HHS Public Access

Author manuscript

Alzheimers Dement. Author manuscript; available in PMC 2021 January 01.

Published in final edited form as:

Alzheimers Dement. 2020 January ; 16(1): 11–21. doi:10.1016/j.jalz.2019.01.012.

Assessment of executive function declines in presymptomatic and mildly symptomatic familial frontotemporal dementia: NIH-EXAMINER as a potential clinical trial endpoint

A full list of authors and affiliations appears at the end of the article.

Abstract

Introduction: Identifying clinical measures that track disease in the earliest stages of frontotemporal lobar degeneration (FTLD) is important for clinical trials. Familial FTLD provides a unique paradigm to study early FTLD. Executive dysfunction is a clinically relevant hallmark of FTLD and may be a marker of disease progression.

Methods: Ninety-three mutation carriers with no symptoms or minimal/questionable symptoms (*MAPT*, n = 31; *GRN*,n = 28; *C9orf72*,n = 34; Clinical Dementia Rating scale plus NACC FTLD Module <1) and 78 noncarriers enrolled through Advancing Research and Treatment in Frontotemporal Lobar Degeneration/Longitudinal Evaluation of Familial Frontotemporal Dementia Subjects studies completed the Executive Abilities: Measures and Instruments for Neurobehavioral Evaluation and Research (NIH-EXAMINER) and the UDS neuropsychological battery. Linear mixed-effects models were used to identify group differences in cognition at baseline and longitudinally. We examined associations between cognition, clinical functioning, and magnetic resonance imaging volumes.

Results: NIH-EXAMINER scores detected baseline and differences in slopes between carriers and noncarriers, even in carriers with a baseline Clinical Dementia Rating scale plus NACC FTLD Module = 0. NIH-EXAMINER declines were associated with worsening clinical symptoms and brain volume loss.

Discussion: The NIH-EXAMINER is sensitive to cognitive changes in presymptomatic familial FTLD and is a promising surrogate endpoint.

Keywords

Neuropsychology; Genetic; Progranulin; Cognition; Primary progressive aphasia; Semantic variant; Nonfluent variant; Behavioral variant; Working memory; Set-shifting; Inhibition; Fluency; Progressive supranuclear palsy; Corticobasal syndrome; Tau

*Corresponding author. Tel.: 11 415 502 7201; Fax: 11 415 476 2921. Adam.Staffaroni@ucsf.edu.

[1]Joint last authors.

Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jalz.2019.01.012.

1. Background

Neurodegenerative diseases, such as Alzheimer's disease (AD) and frontotemporal lobar degeneration (FTLD), are major public health concerns in our growing aging population. A concerted effort is underway to develop disease-modifying treatments, but recent trials have failed to demonstrate efficacy in the symptomatic phases [1,2]. Recently, pharmaceutical trials have shifted their focus to patients in the presymptomatic stages of disease [3], based on the lack of efficacy in the symptomatic stages and promising work in preclinical animal models [4]. Patients with autosomal dominant mutations that cause neurodegeneration offer the opportunity to study treatments in the earliest phases of illness.

About 30% of FTLD cases are familial (f-FTLD), most often due to mutations in the *C9orf72*, *GRN*, or *MAPT* genes [5]. Detailed knowledge of the molecular pathophysiology of these mutations has resulted in more refined therapeutic targets [6]. Thus, trials in the presymptomatic or questionably symptomatic phases of f-FTLD are expected in the near future [6]. In anticipation of such studies, we are faced with the challenge of validating potential endpoints in presymptomatic and mildly symptomatic mutation carriers, in whom symptoms are particularly subtle and difficult to identify and monitor.

Tracking cognition in f-FTLD is further complicated by the diversity of phenotypes that manifest; these include behavioral variant of frontotemporal dementia (bvFTD), primary progressive aphasia (PPA), motor neuron disease, and parkinsonism. In symptomatic FTLD, neuropsychological changes can be appreciated in several cognitive domains. Although episodic memory deficits are appreciated in bvFTD [7,8] and language deficits are required to diagnose PPA [9], executive function deficits are common across clinical syndromes [10–13]. Relatively less is known about the presymptomatic phases of f-FTLD, but emerging literature suggests that early executive deficits may be a primary cognitive feature [14–16].

Executive dysfunction can be challenging to evaluate with a single measure because this umbrella term comprises several subdomains, such as working memory, set-shifting, and inhibition. The Executive Abilities: Measures and Instruments for Neurobehavioral Evaluation and Research (NIH-EXAMINER) is a psychometrically validated, computerized battery developed to quantify many facets of executive functions [17]. The core battery includes six subtests combined using item response theory (IRT) to calculate an overall Executive Composite score and three factor scores. The NIH-EXAMINER is sensitive to executive dysfunction in symptomatic, sporadic FTLD [12]. Given its comprehensive and IRT-based approach to measuring executive functions, we hypothesized that the NIH-EXAMINER will be more sensitive to cognitive changes in early f-FTLD than a standard paper-and-pencil test, Trail Making Test (TMT), Part B.

The goal of the present study was to assess the ability of the NIH-EXAMINER to detect cognitive changes in the earliest stages of f-FTLD, using the Longitudinal Evaluation of Familial Frontotemporal Dementia Subjects (LEFFTDS; U01AG045390) and Advancing Research and Treatment in Frontotemporal Lobar Degeneration (ARTFL; U54NS092089) cohorts. These cohorts have been established by a consortium of 18 centers in the US and Canada, which follows f-FTLD family members, both mutation carriers and noncarriers,

longitudinally. The present work investigates differences in baseline and longitudinal executive function between early-stage f-FTLD mutation carriers and a cohort of noncarrier family members. We examined the NIH-EXAMINER Executive Composite score and three factor scores, as well as a traditional paper-and-pencil measure of executive functions and processing speed. As episodic memory is known to be a common feature in bvFTD, we also investigated visual and verbal memory measures as potential endpoints. The results of this work will help inform endpoint selection for future clinical trials that enroll patients in the earliest stages of f-FTLD.

2. Methods

2.1. Study participants

Participants were 169 members of families affected by genetic forms of FTLD who were enrolled in the LEFFTDS and ARTFL studies, which include annual longitudinal evaluations. Participants for this study were enrolled if at least one first-degree relative had a mutation in the *MAPT, GRN*, or *C9orf72* genes. In the present study, carrier inclusion was based on the functional rating from the CDR® Dementia Staging Instrument plus Behavior and Language domains from the NACC FTLD Module (CDR® plus NACC FTLD; Olney et al., this issue) scale. This measure of functional impairment includes ratings of six domains of cognition and daily function that are included in the traditional CDR domains, plus two additional domains assessing core features of FTLD: language and behavior. Mutation carriers were included if they were deemed to be asymptomatic (CDR® plus NACC FTLD = 0) or mildly/questionably symptomatic (CDR® plus NACC FTLD = 0.5) at baseline. Noncarrier family members who met study inclusion/exclusion criteria were included as controls given their similar early environment, genetic background, and demographics. Participants provided informed consent before study procedures, and the study was conducted in accordance with Internal Review Board approval.

2.2. Measures

2.2.1. Neuropsychological evaluation—All patients enrolled in the ARTFL/LEFFTDS protocol were administered the neuropsychological battery from the Uniform Data Set (UDSNB), version 3 [18]. This battery includes the Montreal Cognitive Assessment (MoCA), a screen of general cognitive functioning. Participants also received the TMT [19]. In part A of this timed test, participants connect letters in order as quickly as possible. In part B, participants alternate between connecting letters and numbers in sequential order. Part A measures processing speed, whereas part B requires set-shifting, an element of executive functioning. The UDSNB includes two measures of phonemic fluency and two measures of category fluency, which were summed together to create a UDSNB Verbal Fluency score to determine whether a standard paper-and-pencil measure of verbal fluency performed similar to the NIH-EXAMINER, IRT-derived fluency composite. Memory measures included the California Verbal Learning Test, Short Form [20], a nine-item list learning task. The outcome was free recall after a 10-minute delay. Visual memory was quantified as the number of correct items recalled 10 minutes after copying the Benson Figure [18].

2.2.2. NIH-EXAMINER—The NIH-EXAMINER is a computerized battery developed to be a clinical trial endpoint. Six subtests were administered to ARTFL/LEFFTDS participants and combined to form an Executive Composite score using the IRT, as well as three factor scores: Working Memory, Cognitive Control, and Fluency factors. The NIH-EXAMINER scoring program computes a standard error of measurement for each composite score for each individual. Consistent with recommendations from the normative study [17], we removed an individual's data for any composite score if that score's standard error was greater than 0.75 (Executive Composite, n = 1; Working Memory, n = 26). For each individual, all other composites scores below the standard error threshold were retained. Descriptions of each subtest are presented in the supplemental materials and initial publication [17].

2.2.3. FTLD-specific Clinical Dementia Rating scale—Disease severity was defined using the CDR® plus NACC FTLD [21]. The eight domain scores were summarized to create a global score using a recently developed algorithm (Olney et al., this issue). In addition, each individual domain was scored on a scale from 0 to 3, and the raw values from each domain were summed to create the CDR® plus NACC FTLD Sum of Boxes (CDR® plus NACC FTLD-SB), an integer (0–24) measure of symptom severity.

2.3. Genetic testing

All participants had genetic testing at the same laboratory at the University of California, Los Angeles using published methods (Ramos, this issue); a brief description is also included as a supplement in this article.

2.4. Neuroimaging

Participants were scanned at 3 tesla on magnetic resonance imaging scanners from one of three vendors: Philips Medical Systems, Siemens, or General Electric Medical Systems. A standard imaging protocol [22] was used by all centers and managed and reviewed for quality by a core group at the Mayo Clinic, Rochester. To create four lobar regions of interest, we summed all modulated gray matter atlas regions of interest bilaterally within each lobe.

2.5. Statistical analysis

We fitted linear mixed-effects models allowing for random intercepts and slopes in modeling longitudinal trajectories. Our primary outcomes of interest were the NIH-EXAMINER Executive Composite and TMT-B, evaluated in separate models. The primary predictors were group, time (in years, as a continuous variable), and the interaction between group (carriers vs. noncarriers) and time, allowing for assessment of group differences at baseline and in rates of change. The models also covaried for baseline age, education, and gender, as well as the interaction of each of these terms with time. We assessed baseline differences via the group effect at time zero (baseline) and differential rates of decline between carriers and noncarriers by examining the group by time interaction. Secondary analyses also examined each of the three subcomponents of the NIH-EXAMINER composite (i.e., Working Memory, Cognitive Control, and Fluency) to explore which components might be driving observed effects in the primary EXAMINER score. We also secondarily examined standard

neuropsychological measures of memory (California Verbal Learning Test and Benson Recall), processing speed (TMT-A), and verbal fluency (UDS Verbal Fluency score), as well as the CDR® plus NACC FTLD-SB in separate models. We observed some non-normality of TMT-B residuals; log transformation led to residuals that were approximately normal. We ran a sensitivity analysis using the log-transformed variable, and the same pattern of results remain. We report nontransformed data to enhance interpretability of the parameter estimates.

Effect sizes for each measure were evaluated by calculating sample sizes (per arm) required to detect 25% and 40% reductions in decline [23], using 10,000-fold bootstrapping as described in Supplementary Methods.

In follow-up analyses, we assessed the associations between the NIH-EXAMINER Executive Composite score, CDR® plus NACC FTLD-SB, and the four lobar volumes (see Supplementary Methods for details). We also analyzed the association between the Executive Composite and lobar volumes in the noncarrier controls to further validate the association between this measure and neural tissue.

To mimic the conditions of clinical trial enrolling presymptomatic carriers, we conducted follow-up analyses only including carriers with a baseline CDR® plus NACC FTLD-SB = 0. As most trials use two measurements (i.e., pre- and post-test) acquired over a ~1-year time frame, we also restricted our sample to those whose second visit was acquired within 1.5 years of baseline. These two conditions were applied to create a restricted data set that was used for the sensitivity analyses.

3. Results

3.1. Demographics, genetic, and clinical characteristics

Participants were 93 mutation carriers (31 *MAPT*, 28 *GRN*, and 34 *C9orf72*), 66 of whom had follow-up data. Seventy-eight family members without a mutation (noncarriers) were included as a comparison group, 43 with follow-up data. Demographics are presented in Table 1.

3.2. Group differences in neuropsychological performances

Group differences in baseline cognition and longitudinal cognitive slopes are presented in Table 2. Please see Supplementary Table 1 for a description of baseline performances and rates of change for carriers and noncarriers separately. At baseline, mutation carriers performed worse than noncarriers on the Executive Composite, and there was a statistically significant group by time interaction, indicating that carriers had a faster declining longitudinal change (steeper slope) on the Executive Composite (Fig. 1A). A preliminary exploration of Executive Composite decline by mutation type (i.e., *C9orf72*, *MAPT*, *PGN*) did not find a statistically significant difference in their slopes ($b = .1$, $P = .086$, 95% confidence interval [CI] [−.02, .24]). For TMT-B, although neither baseline nor longitudinal differences reached statistical significance, both were in the expected direction. The same pattern of results was observed for Trails A, with both baseline and longitudinal differences reaching statistical significance. Similar to the Executive Composite, carriers performed

worse than noncarriers at baseline and showed greater increases in functional impairments (CDR® plus NACC FTLD-SB) over time.

In addition, we investigated whether any of the three subtests comprising the Executive Composite differed between carriers and noncarriers. For the Fluency factor score, there was a statistically significant difference in the longitudinal trajectories between groups, in the expected direction. We also looked at a summary score of UDSNB Verbal Fluency measures. Similar to the EXAMINER Fluency factor score, there was a statistically significant difference in the longitudinal trajectories between groups, in the expected direction. Baseline differences in UDSNB Verbal Fluency were also in the expected direction but did not reach statistical significance. For the Control factor, carriers exhibited worse baseline performance than noncarriers, and estimated group differences in rate of decline were in the expected direction, although not statistically significant. For the Working Memory factor, both baseline and longitudinally, results were in the expected direction but did not reach statistical significance. For measures of visual and verbal episodic memory, baseline and longitudinal differences on both measures were in the expected direction not statistically significant.

3.3. Sample size estimates

We calculated the sample size (per arm) required to detect a moderate (40%) reduction in decline in a 1-year clinical trial (power = .80, alpha = .05), assuming 20% attrition. Sample size estimates (Table 3) were generally lower when the sample was restricted to those with a baseline CDR® plus NACC FTLD = 0.5, although the differences did not reach statistical significance based on the 95% CI. NIH-EXAMINER composite and factor scores and the CDR® plus NACC FTLD-SB were among the largest effect sizes regardless of the inclusion criteria.

3.4. Follow-up analyses

NIH-EXAMINER performance was analyzed in carriers (n = 66) with a baseline CDR® plus NACC FTLD = 0 and a follow-up assessment within 1.5 years of baseline (Fig. 1B), compared with 64 noncarriers. Mutation carriers continued to show a significantly more negative slope on the Executive Composite than noncarriers ($b = -0.23$, $P = .006$, 95% CI [−0.39, −0.06]). Baseline performance did not differ significantly ($b = -0.10$, $P = 0.368$, 95% CI [−0.31, 0.11]). For TMT-B, although these carriers performed worse at baseline than noncarriers ($b = 8.36$, $P = .015$, 95% CI [1.61, 15.12]), longitudinal trajectories did not statistically differ ($b = 8.37$, $P = .11$, 95% CI [−1.9, 18.64]). The model for the CDR® plus NACC FTLD-SB did not converge possibly because only 5 of 43 asymptomatic carriers showed any change between baseline and follow-up.

To further support the clinical significance of the NIH-EXAMINER, we evaluated its association with the CDR® plus NACC FTLD-SB and brain volumes (Table 4). In mutation carriers, those with higher mean Composite scores showed higher SB scores ($b = -1.13$, $P < .001$, 95% CI [−1.49, −1.72]), and those with greater longitudinal executive declines showed steeper increases in CDR® plus NACC FTLD-SB (more functional loss), ($b = -2.33$, $P < .001$, 95% CI [−2.93, −1.72]). Within-person declines in the Executive Composite were

associated with significantly greater volume loss over time in frontal and parietal lobes; relationships were also in the expected direction for occipital and temporal lobes but were not statistically significant. Between-person estimates showed that greater volume (averaged across timepoints) in all lobes was associated with better executive performance. In noncarrier controls (Table 4), greater volume in all lobes was associated with Executive Composite scores (between-person), although longitudinal, intraindividual associations between the composite and volume loss did not reach statistical significance.

4. Discussion

This study evaluated longitudinal changes in executive functions, processing speed, and memory in the earliest stages of f-FTLD using the NIH-EXAMINER and paper-and-pencil measures. At baseline, mutation carriers performed worse on the NIH-EXAMINER Executive Composite than did noncarrier family members. Nonmutation carriers appeared to improve over time, possibly due to practice effects. Carriers showed significantly steeper, negative longitudinal trajectories on this composite compared with nonmutation carriers. This finding remained statistically significant when the sample was restricted to the first two visits of carriers without any observable symptoms at baseline (CDR® plus NACC FTLD = 0). Moreover, in a clinical trial using the NIH-EXAMINER, the sample size required to detect a treatment effect would be over 50% less than a study using TMT-B as the endpoint. We further assessed the clinical relevance of the NIH-EXAMINER by analyzing its association with the CDR® plus NACC FTLD-SB. Consistent with expectations, those with greater functional impairment performed worse on the composite and greater within-person NIH-EXAMINER change tracked with longitudinal functional decline. The association of the NIH-EXAMINER with atrophy rates provided another measure of the validity of the Executive Composite, suggesting an association with the underlying disease neurobiology. Taken together, these results provide evidence that mutation carriers show detectable, early declines in executive functions and suggest that the NIH-EXAMINER has potential as a sensitive, surrogate endpoint for clinical trials of presymptomatic and mildly symptomatic f-FTLD. Although the CDR® plus NACC FTLD-SB was also able to detect longitudinal changes in the entire sample, when limiting the sample to those at the very earliest stages (global CDR® plus NACC FTLD = 0), very few people showed any change. This suggests that the CDR® plus NACC FTLD-SB may perform well in trials including carriers at the mild cognitive impairment stage, whereas it may not be sufficiently sensitive in trials enrolling asymptomatic carriers.

The NIH-EXAMINER was designed as a clinical trial endpoint to provide a more psychometrically robust composite score, compared with standard neuropsychological assessments [17]. We demonstrate that the NIH-EXAMINER is sensitive to detecting early cognitive changes in presymptomatic and mildly/questionably symptomatic mutation carriers, consistent with the earlier demonstration of its utility in symptomatic FTLD [12]. Convergent validity is demonstrated by showing longitudinal associations with functional independence and atrophy. This adds to prior research indicating that the NIH-EXAMINER Executive Composite correlates with real-world executive behavior and dorsolateral prefrontal volumes [24]. The advantage of the NIH-EXAMINER may stem in part from the wide range of executive constructs that are captured. This multidomain assessment is also

structured for modularity, such that individual subtests can be administered in isolation. For example, if validation studies suggest the Verbal Fluency composite produces the largest effect sizes in a certain genetic variant, that composite could be used as a trial endpoint, reducing trial and participant burden. Moreover, the NIH-EXAMINER uses IRT methods [25,26] to generate composite scores; these methods allow for composite construction even in the absence of certain subtests, making it particularly useful for longitudinal studies such as clinical trials. All NIH-EXAMINER components, in English and Spanish, are in the public domain and freely available to qualified users at http://memory.ucsf.edu/resources/examiner.

This study contributes to a growing body of literature characterizing cognitive trajectories in the initial phases of f-FTLD. Jiskoot et al. [27] published two longitudinal studies of a cohort of 46 presymptomatic *MAPT* and *GRN* mutation carriers with 2 years and 4 years of follow-up data [28]. At 4-year follow-up, although declines were observed in memory, language, and social cognition scores, no differences between carriers and controls were seen in the in longitudinal trajectories of scores derived from paper-and-pencil executive function measures. However, longitudinal decline in executive functions was observed in those *GRN* and *MAPT* mutation carriers who later developed symptoms. An earlier cross-sectional study (78 asymptomatic carriers) showed executive function differences between noncarriers and carriers (*MAPT* and *GRN*) in the presymptomatic stage [14], replicating the results of several smaller studies in carriers of *GRN* (n's = 8 and 13) [29,30] and *MAPT* (n's = 4 and 10) [15,16] mutations, respectively. Our work buttresses findings that declines in processing speed (TMT-A) and executive functions are detectable in the early stages of f-FTLD and builds on these works by showing these declivities are associated with longitudinal changes in clinical status and brain volumes. Furthermore, our study includes carriers of the *C9orf72* expansion, whereas many prior studies did not. In contrast to the study by Jiskoot et al. described previously [28], we did not find statistically significant longitudinal differences in episodic memory, although the coefficients were in the expected direction. Follow-up analyses suggested that the verbal fluency domain of executive functions appears to be a particularly affected in early stages of f-FTLD, and the NIH-EXAMINER Fluency factor produces the most encouraging effect sizes for clinical trials. Given that the Fluency factor and TMT-A both rely on processing speed, follow-up studies of processing speed measures in this cohort may be warranted.

This study has several limitations. First, we group the three major classes of f-FTLD mutations in a single analysis to maximize power. As sample sizes continue to grow in this and other cohorts, these findings should be replicated in larger groups of each genetic variant to confirm the generalizability of the NIH-EXAMINER for trials enrolling carriers of particular mutation types. A second limitation is the large sample size required to detect a treatment effect in the early phases of f-FTLD. It is important to note that this calculation was based on a convenience sample, as we did not limit inclusion to those most likely to exhibit clinical change during the study period. The mean age of our cohort is 46 years, which is younger than the mean age of onset for f-FTLD mutations (50 to early 60s; Olney, this issue) [31]. Our recent work [32] suggests that brain atrophy may improve the ability to predict which mutation carriers are most likely to convert to dementia, thereby improving power and reducing the number of participants required to detect an effect. Further work will

be needed to validate the NIH-EXAMINER in the symptomatic phases of FTLD; we refer readers to our study on other potential clinical and neuroimaging endpoints in symptomatic FTLD [33].

Despite its limitations, the present study adds to our knowledge of cognition in presymptomatic and mildly/questionably symptomatic f-FTLD and provides indications that the NIH-EXAMINER is well suited to detect early changes in a heterogeneous group of f-FTLD mutation carriers and is associated with the neurobiology of f-FTLD. Given the relatively large sample sizes required for a trial in mutations carriers with CDR® plus NACC FTLD = 0 and 0.5, however, improved enrichment strategies for enrolling patients closest to developing unequivocal dementia, major refinements, new scales, or different methodologic approaches may be necessary to measure clinical changes in presymptomatic to very early symptomatic trial participants. Regardless, the results are encouraging and suggest that further study of the NIH-EXAMINER as a potential surrogate endpoint for f-FTLD is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Authors

Adam M. Staffaroni[a,*], Lynn Bajorek[a], Kaitlin B. Casaletto[a], Yann Cobigo[a], Sheng-Yang M. Goh[a], Amy Wolf[a], Hilary W. Heuer[a], Fanny M. Elahi[a], Peter A. Ljubenkov[a], Reilly Dever[a], John Kornak[b], Brian Appleby[c], Jessica Bove[d], Yvette Bordelon[e], Patrick Brannelly[f], Danielle Brushaber[g], Christina Caso[h], Giovanni Coppola[e,i], Christina Dheel[j], Bradford C. Dickerson[k], Susan Dickinson[l], Sophia Dominguez[d], Kimiko Domoto-Reilly[h], Kelly Faber[m], Jessica Ferrall[n], Julie A. Fields[o], Ann Fishman[p], Jamie Fong[a], Tatiana Foroud[m], Leah K. Forsberg[j], Ralitza Gavrilova[j], Debra Gearhart[j], Behnaz Ghazanfari[q,r], Nupur Ghoshal[s], Jill Goldman[t,u], Jonathan Graff-Radford[j], Neill Graff-Radford[v], Ian Grant[w], Murray Grossman[d], Dana Haley[v], Ging-Yuek Hsiung[x], Edward D. Huey[t,u], David J. Irwin[d], David T. Jones[j], Lynne Jones[y], Kejal Kantarci[z], Anna Karydas[a], Daniel I. Kaufer[n], Diana R. Kerwin[aa,bb], David S. Knopman[j], Ruth Kraft[j], Walter K. Kremers[g], Walter A. Kukull[cc], Irene Litvan[dd], Diane Lucente[k], Codrin Lungu[ee], Ian R. Mackenzie[ff], Miranda Maldonado[e], Masood Manoochehri[t], Scott M. McGinnis[k], Emily McKinley[gg], Mario F. Mendez[e,i], Bruce L. Miller[a], Namita Multani[q,r], Chiadi Onyike[hh], Jaya Padmanabhan[k], Alex Pantelyat[ii], Rodney Pearlman[jj], Len Petrucelli[kk], Madeline Potter[m], Rosa Rademakers[kk], Eliana Marisa Ramos[i], Katherine P. Rankin[a], Katya Rascovsky[d], Erik D. Roberson[gg], Emily Rogalski[ll], Pheth Sengdy[x], Leslie M. Shaw[mm], Jeremy Syrjanen[g], M. Carmela Tartaglia[q,r], Nadine Tatton[l], Joanne Taylor[a], Arthur Toga[nn], John Q. Trojanowski[mm], Sandra Weintraub[w], Ping Wang[a], Bonnie Wong[k], Zbigniew Wszolek[v], Adam L. Boxer[a], Brad F. Boeve[j], Joel H. Kramer[a,1], Howard J. Rosen[a,1]

ARTFL/LEFFTDS consortium

Affiliations

[a]Department of Neurology, Memory and Aging Center, University of California, San Francisco, San Francisco, CA, US

[b]Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, CA, USA

[c]Department of Neurology, Case Western Reserve University, Cleveland, OH, USA

[d]Department of Neurology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

[e]Department of Neurology, University of California, Los Angeles, Los Angeles, CA, USA

[f]Tau Consortium, Rainwater Charitable Foundation, Fort Worth, TX, USA

[g]Department of Health Sciences Research, Mayo Clinic, Rochester, MN, USA

[h]Department of Neurology, University of Washington, Seattle, WA, USA

[i]Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, Los Angeles, CA, USA

[j]Department of Neurology, Mayo Clinic, Rochester, MN, USA

[k]Department of Neurology, Frontotemporal Disorders Unit, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

[l]Association for Frontotemporal Degeneration, Radnor, PA, USA

[m]National Cell Repository for Alzheimer's Disease (NCRAD), Indiana University, Indianapolis, IN, USA

[n]Department of Neurology, University of North Carolina, Chapel Hill, NC, USA

[o]Department of Psychiatry and Psychology, Mayo Clinic, Rochester, MN, USA

[p]School of Medicine, Department of Psychiatry, Johns Hopkins University, Baltimore, MD, USA

[q]Tanz Centre for Research in Neurodegenerative Diseases, University of Toronto, Toronto, Ontario, Canada

[r]Division of Neurology, Department of Medicine, University of Toronto, Toronto, Ontario, Canada

[s]Departments of Neurology and Psychiatry, Washington University School of Medicine, Washington University, St. Louis, MO, USA

[t]Department of Neurology, Columbia University, New York, NY, USA

[u]Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Columbia University, New York, NY, USA

[v]Department of Neurology, Mayo Clinic, Jacksonville, FL, USA

[w]Feinberg School of Medicine, Department of Neurology, Northwestern University, Chicago, IL, USA

[x]Division of Neurology, Deptartment of Medicine, University of British Columbia, Vancouver, British Columbia, Canada

[y]Department of Radiology, Washington University School of Medicine, Washington University, St. Louis, MO, USA

[z]Department of Radiology, Mayo Clinic, Rochester, MN, USA

[aa]Department of Neurology and Neurotherapeutics, Center for Alzheimer's and Neurodegenerative Diseases, The University of Texas, Southwestern Medical Center at Dallas, Dallas, TX, USA

[bb]Department of Internal Medicine, The University of Texas, Southwestern Medical Center at Dallas, Dallas, TX, USA

[cc]National Alzheimer Coordinating Center (NACC), University of Washington, Seattle, WA, USA

[dd]Department of Neurosciences, Parkinson and Other Movement Disorders Center, University of California, San Diego, San Diego, CA, USA

[ee]National Institute of Neurological Disorders and Stroke (NINDS), Bethesda, MD, USA

[ff]Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, British Columbia, Canada

[gg]Department of Neurology, Alzheimer's Disease Center, University of Alabama at Birmingham, Birmingham, AL, USA

[hh]Department of Geriatric Psychiatry and Neuropsychiatry, Johns Hopkins University, Baltimore, MD, USA

[ii]School of Medicine, Department of Neurology, Johns Hopkins University, Baltimore, MD, USA

[jj]Bluefield Project, San Francisco, CA, USA

[kk]Department of Neurosciences, Mayo Clinic, Jacksonville, FL, USA

[ll]Feinberg School of Medicine, Department of Psychiatry and Behavioral Sciences, Northwestern University, Chicago, IL, USA

[mm]Perelman School of Medicine, Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, PA, USA

[nn]Departments of Ophthalmology, Neurology, Psychiatry and the Behavioral Sciences, Radiology and Engineering, Laboratory of Neuroimaging (LONI), USC, Los Angeles, CA, USA

Acknowledgments

The authors extend our appreciation to Drs. John Hsiao and Dallas Anderson from the National Institute on Aging, Drs. Marg Sutherland and Codrin Lungu from the National Institute of Neurological Disorders and Stroke, the staff of all centers, and particularly to our patients and their families for their participation in this protocol. This work is supported by the National Institutes of Health [grants AG045390, NS092089, AG032306, AG021886, AG016 976, and K24AG045333] and the Larry L. Hillblom Foundation (2018-A-025-FEL). Samples from the National Centralized Repository for Alzheimer Disease and Related Dementias, which receives government support under a cooperative agreement grant (U24 AG21886) awarded by the National Institute on Aging (NIA), were used in this study.

A.M.S. receives research funding from the Larry H. Hillblom foundation and support from the NIH. K.B.C. receives research support from the NIH and Larry H. Hillblom foundation. H.H. receives research support from NIH. B.A. receives research support from CDC. P.B. is employed by the Rainwater Charitable Foundation. G.C. receives research support from NIH. B.D. receives research support from NIH. S.D. is a staff member at the Association for Frontotemporal Degeneration and a member of the National Institute for Neurological Disorders and Stroke Advisory Council. K.F. receives research support from NIH. J. Fields receives research support from NIH. T.F. receives research support from NIH. L.F. receives research support from NIH. R.G. receives research support from NIH. N.G. has participated or is currently participating in clinical trials of antidementia drugs sponsored by the following companies: Bristol-Myers Squibb, Eli Lilly/Avid Radiopharmaceuticals, Janssen Immunotherapy, Novartis, Pfizer, Wyeth, SNIFF (The Study of Nasal Insulin to Fight Forgetfulness) study, and A4 (The Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease) trial. She receives research support from Tau Consortium and Association for Frontotemporal Dementia and is funded by the NIH. J.G. is serving as a consultant to the Novartis Alzheimer's Prevention Advisory Board. She receives research support from NIH, HDSA, New York State Department of Health (RFA # 1510130358). J.G.-R. receives research support from the NIH. N.G.-R. receives royalties from UpToDate and has participated in multicenter therapy studies sponsored by Biogen, TauRx, AbbVie, Novartis, and Lilly. He receives research support from NIH. M.G. receives grant support from NIH, Avid, and Piramal; participates in clinical trials sponsored by Biogen, TauRx, and Alector; serves as a consultant to Bracco and UCB; and serves on the Editorial Board of *Neurology*. G.-Y.H. has served as an investigator for clinical trials sponsored by AstraZeneca, Eli Lilly, and Roche/Genentech. He receives research support from Canadian Institutes of Health Research and the Alzheimer Society of British Columbia. E.H. receives research support from NIH. D.I. receives support from NIH, BrightFocus Foundation, and Penn Institute on Aging. D.J. receives research support from NIH and the Minnesota Partnership for Biotechnology and Medical Genomics. K.K. served on the Data Safety Monitoring Board for Takeda Global Research & Development Center, Inc.; served on the data monitoring boards of Pfizer and Janssen Alzheimer Immunotherapy; and received research support from the Avid Radiopharmaceuticals, Eli Lilly, the Alzheimer's Drug Discovery Foundation, and NIH. D. Kerwin has served on an advisory board for AbbVie and as a site PI for studies funded by Roche/Genentech, AbbVie, Avid, Novartis, Eisai, Eli Lilly, and UCSF. D. Knopman serves on the DSMB of the DIAN-TU study; is a site PI for clinical trials sponsored by Biogen, Lilly, and the University of Southern California; and is funded by NIH. J. Kornak has provided expert witness testimony for Teva Pharmaceuticals in *Forest Laboratories Inc. et al. v. Teva Pharmaceuticals USA, Inc.*, Case Nos. 1:14-cv-00121 and 1:14-cv-00686 (D. Del. filed Jan. 31, 2014 and May 30, 2014), regarding the drug memantine, and for Apotex/HEC/Ezra in *Novartis AG et al. v. Apotex Inc.*, No. 1:15-cv-975 (D. Del. filed Oct. 26, 2015, regarding the drug Fingolimod. He has also given testimony on behalf of Puma Biotechnology in *Hsingching Hsu et al. vs. Puma Biotechnology, INC., et al.* 2018, regarding the drug neratinib. He receives research support from the NIH. W. Kremers receives research funding from AstraZeneca, Biogen, Roche, DOD, and NIH. W. Kukull receives research support from NIH. I.L. receives research support from NIH, Parkinson Study Group, Parkinson Foundation, Michael J Fox Foundation, AVID Pharmaceuticals, C2N Diagnostics/AbbVie, and Bristol-Myers Squibb. She was a member of the Biogen and Bristol-Myers Squibb Advisory Boards, Biotie/Parkinson Study Group Medical Advisory Board, and a consultant for Toyama Pharmaceuticals; receives salary from the University of California San Diego; and serves as a editor in Frontiers in Neurology. D.L. receives research support from NIH. C.L. receives honoraria for editorial work from Elsevier, Inc. I.M. receives research funding from Canadian Institutes of Health Research. S.McG. has served as an investigator for clinical trials sponsored by AbbVie, Allon Therapeutics, Biogen, Bristol-Myers Squibb, C2N Diagnostics, Eisai Inc., Eli Lilly and Co., Genentech, Janssen Pharmaceuticals, Medivation, Merck, Navidea Biopharmaceuticals, Novartis, Pfizer, and TauRx Therapeutics. He receives research support from NIH. B.M. receives research support from NIH. A.P. receives research support from NIH (NIA/NINDS). R.P. employed by The Bluefield Project. L.P. receives research support from NIH. M.P. receives research support from NIH. R.R. receives research funding from NIH and the Bluefield Project to Cure Frontotemporal Dementia. K. Rankin receives research support from NIH. K. Rascovsky receives research support from NIH. E.D.R. receives research support from NIH, Bluefield Project to Cure Frontotemporal Dementia, Alzheimer's Association, BrightFocus Foundation, Biogen, and Alector and owns intellectual property related to tau. L.S. receives research support from NIH. N.T. employed by the Association for Frontotemporal Degeneration. A.T. receives research support from the NIH and the Alzheimer's Association. J. Trojanowski may accrue revenue in the future on patents submitted by the University of Pennsylvania, wherein he is a coinventor and received revenue from the sale of Avid to Eli Lily as a coinventor on Ab amyloid imaging–related patents submitted by the University of Pennsylvania. He receives research support from the NIH and several nonprofits. S.W. receives research support from the NIH. B.W. receives research support from the NIH. Z.W. is

supported by the NIH, Mayo Clinic Center for Regenerative Medicine, the gift from Carl Edward Bolch, Jr., and Susan Bass Bolch, The Sol Goldman Charitable Trust, and Donald G. and Jodi P. Heeringa. He has also received grant funding support from Allergan, Inc. (educational grant), and AbbVie (medication trials). A.B. receives research support from NIH, the Tau Research Consortium, the Association for Frontotemporal Degeneration, Bluefield Project to Cure Frontotemporal Dementia, Corticobasal Degeneration Solutions, the Alzheimer's Drug Discovery Foundation, and the Alzheimer's Association. He has served as a consultant for Aeton, AbbVie, Alector, Amgen, Arkuda, Ionis, Iperian, Janssen, Merck, Novartis, Samumed, Toyama, and UCB and received research support from Avid, Biogen, BMS, C2N, Cortice, Eli Lilly, Forum, Genentech, Janssen, Novartis, Pfizer, Roche, and TauRx. B.B. has served as an investigator for clinical trials sponsored by GE Healthcare and Axovant. He receives royalties from the publication of a book entitled *Behavioral Neurology of Dementia* (Cambridge Medicine, 2009, 2017). He serves on the Scientific Advisory Board of the Tau Consortium. He receives research support from NIH, the Mayo Clinic Dorothy and Harry T. Mangurian Jr. Lewy Body Dementia Program, and the Little Family Foundation. J. Kramer receives research support from NIH. H.R. has received research support from Biogen Pharmaceuticals, has consulting agreements with Wave Neuroscience and Ionis Pharmaceuticals, and receives research support from NIH. L.B., Y.C., S.G., A.W., F.M.E., J.B., D.B., C.D., R.D., J. Fong, D.G., D.H., L.J., A.K., R.K., M.L., M.M., E.R., P.S., J.S., and J. Taylor have nothing to disclose.

References

[1]. Salloway S, Sperling R, Fox NC, Blennow K, Klunk W, Raskind M, et al. Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease. N Engl J Med 2014;370:322–33. [PubMed: 24450891]

[2]. Vandenberghe R, Rinne JO, Boada M, Katayama S, Scheltens P, Vellas B, et al. Bapineuzumab for mild to moderate Alzheimer's disease in two global, randomized, phase 3 trials. Alzheimers Res Ther 2016;8:18. [PubMed: 27176461]

[3]. Sperling RA, Rentz DM, Johnson KA, Karlawish J, Donohue M, Salmon DP, et al. The A4 Study: Stopping AD Before Symptoms Begin? Sci Transl Med 2014;6:228fs13.

[4]. McDade E, Bateman RJ. Stop Alzheimer's before it starts. Nature 2017;547:153–5. [PubMed: 28703214]

[5]. Rohrer JD, Guerreiro R, Vandrovcova J, Uphill J, Reiman D, Beck J, et al. The heritability and genetics of frontotemporal lobar degeneration. Neurology 2009;73:1451–6. [PubMed: 19884572]

[6]. Tsai RM, Boxer AL. Therapy and clinical trials in frontotemporal dementia: past, present, and future. J Neurochem 2016;138:211–21. [PubMed: 27306957]

[7]. Poos JM, Jiskoot LC, Papma JM, van Swieten JC, van den Berg E. Meta-analytic Review of Memory Impairment in Behavioral Variant Frontotemporal Dementia. J Int Neuropsychol Soc 2018;24:593–605. [PubMed: 29552997]

[8]. Mansoor Y, Jastrzab L, Dutt S, Miller BL, Seeley WW, Kramer JH. Memory Profiles in Pathology or Biomarker Confirmed Alzheimer Disease and Frontotemporal Dementia. Alzheimer Dis Assoc Disord 2014;29:135–40.

[9]. Gorno-Tempini ML, Hillis AE, Weintraub S, Kertesz A, Mendez M, Cappa SF, et al. Classification of primary progressive aphasia and its variants. Neurology 2011;76:1006–14. [PubMed: 21325651]

[10]. Kramer JH, Jurik J, Sha SJ, Rankin KP, Rosen HJ, Johnson JK, et al. Distinctive neuropsychological patterns in frontotemporal dementia, semantic dementia, and Alzheimer disease. Cogn Behav Neurol 2003;16:211–8. [PubMed: 14665820]

[11]. Patel AN, Sampson JB. Cognitive Profile of C9orf72 in Frontotemporal Dementia and Amyotrophic Lateral Sclerosis. Curr Neurol Neurosci Rep 2015;15:59. [PubMed: 26198888]

[12]. Possin KL, Feigenbaum D, Rankin KP, Smith GE, Boxer AL, Wood K, et al. Dissociable executive functions in behavioral variant frontotemporal and Alzheimer dementias. Neurology 2013;80:2180–5. [PubMed: 23658382]

[13]. Macoir J, Lavoie M, Laforce R, Brambati SM, Wilson MA. Dysexecutive Symptoms in Primary Progressive Aphasia: Beyond Diagnostic Criteria. J Geriatr Psychiatry Neurol 2017;30:151–61. [PubMed: 28355946]

[14]. Rohrer JD, Nicholas JM, Cash DM, van Swieten J, Dopper E, Jiskoot L, et al. Presymptomatic cognitive and neuroanatomical changes in genetic frontotemporal dementia in the Genetic Frontotemporal dementia Initiative (GENFI) study: a cross-sectional analysis. Lancet Neurol 2015;14:253–62. [PubMed: 25662776]

[15]. Ferman T, McRae C, Arvanitakis Z, Tsuboi Y, Vo A, Wszolek Z. Early and pre-symptomatic neuropsychological dysfunction in the PPND family with the N279K tau mutation. Parkinsonism Relat Disord 2003;9:265–70. [PubMed: 12781592]

[16]. Geschwind DH, Robidoux J, Alarcón M, Miller BL, Wilhelmsen KC, Cummings JL, et al. Dementia and neurodevelopmental predisposition: cognitive dysfunction in presymptomatic subjects precedes dementia by decades in frontotemporal dementia. Ann Neurol 2001;50:741–6. [PubMed: 11761471]

[17]. Kramer JH, Mungas D, Possin KL, Rankin KP, Boxer AL, Rosen HJ, et al. NIH EXAMINER: conceptualization and development of an executive function battery. J Int Neuropsychol Soc 2014;20:11–9. [PubMed: 24103232]

[18]. Weintraub S, Besser L, Dodge HH, Teylan M, Ferris S, Goldstein FC, et al. Version 3 of the Alzheimer Disease Centers' Neuropsychological Test Battery in the Uniform Data Set (UDS). Alzheimer Dis Assoc Disord 2017;1 10.1097/WAD.0000000000000223. [PubMed: 28121634]

[19]. Army Individual Test Battery Manual of Directions and Scoring 1944 Washington, DC: War Department, Adjunct General's Office; 1944.

[20]. Delis DC, Kramer JH, Kaplan E, Ober BA. California Verbal Learning Test - second edition. Adult version. Manual 2000 San Antonio, Tex: Psychological Corporation; 2000.

[21]. Knopman DS, Kramer JH, Boeve BF, Caselli RJ, Graff-Radford NR, Mendez MF, et al. Development of methodology for conducting clinical trials in frontotemporal lobar degeneration. Brain 2008; 131:2957–68. [PubMed: 18829698]

[22]. Weiner MW, Veitch DP, Aisen PS, Beckett LA, Cairns NJ, Green RC, et al. The Alzheimer's Disease Neuroimaging Initiative 3: Continued innovation for clinical trial improvement. Alzheimer's Dement 2017;13:561–71. [PubMed: 27931796]

[23]. Sakpal TV. Sample size estimation in clinical trial. Perspect Clin Res 2010;1:67–9. [PubMed: 21829786]

[24]. Possin KL, Lamarre AK, Wood KA, Mungas DM, Kramer JH. Ecological Validity and Neuroanatomical Correlates of the NIH EXAMINER Executive Composite Score. J Int Neuropsychol Soc 2018;20:20–8.

[25]. Hambleton RK, Swaminathan H, Rogers HJ. Fundamentals of Item Response Theory 1991. Newbury Park, CA: Sage Publications; 1991.

[26]. Mungas D, Reed BR, Kramer JH. Psychometrically matched measures of global cognition, memory, and executive function for assessment of cognitive decline in older persons. Neuropsychology 2003;17:380–92. [PubMed: 12959504]

[27]. Jiskoot LC, Dopper EGP, Heijer T den, Timman R, van Minkelen R, van Swieten JC, et al. Presymptomatic cognitive decline in familial frontotemporal dementia. Neurology 2016;87:384–91. [PubMed: 27358337]

[28]. Jiskoot LC, Panman JL, van Asseldonk L, Franzen S, Meeter LHH, Donker Kaat L, et al. Longitudinal cognitive biomarkers predicting symptom onset in presymptomatic frontotemporal dementia. J Neurol 2018;265:1381–92. [PubMed: 29627938]

[29]. Barandiaran M, Estanga A, Moreno F, Indakoetxea B, Alzualde A, Balluerka N, et al. Neuropsychological Features of Asymptomatic c.709-1G>A Progranulin Mutation Carriers. J Int Neuropsychol Soc 2012;18:1086–90. [PubMed: 23158232]

[30]. Hallam BJ, Jacova C, Hsiung G-YR, Wittenberg D, Sengdy P, Bouchard-Kerr P, et al. Early Neuropsychological Characteristics of Progranulin Mutation Carriers. J Int Neuropsychol Soc 2014;20:694–703. [PubMed: 24993774]

[31]. Woollacott IOC, Rohrer JD. The clinical spectrum of sporadic and familial forms of frontotemporal dementia. J Neurochem 2016; 138:6–31. [PubMed: 27144467]

[32]. Staffaroni AM, Cobigo Y, Goh SYM, Kornak J, Bajorek L, Chiang K, et al. Individualized atrophy scores predict dementia onset in familial frontotemporal lobar degeneration. Alzheimer Dement 2019; in press. 10.1016/j.jalz.2019.04.007.

[33]. Staffaroni AM, Ljubenkov PA, Kornak J, Cobigo Y, Datta S, Marx G, et al. Longitudinal Multimodal Imaging and Clinical Endpoints for Frontotemporal Dementia Clinical Trials. Brain 2019; 142:443–59. [PubMed: 30698757]

RESEARCH IN CONTEXT

1. Systematic review: The authors present a summary of the existing literature (using PubMed) that has investigated cognition in the presymptomatic phases of familial frontotemporal lobar degeneration (f-FTLD). There is a small body of research with few longitudinal studies, and many studies have not included carriers of the *C9orf72* expansion. No studies were found that provided details (i.e., sample size estimates) about the utility of neuropsychological measures as clinical trial endpoints in the earliest stages of f-FTLD.
2. Interpretation: Our findings indicate that longitudinal changes in executive function can be detected in the presymptomatic and mildly/questionably symptomatic stages of f-FTLD. The NIH-EXAMINER (Executive Abilities: Measures and Instruments for Neurobehavioral Evaluation and Research) appears to be particularly well suited as a clinical trial endpoint.
3. Future directions: Sample size estimates for detecting an effect in presymptomatic mutation carriers are relatively large, suggesting that strategies for recruiting mutation carriers who are close to conversion will be important for clinical trials targeting these earliest stages of disease.

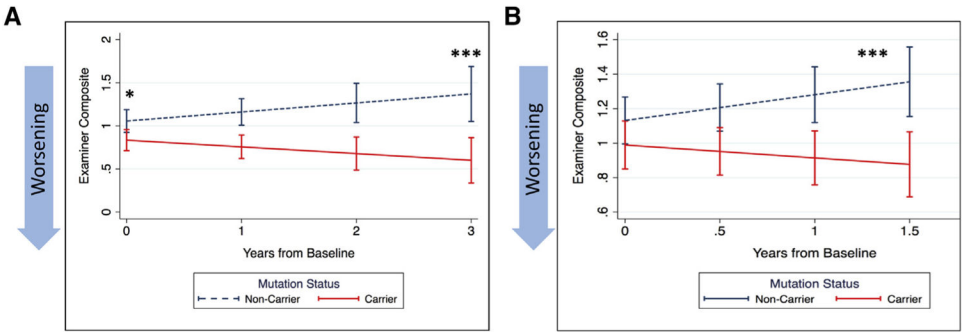

Fig. 1.

Baseline differences and longitudinal executive function declines are detectable in presymptomatic and mildly/questionably symptomatic familial FTLD using the NIH-EXAMINER. NOTE. These figures display fitted regression lines of each group's mean trajectory estimated by the fixed, carrier status by time interaction term in the linear mixed-effects model. Error bars represent the 95% confidence intervals. * indicates baseline differences ($P = .016$). *** indicates longitudinal differences ($P<.009$). (A) This sample includes 93 mutation carriers with a global CDR® plus NACC FTLD = 0 or 0.5 at their baseline visit. Mutation carriers are compared with 78 noncarrier controls using linear mixed-effects models. This figure displays the fitted results of the mutation status by time interaction from a linear mixed-effects model, showing mutation carriers had a significantly more negative slope on the Executive Composite than noncarriers and significantly poorer performance at baseline. EXAMINER Executive Composite scores are displayed on the y-axis in z-score units. The arrow indicates that lower scores are associated with poorer performance. (B) This sample includes 66 mutation carriers with a global CDR® plus NACC FTLD = 0 at their baseline visit, compared with 64 noncarrier controls. This figure displays the fitted results of the mutation status by time interaction from a linear mixed-effects model. Mutation carriers showed a significantly more negative slope on the Executive Composite than noncarriers. Baseline performance did not differ significantly. The y-axis is in z-score units; the arrow signifies that lower scores on this composite indicate poorer performance. Abbreviations: FTLD, frontotemporal lobar degeneration; CDR® plus NACC FTLD, Clinical Dementia Rating scale plus National Alzheimer Coordinating Center FTLD Module; NIH-EXAMINER, NIH–Executive Abilities: Measures and Instruments for Neurobehavioral Evaluation and Research.

Table 1

Participant demographics

Measure	Mutation carriers	Noncarriers
N	93	78
n with longitudinal data	66	49
Total observations	182	137
Visits per person (range)	1.9 (1–3)	1.6 (1–3)
Age (SD)	46.0 (13.9)	48.8 (13.4)
Education (SD)	15.8 (2.3)	15.3 (2.7)
Male [n (%)]	49 (52.7)	37 (47.4)
Baseline cognition		
MoCA	26.71 (2.74)	26.95 (2.45)
CDR® plus NACC FTLD = 0 [n(%)]	64 (68.8)	64 (83.1)
CDR® plus NACC FTLD = 0.5 [n(%)]	29 (31.18)	13 (16.9)

NOTE. Parenthetic values are standard deviations (SDs) unless otherwise noted.

Abbreviations: FTLD, frontotemporal lobar degeneration; CDR® plus NACC FTLD, Clinical Dementia Rating scale plus National Alzheimer Coordinating Center FTLD Module; MoCA, Montreal Cognitive Assessment.

Table 2

Baseline and longitudinal differences in neuropsychological performances between carriers and noncarriers

	Baseline differences		Differences in slope	
	***b* (95% CI)**	***p***	***b* (95% CI)**	***p***
NIH-EXAMINER				
Executive Composite	0.22 (−0.4, −0.04)	.016	−0.18 (−0.32, −0.05)	.008
Factor scores				
Working Memory	−0.12 (−0.33, 0.09)	.252	0.03 (−0.15, 0.21)	.747
Cognitive Control	−0.3 (20.49, −0.12)	.001	−0.11 (−0.23, 0.02)	.086
Fluency factor	−.07 (−0.27, 0.14)	.51	20.25 (−0.41, −0.08)	.003
CDR® plus NACC FTLD-SB	0.21 (0.04, 0.37)	.014	0.43 (0.07, 0.79)	.018
UDSNB measures				
Trails A	2.91 (0.67, 5.14)	.011	2.29 (0.01, 4.56)	.049
Trails B	8.24 (20.08, 16.56)	.052	9.79 (−0.31, 19.89)	.057
Verbal Fluency	−0.91 (−5.44, 3.62)	.694	23.37 (−6.15, −0.58)	.018
CVLT-SF 10′ Delay	−0.39 (−0.98, 0.2)	.196	20.28 (−0.75, 0.19)	.238
Benson Delayed Recall	−0.55 (−1.31, 0.2)	.151	20.32 (−0.98, 0.34)	.338

NOTE. *b* is the unstandardized parameter estimate, with noncarriers = 0 and carriers = 1.

Abbreviations: CVLT-SF, California Verbal Learning Test, Short Form; FTLD, frontotemporal lobar degeneration; CDR® plus NACC FTLD-SB, Clinical Dementia Rating scale plus National Alzheimer Coordinating Center FTLD Module Sum of Boxes; NIH-EXAMINER, NIH–Executive Abilities: Measures and Instruments for Neurobehavioral Evaluation and Research; UDSNB, neuropsychological battery from the Uniform Data Set.

Table 3

Estimated sample sizes to detect therapeutic effects in f-FTLD for trials with two different enrollment criteria based on baseline CDR® plus NACC FTLD

	Baseline CDR® plus NACC FTLD 0 or 0.5		Baseline CDR® plus NACC FTLD = 0.5	
Cognitive measure	***n***	**Sample size (95% confidence interval)**	***n***	**Sample size (95% confidence interval)**
NIH-EXAMINER				
Executive Composite	66	2336 (565, >100,000)	19	539 (142, 85,401)
Fluency factor	63	898 (330, 11,085)	17	245 (89, 3324)
Cognitive Control	60	15,271 (1411, >100,000)	18	>100,000 (>100,000, NE)
Working Memory	55	1507 (379, >100,000)	17	4208 (223, >100,000)
CDR® plus NACC FTLD-SB	61	1018 (559, 2586)	18	514 (290, 1374)
UDS measures				
TMT Part A	64	966 (343, 16,290)	17	1162 (251, >100,000)
TMT Part B	63	2135 (677, >100,000)	16	1118 (153, >100,000)
UDSNB Verbal Fluency	63	1721 (470, >100,000)	17	362 (126, 11,563)

NOTE. This table presents sample size estimates for each arm of a clinical trial to detect a moderate (40%) reduction in slope, assuming power = 0.8, alpha = .05, and 20% attrition rate. 95% Confidence intervals were calculated using a 10,000-fold bootstrap procedure. NE denotes not estimated by the bootstrapping procedure.

Abbreviations: FTLD, frontotemporal lobar degeneration; CDR® plus NACC FTLD, Clinical Dementia Rating scale plus National Alzheimer Coordinating Center FTLD Module; CDR® plus NACC FTLD-SB, Clinical Dementia Rating scale plus National Alzheimer Coordinating Center FTLD Module Sum of Boxes; NIH-EXAMINER, NIH–Executive Abilities: Measures and Instruments for Neurobehavioral Evaluation and Research; TMT, Trail Making Test; UDSNB, neuropsychological battery from the Uniform Data Set.

Table 4

Associations of the NIH-EXAMINER Executive Composite with lobar volumes

	b coefficient	*P* value	95% CI
Mutation carriers			
Frontal			
Within-person *	2386.65	.001	996.91, 3776.39
Between-person *	2616.41	.03	260.51, 4972.32
Parietal			
Within-person *	1118.90	<.001	499.43, 1738.39
Between-person *	1325.34	.011	306.57, 2344.11
Temporal			
Within-person	581.14	.056	−15.07, 1177.36
Between-person *	1234.14	.032	106.83, 2361.44
Occipital			
Within-person	232.96	.08	−28.27, 494.20
Between-person *	597.59	.011	134.17, 1061.02
Noncarriers			
Frontal			
Within-person	−691.05	.463	−2536.44, 1154.35
Between-person *	6181.13	.002	2309.18, 10,053.07
Parietal			
Within-person	−313.87	.588	−1450.82, 823.09
Between-person *	2365.52	.004	775.49, 3955.55
Temporal			
Within-person	−933.83	.082	−1985.83, 118.17
Between-person *	2596.59	.002	951.58, 4241.59
Occipital			
Within-person	290.31	.715	−574.63, 394.00
Between-person *	1256.67	.002	470.06, 2043.28

NOTE. Within-person results (unstandardized b) indicate the change in brain volume (mm^3) associated with a 1 z-score loss of NIH-EXAMINER Composite performance over time. Between-person results (unstandardized b) indicate overall relationships, across visits, among lobar volumes (mm^3) and NIH-EXAMINER Composite performance.

Abbreviations: NIH-EXAMINER, NIH–Executive Abilities: Measures and Instruments for Neurobehavioral Evaluation and Research.

* $P < .05$.