

Revised Self-Monitoring Scale

A potential endpoint for frontotemporal dementia clinical trials

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Abstract

Objective

To investigate whether the Revised Self-Monitoring Scale (RSMS), an informant measure of socioemotional sensitivity, is a potential clinical endpoint for treatment trials for patients with behavioral variant frontotemporal dementia (bvFTD).

Methods

We investigated whether RSMS informant ratings reflected disease severity in 475 participants (71 bvFTD mutation+, 154 bvFTD mutation−, 12 behavioral mild cognitive impairment [MCI] mutation+, 98 asymptomatic mutation+, 140 asymptomatic mutation−). In a subset of 62 patients (20 bvFTD mutation+, 35 bvFTD mutation−, 7 MCI mutation+) who had at least 2 time points of T1-weighted images available on the same 3T scanner, we examined longitudinal changes in RSMS score over time and its correspondence to progressive gray matter atrophy.

Results

RSMS score showed a similar pattern in mutation carriers and noncarriers, with significant drops at each stage of progression from asymptomatic to very mild, mild, moderate, and severe disease ($F_{4,48} = 140.10, p < 0.001$) and a significant slope of decline over time in patients with bvFTD ($p = 0.004$, 95% confidence interval [CI] −1.90 to −0.23). More rapid declines on the RSMS corresponded to faster gray matter atrophy predominantly in the salience network (SN), and RSMS score progression best predicted thalamic volume in very mild and mild disease stages of bvFTD. Higher RSMS score predicted more caregiver burden ($p < 0.001$, 95% CI −0.30 to −0.11).

Conclusions

The RSMS is sensitive to progression of both socioemotional symptoms and SN atrophy in patients with bvFTD and corresponds directly to caregiver burden. The RSMS may be useful in both neurologic practice and clinical trials aiming to treat behavioral symptoms of patients with bvFTD.

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Glossary

ACC = anterior cingulate cortex; **AI** = anterior insula; **ARTFL** = Advancing Research and Treatment in Frontotemporal Lobar Degeneration; **bvFTD** = behavioral variant frontotemporal dementia; **CI** = confidence interval; **FTLD** = frontotemporal lobar degeneration; **LEFFTDS** = Longitudinal Evaluation of Familial Frontotemporal Dementia Subjects; **LME** = linear mixed-effects; **MCI** = mild cognitive impairment; **NACC** = National Alzheimer's Coordinating Center; **OFC** = orbitofrontal cortex; **ROI** = region of interest; **RSMS** = Revised Self-Monitoring Scale; **SAN** = semantic-appraisal network; **SN** = salience network; **TP** = temporal pole; **UCSF FTD PPG** = University of California, San Francisco Frontotemporal Dementia Program Project Grant.

Behavioral variant frontotemporal dementia (bvFTD) belongs to a heterogeneous group of frontotemporal lobar degeneration (FTLD) syndromes that are each characterized by deficits in behavior, language, and motor function. bvFTD selectively targets the salience network (SN)¹ and semantic-appraisal network (SAN),² and drastic alterations in social behavior such as loss of empathy are the hallmark symptoms occurring early in the disease.^{3,4} There are currently no Food and Drug Administration–approved treatments for bvFTD and other FTLD syndromes, but the first clinical trials targeting the 2 most common FTLD proteinopathies, FTLD-tau and FTLD-TDP,⁵ are now being conducted. Because the initial symptoms of bvFTD are exclusively behavioral⁶ and not cognitive and because current clinical trials focus on pre-symptomatic stages,⁷ psychometrically valid tests are required to detect the earliest socioemotional changes and to accurately measure symptom and neuroanatomic progression.

The goal of this study was to investigate whether the Revised Self-Monitoring Scale (RSMS),⁸ an informant-completed measure of socioemotional sensitivity, may be a potential clinical endpoint for treatment trials for patients with bvFTD. We examined whether RSMS score reflects disease severity and whether rate of progression differs between FTLD mutation carriers and noncarriers. In addition, we investigated whether RSMS score declines over time in patients with bvFTD and whether this change corresponds to progressive gray matter atrophy. On the basis of our previous cross-sectional work showing that lower RSMS score is associated with greater atrophy and lower functional connectivity in the SN in bvFTD,^{9,10} we hypothesized that a drop in RSMS score over time would correspond to progressive atrophy predominantly in regions of the SN.

Methods

Participants

For the initial analysis examining whether RSMS rating reflects disease severity (CDR analysis), 475 participants were included from 3 parent studies: University of California, San Francisco Frontotemporal Dementia Program Project Grant (UCSF FTD PPG) study, as well as the multisite Longitudinal Evaluation of Familial Frontotemporal Dementia Subjects (LEFFTDS) and Advancing Research and Treatment in Frontotemporal Lobar Degeneration (ARTFL) studies

(rare diseasesnetwork.org/cms/artfl/) between 2009 and 2019. These included 71 patients diagnosed with bvFTD who carried a mutation in 1 of the 3 main autosomal dominant FTD genes (36 *C9orf72*, 26 *MAPT*, 9 *GRN*), 154 noncarriers with clinical bvFTD,⁶ 12 patients with a diagnosis of behavioral mild cognitive impairment (MCI) who were mutation carriers (5 *C9orf72*, 3 *MAPT*, 4 *GRN*), 98 asymptomatic mutation-positive adults, and 140 asymptomatic mutation-negative adults from families with a known FTLD gene mutation. Patients were diagnosed with behavioral MCI if they had 1 or 2 of the following key symptoms as required for possible bvFTD⁶: disinhibition, apathy or inertia, loss of sympathy/empathy, ritualistic/compulsive behavior, or hyperorality and appetite changes, and no cognitive domain impaired other than behavior. Patients were diagnosed after comprehensive neurologic, neuroimaging, genetic, and neuropsychological assessments that did not include the RSMS. Each participant had an informant who was a first-degree family member or friend who had known the participant for ≥5 years. Participants were included only if they had at least 1 RSMS informant rating available; administration of this measure was standard for all patients, and attempts were made to collect yearly follow-up RSMS score on all participants regardless of diagnostic status or disease severity. When participants had >1 RSMS time point available, only the first time point within the same disease stage level was included in the first analysis.

For the second set of analyses examining how RSMS score changes longitudinally over the course of disease progression in bvFTD (time analysis) and whether change over time corresponds to progression in gray matter atrophy, a subset of the above sample was analyzed that included only the patients who had at least 2 time points at which a structural imaging scan of sufficient quality was collected on the same 3T scanner. This subsample consisted of 62 patients, including 20 mutation carriers with bvFTD (10 *C9orf72*, 8 *MAPT*, 2 *GRN*),⁶ 35 noncarriers with bvFTD,⁶ and 7 mutation carriers with a diagnosis of behavioral MCI (2 *C9orf72*, 3 *MAPT*, 2 *GRN*). The average time interval between RSMS score collection and structural imaging was 4.80 ± 3.61 days. We also included a control sample of 53 neurologically and cognitively healthy older adults (age [mean \pm SD] 68.73 ± 6.10 years, male/female 25/29) from the Hillblom Network Program. Table 1 shows the demographic and clinical characteristics.

Table 1 Demographic and clinical characteristics of diagnostic groups

Mean (SD)	Asymptomatic mutation–	Asymptomatic mutation+	bvFTD mutation–	bvFTD mutation+	Behavioral MCI mutation+	Statistics	<i>p</i> Value
No.	140	98	154	71	12	—	—
No. of observations	140	98	169	104	16	—	—
No. of time points	1.01 (0.08)	1.06 (0.32)	1.10 (0.30)	1.31 (0.47) ^b	1.58 (0.67) ^b	$F_{4,470} = 19.27$	<0.001
Age, y^a	48.56 (12.88)	43.19 (14.60) ^b	63.54 (9.24) ^b	58.56 (9.43) ^b	57.08 (13.01) ^b	$F_{4,470} = 56.49$	<0.001
Sex, M/F, n	52/88	46/52	96/58	36/35	6/6	$\chi^2_{4,470} = 19.00$	<0.001
Education, y	15.56 (2.56)	15.82 (2.57)	15.90 (3.01)	15.26 (2.51)	15.33 (2.64)	$F_{4,470} = 0.84$	0.502
CDR plus NACC FTLD score^a	0	0	1.56 (0.67) ^b	1.61 (0.74) ^b	0.54 (0.14) ^b	$F_{2,286} = 20.22$	<0.001

Abbreviations: bvFTD = behavioral variant frontotemporal dementia; MCI = Mild Cognitive Impairment; NACC = National Alzheimer's Coordinating Center; CDR plus NACC FTLD = CDR Dementia Staging Instrument plus Behavior and Language domains from the NACC Frontotemporal Lobar Degeneration Module.

No. of patients with bvFTD and MCI with 2 time points (Revised Self-Monitoring Scale and MRI): 35. No. of patients with 3 time points: 18. No. of patients with ≥4 time points: 9. No. of total observations = 166. Group differences in age, sex, education, and CDR plus NACC FTLD rating were analyzed with Tukey post hoc tests.

^a Group means/SDs were derived from only the first assessment for each participant.

^b Group differs from asymptomatic noncarriers at $p < 0.05$.

Standard protocol approvals, registrations, and patient consents

The parent studies (UCSF FTD PPG, LEFFTDS, ARTFL) were conducted in accordance with Institutional Review Board approval from each study institution, and all participants and their informants gave their consent to participate and to share data.

Behavioral, functional, and caregiver measures

The RSMS⁸ is a thoroughly validated 13-item questionnaire that measures sensitivity and responsiveness to subtle emotional expressions during face-to-face interactions. Sample items include “In conversations, the subject is sensitive to even the slightest change in the facial expression of the other person he/she is conversing with,” and “In social situations, the subject has the ability to alter his/her behavior if he/she feels that something else is called for.” The questionnaire has good psychometric characteristics, including internal consistency, retest reliability, and construct validity,^{11–13} and has previously been used to investigate brain-behavior relationships in both healthy and clinical populations.^{9,10,14} Informants rated patients on each item on a 6-point Likert scale, ranging from “certainly, always false” to “certainly, always true.”

The CDR Dementia Staging Instrument plus Behavior and Language domains from the National Alzheimer's Coordinating Center (NACC) FTLD Module (CDR plus NACC FTLD) was included as a proxy of disease severity. This measure is an extension of the standard CDR,¹⁵ which assesses functional impairment in 6 domains (memory, orientation, judgment and problem solving, community affairs, home and hobbies, personal care) and includes 2 additional domains that are predominantly affected in

FTLD: behavior and language.¹⁶ The score ranges between 0 (no functional impairment) and 3 (severe functional impairment).

The Zarit Burden Interview¹⁷ is a 22-item self-report measure that assesses caregiver burden in different areas, including behavioral symptoms and functional status of the patient, interpersonal relationships, finances, physical health, and social life. The questionnaire was used to test our hypothesis that lower socioemotional sensitivity in patients with bvFTD would be associated with higher caregiver burden.

Behavioral data analysis

CDR analysis: RSMS rating by CDR plus NACC FTLD stage

Group differences on potentially confounding covariates, including age, sex, and education, were analyzed with general linear models in SAS (Proc GLM; SAS Institute Inc, Cary, NC). To investigate whether RSMS score significantly worsened with increasing CDR plus NACC FTLD stage and whether rate of decline differed between carriers and noncarriers, we performed linear mixed-effects (LME) models in SAS (Proc Mixed) with random intercepts and slopes, which accounted for individual differences in baseline RSMS score and rate of progression. The use of LME models also allowed us to use the full sample ($n = 475$, 527 observations), including individuals who had only 1 time point and those without concurrent MRI. Group (carriers vs noncarriers), CDR plus NACC FTLD score (asymptomatic, very mild, mild, moderate, severe), and the interaction between group and CDR plus NACC FTLD score were included in the model, controlling for age at first assessment and sex. A priori power analysis showed that standard $\alpha = 0.05$ level tests with 475 participants had power >0.8 to detect small effect sizes of 0.03.

Time analysis: Pattern of longitudinal RSMS score change in bvFTD

The statistical assumptions underlying our second set of analyses required that only patients with bvFTD and MCI who had ≥ 2 time points of both RSMS and MRI data of sufficient quality and on the same scanner could be included; thus, the smaller set ($n = 62$, 166 observations) was used. Generalized linear models were performed to assess group differences in age at symptom onset, disease duration since symptom onset, sex, and education. To examine whether RSMS score declined over time, we performed LME models with disease duration, group (carriers vs noncarriers), and the interaction of disease duration by group included as predictors in the model. A priori power analysis showed that standard $\alpha = 0.05$ level tests with 62 patients had power >0.8 to detect medium effect sizes of 0.23. To determine whether these rates of RSMS score decline differed on the basis of level of disease severity at baseline presentation, we assigned patients to 3 groups based on their baseline CDR plus NACC FTLD score (0.5 = very mild, 1 = mild, 2/3 = moderate and severe). LME models were performed with disease duration, severity group, and the disease duration by group interaction included in the model. Age at symptom onset and sex were entered as covariates of no interest. To model the stability of RSMS score in the comparison group of healthy older adults, we calculated each control's RSMS slope across all time points and derived the group's average.

Context analysis: Relationship between RSMS rating and caregiver burden

To investigate whether RSMS score would correspond with clinically meaningful factors in their living environment, we took the first RSMS rating of each patient with bvFTD (carriers $n = 77$, noncarriers $n = 104$) and behavioral MCI ($n = 13$) who had a valid Zarit score within 90 days of RSMS data collection. A generalized linear model was performed to assess whether Zarit score significantly predicted RSMS score, controlling for age at symptom onset and sex.

Neuroimaging

Participants underwent structural imaging using 3T scanners from 1 of 3 vendors: Siemens (Munich, Germany), Philips Medical Systems (Best, the Netherlands), or General Electric Medical Systems (Chicago, IL). A standard imaging acquisition protocol was used at all centers, managed and reviewed for quality by a core group at the Mayo Clinic (Rochester, MN). A T1-weighted 3D magnetization-prepared rapid gradient echo sequence was used to obtain the T1-weighted images, with parameters as follows: $240 \times 256 \times 256$ matrix, ≈ 170 slices, and voxel size $1.05 \times 1.05 \times 1.25$ mm³; flip angle, echo time, and repetition time varied by vendor. Preprocessing was performed in SPM12 (fil.ion.ucl.ac.uk/spm/). In brief, the images were visually inspected for artifacts, bias corrected, tissue classified (gray matter, white matter, CSF segments) with unified segmentation,¹⁸ and modulated by multiplying the jacobian determinants of the time points with the intra-subject averaged tissues.¹⁹ A group template was generated from the averaged within-subject tissue segments with a Large Deformation

Diffeomorphic Metric Mapping framework.²⁰ 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.

Longitudinal voxel-wise and region of interest-based analysis

The voxel-wise longitudinal atrophy trajectories of each subject and the entire group were modeled using a hierarchical Bayesian LME model. In brief, the model rested on 2 hierarchical levels: single-subject trajectory and the group's trajectory. The trajectory was described as a degree $D = 1$ polynomial, for example, the j th time point of subject i had a gray matter density in 1 voxel y_{ij} such as $y_{ij} = \sum_{d=0}^D \theta_{id}^{(1)} t_j^d + \varepsilon_{ij}^{(1)}$, which was fitted with a design matrix $X^{(1)}$ where t_j was the subject's age at the time point j acquisition day, and $\theta^{(1)}$ and $\varepsilon^{(1)}$ were the first-level vectors of parameters and noise. The complete model was $y = X^{(1)}\theta^{(1)} + \varepsilon^{(1)}$; $X^{(1)}$ and $\varepsilon^{(1)}$ corresponded to the first-level design matrix and noise. The second level was modeled by $\theta^{(1)} = X^{(2)}\theta^{(2)} + \varepsilon^{(2)}$, where $X^{(2)}$, $\theta^{(2)}$, and $\varepsilon^{(2)}$ corresponded to the second-level design matrix, parameters, and noise. At each level, the noise distribution was drawn from a centered gaussian: $\varepsilon^{(u)} \sim N(0, C_\varepsilon^{(u)})$, where $C_\varepsilon^{(u)}$ was the hierarchical level u covariance matrix.

To test our hypothesis that rate of RSMS score progression in different disease stages would correspond to change in gray matter volume in regions of the SN and SAN, the Desikan brain atlas was used to define bilateral regions of interest (ROIs) in the SN (anterior insula [AI], dorsal anterior cingulate cortex [ACC], thalamus, amygdala, and brainstem) and SAN (temporal pole [TP], orbitofrontal cortex [OFC], subgenual ACC, caudate, and nucleus accumbens).

Brain-behavior analyses

Time analysis: Longitudinal relationship between RSMS rating and brain volume

To examine whether a greater drop in RSMS score would correspond to more rapid volume loss in SN regions, we performed a linear regression analysis in SPM12, investigating whether each patient's slope of change in RSMS score significantly predicted the voxel-wise slope of change in gray matter volume. To investigate whether patients with different levels of disease severity at baseline showed different relationships between change in RSMS score and change in gray matter volume, LME models were performed for each SN and SAN ROI. The ROI volume, severity group (very mild, mild, moderate/severe), and the interaction between ROI and group were entered as predictors, controlling for age at symptom onset, sex, disease duration, and total intracranial volume.

Data availability

Anonymized data will be shared on request from any qualified investigator for the purposes of replicating procedures and results.

Results

Demographic and clinical features

The demographics of the full sample ($n = 475$) are shown in table 1. The longitudinal analysis was performed in a subset consisting of patients with bvFTD and MCI ($n = 62$). In the smaller group, mutation carriers had an earlier age at symptom onset, but the groups did not differ in other factors, including disease duration.

RSMS score by CDR plus NACC FTLD stage and its relationship to caregiver burden

CDR analysis

To identify the typical RSMS scores that are predicted to occur at each level of disease severity in patients with bvFTD, we performed an LME model in the full sample of carriers and noncarriers with bvFTD, carriers with behavioral MCI, and asymptomatic carriers and noncarriers. Our results showed a main effect of CDR plus NACC FTLD score ($F_{4,48} = 140.10$, $p < 0.001$) in which RSMS score decreased significantly at each stage as CDR worsened, but no interaction was found between mutation status and CDR plus NACC FTLD score, indicating that mutation status did not influence the timing of RSMS score (figure 1). The same significant main effect was found when the data were reanalyzed including only the first time point for each patient ($F_{4,468} = 137.41$, $p < 0.001$), suggesting that the use of additional time points for some of the patients did not bias the result.

Context analysis

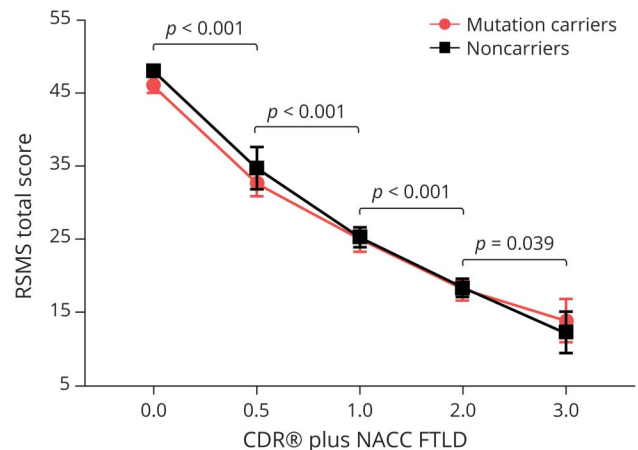
To assess whether lower socioemotional sensitivity would be associated with higher caregiver burden, we examined patients' initial RSMS ratings, controlling for age at symptom onset and sex. As expected, our analysis showed that lower RSMS score was significantly associated with higher Zarit burden score ($F_{1,190} = 17.57$, $p < 0.001$, estimate -0.21 , 95% confidence interval [CI] -0.30 to -0.11).

Longitudinal change over time of RSMS score in bvFTD

Time analysis

We then examined our subsample of patients with bvFTD and behavioral MCI who had complete longitudinal data (average time interval 0.98 ± 1.12 years) and performed LME model analysis to investigate whether RSMS score would significantly decrease over time. Consistent with the CDR plus NACC FTLD analysis, we found a significant main effect of disease duration ($F_{1,59} = 8.90$, $p = 0.004$, estimate -0.73 , 95% CI -1.90 to -0.23 ; figure 2A) in which RSMS score decreases linearly in patients at a rate of 5 points per year (average RSMS score slope per year -2.13 ± 1.29), but there was no main effect of mutation status, and the interaction between mutation status and disease duration was not significant. To determine whether the small number of patients with >2 time points skewed this result, we performed the same analysis but included only the first 2 time

Figure 1 RSMS score reflects disease severity independently of mutation status



Linear mixed-effects model analysis ($n = 475$) revealed a significant main effect of CDR Dementia Staging Instrument plus Behavior and Language domains from the National Alzheimer's Coordinating Center Frontotemporal Lobar Degeneration Module (CDR plus NACC FTLD) ($F_{4,48} = 140.10$, $p < 0.001$), showing that average Revised Self-Monitoring Scale (RSMS) score dropped significantly between asymptomatic (CDR plus NACC FTLD score 0) and very mildly symptomatic (CDR plus NACC FTLD score 0.5) stages ($t = 4.99$, $p < 0.001$, estimate 10.58, 95% confidence interval [CI] 6.32–14.85), between very mild (CDR plus NACC FTLD score 0.5) and mild (CDR plus NACC FTLD score 1) stages ($t = -5.48$, $p < 0.001$, estimate -12.02 , 95% CI -16.43 to -7.61), between mild (CDR plus NACC FTLD score 1) and moderate (CDR plus NACC FTLD score 2) stages ($t = 4.46$, $p < 0.001$, estimate 6.50, 95% CI 3.57–9.43), and between moderate and severe stages ($t = 2.12$, $p < 0.039$, estimate 4.93, 95% CI 0.25–9.61) in both mutation carriers and noncarriers. Age at first assessment and sex were included as covariates of no interest.

points of each patient ($n = 62$, 122 observations), and the results remained consistent, including a significant effect of disease duration ($F_{1,59} = 9.88$, $p = 0.003$, estimate -1.26 , 95% CI -2.21 to -0.30).

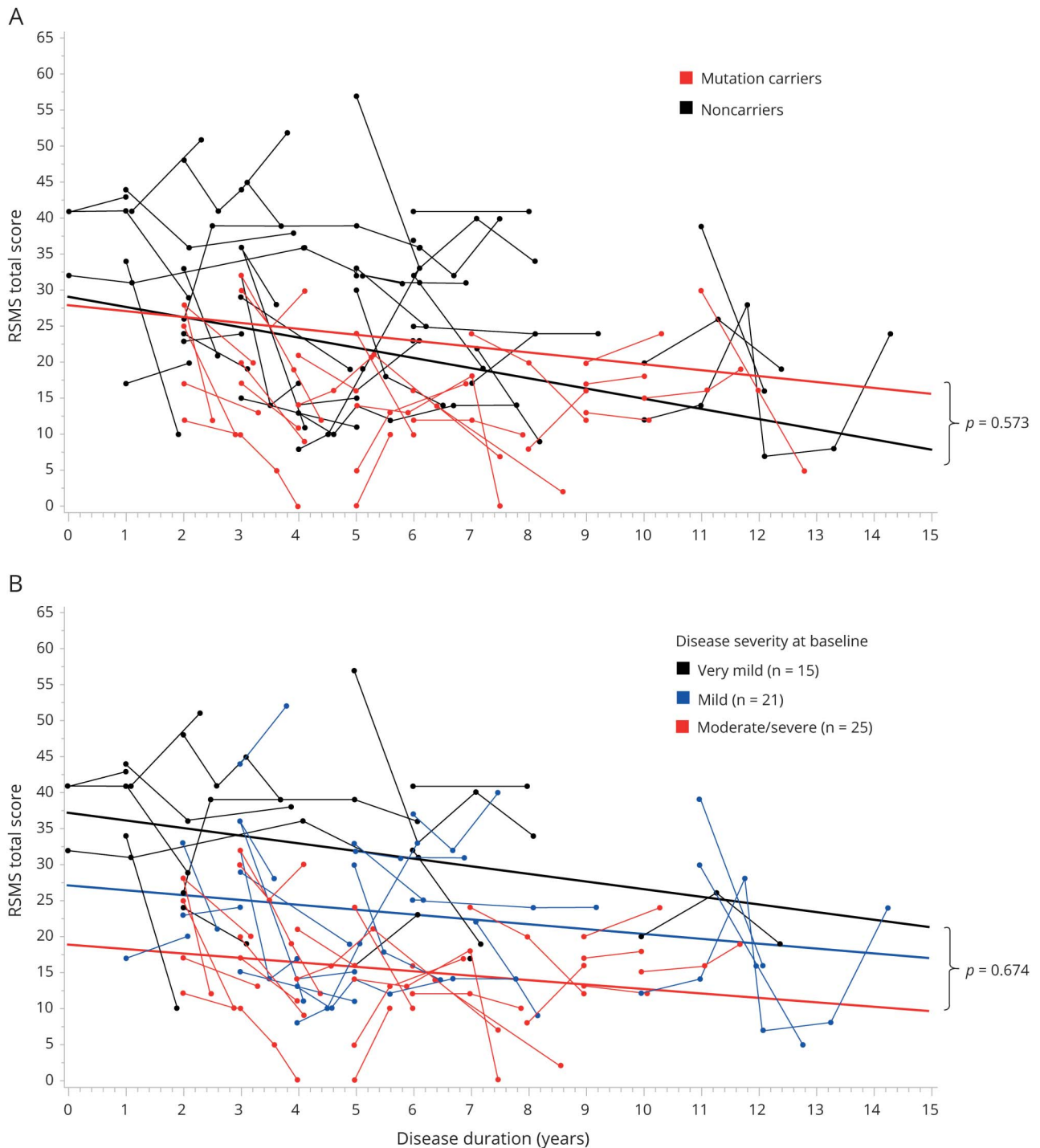
For comparison, the average slope of longitudinal change (0.90 ± 0.92) in RSMS score in the healthy control group was flat. We then examined whether patients with different levels of disease severity at baseline showed different slopes of progression on the RSMS. Patients were divided into very mild (CDR plus NACC FTLD score 0.5, average time interval 2.01 ± 1.43 years), mild (CDR plus NACC FTLD score 1, average time interval 1.53 ± 0.94 years), and moderate/severe (CDR plus NACC FTLD score 2/3, average time interval 1.25 ± 0.66 years) disease stage groups at baseline, but no disease duration by disease stage interaction was found (figure 2B).

Longitudinal relationship between RSMS score and gray matter volume in bvFTD

Time analysis

We then investigated whether the drop in RSMS score corresponded to progressive gray matter loss in bvFTD. Our voxel-wise analysis demonstrated that more rapid declines on the RSMS were associated with faster progression of gray matter atrophy in regions of the SN and SAN, including the

Figure 2 RSMS score shows linear declines over time in behavioral variant frontotemporal dementia

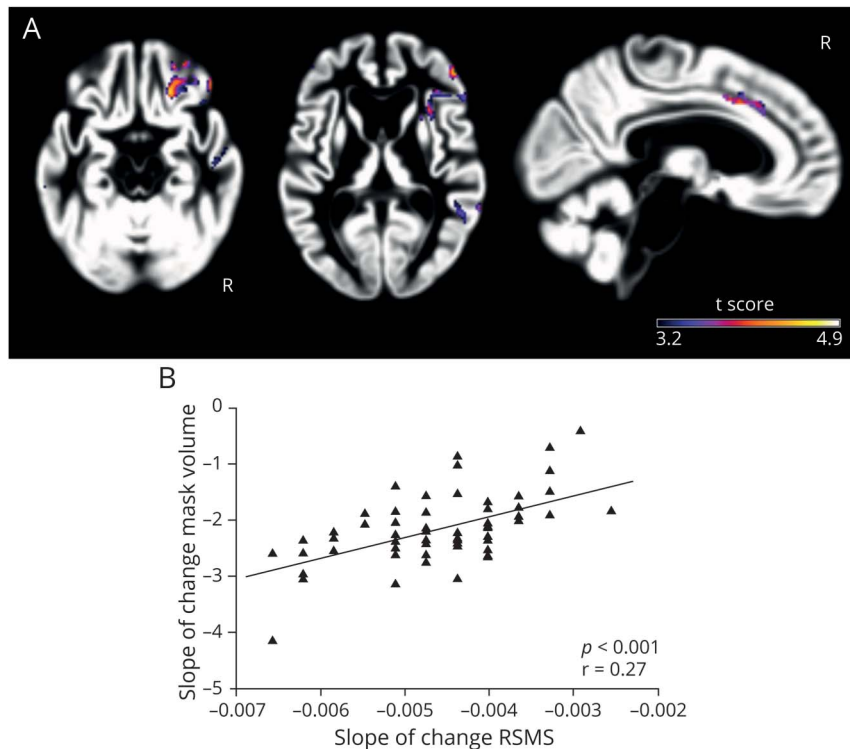


(A) Linear mixed-effects model analysis in the full longitudinal subsample ($n = 62$) revealed a significant main effect of disease duration ($F_{1,59} = 8.90$, $p = 0.004$, estimate -0.73 , 95% confidence interval -1.90 to -0.23), showing that Revised Self-Monitoring Scale (RSMS) score significantly worsened over time. Rate of RSMS score progression did not differ significantly between mutation carriers and noncarriers. (B) When patients were assigned to 3 groups based on their baseline disease stage (very mild, mild, moderate to severe) measured by the CDR plus National Alzheimer's Coordinating Center Frontotemporal Lobar Degeneration Module, no significant interaction was found between disease duration and disease stage group, suggesting that the RSMS score progresses at a similar rate in patients who are in different disease stages at baseline. Age at symptom onset and sex were included as covariates of no interest.

right AI, dorsal ACC, and OFC ($p < 0.001$, uncorrected) (figure 3A and table 2). Next, we binarized the uncorrected statistical t map of the RSMS score–gray matter relationship and calculated each patient's average annual slope of change

in gray matter volume within that binarized mask. A generalized linear model was performed to assess whether annual gray matter loss predicted annual change in RSMS score, controlling for age at symptom onset, sex, disease duration,

Figure 3 More rapid decline on the RSMS corresponded to faster progression of salience network atrophy



(A) Voxel-wise analysis in the full longitudinal subsample ($n = 62$) showed that a higher drop in Revised Self-Monitoring Scale (RSMS) score was significantly associated with more gray matter volume loss in the right anterior insula, dorsal anterior cingulate cortex, and orbitofrontal cortex ($p < 0.001$, uncorrected). (B) A general linear model confirmed this result by showing that a higher annual drop in RSMS score significantly predicted ($F_{1,56} = 13.47$, $p < 0.001$, estimate 753.96, 95% confidence interval 342.38–1,165.54) more annual volume loss within the binarized statistical t map derived from the voxel-wise analysis. Age at symptom onset, sex, disease duration, and total intracranial volume were included as covariates of no interest.

and total intracranial volume. The results showed that more rapid yearly worsening on the RSMS was significantly associated with faster gray matter volume loss in these regions ($F_{1,56} = 13.47$, $p < 0.001$, estimate 753.96, 95% CI 342.38–1,165.54) (figure 3B), confirming the presence and direction of the relationship revealed in the voxel-wise analysis.

We next examined whether patients with very mild, mild, and moderate/severe disease severity showed different degrees of correspondence between change in RSMS score and change in any predefined ROI within the SN and SAN. LME models were performed for each ROI, revealing a significant main effect in the thalamus ROI ($F_{1,37} = 9.73$, $p = 0.004$). Although nonsignificant, there was some evidence to suggest a meaningful interaction between thalamus and severity subgroup ($F_{2,37} = 2.89$, $p = 0.07$), showing that RSMS score progression corresponds to thalamic volume primarily in very mild and mild disease stages but to a lesser degree in moderate/severe disease stages. A sensitivity analysis dividing patients by speed of progression and comparing only the highest ($n = 12$) and lowest ($n = 12$) speed quartiles yielded the same result, suggesting that both groups had the same linear effect of thalamic volume on RSMS score. These effects lost significance after the exclusion of 12 *C9orf72* carriers (30 observations) from the analysis, potentially because of the enrichment of early thalamic atrophy in this group. No significant main effects or interactions were found for the other SN and SAN ROIs.

Discussion

This study shows that both level of disease severity and disease duration in bvFTD are reflected in ratings on the RSMS and that change in RSMS score over time corresponds to progressive gray matter atrophy in mutation carriers and noncarriers with bvFTD. We found that the measure is sensitive to the earliest socioemotional changes occurring during the conversion from the asymptomatic to very mildly symptomatic stage, as well as to later disease progression. Patients with bvFTD who were in different disease stages at baseline showed similar rates of change in RSMS score over time. For an outcome measure in clinical trials, the roughly linear rate of progression across disease severity is a desirable feature. Faster decline on the RSMS predicted greater atrophy, particularly in the SN but also in the SAN. This study highlights that the RSMS is a valid measure to monitor symptoms and corresponding SN progression of patients with bvFTD, both in neurologic practice and in clinical trials aiming to modify socioemotional symptoms of patients with presumed tau- and TDP-related proteinopathies.

Our behavioral analyses revealed 4 main findings. First, our results showed that RSMS score significantly declines with progression across disease stage categories from asymptomatic to very mild, mild, moderate, and severe, and it declines over time regardless of categorical disease stage in patients

Table 2 Regions in which progressive atrophy corresponded to progressive drop in RSMS score

Brain regions	Cluster size, n	x	y	z	t Value
Right frontoinsula cortex	1,297	48	20	-4	4.87
Right OFC	a	20	24	-14	4.70
Right dorsal ACC	103	5	5	39	4.43
Right fusiform cortex	155	42	-22	-27	4.36
Left dorsal ACC	82	-1	-3	39	4.29
Right inferior temporal gyrus	49	51	-10	-34	4.27
Left middle temporal gyrus	24	-63	-33	-9	4.19
Subgenual ACC	50	0	27	-6	4.17
Left middle frontal gyrus	18	-37	11	32	4.15
Left inferior temporal gyrus	33	-43	-16	-32	4.12
Right middle temporal gyrus	77	63	-27	-2	4.0
Right precentral gyrus	14	41	-9	40	3.78
Right superior temporal gyrus	23	53	0	-20	3.78
Right posterior middle temporal gyrus	50	50	-51	8	3.69
Right posterior cingulate cortex	11	2	-21	38	3.60

Abbreviations: ACC = anterior cingulate cortex; OFC = orbitofrontal cortex; RSMS = Revised Self-Monitoring Scale.

^a Part of the larger cluster given in the above row.

with bvFTD. Second, we found that the rate of progression did not differ significantly between mutation carriers and noncarriers, which is consistent with previous studies showing that carriers and noncarriers with bvFTD have similar clinical profiles and overlapping atrophy in regions of the SN.^{22,23} There is currently no evidence that age at disease onset affects the severity of behavioral symptoms in patients with bvFTD, which is in line with our finding that carriers and noncarriers in the longitudinal subsample had different ages at disease onset but showed the same rate of progression. Third, we found that individuals with bvFTD who were in very mild, mild, or moderate to severe disease stage at baseline showed the same slope of linear decline in RSMS score over time. This indicates that the RSMS is a useful clinical test to measure socioemotional progression throughout the disease process in both mutation carriers and noncarriers. A clinical trial of symptom progression in patients with bvFTD requires a measure that is sensitive to the progression of behavioral symptoms at different stages of the disease process.²⁴ Finally, we found that lower RSMS score significantly predicted higher caregiver distress and burden, emphasizing that the RSMS measures a key socioemotional symptom affecting the well-being of caregivers and families. This finding is consistent with previous studies showing that in patients with bvFTD and other neurodegenerative syndromes, both a patient's behavioral and neuropsychiatric symptoms and the quality of the patient-caregiver relationship are associated with caregiver stress.^{25,26}

Our voxel-wise analysis showed that a faster decline in RSMS score is reflected in a greater progression of atrophy in individual regions of the SN, including the AI, dorsal ACC, and thalamus. The AI and dorsal ACC are the hub regions of the SN that work together with subcortical regions, including the thalamus, hypothalamus, amygdala, and periaqueductal gray, to integrate and interpret interoceptive, autonomic signals and to adjust arousal and attention on the basis of perceived relevance.^{1,27} Specifically, the AI (sensory limbic) is involved in emotional awareness, the dorsal ACC (motor limbic) mediates behavior initiation, and the role of the thalamus is to bind the SN circuit together.^{1,28} In addition to the SN, we found that decline in socioemotional sensitivity corresponded to progressive atrophy in the OFC and subgenual ACC, which belong to the SAN.² The SAN has its key node in the right TP, which stores multimodal concepts, including social ones such as emotions, faces, and biographies.^{29,30} The right TP is intrinsically connected with regions related to reward and hedonics, including the OFC, subgenual ACC, caudate, and nucleus accumbens.² The interplay between these regions mediates personal evaluations of social semantic concepts, which includes tagging concepts with complex hedonic evaluations and resolving ambiguity about the semantic identity of the concepts based on viscerally experienced valence (this is disgust, not amusement).³¹ These results also support previous cross-sectional studies showing that gray matter atrophy and functional connectivity changes in the SN and SAN correspond to characteristic bvFTD social symptoms, including loss of

empathy^{32,33} and interpersonal warmth,^{34,35} as well as disrupted emotion recognition, reactivity, and experience.^{36–38}

Although patients with different disease severities at baseline showed similar rates of RSMS score progression, our ROI analysis showed that thalamic volume was the region that was most consistently predictive of RSMS score change in very mild and mild disease stages of bvFTD and became less predictive in patients with moderate to severe disease severity. One reason for this may be that the thalamic volume loss was so extensive in later disease stages that it reached a plateau so that no brain-behavior relationship was detectable anymore. Another possible explanation is that our linear statistical approach did not adequately model this brain-behavior relationship in later disease stages when brain volume loss may accelerate disproportionately compared to earlier disease stages.³⁹ In addition, the finding that the thalamus plays a critical role for progression of social symptoms in patients with bvFTD supports previous evidence showing that thalamic atrophy causes functional connectivity changes in the SN in *C9orf72* carriers with bvFTD⁴⁰ and is frequently associated with early neuropsychiatric symptoms.^{41,42} This result is also consistent with our previous work demonstrating that functional connectivity between the right AI and subcortical regions, including the thalamus, predicts socioemotional sensitivity in healthy older adults and in patients with early neurodegenerative disease.⁹ Because previous studies have shown that thalamic atrophy is closely linked to the *C9orf72* mutation,^{23,43} we performed a post hoc analysis excluding the 12 *C9orf72* carriers and found that thalamic volume no longer significantly predicted decline in RSMS score, suggesting that the *C9orf72* subtype was a major driver of this finding in our sample. However, because thalamic atrophy is also found in very early stages of patients with sporadic bvFTD⁴⁴ and in *GRN* and *MAPT* carriers,⁴⁵ we cannot exclude that there may also be a relationship between RSMS score and thalamus across both patients with sporadic bvFTD and those with genetic bvFTD that we were not able to detect because of insufficient power; thus, future studies in larger samples are likely warranted to resolve this issue.

Our previous cross-sectional⁹ and current longitudinal findings confirm that the RSMS is a valid clinical measure to assess the progression of both symptoms and neural network changes in patients with bvFTD in both neurologic practice and research. We have recently shown that the RSMS shows high interindividual variability and is not susceptible to ceiling or floor effects, both in healthy participants across the lifespan and in patients with neurodegenerative disease,⁹ psychometric qualities that are required for measures to be used to assess symptom progression in therapeutic trials targeting patients with different disease severities.²⁴ In addition, our previous and current work confirms that the RSMS can be administered quickly as an informant questionnaire to identify patients with bvFTD in the earliest stage of disease and thus could be used to enroll very mildly symptomatic patients in clinical trials on the basis of behavioral phenotype. Moreover, the present results show that the RSMS can measure socioemotional and cortico-

subcortical SN progression in both mutation carriers and noncarriers with bvFTD syndrome, including in patients who are in very early disease stage. Finally, this study showed that greater loss of socioemotional sensitivity is associated with higher levels of distress for caregivers and families. Thus, a clinical trial that achieves a delay or remission of the socioemotional symptoms measured by the RSMS may directly affect quality of life for caregivers by reducing their burden.

Our study has some limitations. One limitation was that the number of patients in this study with any of the 3 FTD mutations yielded insufficient power to investigate our longitudinal brain-behavior relationships separately in these subgroups. Another limitation always inherent to longitudinal analyses was the manner in which interindividual variation in patient factors may have influenced our statistical models, including age at symptom onset, disease stage at baseline, rate of progression, and number of and interval between time points. Although we used LME model analyses to account for this statistical noise, we cannot be certain that our models were able to adequately correct for all interindividual variability. Another consideration is that, while our analyses found a significant linear relationship between RSMS score and both disease stage and time, it is possible that, with the increased power afforded by additional data collection in future studies, this linear relationship may actually turn out to be more nuanced, and sigmoid models should be evaluated. Finally, because our behavioral analyses suggest a linear progression of RSMS score, we used linear statistical models to investigate our brain-behavior relationships in all disease stages. However, this statistical approach may not be appropriate to model our brain-behavior relationships in later disease stages because the rate of progression in gray matter atrophy may be different from earlier disease stages.³⁹ It is also possible that baseline atrophy and overall rate of progression differ among carriers and noncarriers, as well as among the 3 different FTD mutations.^{46,47}

The RSMS is a brief but effective informant questionnaire that clinicians and clinical researchers can use to identify the earliest changes in socioemotional behavior in patients with bvFTD and to monitor the progression of both symptoms and damage to vulnerable brain networks throughout the disease. Our findings suggest that this scale measures a valuable clinical endpoint in treatment trials conducted for patients with the predominantly bvFTD syndrome and potentially other neurodegenerative diseases.

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Adam Staffaroni, PhD	University of California, San Francisco	Statistical analysis, revising the manuscript for intellectual content
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Neill Graff-Radford, MD	Mayo Clinic, Rochester, MN	Revising the manuscript for intellectual content
Murray Grossman, MD, EdD	University of Pennsylvania, Philadelphia	Revising the manuscript for intellectual content
Hilary Heuer, PhD	University of California, San Francisco	Acquisition of data, revising the manuscript for intellectual content
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Appendix (continued)

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Sandra Weintraub, PhD	Northwestern University, Chicago, IL	Revising the manuscript for intellectual content
Brad Boeve, MD	Mayo Clinic, Rochester, MN	Data interpretation, revising the manuscript for intellectual content
Adam Boxer, MD, PhD	University of California, San Francisco	Data interpretation, revising the manuscript for intellectual content
Howard Rosen, MD	University of California, San Francisco	Data interpretation, revising the manuscript for intellectual content

Appendix (continued)

Name	Location	Contribution
Katherine Rankin, PhD	University of California, San Francisco	Data acquisition, study design and concept, statistical analysis, data interpretation, revising the manuscript for intellectual content

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