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Sensitivity of the Social Behavior Observer Checklist to Early Symptoms of Patients With Frontotemporal Dementia

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Abstract

Background and Objectives

Changes in social behavior are common symptoms of frontotemporal lobar degeneration (FTLD) and Alzheimer disease syndromes. For early identification of individual patients and differential diagnosis, sensitive clinical measures are required that are able to assess patterns of behaviors and detect syndromic differences in both asymptomatic and symptomatic stages. We investigated whether the examiner-based Social Behavior Observer Checklist (SBOCL) is sensitive to early behavior changes and reflects disease severity within and between neurodegenerative syndromes.

Methods

Asymptomatic individuals and patients with neurodegenerative disease were selected from the multisite ALLFTD cohort study. In a sample of participants with at least 1 time point of SBOCL data, we investigated whether the Disorganized, Reactive, and Insensitive subscales of the SBOCL change as a function of disease stage within and between these syndromes. In a longitudinal subsample with both SBOCL and neuroimaging data, we examined whether change over time on each subscale corresponds to progressive gray matter atrophy.

Results

A total of 1,082 FTLD pathogenic variant carriers and noncarriers were enrolled (282 asymptomatic, 341 behavioral variant frontotemporal dementia, 114 semantic and 95 nonfluent variant primary progressive aphasia, 137 progressive supranuclear palsy, and 113 Alzheimer disease syndrome). The Disorganized score increased between asymptomatic to very mild ($p = 0.016$, estimate $= -1.10$, 95% CI $= -1.99$ to -0.22), very mild to mild ($p = 0.013$, estimate $= -1.17$, 95% CI $= -2.08$ to -0.26), and mild to moderate/severe ($p < 0.001$, estimate $= -2.00$, 95% CI $= -2.55$ to -1.45) disease stages in behavioral variant frontotemporal dementia regardless of pathogenic variant status. Asymptomatic *GRN* pathogenic gene variant carriers showed more reactive behaviors (preoccupation with time: $p = 0.001$, estimate $= 1.11$, 95% CI $= 1.06$ to 1.16; self-consciousness: $p = 0.003$, estimate $= 1.77$, 95% CI $= 1.52$ to 2.01) than asymptomatic noncarriers (estimate $= 1.01$, 95% CI $= 0.98$ to 1.03; estimate $= 1.31$, 95% CI $= 1.20$ to 1.41). The Insensitive score increased to a clinically abnormal level in advanced stages of behavioral variant frontotemporal dementia ($p = 0.003$, estimate $= -0.73$, 95% CI $= -1.18$ to -0.29). Higher scores on each subscale corresponded with higher caregiver burden ($p < 0.001$). Greater change over time corresponded to greater fronto-subcortical atrophy in the semantic-appraisal and fronto-parietal intrinsically connected networks.

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

ACC = anterior cingulate cortex; AD = Alzheimer disease; bvFTD = behavioral variant frontotemporal dementia; C9orf72 = chromosome 9 open reading frame 72; GRN = progranulin; FPN = fronto-parietal network; FTLD = frontotemporal lobar degeneration; IQR = interquartile range; LME = linear mixed effects; MAPT = microtubule-associated protein tau; NACC = National Alzheimer's Coordinating Center; nfvPPA = nonfluent variant primary progressive aphasia; OFC = orbitofrontal cortex; PSP = progressive supranuclear palsy; ROI = region of interest; SAN = semantic-appraisal network; SBOCL = Social Behavior Observer Checklist; SN = salience network; svPPA = semantic variant primary progressive aphasia.

Discussion

The SBOCL is sensitive to early symptoms and reflects disease severity, with some evidence for progression across asymptomatic and symptomatic stages of FTLD syndromes; thus, it may hold promise for early measurement and monitoring of behavioral symptoms in clinical practice and treatment trials.

Classification of Evidence

This study provides Class II evidence that the SBOCL is sensitive to early behavioral changes in FTLD pathogenic variants and early symptomatic individuals in a highly educated patient cohort.

Alterations in behavior frequently occur in frontotemporal lobar degeneration (FTLD) and Alzheimer disease (AD) syndrome[1-3] and are an important determinant of caregiver burden.[4,5] However, the pattern and rate of progression of behavioral symptoms, as well as the underlying neuroanatomical changes, differ among syndromes. Furthermore, there is evidence showing that the 3 major genes that cause FTLD (chromosome 9 open reading frame 72 [C9orf72], progranulin [GRN], and microtubule-associated protein tau [MAPT]) are associated with distinct patterns of behavior and neuronal changes in insulo-cingular, temporal, and parietal networks.[6-8]

The optimal time point to diagnose patients and start a therapeutic drug is in the earliest disease stage, ideally in the presymptomatic phase. Thus, diagnostic evaluations must include clinical measures that are sensitive to detect subtle behavior changes in asymptomatic FTLD pathogenic variant carriers and early symptomatic individuals. In addition, to monitor symptom progression in clinical practice and treatment trials, measures are needed that can accurately represent behavior changes over time in different clinical syndromes. This is an exciting time because large cross-sectional and longitudinal data sets of both behavior and neuroimaging data are starting to become available from cross-site studies (ALLFTD and GENFI) that can more comprehensively address these questions.

In the past decade, researchers have developed and validated face-to-face tests, self-report measures, and informant questionnaires to assess individual behavioral symptoms in patients with FTLD and AD such as loss of empathy, coldness, and apathy.[9-12] However, until now, few examiner-based observational measures have been used to assess constellations of behavioral symptoms that spontaneously occur during clinical interactions with these patients (e.g., a cognitive evaluation)[13,14] and that reflect distinct patterns of behavior

change in different neurodegenerative syndromes. Because they are completed by the clinician, such observation-based measures might be particularly suited to practical use with this population because they do not rely on the cognitive capacity of the patient or the availability of a reliable informant.

A recent cross-sectional validation study[15] has shown that patients with the FTLD and AD syndromes have partially overlapping but distinct profiles for a broad range of behaviors measured by the observation-based Social Behavior Observer Checklist (SBOCL). This work has also found that these behaviors can be grouped into 3 symptom categories (Disorganized, Reactive, and Insensitive) that each correspond to atrophy in regions of the salience (SN),[16] semantic-appraisal (SAN),[17] and fronto-parietal (FPN)[18] networks underlying behavior changes in FTLD.[19,20]

The primary research question of this follow-up study was to investigate whether the SBOCL subscales reflect disease severity in neurodegenerative disease syndromes, with a particular focus on very early changes occurring between the asymptomatic and very mildly symptomatic stages of behavioral variant frontotemporal dementia (bvFTD).

Methods

Participants

We enrolled 1,082 participants from 3 multisite collaborative studies between 2009 and 2019. These included 341 patients diagnosed with bvFTD[21] (107 carried a pathogenic variant in 1 of the 3 FTLD-associated genes C9orf72, GRN, and MAPT [pathogenic variant+]), 114 with semantic variant primary progressive aphasia (svPPA)[22] (2 pathogenic variant+), 95 patients with nonfluent variant primary progressive aphasia

(nfvPPA)[22] (6 pathogenic variant+), 137 patients with progressive supranuclear palsy (PSP)[23] (1 pathogenic variant+), a non-FTLD dementia control group of 113 patients with AD [24] (2 pathogenic variant+), and 282 asymptomatic individuals (115 pathogenic variant+). Participants were diagnosed after comprehensive neurologic, neuropsychologic, neuroimaging, and genetic assessments that did not include the SBOCL. All participants were required to have at least 1 time point of SBOCL data available. A subset of 73 patients (16 asymptomatic and 149 symptomatic observations) had at least 2 time points of both SBOCL data and MRI scans of sufficient quality performed on the same scanner. The median time interval was 0 days between SBOCL data collection and MRI scanning (interquartile range [IQR] = 1 day, max = 126 days) and 186 days between 2 consecutive MRI scans (IQR = 383 days, max = 821 days). Demographic and clinical characteristics are presented in Table 1.

The studies were conducted in accordance with IRB approval from each study institution, and all participants and their informants gave their consent to participate and to share data.

Behavioral and Functional Measures

The SBOCL measures social behavior as observed by an examiner. The raters were clinical research staff or psychometrists who were blind to the final diagnostic designation at the time the SBOCL was completed. The SBOCL consists of 14 descriptors of various behaviors that the patient may enact during a 30–60-minute cognitive evaluation. The examiner provides a subjective rating (not at all, a little bit, moderately, or severely) of each descriptor based on their interaction with the participant. Each behavior has a variable number of checklist items representing a frequency count of the behavior (never, once, 2–3 times, and 4+ times). In our recent validation study,[15] we showed that the 14 descriptors and checklist items have high inter-rater reliability and can be grouped into 3 symptom clusters: (1) disorganized (failed to adapt to structure, stimulus-bound, perseverative, decreased initiation, fluctuations, and diminished social engagement), (2) reactive (overly self-conscious, anxious, overly dependent, labile emotional reactivity, and preoccupied with time), and (3) insensitive (too little self-conscious, insensitive to other's embarrassment, and overly disclosing/inappropriately familiar). Following the methods of our validation study,[15] for each participant, we created 3 cluster severity scores which were used in our statistical analyses. First, each behavior's severity score was derived by multiplying each descriptor score ("degree") with the maximum score across the checklist items for that behavior ("frequency"). Second, each cluster severity score was calculated using the mean severity score of all behaviors that belong to the cluster (scores ranged from 1 to 16).

The CDR Dementia Staging Instrument plus Behavior and Language domains from the National Alzheimer's Coordinating Center (NACC) FTLD Module (CDR plus NACC FTLD) were included as a proxy of disease severity. This informant measure is an extension of the standard CDR[25] and includes 2 additional domains that are predominantly affected in FTLD: behavior and language.[26] Each patient's CDR plus NACC FTLD global score was calculated according to the scoring rules described by Miyagawa et al.,[27] with global score ranging from 0 (normal), 0.5 (very mildly impaired), 1 (mildly impaired), 2 (moderately impaired) to 3 (severely impaired).

The Zarit Burden Interview[28] is a 22-item informant measure yielding scores ranging from 0 to 88 that assesses caregivers' self-reported burden in different areas, including behavioral symptoms and functional status of the patient, interpersonal relationships, finances, physical health, and social life.

Behavioral Data Analysis

Subscale Scores in Asymptomatic Pathogenic Variant Carriers

To investigate whether the SBOCL scores are sensitive to detect any subtle behavior differences between individuals in any of the asymptomatic pathogenic variant carrier groups (C9orf72, GRN, and MAPT) and asymptomatic noncarriers, we performed linear modeling in SAS version 9.4 (Proc GLM) for each score, covarying for pathogenic variant status (C9orf72, GRN, MAPT, and noncarriers), age at first evaluation, and sex. We also performed secondary exploratory modeling using each descriptor item as an outcome.

Subscale Scores by CDR Plus NACC FTLD Stage

To examine whether the scores changed as a function of disease stage from asymptomatic to very mild, mild, moderate, and severe disease and whether the rate of change differed between asymptomatic and symptomatic carriers and noncarriers, we performed linear mixed effects (LME) modeling in SAS (Proc mixed) with random intercepts and slopes, which accounts for individual differences in baseline scores, and allowed us to include individuals who had only 1 time point available. We included only patients with bvFTD (n = 341, observations = 387) and asymptomatic participants (n = 282, observations = 282) because only 5% of all pathogenic variant carriers had a diagnosis of svPPA, nfvPPA, PSP, or AD (Table 1). Because of the small numbers of patients with severe disease stage (CDR plus NACC FTLD global score = 3), patients who were in moderate (CDR plus NACC FTLD global score = 2) and severe disease stages were assigned to the same group. CDR plus NACC FTLD global score (asymptomatic, very mild, mild, and moderate/severe), group (carriers vs noncarriers), and the interaction between CDR plus NACC FTLD global score and group were included in the model, controlling for age at first evaluation and sex.

To investigate whether the scores significantly increased as a function of disease stage within each syndrome, we performed LME model analysis across all diagnostic groups (asymptomatic, bvFTD, svPPA, nfvPPA, PSP, and AD; n = 799, 883 observations), with diagnostic group, CDR plus NACC FTLD global score, the interaction diagnostic group by CDR plus NACC FTLD global score, age at symptom onset, and sex included in the model.

Table 1 Demographic and Clinical Characteristics of Diagnostic Groups at Baseline

	Asymptomatic	bvFTD	svPPA	nfvPPA	PSP	AD	p Value
n	282	341	114	95	137	113	—
Pathogenic variant status, +/−	115/167	107/234	2/112	6/89	1/136	2/111	—
C9orf72	46	54	1	0	0	0	—
GRN	29	21	1	6	0	2	—
MAPT	40	32	0	0	1	0	—
Age, y, mean ± SD	45.6 (13.7)	62.0 (9.5)[a]	65.4 (6.8)[a]	68.0 (8.3)[a]	69.3 (6.9)[a]	65.2 (9.2)[a]	<0.001
Sex, M/F	112/170	196/145	54/60	34/61	73/64	59/54	<0.001
Education, mean ± SD	15.7 (2.5)	15.8 (2.8)	17.5 (8.5)[a]	15.8 (3.1)	16.2 (2.9)	16.4 (2.5)	<0.001
CDR plus NACC FTLD, mean ± SD	0	1.6 (0.7)[a]	1.2 (0.6)[a]	1.0 (0.6)[a]	1.4 (0.7)[a]	1.2 (0.6)[a]	<0.001

Abbreviations: AD = Alzheimer disease; bvFTD = behavioral variant frontotemporal dementia; CDR plus NACC FTLD = CDR Dementia Staging Instrument plus Behavior and Language domains from the NACC FTLD Module; *C9orf72* = chromosome 9 open reading frame 72; *GRN* = progranulin; *MAPT* = microtubule-associated protein tau; nfvPPA = nonfluent variant primary progressive aphasia; PSP = progressive supranuclear palsy; svPPA = semantic variant primary progressive aphasia.
Group differences in age at first evaluation, sex, education, and CDR plus NACC FTLD global rating were analyzed using Tukey post hoc tests.
[a] Group differs from asymptomatic noncarriers at $p < 0.05$.

Longitudinal Pattern of Change in Subscale Scores

We had 73 patients (16 asymptomatic and 149 symptomatic observations) who had at least 2 time points of SBOCL data and 2 MRI scans available. However, the sample sizes within each syndrome were small and ranged between 8 and 27 patients, so we performed our longitudinal analyses grouping across all syndromes. To examine whether scores would significantly increase over time with disease progression, we performed LME models for each subscale with disease duration since symptom onset, age at symptom onset, and sex included as predictors (which we will refer to as the "Main effects model"). To determine whether the predictor diagnostic group (5 levels) disproportionately affected the main effects results, we performed a second analysis for each subscale in which k-1 = 4 diagnostic groups were binarized and added as additional confounds to the main effects analysis (termed "Diagnostic confound model").[29]

Relationship to Caregiver Burden

To examine whether the SBOCL measures behaviors that are burdensome for caregivers, we took the first score of each subscale and each participant who had a valid Zarit score within 90 days of SBOCL collection (n = 193). A linear model was performed to assess whether the Zarit score was a predictor of each score, controlling for age at first evaluation and sex.

Neuroimaging

Participants underwent structural imaging using 3T scanners from 1 of 3 vendors: Siemens, Philips Medical System, or General Electric Medical Systems. A standard imaging acquisition protocol was used at all centers, managed, and reviewed for quality by a core group at the Mayo Clinic, Rochester. A T1-weighted 3D magnetization–prepared rapid gradient echo sequence was used to obtain the T1-weighted images, with parameters as follows: 240 × 256 × 256 matrix, approximately 170 slices, voxel size = 1.05 × 1.05 × 1.25 mm³, flip angle, echo time, and repetition time varied by vendor. Preprocessing was performed in Statistical Parametric Mapping 12 (fil.ion.ucl.ac.uk/spm/). In brief, the images were visually inspected for artifacts, bias-corrected, and tissue classified (gray matter, white matter, and CSF segments) using unified segmentation[30] and modulated by multiplying the time points' Jacobian determinants with the intrasubject averaged tissues.[31] A group template was generated from the averaged within-subject tissue segments using a large deformation diffeomorphic metric mapping framework.[32] The modulated intrasubject gray and white matter images were normalized to the group template and smoothed with a 10-mm full-width at half maximum Gaussian kernel.

To test our hypothesis that the rate of SBOCL worsening would correspond to loss of predominantly frontotemporal gray matter volume in patients,[15] we defined bilateral regions of interest (ROIs) in the SN, SAN, and FPN using the Desikan brain atlas.[33] The SN ROIs included the bilateral anterior insula, dorsal anterior cingulate cortex (ACC), thalamus, and amygdala. The SAN ROIs were defined in the bilateral temporal pole, orbitofrontal cortex (OFC), subgenual ACC, caudate, and nucleus accumbens. The FPN ROIs included the bilateral middle frontal gyrus, supramarginal gyrus, and inferior parietal cortex. For each subscale and each ROI, we performed LME models in SAS and entered ROI, disease duration, age at symptom onset, sex, and total intracranial volume in each model (main effects model). We also added the diagnostic group to the analysis to assess whether our brain-behavior relationships were generalizable (diagnostic confound model). The statistical threshold for all brain-behavior analyses was set at $p < 0.01$. We also performed

Figure 1 Reactive Subscale Scores in Asymptomatic Individuals
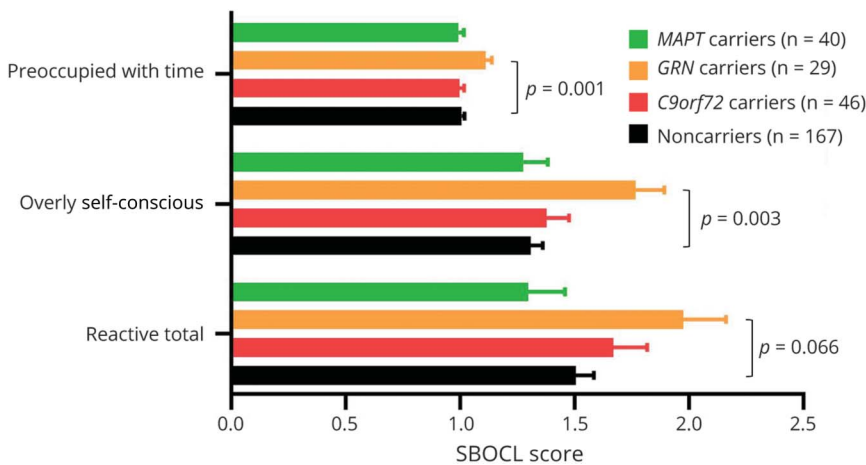
Asymptomatic GRN pathogenic variants are more preoccupied with time and more self-conscious than asymptomatic noncarriers. Linear models showed that asymptomatic *GRN* pathogenic variant carriers had significantly higher score than asymptomatic noncarriers on 2 checklist items that belong to the Reactive subscale: "Preoccupied with time" ($p = 0.001$; *GRN*: 1.11 ± 0.03, 95% CI = 1.06–1.16; noncarriers: 1.01 ± 0.01, 95% CI = 0.98–1.03) and overly self-conscious ($p = 0.003$; *GRN*: 1.77 ± 0.13, 95% CI = 1.52–2.01; noncarriers: 1.31 ± 0.05, 95% CI = 1.20–1.41). No significant differences were found between asymptomatic *C9orf72* carriers and asymptomatic noncarriers or between asymptomatic *MAPT* carriers and asymptomatic noncarriers. *C9orf72* = chromosome 9 open reading frame 72; *GRN* = progranulin; *MAPT* = microtubule-associated protein tau; SBOCL = Social Behavior Observer Checklist.

an error check to identify any artifact introduced by using scanners at different institutions by rerunning all analyses while including institution as a confound.

Data Availability

Anonymized data can be requested at allftd.org/data and will be shared on request from any qualified investigator for the purposes of replicating procedures and results.

Results

Demographic and Clinical Characteristics

The diagnostic groups significantly differed regarding mean age at first evaluation, sex, and education (Table 1). The maximum estimated difference in education was 1.5 school years (mean scores ranged between 15.7 and 17.5 years), thus unlikely to reflect clinically meaningful differences in this highly educated sample; therefore, only age at first evaluation and sex were included as variables to be covaried for in all statistical analyses. The diagnostic groups in the fully longitudinal subsample significantly differed regarding age at symptom onset, but disease duration, sex, and education did not reach statistical significance.

SBOCL Scores in Asymptomatic Pathogenic Variant Carriers and Asymptomatic Noncarriers

Pathogenic variant status (*C9orf72*, *GRN*, *MAPT*, and noncarriers) was a significant predictor ($p = 0.041$) of the Reactive score. Post hoc Dunnett-Hsu tests revealed $p = 0.66$ for the group comparison between asymptomatic *GRN* pathogenic variant carriers (mean ± SE: 1.97 ± 0.19, 95% CI = 1.60–2.34) and asymptomatic noncarriers (1.51 ± 0.08, 95% CI = 1.35–1.66) (Figure 1). Next, we performed a linear model for each checklist item in the Reactive subscale (overly self-conscious, anxious, overly dependent, labile emotional reactivity, and preoccupied with time). Asymptomatic *GRN* pathogenic variant carriers had

higher score on the "Preoccupied with time" ($p = 0.001$, 1.11 ± 0.03, 95% CI = 1.06–1.16) and "Overly self-conscious" ($p = 0.003$, 1.77 ± 0.13, 95% CI = 1.52–2.01) items than asymptomatic noncarriers (1.01 ± 0.01, 95% CI = 0.98–1.03; 1.31 ± 0.05, 95% CI = 1.20–1.41). No significant results were revealed for asymptomatic *C9orf72* and *MAPT* pathogenic variant carriers or for any asymptomatic carrier group with the Disorganized and Insensitive subscales.

SBOCL Scores by Disease Severity in Asymptomatic and Symptomatic Pathogenic Variant Carriers and Asymptomatic Noncarriers

Subscale Scores by CDR Plus NACC FTLD Stage

The Disorganized score was a significant predictor of CDR plus NACC FTLD ($p < 0.001$) in the main effects model (subscale score = CDR plus NACC FTLD + covariates; Figure 2A), showing that the score increased at each stage from asymptomatic to very mild ($p = 0.016$, estimate = −1.10, 95% CI = −1.99 to −0.22), very mild to mild ($p = 0.013$, estimate = −1.17, 95% CI = −2.08 to −0.26), and mild to moderate/severe ($p < 0.001$, estimate = −2.00, 95% CI = −2.55 to −1.45) disease. The main effect CDR plus NACC FTLD remained significant ($p < 0.001$) in the Interaction model (subscale score = CDR plus NACC FTLD + pathogenic variant status + interaction term + covariates). We also found an interaction for CDR plus NACC FTLD by pathogenic variant status ($p = 0.037$), demonstrating that the score increased from asymptomatic to very mild stage in noncarriers ($p = 0.024$, estimate = −1.78, 95% CI = −3.28 to −0.28) and from mild to moderate/severe stage in both pathogenic variant carriers ($p < 0.001$, estimate = −2.61, 95% CI = −3.64 to −1.58) and noncarriers ($p < 0.001$, estimate = −1.76, 95% CI = −2.49 to −1.03). The Reactive subscale was a significant predictor of CDR plus NACC FTLD in the main effects model ($p < 0.001$), showing that the score increased only from asymptomatic to very mild disease stage ($p = 0.013$, estimate = −0.72, 95% CI = −1.28 to −0.16) (Figure 2B). The interaction between CDR plus

Figure 2 BvFTD Patients With a Reference Group of Asymptomatic Individuals
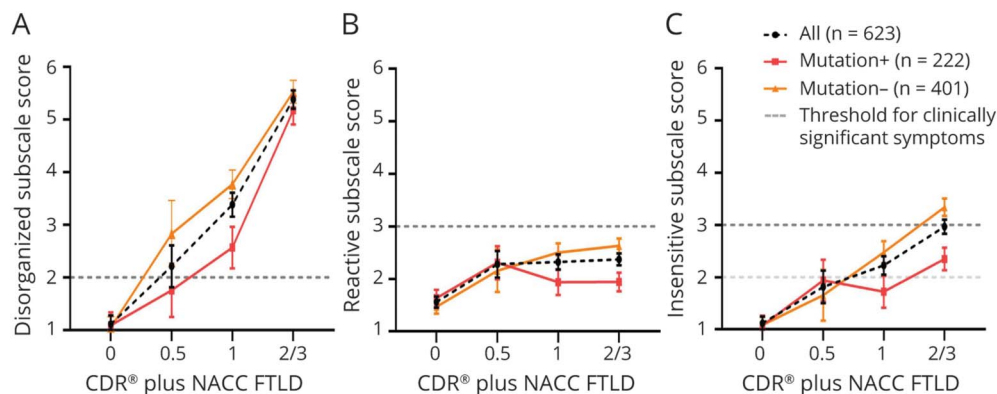
Of the 3 SBOCL subscales, the disorganized subscale best reflects disease severity in a sample of asymptomatic individuals and patients with bvFTD, regardless of whether they are pathogenic variant carriers or noncarriers. (A) The main effects model showed that CDR plus NACC FTLD was a significant predictor of the Disorganized score, showing that the score increased at each stage of disease severity from asymptomatic to very mild ($p = 0.016$, estimate = −1.10, 95% CI = −1.99 to −0.22), from very mild to mild ($p = 0.013$, estimate = −1.17, 95% CI = −2.08 to −0.26), and from mild to moderate/severe ($p < 0.001$, estimate = −2.00, 95% CI = −2.55 to −1.45) disease stage across pathogenic variant carriers and noncarriers. The interaction model incorporating pathogenic variant status showed that the score increased from asymptomatic to very mildly symptomatic stage in noncarriers ($p = 0.024$, estimate = −1.78, 95% CI = −3.28 to −0.28). (B) The Reactive score was a predictor of CDR plus NACC FTLD in the main effects analysis, showing that the score increased only in the very earliest disease stage, during the conversion from asymptomatic to very early symptomatic stage ($p = 0.013$, estimate = −0.72, 95% CI = −1.28 to −0.16). The interaction between CDR plus NACC FTLD and pathogenic variant status was not significant. (C) The Insensitive score was a predictor of CDR plus NACC FTLD in both the main effects and interaction models, showing that the score increased from asymptomatic to very mild disease ($p = 0.049$, estimate = −0.70, 95% CI = −1.39 to 0.00) and from mild to moderate/severe ($p = 0.001$, estimate = −0.74, 95% CI = −1.17 to −0.31) disease across pathogenic variant carriers and noncarriers. The interaction analysis showed that the significant increase from mild to moderate/severe disease stage occurred primarily in the noncarrier group. The gray line represents the threshold for clinically significant symptoms found in our cross-sectional validation study.[15] The lower line in part C shows an updated, suggested threshold derived on the basis of these findings across different disease stages within syndromes, which differs from the threshold initially suggested in the earlier, cross-sectional validation paper. bvFTD = behavioral variant frontotemporal dementia; SBOCL = Social Behavior Observer Checklist.

NACC FTLD and pathogenic variant status did not reach statistical significance. Similar results were revealed for the Insensitive subscale, including a main effect of CDR plus NACC FTLD in the main effects model ($p < 0.001$) but no interaction of CDR plus NACC FTLD by pathogenic variant status (Figure 2C). The score increased from asymptomatic to very mild disease stage ($p = 0.049$, estimate = −0.70, 95% CI = −1.39 to 0.00) and from mild to moderate/severe disease stage ($p = 0.001$, estimate = −0.74, 95% CI = −1.17 to −0.31). The Interaction model showed that only the increase from mild to moderate/severe disease stages in noncarriers was statistically significant ($p = 0.007$, estimate = −0.87, 95% CI = −1.43 to −0.30).

SBOCL Scores by Disease Severity Within Neurodegenerative Syndromes

Subscale Scores by CDR Plus NACC FTLD Stage
For the Disorganized subscale, we found a main effect of CDR plus NACC FTLD ($p < 0.001$) and a significant interaction CDR plus NACC FTLD by the diagnostic group ($p = 0.021$). The main effect of the diagnostic group did not reach statistical significance (Figure 3A). In patients with bvFTD, the Disorganized score increased from very mild to mild stages ($p = 0.019$, estimate = 1.15, 95% CI = 0.22–2.07) and from mild to moderate/severe stages ($p < 0.001$, estimate = −2.04, 95% CI = −2.59 to −1.47). In patients with nfvPPA ($p = 0.002$, estimate = −2.46, 95% CI = −3.85 to −1.06) and AD ($p = 0.003$, estimate = −1.83, 95% CI = −2.90 to −0.76), the score increased only from mild to moderate/severe stages. No

significant effects were found in patients with svPPA and PSP. For the Reactive subscale, only the main effect of the diagnostic group reached statistical significance ($p < 0.001$), primarily because patients with AD and svPPA had higher reactive scores than other diagnostic groups at multiple disease stages (Figure 3B). For the Insensitive subscale, our results revealed a main effect of CDR plus NACC FTLD ($p = 0.007$) and diagnostic group ($p < 0.001$). Although the interaction was not significant, in bvFTD patients, the score increased from early to moderate/severe disease stages ($p = 0.002$, estimate = −0.74, 95% CI = −1.13 to −0.35) (Figure 3C).

Relationship Between SBOCL Scores and Caregiver Burden
As expected, we found that higher scores on the (1) Disorganized ($p < 0.001$, estimate = 0.05, 95% CI = 0.04–0.06), (2) Reactive ($p < 0.001$, estimate = 0.02, 95% CI = 0.01–0.03), and (3) Insensitive ($p < 0.001$, estimate = 0.02, 95% CI = 0.01–0.03) subscales predict higher Zarit burden score.

Longitudinal Progression of Subscale Scores Across Syndromes

Subscale Scores Over Time
In the longitudinal sample of symptomatic pathogenic variant carriers and symptomatic noncarriers (n = 73), disease duration was a predictor of the Disorganized score ($p = 0.042$, estimate = 0.06, 95% CI = 0.00–0.12), controlling for age at symptom onset and sex. This main effect remained significant ($p = 0.009$, estimate = 0.09, 95% CI = 0.02–0.15) after

Figure 3 Subscale Scores Across Disease Stages Within Syndromes
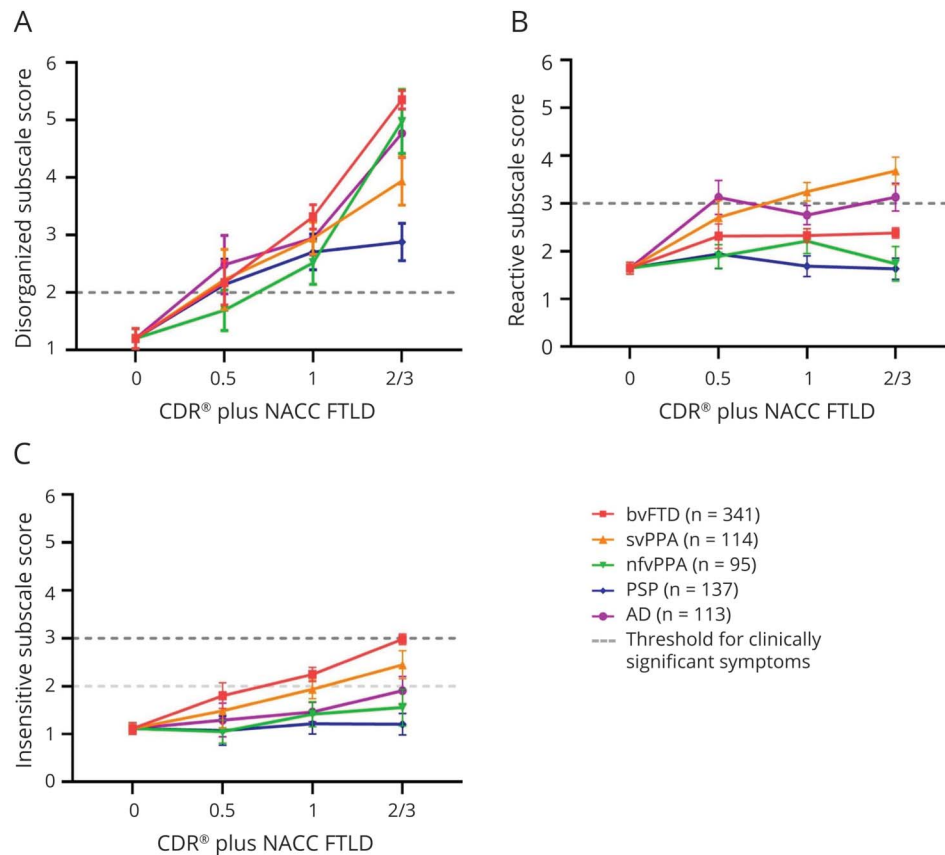
Disorganized and insensitive subscales are sensitive to disease progression in patients with bvFTD. (A) CDR plus NACC FTLD was a significant predictor of the Disorganized score, but the interaction of CDR plus NACC FTLD by diagnostic group was not significant. The results show that the subscale can detect early behavior changes occurring between very mild and mild disease stage ($p = 0.019$, estimate = 1.15, 95% CI = 0.22–2.07) in patients with bvFTD. In addition, the Disorganized score increased from mild to moderate/severe disease stage in patients with bvFTD ($p < 0.001$, estimate = −2.04, 95% CI = −2.59 to −1.47), nfvPPA ($p = 0.002$, estimate = −2.46, 95% CI = −3.85 to −1.06), and AD ($p = 0.003$, estimate = −1.83, 95% CI = −2.90 to −0.76). (B) The diagnostic group was a significant predictor ($p < 0.001$) of the Reactive score, showing that patients with AD and svPPA had significantly higher scores than other diagnostic groups at multiple disease stages. (C) Both CDR plus NACC FTLD ($p = 0.007$) and diagnostic group ($p < 0.001$) was a significant predictor of the Insensitive score. The only significant within-group effect of diagnosis was the increase from early to moderate/severe disease stage in patients with bvFTD ($p = 0.002$, estimate = −0.74, 95% CI = −1.13 to −0.35). The upper gray line represents the threshold for clinically significant symptoms found in our cross-sectional validation study.[15] The lower line in part C shows an updated, suggested threshold derived on the basis of these findings across different disease stages within syndromes, which differs from the threshold initially suggested in the earlier, cross-sectional validation paper. AD = Alzheimer disease; bvFTD = behavioral variant frontotemporal dementia; nfvPPA = nonfluent variant primary progressive aphasia; PSP = progressive supranuclear palsy; svPPA = semantic variant primary progressive aphasia.

accounting for group membership, suggesting that it generalizes across neurodegenerative syndromes. The analysis of the relationship between disease duration and the Insensitive subscale revealed $p = 0.051$ (estimate = 0.06, 95% CI = −0.01 to 0.11) in the main effects model and $p = 0.061$ (estimate = 0.05, 95% CI = −0.00 to 0.11) in the diagnostic confound model. No significant effects of disease duration were revealed for the Reactive subscale.

Longitudinal Relationship Between Subscale Scores and Gray Matter Atrophy

The main effects analysis showed that greater increase in the Disorganized subscale corresponded to more rapid volume loss in regions of the SAN, including the bilateral nucleus accumbens, medial OFC, and lateral OFC, as well as the left rostral ACC (Table 2). The left nucleus accumbens, left medial OFC, and bilateral lateral OFC remained significant predictors in the diagnostic confound models. One region of the SN, the right thalamus, was a significant predictor of the Disorganized score, although this effect did not reach statistical significance when diagnosis was added to the analysis. More volume loss in the bilateral middle frontal gyrus of the FPN corresponded to greater increase on the Disorganized subscale in both models. The only region that was significantly associated with the Reactive score was the left nucleus accumbens, but this effect did not reach statistical significance in the diagnostic confound model. Similarly, we found that the Insensitive score significantly predicts the left nucleus accumbens and right medial OFC only in the main effects models. No regional differences in these results were seen when institution was added as a confound.

Table 2 Longitudinal Relationships Between the SBOCL Subscales and Gray Matter Volume in the SN, SAN, and FPN

Subscale	Region	Main effects model			Diagnostic confound model		
		b coefficient	95% CI	p Value	b coefficient	95% CI	p Value
Disorganized	Right nucleus accumbens	−0.0074	−0.0125 to −0.0023	0.007			>0.01
	Left nucleus accumbens	−0.0065	−0.0105 to −0.0025	0.003	−0.0071	−0.0112 to −0.0031	0.002
	Right medial OFC	−0.0009	−0.0014 to −0.0004	0.002			>0.01
	Left medial OFC	−0.0008	−0.0013 to −0.0003	0.003	−0.0007	−0.0012 to −0.0002	0.008
	Right lateral OFC	−0.0006	−0.0010 to −0.0003	0.001	−0.0005	−0.0009 to −0.0001	0.009
	Left lateral OFC	−0.0007	−0.0011 to −0.0004	0.001	−0.0006	−0.0011 to −0.0002	0.004
	Left rostral ACC	−0.0012	−0.0020 to −0.0005	0.004			>0.01
	Right thalamus	−0.0010	−0.0016 to −0.0004	0.003			>0.01
	Right middle frontal gyrus	−0.0004	−0.0006 to −0.0002	0.002	−0.0004	−0.0006 to −0.0001	0.005
	Left middle frontal gyrus	−0.0005	−0.0007 to −0.0002	0.004	−0.0004	−0.0007 to −0.0001	0.009
Reactive	Left nucleus accumbens	−0.0044	−0.0077 to −0.0012	0.010			>0.01
Insensitive	Left nucleus accumbens	−0.0048	−0.0083 to −0.0014	0.008			>0.01
	Right medial OFC	−0.0006	−0.0011 to −0.0002	0.008			>0.01

Abbreviations: ACC = anterior cingulate cortex; FPN = fronto-parietal network; OFC = orbitofrontal cortex; ROI = region of interest; SAN = semantic-appraisal network; SBOCL = Social Behavior Observer Checklist; SN = salience network.
Main effects models included ROI, disease duration, age at symptom onset, sex, and total intracranial volume. In the Diagnostic confound models, the variable diagnostic group was parametrized and added to the model. The statistical threshold was set at $p < 0.01$.

Discussion

This study shows that the examiner-based SBOCL is sensitive to some behavior differences even among asymptomatic individuals and shows distinct patterns of differences across each disease stage in neurodegenerative syndromes. We also found that the SBOCL measures symptoms that are burdensome for caregivers. Greater change on the SBOCL over time corresponds to greater volume loss in the SAN and FPN brain networks. The SBOCL is a valuable addition to a clinical evaluation because it is sensitive to early changes and can be administered by a psychometrist without training in behavior assessment. The measure is already being collected as a clinical research measure at a national level as part of the NACC FTLD module battery[34] and has been incorporated into the freely available TabCAT software program.[35]

For early stage identification and classification of patients with bvFTD in treatment trials and for determination of treatment efficacy, clinical measures are required that can detect subtle behavior changes in the earliest disease stage. Two previous studies have shown that assessments of executive functioning, language, and episodic memory can detect cognitive differences between presymptomatic FTLD pathogenic variant carriers and presymptomatic noncarriers, both at baseline and with progression over time.[36,37] However, other studies did not find any cognitive differences between asymptomatic FTLD pathogenic variant carriers and asymptomatic noncarriers.[38] We found that asymptomatic GRN pathogenic variant carriers had an altered pattern of observed behaviors (increased levels of self-consciousness and preoccupation with time) compared with asymptomatic noncarriers and also compared with asymptomatic C9orf72 pathogenic variant carriers and MAPT pathogenic variant carriers. This supports 2 longitudinal studies showing that emotion reading[39] and theory of mind[40] abilities of GRN pathogenic variant carriers significantly declined over time during the presymptomatic phase. This distinct SBOCL pattern seen in GRN pathogenic variant carriers is consistent with previously reported neuroanatomical differences among presymptomatic FTLD carriers with C9orf72, GRN, and MAPT pathogenic variants, including differences in functional connectivity in the SN and FPN,[7,41,42] white matter integrity in the frontotemporal lobe,[43,44] and gray matter atrophy in fronto-temporal and thalamic regions.[38] In addition, a recent longitudinal multimodal neuroimaging study showed that gray and white matter changes evolve more rapidly in GRN compared with MAPT converters,[43] which may have contributed to the behavioral differences we found between the 3 gene groups.

The SBOCL is not only sensitive to early behavior changes in asymptomatic GRN pathogenic variant carriers but also increases as a function of disease stage, with some evidence for progression between asymptomatic and very mild, as well as very mild and mild stages of bvFTD. This is an important finding because sensitive tests are required for early and accurate diagnosis of patients, particularly with disease-modifying treatments on the horizon.

Several analytic approaches converged to show that the SBOCL Disorganized subscale is sensitive to changes in

clinically significant behaviors in patients with bvFTD. Although this result was not specific to bvFTD and was found in other neurodegenerative syndromes as well, reducing the measure's utility for differential diagnosis, its value for early identification and to some extent for measurement of disease progression in bvFTD is not diminished. First, the score increased over time across disease groups and as a function of disease stage across all pathogenic variant carriers and noncarriers. Second, although each syndrome showed a different pattern of change on the Disorganized score, only patients with bvFTD had a significant increase at each stage of disease. By contrast, in patients with nfvPPA and AD, the score increased only in later disease stages, and the increase in patients with svPPA was not statistically significant. The average score of patients with PSP was in the clinically elevated range at each disease stage but remained relatively flat across disease progression.

We also found that the Insensitive subscale changed with advancing disease in different syndromes, although to a lesser degree than the Disorganized subscale. The longitudinal analysis showed that, overall, the Insensitivity score increased over time across all patients. Specifically, in patients with bvFTD, the score increased after the mild disease stage but only reached the clinically significant (i.e., abnormal) threshold in moderate to severe disease stages. Although the Insensitive score quantitatively increased as a function of disease stage in patients with svPPA, the effects did not reach statistical significance. By contrast, the SBOCL Reactive subscale was not sensitive to disease severity in any syndrome, but the scores of the patients with AD and svPPA were higher compared with the other patient groups and were in the clinically significant range. This is consistent with previous research and clinical observations showing that patients with AD and svPPA have higher levels of emotional contagion, anxiety, and worry.[2,12]

Two different approaches (LME models and overall slopes over time) showed that more rapid change on the SBOCL Disorganized subscale was associated with greater volume loss in the SAN (bilateral OFC, left nucleus accumbens) and FPN (bilateral middle frontal gyrus). The SAN mediates personal evaluations of semantic entities, including social percepts such as emotions and faces.[45] The OFC and nucleus accumbens are responsible for complex hedonic evaluations and interact with the anterior temporal lobe to apply these evaluations to social concepts.[46,47] By contrast, the FPN that is recruited by the SN[48] is responsible for top-down control of attention and executive functioning and helps to exert task control in social cognition.[18,49] The role of the middle frontal gyrus is to maintain stable cognitive control, whereas parietal regions of the FPN are involved in adaptive control.[18] These findings suggest that patients in our study who show worsening on the Disorganized subscale over time may have altered evaluations of social interactions and difficulties maintaining focused attention on social stimuli. In contrast to the Disorganized subscale, change on the SBOCL Reactive and Insensitive scores did not correspond to change in gray matter volume in a generalizable

manner, despite significant brain-behavior relationships in cross-sectional models.[15] We did not expect that change in the Reactive subscale would correspond with change in gray matter volume in the longitudinal sample because the score did not increase over time. One possible reason why we did not detect any significant relationships between change on Insensitive score and change in gray matter volume may be that we had insufficient behavioral variability in patients with nfvPPA, AD, and PSP, which may have reduced our statistical power to detect meaningful longitudinal brain-behavior relationships.

Desired features for an outcome measure in treatment trials include sensitivity to behavioral and neuroanatomical change over time and clinical meaningfulness (improvement on the measure might correspond with changes in the functional status of the patient or caregiver burden). We found that the SBOCL, particularly the Disorganized subscale, fulfills each of these criteria because it worsens over time, corresponds to progressive gray matter atrophy, and measures symptoms that are burdensome for caregivers. This suggests that the SBOCL may be a promising end point for FTLD clinical trials.

Clinician-based ratings are an effective way to assess social behavior because they can be administered independent of the cognitive status of patients and the availability of a reliable informant. The SBOCL is a particularly useful measure because it can be used by any examiner without specialized clinical training. However, 1 caveat of the SBOCL is that it is simply a thin-slice behavior observation, meaning that the absence of a certain behavior during a 30–60-minute patient interaction does not guarantee that the patient never enacts the behavior. Another limitation is that we did not have longitudinal data for asymptomatic sporadic cases before they converted to the symptomatic stage; thus, these findings in the genetic cases may not be generalizable to the nongenetic group. A longitudinal design would have allowed us to determine whether differences in time to disease onset between C9orf72, GRN, and MAPT pathogenic variant carriers had an impact on our results and would have the additional benefit of identifying any differences in initial symptom presentation between causative gene groups. Finally, because we did not split patients with bvFTD into different anatomic subtypes, we cannot draw any conclusions about whether the measure is more sensitive to early behavior changes in some subtypes than others.

Despite these limitations, our findings suggest that the SBOCL, and particularly the Disorganized subscale, may be used for early identification of bvFTD, to track changes in social behavior across different disease stages and over time, and to differentiate bvFTD from other FTLD and AD syndromes based on their pattern and trajectory of observed behaviors. This study shows that the SBOCL can be used to monitor symptom and neuroanatomical progression across asymptomatic and symptomatic disease

stages of bvFTD, highlighting that the measures may be suitable for use in neurologic practice and upcoming clinical trials for patients with bvFTD.

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Disclosure

Publication History

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References

1. Kumfor F, Irish M, Leyton C, et al. Tracking the progression of social cognition in neurodegenerative disorders. *J Neurol Neurosurg Psychiatry*. 2014;85(10):1076-1083.
2. Mega MS, Cummings JL, Fiorello T, Gornbein J. The spectrum of behavioral changes in Alzheimer's disease. *Neurology*. 1996;46(1):130-135.
3. Shany-Ur T, Poorzand P, Grossman SN, et al. Comprehension of insincere communication in neurodegenerative disease: lies, sarcasm, and theory of mind. *Cortex*. 2012;48(10):1329-1341.
4. Brown CL, Lwi SJ, Goodkind MS, et al. Empathic accuracy deficits in patients with neurodegenerative disease: association with caregiver depression. *Am J Geriatr Psychiatry*. 2018;26(4):484-493.
5. Mioshi E, Foxe D, Leslie F, et al. The impact of dementia severity on caregiver burden in frontotemporal dementia and Alzheimer disease. *Alzheimer Dis Assoc Disord*. 2013;27(1):68-73.
6. Cash DM, Bocchetta M, Thomas DL, et al. Patterns of gray matter atrophy in genetic frontotemporal dementia: results from the GENFI study. *Neurobiol Aging*. 2018;62:191-196.
7. Lee SE, Sias AC, Kosik EL, et al. Thalamo-cortical network hyperconnectivity in preclinical progranulin mutation carriers. *Neuroimage Clin*. 2019;22:101751.
8. Sellami L, Bocchetta M, Masellis M, et al. Distinct neuroanatomical correlates of neuropsychiatric symptoms in the three main forms of genetic frontotemporal dementia in the GENFI cohort. *J Alzheimers Dis*. 2018;65(1):147-163.
9. Kumfor F, Zhen A, Hodges JR, Piguet O, Irish M. Apathy in Alzheimer's disease and frontotemporal dementia: distinct clinical profiles and neural correlates. *Cortex*. 2018;103:350-359.
10. Rankin KP, Gorno-Tempini M, Allison SC, et al. Structural anatomy of empathy in neurodegenerative disease. *Brain*. 2006;129(pt 11):2945-2956.
11. Sollberger M, Stanley CM, Wilson SM, et al. Neural basis of interpersonal traits in neurodegenerative diseases. *Neuropsychologia*. 2009;47(13):2812-2827.
12. Sturm VE, Yokoyama JS, Seeley WW, Kramer JH, Miller BL, Rankin KP. Heightened emotional contagion in mild cognitive impairment and Alzheimer's disease is associated with temporal lobe degeneration. *Proc Natl Acad Sci USA*. 2013;110(24):9944-9949.
13. Cummings JL, Mega M, Gray K, Thompson-Rosenberg J, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology*. 1994;44(12):2308-2314.
14. Mendez MF, Fong SS, Shapira JS, et al. Observation of social behavior in frontotemporal dementia. *Am J Alzheimers Dis Other Dement*. 2014;29(3):215-221.
15. Rankin KP, Toller G, Gavron L, et al. Social behavior observer checklist: patterns of spontaneous behaviors differentiate patients with neurodegenerative disease from healthy older adults. *Front Neurol*. 2021;12:683162.
16. Seeley WW, Menon V, Schatzberg AF, et al. Dissociable intrinsic connectivity networks for salience processing and executive control. *J Neurosci*. 2007;27(9):2349-2356.
17. Seeley WW, Zhou J, Kim EJ. Frontotemporal dementia: what can the behavioral variant teach us about human brain organization? *Neuroscientist*. 2012;18(4):373-385.
18. Dosenbach NU, Fair DA, Miezin FM, et al. Distinct brain networks for adaptive and stable task control in humans. *Proc Natl Acad Sci USA*. 2007;104(26):11073-11078.
19. Yang WFZ, Toller G, Shdo S, et al. Resting functional connectivity in the semantic appraisal network predicts accuracy of emotion identification. *Neuroimage Clin*. 2021;31:102755.
20. Rosen HJ, Allison SC, Schauer GF, Gorno-Tempini M, Weiner MW, Miller BL. Neuroanatomical correlates of behavioural disorders in dementia. *Brain*. 2005;128(pt 11):2612-2625.
21. Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain*. 2011;134(pt 9):2456-2477.
22. Gorno-Tempini ML, Hillis AE, Weintraub S, et al. Classification of primary progressive aphasia and its variants. *Neurology*. 2011;76(11):1006-1014.
23. Litvan I, Agid Y, Goetz C, et al. Accuracy of the clinical diagnosis of corticobasal degeneration: a clinicopathologic study. *Neurology*. 1997;48(1):119-125.
24. Jack CR Jr, Bennett DA, Blennow K, et al. NIA-AA research framework: toward a biological definition of Alzheimer's disease. *Alzheimers Dement*. 2018;14(4):535-562.
25. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology*. 1993;43(11):2412-2414.
26. Knopman DS, Weintraub S, Pankratz VS. Language and behavior domains enhance the value of the clinical dementia rating scale. *Alzheimers Dement*. 2011;7(3):293-299.
27. Miyagawa T, Brushaber D, Syrjanen J, et al. Utility of the global CDR plus NACC FTLD rating and development of scoring rules: data from the ARTFL/LEFFTDS Consortium. *Alzheimers Dement*. 2020;16(1):106-117.
28. Zarit SH, Reever KE, Bach-Peterson J. Relatives of the impaired elderly: correlates of feelings of burden. *Gerontologist*. 1980;20(6):649-655.
29. Rankin KP, Salazar AM, Gorno-Tempini M, et al. Detecting sarcasm from paralinguistic cues: anatomic and cognitive correlates in neurdegenerative disease. *Neuroimage*. 2009;47(4):2005-2015.
30. Ashburner J, Friston KJ. Unified segmentation. *Neuroimage*. 2005;26(3):839-851.
31. Ziegler G, Penny WD, Ridgway GR, Ourselin S, Friston KJ; Alzheimer's Disease Neuroimaging Initiative. Estimating anatomical trajectories with Bayesian mixed-effects modeling. *Neuroimage*. 2015;121:51-68.
32. Ashburner J, Friston KJ. Diffeomorphic registration using geodesic shooting and Gauss–Newton optimisation. *Neuroimage*. 2011;55(3):954-967.
33. Desikan RS, Ségonne F, Fischl B, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage*. 2006;31(3):968-980.
34. National Alzheimer's Coordinating Centers. Accessed January 15, 2021. alz.washington.edu/WEB/forms_ftld.html.
35. TabCAT. 2017. Accessed January 15, 2021. memory.ucsf.edu/research-trials/professional/tabcat 2017.
36. Rohrer JD, Nicholas JM, Cash DM, 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(3):253-262.
37. Staffaroni AM, Bajorek L, Casaletto KB, et al. Assessment of executive function declines in presymptomatic and mildly symptomatic familial frontotemporal dementia: NIH-EXAMINER as a potential clinical trial endpoint. *Alzheimers Dement*. 2020;16(1):11-21.
38. Olney NT, Ong E, Goh SM, et al. Clinical and volumetric changes with increasing functional impairment in familial frontotemporal lobar degeneration. *Alzheimers Dement*. 2020;16(1):49-59.
39. Barandiaran M, Moreno F, de Arriba M, et al. Longitudinal neuropsychological study of presymptomatic c. 709-1G> A progranulin mutation carriers. *J Int Neuropsychol Soc*. 2019;25(1):39-47.
40. Jiskoot LC, Dopper EG, Heijer T, et al. Presymptomatic cognitive decline in familial frontotemporal dementia: a longitudinal study. *Neurology*. 2016;87(4):384-391.
41. Lee SE, Khazenzon AM, Trujillo AJ, et al. Altered network connectivity in frontotemporal dementia with C9orf72 hexanucleotide repeat expansion. *Brain*. 2014;137(pt 11):3047-3060.
42. Premi E, Formenti A, Gazzina S, et al. Effect of TMEM106B polymorphism on functional network connectivity in asymptomatic GRN mutation carriers. *JAMA Neurol*. 2014;71(2):216-221.
43. Jiskoot LC, Panman JL, Meeter LH, et al. Longitudinal multimodal MRI as prognostic and diagnostic biomarker in presymptomatic familial frontotemporal dementia. *Brain*. 2019;142(1):193-208.
44. Sudre CH, Bocchetta M, Cash D, et al. White matter hyperintensities are seen only in GRN mutation carriers in the GENFI cohort. *Neuroimage Clin*. 2017;15:171-180.
45. Kringelbach ML, Rolls ET. The functional neuroanatomy of the human orbitofrontal cortex: evidence from neuroimaging and neuropsychology. *Prog Neurobiol*. 2004;72(5):341-372.
46. Patterson K, Nestor PJ, Rogers TT. Where do you know what you know? The representation of semantic knowledge in the human brain. *Nat Rev Neurosci*. 2007;8(12):976-987.
47. Yeo BT, Krienen FM, Sepulcre J, et al. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *J Neurophysiol*. 2011;106(3):1125-1165.
48. Chiong W, Wilson SM, D'Esposito M, et al. The salience network causally influences default mode network activity during moral reasoning. *Brain*. 2013;136(pt 6):1929-1941.
49. Marek S, Dosenbach NUF. The frontoparietal network: function, electrophysiology, and importance of individual precision mapping. *Dialogues Clin Neurosci*. 2018;20(2):133-140.