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RESEARCH ARTICLE

Extending the phenotypic spectrum assessed by the CDR plus NACC FTLD in genetic frontotemporal dementia

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Abstract

INTRODUCTION: We aimed to expand the range of the frontotemporal dementia (FTD) phenotypes assessed by the Clinical Dementia Rating Dementia Staging Instrument plus National Alzheimer's Coordinating Center Behavior and Language Domains (CDR plus NACC FTLD).

METHODS: Neuropsychiatric and motor domains were added to the standard CDR plus NACC FTLD generating a new CDR plus NACC FTLD-NM scale. This was assessed in 522 mutation carriers and 310 mutation-negative controls from the Genetic Frontotemporal dementia Initiative (GENFI).

RESULTS: The new scale led to higher global severity scores than the CDR plus NACC FTLD: 1.4% of participants were now considered prodromal rather than asymptomatic, while 1.3% were now considered symptomatic rather than asymptomatic or

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prodromal. No participants with a clinical diagnosis of an FTD spectrum disorder were classified as asymptomatic using the new scales.

DISCUSSION: Adding new domains to the CDR plus NACC FTLD leads to a scale that encompasses the wider phenotypic spectrum of FTD with further work needed to validate its use more widely.

KEYWORDS

C9orf72, frontotemporal dementia, genetics, progranulin, tau

Highlights

- The new Clinical Dementia Rating Dementia Staging Instrument plus National Alzheimer's Coordinating Center Behavior and Language Domains neuropsychiatric and motor (CDR plus NACC FTLD-NM) rating scale was significantly positively correlated with the original CDR plus NACC FTLD and negatively correlated with the FTD Rating Scale (FRS).
- No participants with a clinical diagnosis in the frontotemporal dementia spectrum were classified as asymptomatic with the new CDR plus NACC FTLD-NM rating scale.
- Individuals had higher global severity scores with the addition of the neuropsychiatric and motor domains.
- A receiver operating characteristic analysis of symptomatic diagnosis showed nominally higher areas under the curve for the new scales.

1 | BACKGROUND

Frontotemporal dementia (FTD) is a progressive neurodegenerative disorder that results in behavioral, cognitive, motor, and functional deficits. Disease severity is usually measured using either the Clinical Dementia Rating Dementia Staging Instrument plus National Alzheimer's Coordinating Center Behavior and Language Domains (CDR plus NACC FTLD)[1–3] or the FTD Rating Scale (FRS).[4,5] However, neither fully encompass all the multi-domain deficits that are found in FTD.[6–8] This has become increasingly important in recent years as disease-modifying drugs are developed, with trials commonly using the CDR plus NACC FTLD and FRS as either outcome measures or as methods of stratification.[9]

Previous work from our group has investigated the lack of motor and neuropsychiatric elements within clinical rating scales [7,8] using data from the Genetic Frontotemporal Initiative (GENFI) study, which studies the familial forms of FTD, particularly those with mutations in progranulin (*GRN*), chromosome 9 open reading frame 72 (*C9orf72*), and microtubule-associated protein tau (*MAPT*).[10] This work shows that a single motor score can incorporate the clinical symptoms of parkinsonism and amyotrophic lateral sclerosis (ALS) seen across the FTD spectrum.[7] Similarly, a single neuropsychiatric score is required, but including only psychotic features of hallucinations and delusions, and excluding affective symptoms (which fluctuate longitudinally) and other neuropsychiatric features which load with the core behavioral disturbances seen in FTD.[8] We now aim to add both of these novel components to the original CDR plus NACC FTLD scale, alongside a re-evaluation of the language element. The goal of the study is to extend the phenotypic spectrum assessed by the scale, aiming to improve its use as both a staging and outcome measure in forthcoming clinical trials.

2 | METHODS

2.1 | Participants

Participants were recruited from the fifth data freeze of the GENFI study between January 20, 2012 and May 30, 2019, including sites in the UK, Canada, Belgium, Germany, France, Italy, the Netherlands, Portugal, Spain, and Sweden.

The standardized GENFI clinical assessment included a history, examination, cognitive assessment (including Mini-Mental State Examination [MMSE]), FRS, and the CDR plus NACC FTLD rating scale. Mutation carriers were classified into asymptomatic, prodromal, or symptomatic if they scored 0, 0.5, or ≥ 1, respectively, on the CDR plus NACC FTLD global score.

All mutation carriers with baseline clinical data were included: 522 in total, consisting of 221 *C9orf72*, 213 *GRN*, and 88 *MAPT* mutation carriers (CDR plus NACC FTLD 0 = 291 [55.7%], 0.5 = 82

[15.7%], ≥ 1 = 149 [28.5%]). Based on clinician judgement, 165 individuals were classed as symptomatic, and 357 mutation carriers were identified as unaffected (i.e., not yet symptomatic). The control group consisted of 310 mutation-negative family members with a CDR plus NACC FTLD global score of < 1. Demographics of the groups are shown in Table 1.

2.2 | Rating scale analysis

As part of the GENFI clinical assessment, the CDR plus NACC FTLD was administered as per standard protocol (interviewing both the participant and an informant separately) including the core cognitive and functional domain items from the CDR (memory, orientation, judgment and problem solving, community affairs, hobbies, personal care), and the two clinician judgment (global) scores from the NACC FTLD for behavior and language.

Additionally, the GENFI study includes a set of questionnaires consisting of individual behavior, language, neuropsychiatric, and motor symptoms as well as overall global scores for neuropsychiatric and motor features, each scored using a symptom severity scale along the lines of that used in the CDR, that is, 0 (absent), 0.5 (very mild/questionable), 1 (mild), 2 (moderate), and 3 (severe). Of note, for the motor features the questionnaire only includes reported symptoms and not signs found on physical examination.

Prior work from our group has examined the optimal methods for adding both neuropsychiatric and motor components,[7,8] suggesting that the neuropsychiatric score should consist of only psychosis features (i.e., only delusions and visual/auditory hallucinations), and the motor component should be a single score encompassing all the motor symptoms in the GENFI questionnaire. Hence, while there was a global score that could be used for motor symptoms in the current study, there was no global score available for the neuropsychiatric component. We therefore used an algorithm-derived score which consisted of only the individual psychosis symptoms.[8] Adding these two scores to the CDR plus NACC FTLD led to a new scale, which we refer to as the CDR plus NACC FTLD-NM. As with the other CDR scores, both a global score (using the scoring rules outlined in Table S1 in supporting information) and sum of boxes (SOB) score were calculated.

In previous work we have also examined whether it may be helpful to derive the overall score for each FTD-related domain by combining scores from multiple individual symptoms within that domain, rather than relying on a global "feel." The hypothesis is that a more objective (and accurate) score will be given when a clinician individually scores a specific symptom (e.g., apathy, disinhibition, etc.) rather than trying to score a gestalt sense of a heterogeneous domain (e.g., behavior). An overall score is then derived using a specific algorithm which weighs individual symptoms and produces a single score for that domain. We have called these "algorithm-derived" scores here and produced them for behavior (as per Samra et al.[8]), language (as per Supplementary Appendix in supporting information), neuropsychiatric (as per Samra et al.,[8] and the same as used above) and motor (as per Samra et al.[7]) domains. After all the algorithm-derived domain scores were generated, the CDR plus NACC FTLD-NM scale was adjusted to include the six core items from the CDR using the standard methodology (without alteration), and algorithm-derived behavior, neuropsychiatric, motor, and language components using the scoring rules described in Table S1. This formed a new scale, termed CDR plus NACC FTLD-NMI, referencing the "individual" symptoms that the FTD-related domains were derived from, with both global and SOB scores calculated.

See Table 2 for a summary of the CDR scales examined here.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using PubMed. While expanding the range of phenotypes assessed by the Clinical Dementia Rating Dementia Staging Instrument plus National Alzheimer's Coordinating Center Behavior and Language Domains (CDR plus NACC FTLD) has not been investigated systematically, there have been several publications describing neuropsychiatric and motor features in genetic frontotemporal dementia (FTD).
2. **Interpretation**: This cohort study showed adding neuropsychiatric and motor domains to the existing CDR plus NACC FTLD led individuals to enter more severe disease stages. This is consistent with previous studies that highlight the important contribution of symptoms within these domains to FTD disease burden.
3. **Future directions**: This study brings us closer to suitable staging and outcome measures for use in genetic FTD-related clinical trials.

2.3 | Statistical analysis

All statistical analyses were performed using Stata/MP 16.1 unless otherwise specified. All graphs were produced using GraphPad Prism 9 apart from the Sankey diagrams, which were made using SankeyMATIC.

Global and SOB scores were compared between groups for each scale using linear regressions comparing to controls, and logistic regressions between mutation groups, adjusting for age and sex, and 95% bias-corrected bootstrapped confidence intervals with 2000 repetitions where applicable. Sex differences were calculated using a chi-squared test.

Spearman rank correlations were performed to compare both the CDR plus NACC FTLD-NM-SOB and CDR plus NACC FTLD-NMI-SOB to the original CDR plus NACC FTLD and the FRS, as well as with each other. Analyses were performed within the mutation carriers.

TABLE 1 Demographics and clinical scores for all mutation carriers (*C9orf72*, *GRN*, *MAPT*) and mutation-negative controls.

CDR plus NACC FTLD	Controls	All mutation carriers				*C9orf72*				*GRN*				*MAPT*			
		All	0	0.5	1	All	0	0.5	1	All	0	0.5	1	All	0	0.5	1
No. of participants	310	522	289	84	149	221	110	39	72	213	130	31	52	88	49	14	25
% Male	44	44	38	41	58	49	41	41	65	39	35	48	46	45[a]	41	29	64
Age in years	46.0 (12.7)	**50.1 (13.7)**	44.1 (11.9)	**49.9 (12.3)**	**62.0 (9.2)**	**51.2 (13.6)**	44.2 (11.6)	49.9 (11.5)	**62.7 (9.3)**	**51.0 (13.6)**	45.8 (12.2)	**51.8 (13.2)**	**63.5 (7.7)**	45.3 (13.1)[ab]	**39.2 (10.4)[ab]**	45.7 (12.6)	**57.0 (10.1)[ab]**
Education	14.5 (3.3)	**13.9 (3.4)**	14.5 (3.2)	14.0 (3.1)	**12.8 (3.7)**	13.9 (3.2)	14.4 (3.0)	14.1 (2.5)	**13.1 (3.7)**	13.9 (3.7)	14.7 (3.4)	14.0 (4.0)	**11.9 (3.5)[c]**	14.1 (3.3)	14.4 (3.3)	13.5 (2.4)	13.6 (3.8)
MMSE	29.3 (1.0)	**27.1(5.3)**	29.4 (1.0)	**28.4 (2.2)**	**21.9 (7.6)**	**27.2 (4.7)**	29.2 (1.1)	**28.4 (2.2)**	**23.4 (6.6)**	**26.9 (6.0)**	29.4 (0.9)	28.5 (2.4)	**19.3 (8.4)[a]**	**27.4 (5.1)**	29.5 (0.8)	28.2 (2.3)	**22.8 (7.7)**
FRS	96.6 (7.0)	**77.2 (31.0)**	95.8 (7.8)	**87.3 (18.5)**	**38.8 (26.9)**	**71.2 (34.0)[b]**	95.3 (7.7)[b]	**84.5 (20.4)**	**33.1 (25.2)[b]**	**83.0 (27.4)**	97.3 (5.8)	90.5 (15.0)	**45.1 (27.8)**	**78.3 (28.8)**	**93.0 (11.2)[b]**	88.8 (19.5)	**42.9 (27.7)**
CDR plus NACC FTLD Global score	0.1 (0.2)	**0.6 (1.0)**	*0.0 (0.0)*	**0.5 (0.0)**	**2.0 (0.8)**	**0.8 (1.0)[b]**	*0.0 (0.0)*	**0.5 (0.0)**	**2.1 (0.8)**	**0.5 (0.9)**	*0.0 (0.0)*	**0.5 (0.0)**	**1.9 (0.8)**	**0.6 (0.9)**	*0.0 (0.0)*	**0.5 (0.0)**	**1.9 (0.8)**
CDR plus NACC FTLD Sum of boxes	0.2 (0.4)	**3.1 (5.5)**	*0.0 (0.0)*	**1.1 (0.8)**	**10.3 (5.8)**	**3.8 (6.0)[b]**	*0.0 (0.0)*	**1.1 (0.8)**	**10.9 (5.7)**	**2.5 (5.1)**	*0.0 (0.0)*	**1.0 (0.8)**	**9.8 (6.0)**	**2.9 (5.3)**	*0.0 (0.0)*	**1.1 (0.8)**	**9.7 (5.8)**

Note: Age, education, MMSE, FRS, and clinical rating scale scores are shown as mean (standard deviation). Note that FRS was available in 440 mutation carriers (187 *C9orf72*, 178 *GRN*, 75 *MAPT*) and 252 controls. Bold items are significantly different to controls (italicized items are significantly less impaired compared to controls) using linear regression when comparing to controls, logistic regression between mutation groups, and chi-squared for sex differences ($P < 0.005$). Other differences are shown as: [a]Significantly impaired/young/more males compared to *C9orf72*; [b]Significantly impaired/young compared to *GRN*; or [c]Significantly impaired/fewer education years compared to *MAPT* mutation carriers.

Abbreviations: CDR plus NACC FTLD; Clinical Dementia Rating Dementia Staging Instrument plus National Alzheimer's Coordinating Center Behavior and Language Domains; FRS, FTD Rating Scale *GRN*, progranulin; *MAPT*, microtubule-associated protein tau; MMSE, Mini-Mental State Examination.

TABLE 2 A breakdown of the components of the Clinical Dementia Rating scales discussed in this paper.

	CDR	Behavior	Language	Neuropsychiatric	Motor
CDR plus NACC FTLD	Standard algorithm	Global	Global	X	X
CDR plus NACC FTLD-NM	Standard algorithm	Global	Global	Algorithm	Global
CDR plus NACC FTLD-NMI	Standard algorithm	Algorithm	Algorithm	Algorithm	Algorithm

Note: "Global" represents clinician judgement domain scores, while "Algorithm" represents domain scores generated using the algorithm scoring rules outlined in Table S1 in supporting information. The CDR has a standard algorithm which defines the global CDR score.
Abbreviations: CDR plus NACC FTLD; Clinical Dementia Rating Dementia Staging Instrument plus National Alzheimer's Coordinating Center Behavior and Language Domains; CDR plus NACC FTLD-NM, Clinical Dementia Rating Dementia Staging Instrument plus National Alzheimer's Coordinating Center Behavior and Language Domains plus Neuropsychiatric and Motor domains; CDR plus NACC FTLD-NMI, Clinical Dementia Rating Dementia Staging Instrument plus National Alzheimer's Coordinating Center Behavior and Language Domains plus Neuropsychiatric and Motor domains by individual symptoms.

A receiver operating characteristic (ROC) curve analysis was also performed to compare the diagnostic utility of the scales, determining whether they could detect if a participant was symptomatic as per clinician judgement.

2.4 | Ethics approval and consent to participate/publish

All GENFI sites had local ethical approval for the study, and all participants gave written informed consent. Travel and accommodation expenses were covered but participants did not receive a stipend. The London Queen Square Research Ethics Committee reference is 14/0377.

3 | RESULTS

3.1 | Demographics

No significant differences were seen between the mutation groups in years of education apart from *GRN* mutation carriers with a CDR plus NACC FTLD of ≥ 1 who had significantly fewer years in education compared to the equivalent *MAPT* group ($P = 0.038$). There were also significantly more males with a *MAPT* mutation compared to the *C9orf72* group ($Chi^2 = 3.91$, $P = 0.048$; Table 1).

3.2 | Disease severity

The MMSE, FRS, and CDR plus NACC FTLD scores were significantly different from controls in each genetic group ($P < 0.001$). There were no significant differences between the mutation groups overall, apart from the *C9orf72* mutation group, which had significantly impaired FRS ($P < 0.001$) and CDR plus NACC FTLD (Global score: $P = 0.023$, SOB: $P = 0.020$) scores compared to *GRN* mutation carriers.

3.3 | CDR plus NACC FTLD-NM

The CDR plus NACC FTLD-NM significantly positively correlated with the CDR plus NACC FTLD and negatively correlated with the FRS in the combined mutation carrier group ($rho = 0.98$, $P < 0.001$; $rho = -0.77$, $P < 0.001$, respectively), and within the individual mutation groups: *C9orf72* ($rho = 0.97$, $P < 0.001$; $rho = -0.80$, $P < 0.001$), *GRN* ($rho = 0.99$, $P < 0.001$; $rho = -0.75$, $P < 0.001$), and *MAPT* ($rho = 0.98$, $P < 0.001$; $rho = -0.67$, $P < 0.001$).

Compared to the CDR plus NACC FTLD 1.4% of participants were now considered prodromal using the new scale who had previously been considered asymptomatic (Figures 1 and 2A; Table S2 in supporting information). Similarly, 1.3% of participants were now considered symptomatic who had previously been considered asymptomatic or prodromal (Figure 2A). Furthermore, no individuals with a clinician-judged symptomatic diagnosis of ALS/FTD-ALS or a parkinsonian syndrome were classified as asymptomatic anymore (compared to 17.6% and 20.0% for the original CDR plus NACC FTLD; Figure 2A and Figure S1 in supporting information).

3.4 | CDR plus NACC FTLD-NMI

The CDR plus NACC FTLD-NMI significantly positively correlated with the CDR plus NACC FTLD and negatively correlated with the FRS in the combined mutation carrier group ($rho = 0.89$, $P < 0.001$; $rho = -0.75$, $P < 0.001$), and within the mutation groups *C9orf72* ($rho = 0.94$, $P < 0.001$; $rho = -0.80$, $P < 0.001$), *GRN* ($rho = 0.93$, $P < 0.001$; $rho = -0.69$, $P < 0.001$), and *MAPT* ($rho = 0.93$, $P < 0.001$; $rho = -0.66$, $P < 0.001$).

Compared to the CDR plus NACC FTLD 8.5% of participants were now considered prodromal using the new scale who had previously been considered asymptomatic (Figures 1 and 2B; Table S2). Similarly, 2.0% of participants were now considered symptomatic who had previously been considered asymptomatic or prodromal (Figure 2B). Furthermore, no individuals with a clinician-judged symptomatic diagnosis of ALS/FTD-ALS or parkinsonism were classified as asymptomatic anymore (Figure 2B and Figure S2 in supporting information).

3.5 | CDR plus NACC FTLD-NM versus CDR plus NACC FTLD-NMI

The CDR plus NACC FTLD-NM and CDR plus NACC FTLD-NMI scores were significantly positively correlated ($rho = 0.91$, $P < 0.001$).

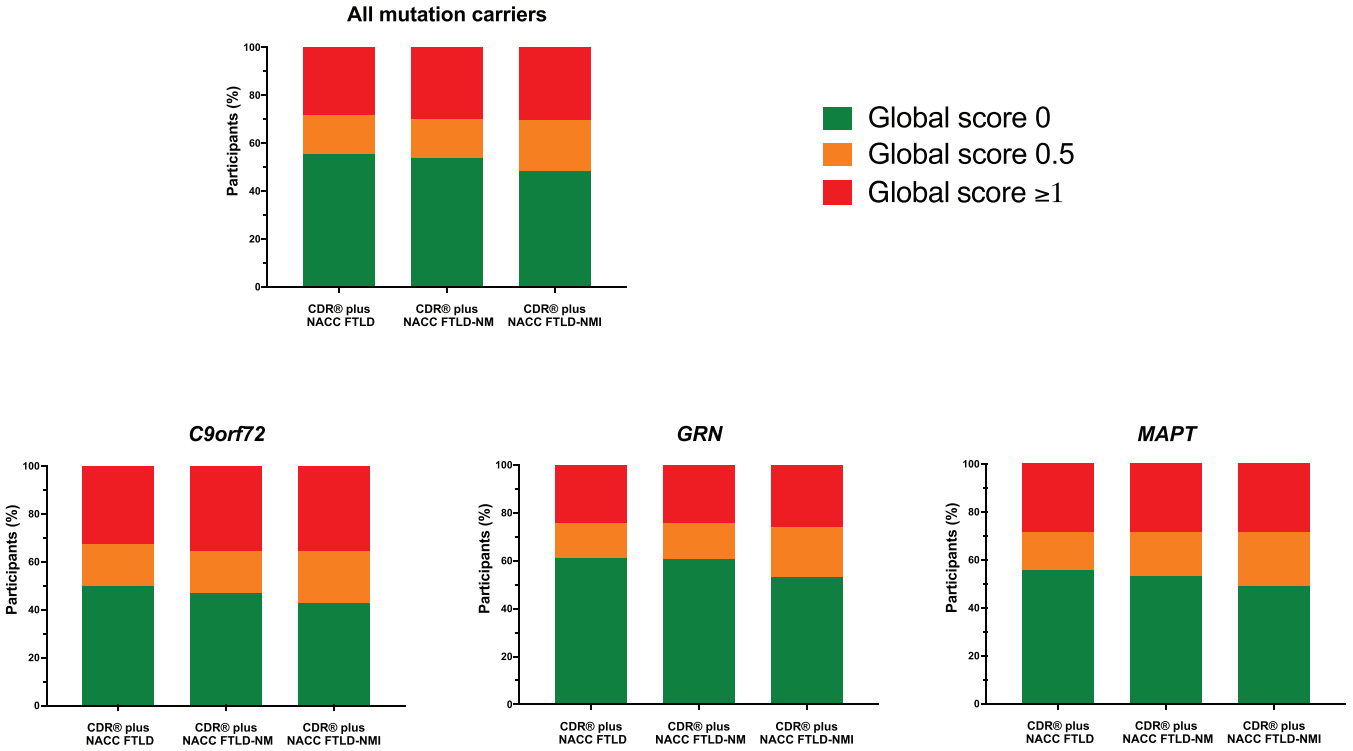

FIGURE 1 Comparison of the overall CDR plus NACC FTLD, CDR plus NACC FTLD-NM, and CDR plus NACC FTLD-NMI scores within mutation carriers stratified by global score (0, 0.5, and ≥ 1). *C9orf72*, chromosome 9 open reading frame 72; CDR plus NACC FTLD; Clinical Dementia Rating Dementia Staging Instrument plus National Alzheimer's Coordinating Center Behavior and Language Domains; CDR plus NACC FTLD-NM, Clinical Dementia Rating Dementia Staging Instrument plus National Alzheimer's Coordinating Center Behavior and Language Domains plus Neuropsychiatric and Motor domains; CDR plus NACC FTLD-NMI, Clinical Dementia Rating Dementia Staging Instrument plus National Alzheimer's Coordinating Center Behavior and Language Domains plus Neuropsychiatric and Motor domains by individual symptoms; *GRN*, progranulin; *MAPT*, microtubule-associated protein tau.

Participants tended to score higher with the -NMI scale, for example, more participants were prodromal and moderately symptomatic with the -NMI scale (23.7% and 7.2% of total participants) compared to the -NM scale (16.7% and 6.7%). However, a small number of cases scored lower on the -NMI scale compared to the -NM scale (see Figure 2C and Table S3 in supporting information).

3.6 | ROC analysis

The area under the curve (AUC) was 0.942 for the CDR plus NACC FTLD, 0.967 for the CDR plus NACC FTLD-NM, and 0.970 for the CDR plus NACC FTLD-NMI (Figure 3).

4 | DISCUSSION

In this study we have shown that the addition of two new modules (for neuropsychiatric and motor symptoms) to the CDR plus NACC FTLD more accurately captures the complete phenotype seen within the FTD spectrum. In particular, it more appropriately places individuals at the correct (often more severe) stage of disease. This is particularly important for those genetic FTD mutation carriers who have primary motor diagnoses, who were previously deemed asymptomatic using the original scale but are now correctly classed as affected. Overall, this suggests that the CDR plus NACC FTLD-NM (or -NMI) may be a potential staging and outcome measure for clinical trials in genetic FTD in preference to the original scale.

A ROC curve analysis identified a nominally higher AUC for the new scales. This is largely driven by the inability of the previous scale to identify those with primary motor diagnoses. Looking at this in more detail, this change is seen predominantly in *C9orf72* and *MAPT* mutation carriers for whom half of those with an FTD spectrum diagnosis within these genetic groups became affected or more severely affected with the new scales. *C9orf72* expansions are particularly associated with the presence of ALS, and many people will develop features of both FTD and ALS[11,12] or even motor features without meeting criteria for ALS.[7,13,14] *MAPT* mutations are associated with the development of parkinsonian disorders including corticobasal syndrome, progressive supranuclear palsy, as well as parkinsonian disorders resembling Parkinson's disease.[15–20] However, similarly to *C9orf72*, a number of people will develop parkinsonian symptoms without meeting criteria for one of the atypical parkinsonian conditions.[7,16,21,22] These new scales will therefore be particularly

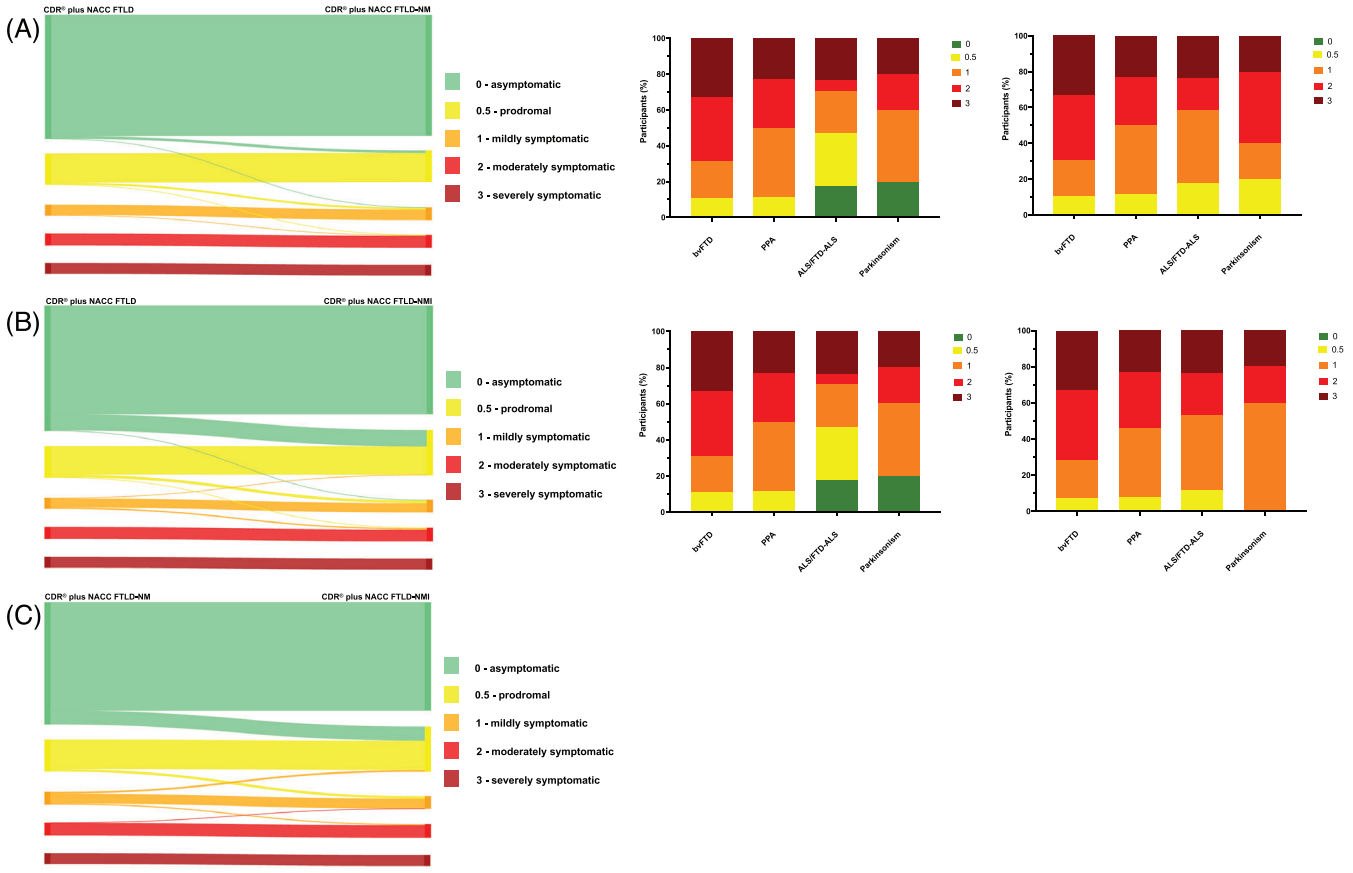

FIGURE 2 A, Comparison of the standard CDR plus NACC FTLD to a new CDR plus NACC FTLD-NM. Left figure shows the change in global score in individual participants and right figure shows the percentage of symptomatic participants with a particular CDR score (left shows standard CDR plus NACC FTLD, right shows new CDR plus NACC FTLD-NM). Diagnoses: bvFTD, behavioral variant frontotemporal dementia; PPA, primary progressive aphasia; ALS/FTD-ALS, amyotrophic lateral sclerosis; Parkinsonism (progressive supranuclear palsy, corticobasal syndrome, or Parkinson's disease). B, Comparison of the standard CDR plus NACC FTLD to a new CDR plus NACC FTLD-NMI. Left figure shows the change in global score in individual participants and right figure shows the percentage of symptomatic participants with a particular CDR score (left shows standard CDR plus NACC FTLD, right shows new CDR plus NACC FTLD-NMI). Diagnoses: bvFTD, behavioral variant frontotemporal dementia; PPA, primary progressive aphasia; ALS/FTD-ALS, amyotrophic lateral sclerosis; Parkinsonism (progressive supranuclear palsy, corticobasal syndrome, or Parkinson's disease). C, Comparison of the CDR plus NACC FTLD-NM to the CDR plus NACC FTLD-NMI showing the change in global score in individual participants.

helpful when considering trials in these two genetic groups moving forward.

Neuropsychiatric symptoms are more common in *C9orf72* expansions but nonetheless occur to a significant extent in the other two genetic groups as well.[8,23–27] The addition of a neuropsychiatric module consisting of psychosis symptoms (which separate out from other behavioral features) to the new scale will therefore be important across the genetic FTD spectrum and not just for the *C9orf72* group. Because of how the module was derived (see Samra et al.[8]), there is no current global neuropsychiatric score based on just the psychosis symptoms, but future versions of the CDR plus NACC FTLD-NM would aim to incorporate this.

There has been a recent focus on better defining the prodromal period of FTD.[28,29] Although this is not yet completely defined, a recent study suggested criteria for prodromal behavioral variant FTD (bvFTD)[28] and incorporated several behavioral items based on sensitivity and specificity analyses—while five of these overlap with the core behavioral features included in the behavioral domain here (and in the Rascovsky bvFTD criteria), two items, irritability/agitation and joviality/gregariousness, are not included in our scale. It may therefore be helpful to include these items in future iterations of the -NMI scale.

The AUC for the two new scales, CDR plus NACC FTLD-NM and CDR plus NACC FTLD-NMI, were very similar, and these two scales were highly correlated. Nonetheless, there were some differences between them, with the CDR plus NACC FTLD-NMI in general scoring people more severely. The trade-off between the two scales is that the CDR plus NACC FTLD-NM is likely to be quicker for clinicians or researchers to complete, with an overall global score generated for behavior, language, and motor symptoms, while the CDR plus NACC FTLD-NMI may be considered more objective, as each module is based on scoring multiple individual symptoms and then using an algorithm to derive a single score.

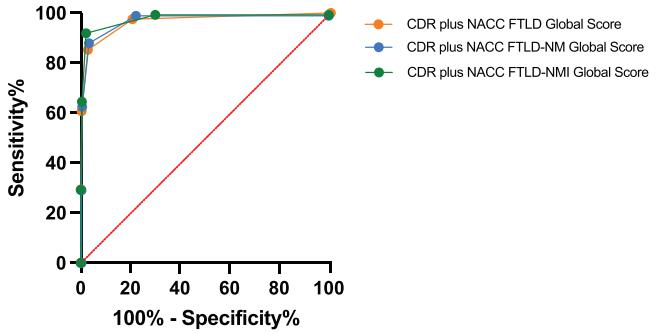

FIGURE 3 Receiver operating characteristic analysis of the utility of the CDR plus NACC FTLD, CDR plus NACC FTLD-NM, and CDR plus NACC FTLD-NMI for detection of clinician-judged symptomatic individuals. The red line represents the line of no discrimination. CDR plus NACC FTLD; Clinical Dementia Rating Dementia Staging Instrument plus National Alzheimer's Coordinating Center Behavior and Language Domains; CDR plus NACC FTLD-NM, Clinical Dementia Rating Dementia Staging Instrument plus National Alzheimer's Coordinating Center Behavior and Language Domains plus Neuropsychiatric and Motor domains; CDR plus NACC FTLD-NMI, Clinical Dementia Rating Dementia Staging Instrument plus National Alzheimer's Coordinating Center Behavior and Language Domains plus Neuropsychiatric and Motor domains by individual symptoms.

4.1 | Limitations

Firstly, although a large genetic FTD cohort was studied there were modest numbers in each group after stratification. Future studies with larger numbers aimed at replicating this work will be helpful. Such studies should also formally assess both intra- and inter-rater variability as well as investigate the longitudinal change in these scales. Further work will be needed to better understand the ability of the scale to detect specific changes in disease stage, for example, to identify phenoconverters. Second, there are a number of limitations of the scales themselves as they are currently set up: the language scale includes a number of individual items that are best assessed by a combination of history and examination, and future versions of the -NMI scale will require a focus on those symptoms assessed best by history; the motor scale is a symptom score only and therefore will not score examination features that are not noted by participants or informants, for example, subtle fasciculations or hyperreflexia that may herald early ALS—future versions of the scale should consider incorporating examination features alongside the history; and finally, although we include functional problems with the hands as an individual item in the motor scale, there are no other measures of the functional impact of motor deficits, which will need to be addressed in future iterations of the scale. Third, the scales have been constructed from the GENFI symptom questionnaires and so future iterations of the -NM and -NMI scales will require fully operationalized instructions on how to derive the global and algorithm-based scores and which symptoms to include within each component. Last, for future versions that might be performed remotely (e.g., by phone or video), there should be some caution over the possibility of missing some features that can only be detected by face-to-face examination (e.g., subtle motor findings).

4.2 | Summary

This study has highlighted the importance of updating the current method of assessing disease severity in FTD to include all symptom domains that can be affected in this disease. Much further work will be needed to be done to ensure this scale is ready for use in clinical trials, including more reliability and validity analyses. However, hopefully this work will be a first crucial step in the development of more appropriate staging and outcome measures in future clinical trials of genetic FTD.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests. Author disclosures are available in the supporting information.

DATA AVAILABILITY STATEMENT

Data will not be shared but is available upon reasonable request. JDR, as Principal Investigator, has full access to all of the data in the study and takes full responsibility for the integrity of the data and accuracy of data analysis.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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