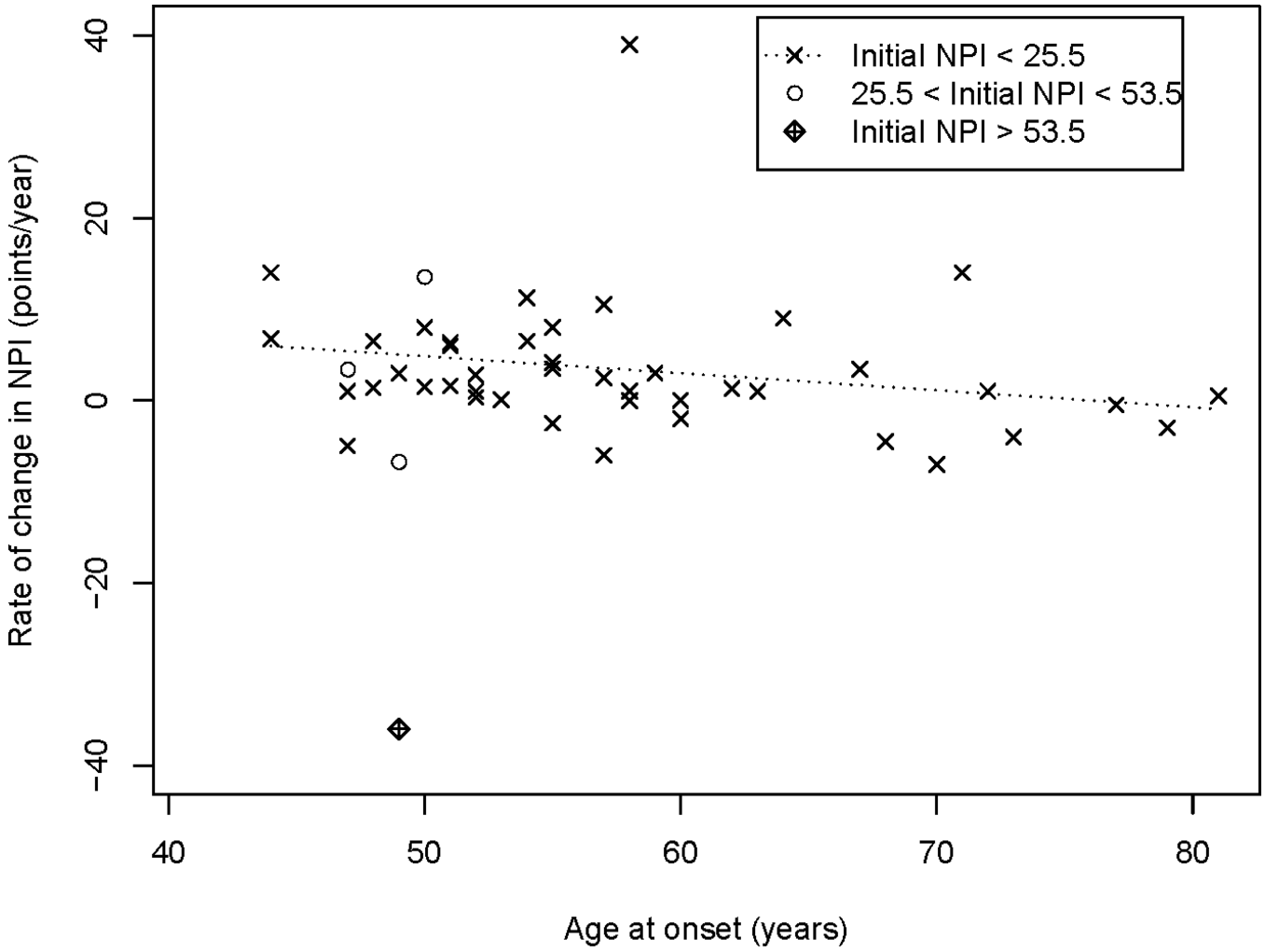

Figure 3.
Yearly change in NPI total score versus age at onset in the AD group. Participants are divided based on initial NPI total score.

Table 1

Demographics of the sample.

	Diagnosis	
	bvFTD	**AD**
Women:men	16:29	23:24
Age at onset (mean, SD)	56, 7	57, 9
Years of education (mean, SD, where available)	16, 3	16, 3
Duration of illness at initial NPI (mean, SD)	4.1, 2.4	3.3, 1.7
Initial NPI total score (Mean, SD)	38.2, 19.9	10.0, 11.7
Time span for NPI tracking (mean in months, SD)	28.5, 16.0	32.0, 18.8
Number of NPIs completed per participant (mean, mode)	2.84, 2	3.06, 3

bvFTD = behavioral variant frontotemporal dementia, AD = probable Alzheimer's disease

Table 2

Genetic testing results for the sample.

Genotype	bvFTD sample (n=45)	AD sample (n=47)
APOE allele		
E3/E3	22 (49%)	15 (32%)
E2/E3	7 (16%)	2 (4%)
E3/E4	10 (22%)	20 (43%)
E4/E4	3 (7%)	7 (15%)
Not tested	3 (7%)	3 (6%)
C9FTDALS		
Positive	7 (16%)	0
Negative	37 (82%)	31 (69%)
Not tested	1 (2%)	14 (31%)
GRN		
Positive	1 (2%)	0
Negative	38 (76%)	33 (70%)
Not tested	6 (13%)	14 (30%)
MAPT		
Positive	1 (2%)	0
Negative	36 (80%)	6 (13%)
Not tested	8 (18%)	41 (87%)
PSEN1		
Positive	1 (2%)	0
Negative	0	4 (9%)
Not tested	44 (98%)	43 (91%)

bvFTD = behavioral variant frontotemporal dementia, AD = probable Alzheimer's disease, APOE=apolipoprotein E, GRN=granulin, MAPT=microtuble-associated protein tau, PSEN1=presenilin 1.

Table 3

Multivariate model of yearly change in total NPI in participants with bvFTD. Bivariate regression results reflect the relative contribution of each dependent variable to the final model.

Independent Variable	Multivariable Linear Regression Model				Bivariate Regression	
	Unstandardized Beta coeffecient	Std. Error	t	Sig.	Unstandardized Beta Coefficient	R^2
(Constant)	57.862	16.903	3.423	0.001	N/A	N/A
Initial NPI performed before or after 6 years duration	−9.152	4.247	−2.155	0.037	−10.989	0.091
Initial NPI total score	−0.551	0.090	−0.692	<0.0001	−0.532	0.447
Onset age	−0.615	0.274	−0.267	0.030	0.077	0.001