

The Revised Self-monitoring Scale Detects Early Impairment of Social Cognition in Genetic Frontotemporal Dementia Within the GENFI Cohort

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Abstract

Background

Although social cognitive dysfunction is a major feature of frontotemporal dementia (FTD) it has been poorly studied in familial forms. A key goal of studies is to detect early cognitive impairment using validated measures in large patient cohorts.

Methods

We used the Revised Self-Monitoring Scale (RSMS) as a measure of socioemotional sensitivity in 730 participants from the Genetic FTD initiative (GENFI) observational study: 269 mutation-negative healthy controls, 193 *C9orf72* expansion carriers, 193 *GRN* mutation carriers and 75 *MAPT* mutation carriers. All participants underwent the standardised GENFI clinical assessment including the 'CDR® plus NACC FTLD' scale and RSMS. The RSMS Total score and its two subscores, socioemotional expressiveness (EX score), and modification of self-presentation (SP score) were measured. Volumetric T1-weighted magnetic resonance imaging was available from 377 mutation carriers for voxel-based morphometry (VBM) analysis.

Results

The RSMS was decreased in symptomatic mutation carriers in all genetic groups but at a prodromal stage only in the *C9orf72* (for the total score and both subscores), and *GRN* (for the modification of self-presentation subscore) groups. RSMS score correlated with disease severity in all groups. The VBM analysis implicated an overlapping network of regions including the orbitofrontal cortex, insula, temporal pole, medial temporal lobe and striatum.

Conclusions

The RSMS indexes socioemotional impairment at an early stage of genetic FTD, and may be a suitable outcome measure in forthcoming trials.

1. Background

Frontotemporal dementia (FTD) is a complex and heterogeneous neurodegenerative disease, manifesting itself as a diverse spectrum of clinical syndromes. However, despite differences in presentation, many people with FTD develop impaired social cognition [1], a set of psychological processes which includes the ability to evaluate social and emotional cues from others and then select an appropriate behavioural response, a phenomenon often referred to as 'socioemotional sensitivity' or 'self-monitoring'. In both healthy and clinical populations, the Revised Self-Monitoring Scale (RSMS) [2] has often been used to study socioemotional sensitivity and responsiveness as well as the neural networks that underlie them [3,4].

Unlike many neurodegenerative diseases, FTD is highly heritable with approximately a third of patients having a causative autosomal dominant genetic mutation [5]. Mutations are most commonly found in one of three genes, chromosome 9 open reading frame 72 (*C9orf72*), progranulin (*GRN*), and microtubule-associated protein tau (*MAPT*) [6], with the most common clinical presentation being behavioural variant FTD (bvFTD) [7]. However, whilst social cognitive dysfunction has been studied extensively in sporadic FTD, few investigations have looked at genetic cohorts exclusively.

The Genetic FTD Initiative (GENFI) is a multicentre natural history study aimed at investigating early biomarkers in a large genetic FTD cohort, including measures of cognition [5]. This study sought to assess whether the RSMS could detect early changes in social cognition and what the underlying neural correlates of the RSMS were in people with mutations in *C9orf72*, *GRN* and *MAPT*.

2. Methods

2.1 Participants

Participants were recruited from the fifth data freeze of GENFI, incorporating data from 24 sites. Of the 849 participants enrolled in the second phase of the study, cross-sectional data on the RSMS was available from 730 participants, consisting of 269 healthy controls (family members who tested negative for the mutation carried within the family), 193 *C9orf72* expansion carriers, 193 *GRN* mutation carriers and 75 *MAPT* mutation carriers (Table 1). All participants provided written informed consent.

2.2 Assessments

All participants were given the standardised GENFI clinical assessment battery including a medical history, physical examination, the Mini-Mental State Examination, and the CDR® Dementia Staging Instrument with National Alzheimer Coordinating Centre Frontotemporal Lobar Degeneration component (CDR® plus NACC FTLD) (Table 1). The CDR® plus NACC FTLD is a clinical measure of disease severity in FTD, consisting of a core six cognitive/functional domains with a further 2 domains addressing behaviour and language [8]. Each domain is rated on a five-point scale ranging from 0 (normal), 0.5 (questionably or minimally impaired), 1 (mildly but definitely impaired), 2 (moderately impaired), to 3 (severely impaired). The sum of ratings across all eight domains is used to generate the CDR® plus NACC FTLD *sum of boxes* (CDR® plus NACC FTLD-SB) (Table 1). A second measure, a *global CDR® plus NACC FTLD* score can also be generated, using a specific algorithm [9]. We used this global score to classify each of the genetic groups cross-sectionally into those who scored 0 (i.e. were asymptomatic), 0.5 (possibly or mildly symptomatic i.e. prodromal), and 1 or more (fully symptomatic mutation carriers).

2.3 Demographics

Demographics are shown in Table 1. There was a significant difference in sex between these groups: symptomatic *C9orf72* carriers had a significantly higher percentage of males than in the mildly symptomatic and asymptomatic *C9orf72* carrier groups and in the controls ($X^2(1) = 4.08, p = 0.044, X^2(1) = 9.12, p = 0.003$ and $X^2(1) = 11.79, p = 0.001$ respectively). There was also a significant difference in age between groups ($F(9,720) = 27.5, p < 0.001$): asymptomatic *MAPT* mutation carriers were significantly younger and mildly symptomatic *GRN* mutation carriers were significantly older than controls ($p < 0.001$ and $p = 0.043$ respectively). All symptomatic mutation carriers were significantly older than controls ($p < 0.001$). Analysis of differences in years spent in education ($F(9,720) = 4.09, p < 0.001$), showed that symptomatic *C9orf72* and *GRN* mutation carriers spent significantly fewer years when compared to controls ($p = 0.003$ and $p < 0.001$ respectively). All analyses were therefore adjusted for sex, age and education.

2.4 Revised Self-Monitoring Scale (RSMS)

The RSMS is a widely used questionnaire made up of 13 items designed to measure an individual's awareness of social behaviour and sensitivity to subtle emotional expressions during face-to-face interaction [10]. Items include 'In conversations, the subject is sensitive to even the slightest change in the facial expression of the person he/she is conversing with' and 'If someone is lying to the subject, he/she usually knows it at once from that person's manner or expression'. Each item is rated by a participant's informant on a 6-point scale, ranging from 'certainly, always false' (0 points) to 'certainly, always true' (6 points). As well as a Total score, two subscores of the RSMS can also be calculated: socioemotional expressiveness i.e. the ability to understand subtle social cues in others (EX score, out of 30), and modification of self-presentation i.e. the ability to change one's behaviour when it is not appropriate for the current social situation (SP score, out of 35).

2.5 Statistical Analysis

Statistical analyses were performed using StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC. In the healthy control group, Spearman rank correlations were performed to assess the relationship between the RSMS Total score, age, sex and education. Cross-sectional RSMS Total, EX and SP scores were compared between groups (healthy controls, and 0, 0.5 and 1+ in each genetic group) using a linear regression model adjusting for age, sex and education, with 95% bias-corrected bootstrapped confidence intervals with 1000 repetitions (to correct for non-normally distributed data).

2.6 Image acquisition and processing

Participants underwent volumetric T1-weighted magnetic resonance imaging according to the harmonized GENFI protocol on a 3T scanner. All images underwent quality control and any scans with movement or artefacts were eliminated from analysis. In addition, any scans displaying moderate to severe vascular disease or any lesion presentation were also excluded. 377 scans were included in the analysis: 151 *C9orf72* expansion carriers, 162 *GRN* mutation carriers and 64 *MAPT* mutation carriers. A Voxel-Based Morphometry (VBM) was subsequently performed using Statistical Parametric Mapping (SPM) 12 software, version 6685 (www.fil.ion.ucl.ac.uk/spm), running under Matlab R2014a (Mathworks, USA). T1-weighted images were normalised and segmented into Grey Matter (GM), White Matter (WM) and Cerebrospinal Fluid (CSF) probability maps using standard procedures and a fast-diffeomorphic image registration algorithm (DARTEL) [11]. Prior to analysis, GM segmentations were then transformed into Montreal Neurological Institute (MNI) space, modulated and smoothed using a Gaussian kernel with 6mm fill-width at half maximum, before applying a mask image as reported in Ridgway et al., 2009 [12]. In order to investigate the neural correlates of socioemotional sensitivity in each genetic group, multiple regression models were performed to explore the relationship of RSMS Total score and GM density in mutation carriers in each genetic group. Age, sex, scanner type and total intracranial volume (TIV, calculated using SPM [13]) were included as nuisance covariates. The Family-Wise Error (FWE) correction for multiple comparisons was set at 0.05. However, if no findings were observed at that strict level of correction, results were reviewed at an uncorrected p value of 0.001.

3. Results

3.1 Healthy control performance on the RSMS

Mean (standard deviation) RSMS Total score was 47.8 (8.4) in controls (Tables S1 and S2). Overall, there was no significant difference between performance in females ($n = 157: 48.5 (8.0)$) and males ($n = 112: 46.8 (9.0)$) ($p = 0.21$). No significant correlations between RSMS Total score and age ($\rho = 0.01, p = 0.87$) or education ($\rho = 0.12, p = 0.06$) were observed.

3.2 Cross-sectional analysis of mutation carriers

Mean RSMS Total scores in all symptomatic (CDR 1+) mutation carriers were significantly lower than in healthy controls (Tables 1 and 2, Figure 1): *C9orf72* 23.5 (12.3), *GRN* 28.6 (12.1), *MAPT* 22.8 (18.9). In the CDR 0.5 groups, the *C9orf72* group also scored significantly lower than controls with a trend for a lower score in the *GRN* group and no difference in the *MAPT* group: *C9orf72* 41.9 (11.4), *GRN* 43.8 (12.1), *MAPT* 50.1 (14.2). No significant differences were observed between the asymptomatic (CDR 0) mutation carrier groups and controls.

Within each genetic group, there was a significantly lower RSMS Total score in the symptomatic group compared with the CDR 0.5 and CDR 0 groups (Tables 1 and 2, Figure 1).

Stratifying by individual global CDR[®] plus NACC FTLD score (0, 0.5, 1, 2 and 3), all genetic groups show decreasing RSMS Total score with increasing CDR (Figure 2).

RSMS EX and SP scores followed a similar pattern as for RSMS Total performance (Table 1, Tables S3 and S4, Figures S1 and S2): mean scores in all symptomatic (CDR 1+) mutation carriers and the *C9orf72* CDR 0.5 group were significantly lower than in healthy controls for both EX and SP scores. However, additionally, the *GRN* CDR 0.5 group had significantly lower mean SP score than controls. Within each genetic group, there was a significantly lower RSMS EX

and SP score in the symptomatic groups compared with the CDR 0.5 and CDR 0 groups, with EX score also lower in the *C9orf72* CDR 0.5 group compared with the CDR 0 group (Tables S3 and S4, Figures S1 and S2).

3.3 Relationship between RSMS and CDR[®] plus NACC FTLD-SB

A strong negative correlation between RSMS Total score and CDR[®] plus NACC FTLD-SB scores was observed for all genetic groups (Figure S3): *C9orf72* ($r = -0.67, p < 0.001$), *GRN* ($r = -0.59, p < 0.001$), *MAPT* ($r = -0.53, p < 0.001$).

3.4 Neural correlates of RSMS in each genetic group

The VBM analysis revealed positive associations of the RSMS total score with grey matter volume corrected for multiple comparisons in the *C9orf72* and *GRN* groups, but only at an uncorrected p value of <0.001 for the *MAPT* group. Overlapping neural correlates were seen in each of the genetic groups, with an association of decreased score with lower grey matter volume in the orbitofrontal lobe, insula, temporal pole, medial temporal lobe and both caudate and putamen (Figure 3, Table S5).

4. Discussion

In this study, we have shown that the RSMS detects social cognitive impairment in genetic FTD, including early difficulties within the CDR 0.5 group of *C9orf72* mutation carriers for the Total score, and for both *C9orf72* and *GRN* mutation carriers for the modification of self-presentation (SP) subscore. RSMS Total score is highly correlated with 'CDR[®] plus NACC FTLD' score and with an overlapping 'social cognitive' network of regions including orbitofrontal, anteromedial temporal, insula and striatal areas.

The results here show that the RSMS score decreases with increasing disease severity as measured by the CDR[®] plus NACC FTLD score, with a significant negative correlation between both scores in each genetic group i.e. RSMS decreases as CDR[®] plus NACC FTLD increases. This relationship has also been described in a recent study [14], although that study did not separate mutation carriers into separate genetic groups.

Carriers of *C9orf72* repeat expansions at CDR 0.5 (i.e. possibly or mildly symptomatic) perform significantly worse on the Total RSMS score and both subscores than controls, whilst *GRN* mutation carriers have a significantly lower SP subscore and a trend to lower Total and EX scores than controls. These results highlight the potential for the RSMS to detect early deficits in social cognition in these genetic cohorts of FTD, prior to phenoconversion to being fully symptomatic.

The profiles of RSMS performance in *MAPT* mutation carriers seem to be somewhat unique. Symptomatic *MAPT* mutation carriers scored much lower at baseline than the other *MAPT* mutation carriers, a result that is consistent with findings from other cross-sectional [5,28–30] and longitudinal [31] familial FTD studies. This could imply that self-monitoring in *MAPT* mutation carriers is relatively stable in early disease stages until soon before or at the point of conversion when there is a rapid decline in social cognitive function, as opposed to a more gradual (and earlier) deterioration in *GRN* and *C9orf72* mutation carriers [32–35].

Previous studies in sporadic FTD have described links between deficits in emotional processing and empathic perspective taking and a 'social cognition network' comprising bifrontal (particularly orbitofrontal), anterior and inferior temporal and insula cortical regions [15–17]. Subcortical structures such as the amygdala and caudate have also been implicated in driving such dysfunction [17]. Results of the VBM analysis in this study highlighted frontal involvement across all mutation carrier groups, in particular the orbitofrontal cortex, a region known to be involved in decision-making and coordinating complex social and emotional behaviours [18–20] with its atrophy and circuitry disruption having been previously described in patients with behavioural variant FTD [21]. Previous studies specifically utilising the RSMS as a tool to measure social cognition have identified a positive association between socioemotional sensitivity and functional connectivity within the brain's salience network, largely between the right anterior insula and both cortical and subcortical nodes [10], as well as between right supramarginal and angular gyri, and right frontal pole [22,23]. Here we demonstrate widespread insula involvement, anteriorly in *C9orf72* and *GRN* mutation carriers and posteriorly in *MAPT* mutation carriers, in addition to anterior cingulate cortex involvement in *GRN* mutation carriers exclusively, another crucial element of the salience network [24].

Other brain regions associated with such behavioural deficits in FTD include the inferior and medial temporal gyri [4], areas particularly involved in emotion perception and recognition. Grey matter volume of the temporal pole was positively correlated with RSMS score in all mutation groups, with *C9orf72* carriers also exhibiting an association with superior temporal gyrus and *GRN* and *MAPT* carriers showing a correlation with inferior temporal gyri specifically. Our results also show an association of the basal ganglia, particularly the caudate and putamen, in all genetic groups. These subcortical regions are also known to be implicated in emotion recognition [25–27], an integral factor in an individual's performance on the RSMS.

Overall, there appears to be a network of brain regions associated with impairment of socioemotional sensitivity in FTD that includes frontal, temporal, insula and striatal areas, including significant crossover with areas involved in the salience network, thus supporting the established role of aberrant saliency detection in FTD-related social cognitive dysfunction.

Limitations

These data should be interpreted in light of some limitations. Despite the large nature of GENFI in comparison to other FTD studies, one limitation lies in the relatively small numbers in some of the groups once stratified. Future studies should aim to replicate these findings in larger cohorts, as well as investigate longitudinal changes in socioemotional sensitivity over time.

Another limitation lies in the design of the RSMS, due to the inclusion of reverse scoring. While every effort is taken to ensure the informant understands how to answer correctly, we cannot eliminate the chance of misinterpretation.

Lastly, while global CDR[®] plus NACC FTLD scoring is a validated and robust tool used to measure disease severity in FTD, the assessment of motor and neuropsychiatric symptoms is not included. With FTD representing a diverse spectrum of symptomatic profiles, a limitation of this study lies in possible mis-categorisation of individuals who might be at a more advanced stage of their disease but present with symptoms that are not specifically addressed by this scale.

5. Conclusions

In summary, this study describes the ability of the RSMS to detect early changes in socioemotional behaviour in distinct genetic cohorts of FTD and illustrates the neural correlates of self-monitoring in these populations. The earliest symptoms of FTD are a product of altered functional connectivity that precedes structural atrophy [36,37] thus tests such as the RSMS that have been shown to correlate well with these functional changes may prove to be the most powerful diagnostically, providing scope to successfully distinguish behavioural symptoms of FTD from psychiatric disorders [38], as well as serving as a potentially useful outcome measure in clinical trials.

Abbreviations

FTD: frontotemporal dementia, RSMS: Revised Self-Monitoring Scale, GENFI: Genetic FTD Initiative, *C9orf72*: chromosome 9 open reading frame 72, *GRN*: progranulin, *MAPT*: microtubule-associated protein tau, CDR[®] plus NACC FTLD: CDR[®] Dementia Staging Instrument with National Alzheimer Coordinating Centre Frontotemporal Lobar Degeneration component, VBM: Voxel-Based Morphometry, bvFTD: behavioural variant FTD, CDR[®] plus NACC FTLD-SB: CDR[®] plus NACC FTLD sum of boxes, EX: RSMS socio-emotional expressiveness subscore, SP: RSMS modification of self-presentation subscore, SPM: Statistical Parametric Mapping, GM: Grey Matter, WM: White Matter, CSF: Cerebrospinal Fluid, DARTEL: fast-diffeomorphic image registration algorithm, MNI: Montreal Neurological Institute, TIV: total intracranial volume, FWE: Family-Wise Error.

Declarations

Ethics approval and consent to participate

Data was collected at GENFI sites under individual ethics approval approved by the local ethics board. Written consent was obtained from all participants before entering the study.

Consent for publication

Consent for publication of data is included within the written consent when entering into the study.

Availability of data and materials

Data are available upon reasonable request. The raw data of this project are part of GENFI and are not publicly available in accordance with the ethical approval. Data can be accessed upon reasonable request to JDR (j.rohrer@ucl.ac.uk).

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

HDF, LLR and JDR designed the study, processed the data, performed analyses, and wrote the first draft of the manuscript. All other authors have collected and helped to analyse data and contributed to the writing and critical revision of the manuscript.

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Tables

Table 1. Demographics and the RSMS Total, EX and SP scores for each genetic group, split by global CDR[®] plus NACC FTLD score (0, 0.5, 1+). N represents number of participants, mean (standard deviation) shown for age, education and cognitive test scores. In the *symptomatic* (1+) groups, MMSE scores were significantly lower in *GRN* carriers than in *C9orf72* carrier group but no other differences were seen, whilst no differences were seen in the CDR[®] plus NACC FTLD-SB.

	N	Sex	Age (years)	Education (years)	MMSE (/30)	CDR plus NACC FTLD SB	RSMS Total (/65)	RSMS EX (/30)	RSMS SP (/35)	
		% male	mean (SD)	mean (SD)	mean (SD)	mean (SD)	mean (SD)	mean (SD)	mean (SD)	
Controls	269	42	46.2 (13.0)	14.4 (3.4)	29.3 (1.1)	0.2 (0.4)	47.8 (8.4)	23.3 (8.4)	24.5 (5.3)	
C9orf72	0	93	41	43.9 (11.6)	14.3 (3.0)	29.1 (1.2)	0.0 (0.0)	22.8 (10.5)	47.1 (10.5)	24.3 (6.0)
	0.5	34	44	49.7 (11.2)	14.0 (2.6)	28.4 (2.2)	1.1 (0.7)	19.8 (11.4)	41.9 (11.4)	22.1 (6.3)
	1+	66	65	62.7 (9.5)	13.0 (3.8)	23.3 (6.8)	11.1 (5.6)	9.6 (12.3)	23.5 (12.3)	14.0 (6.6)
GRN	0	122	34	45.6 (12.2)	14.7 (3.5)	29.5 (0.8)	0.0 (0.0)	23.6 (8.9)	47.9 (8.9)	24.3 (5.9)
	0.5	24	46	51.3 (13.8)	14.0 (4.3)	28.6 (2.3)	0.9 (0.8)	21.6 (10.7)	43.8 (10.7)	22.2 (5.6)
	1+	47	47	63.0 (7.4)	11.7 (3.4)	20.1 (7.7)	9.8 (6.2)	12.9 (12.1)	28.6 (12.1)	15.6 (6.1)
MAPT	0	41	41	38.3 (11.0)	14.3 (3.3)	29.5 (0.8)	0.0 (0.0)	24.0 (9.7)	50.7 (9.7)	26.7 (6.0)
	0.5	13	31	46.4 (12.8)	13.6 (2.5)	28.1 (2.3)	1.1 (0.8)	23.8 (14.2)	50.1 (14.2)	26.3 (7.1)
	1+	21	57	58.9 (9.4)	13.6 (4.0)	21.9 (8.1)	10.3 (6.0)	9.4 (18.9)	22.8 (18.9)	13.4 (9.8)

Table 2. Adjusted mean differences in RSMS Total scores between the genetic groups stratified by global CDR® plus NACC FTLD scores, with 95% bias-corrected confidence intervals. Significant values are shown in bold.

	C9ORF72			GRN			MAPT									
	0	0.5	1+	0	0.5	1+	0	0.5								
Controls	-0.91	-5.34	-22.39	-0.35	-4.05	-17.41	1.99	2.07								
	-3.41	1.60	-9.36	-1.32	-25.72	-19.05	-2.17	1.47	-8.53	0.42	-20.94	-13.88	-1.21	5.19	-5.72	9.1
C9ORF72	0	-4.43	-21.48	0.55	-3.15	-16.50	2.90	2.97								
		-9.10	0.24	-25.68	-17.29	-2.29	3.39	-8.19	1.90	-20.84	-12.17	-0.91	6.71	-5.02	10.1	
	0.5		-17.05	4.99	1.29	-12.07	7.33	7.41								
			-21.93	-12.16	0.61	9.36	-4.54	7.11	-17.17	-6.98	2.19	12.48	-1.18	11.1		
	1+			22.04	18.34	4.98	24.38	24.45								
				18.41	25.66	12.93	23.74	0.40	9.55	19.79	28.97	16.28	31.1			
GRN	0				-3.70	-17.06	2.35	2.42								
					-8.60	1.20	-20.77	-13.35	-1.31	6.00	-5.61	10.1				
	0.5						-13.36	6.05	6.12							
							-18.76	-7.96	0.72	11.38	-2.59	11.1				
	1+						19.41	19.48								
							14.54	24.27	11.10	21.1						
MAPT	0							0.07								
								-7.46	7.1							
	0.5															
	1+															

Figures

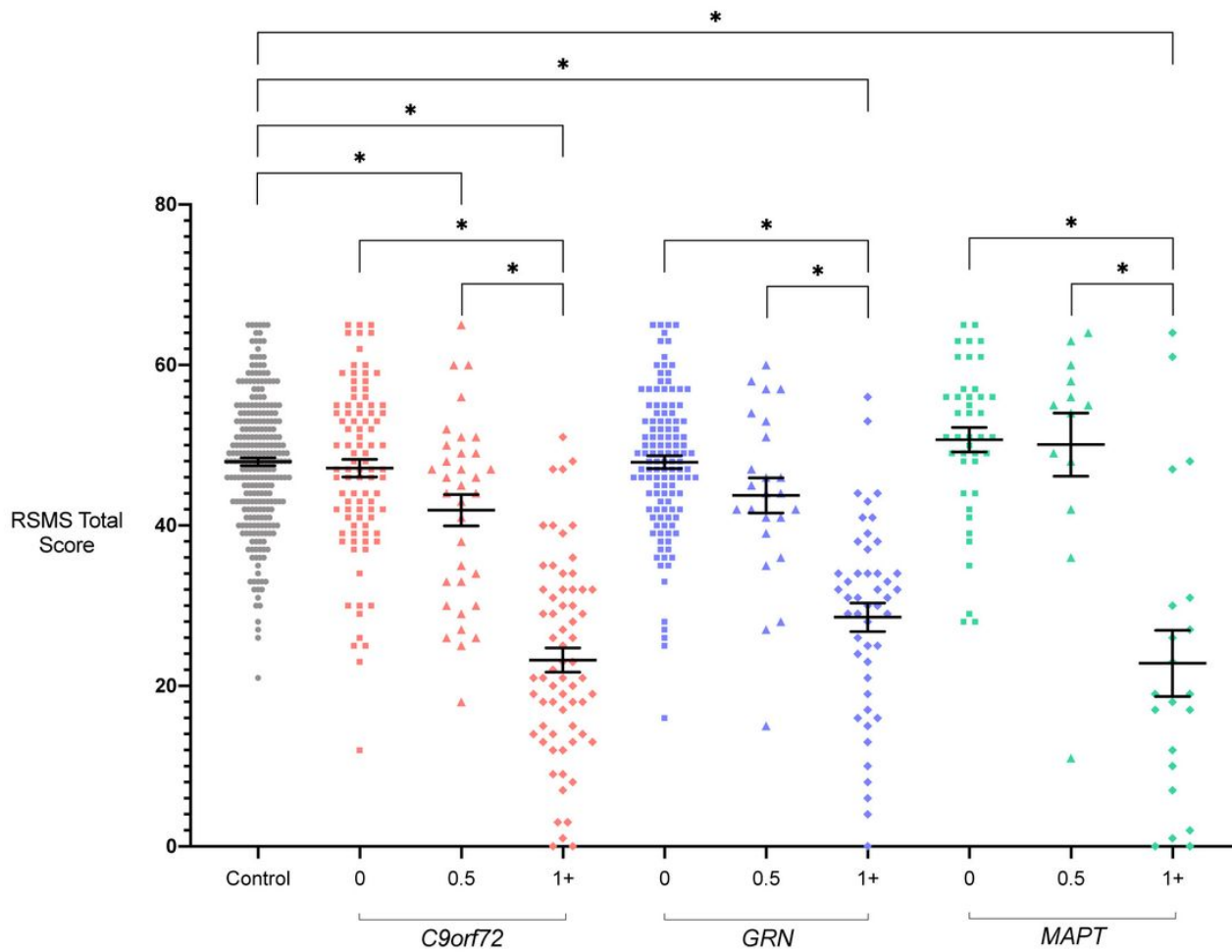


Figure 1
 RSMS Total scores in each genetic group, stratified by global CDR® plus NACC FTLD scores. Significant differences from controls and within each genetic group are starred. Differences between different genetic groups are not shown.

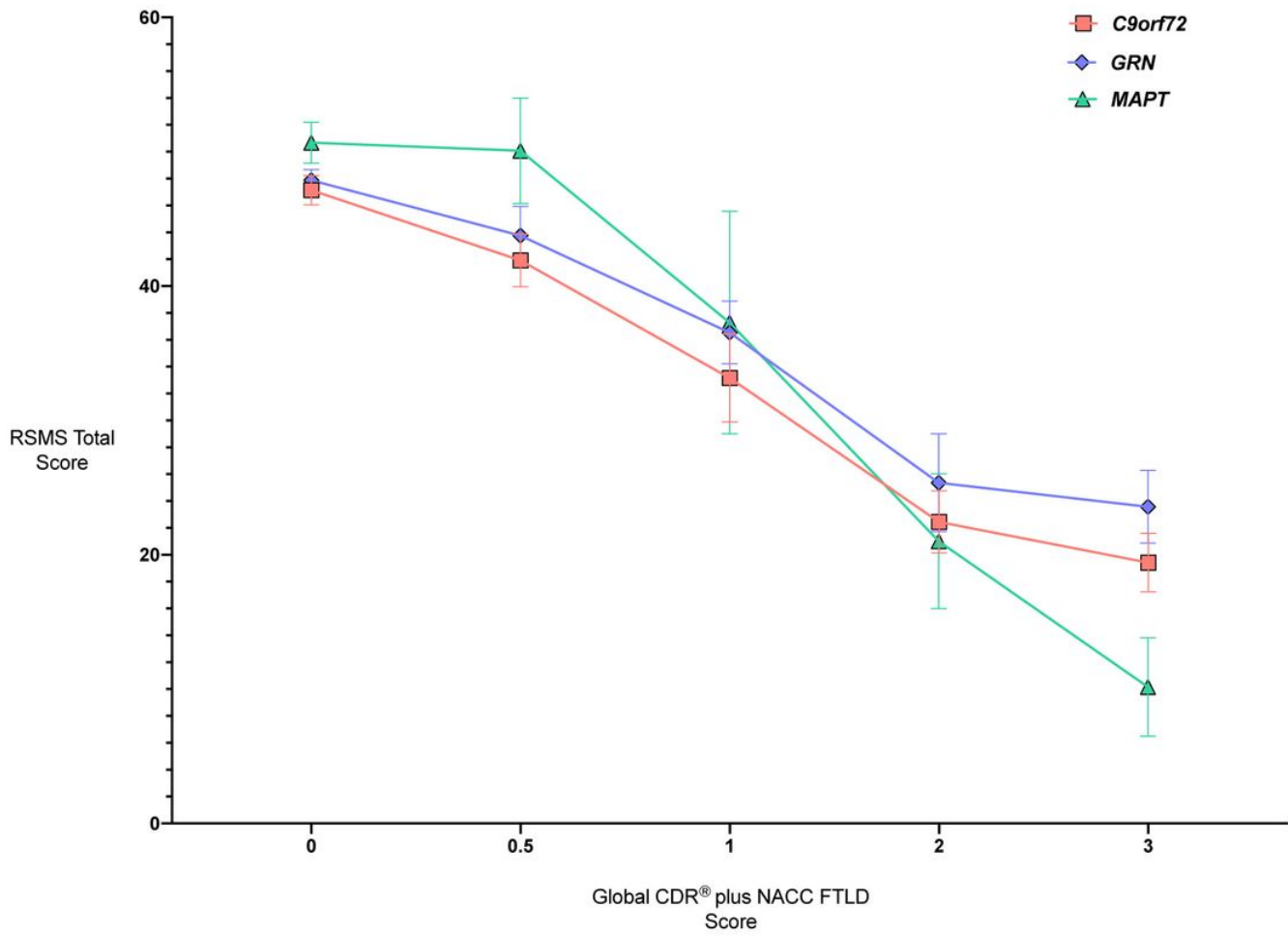


Figure 2

Mean RSMS Total scores in each genetic group by individual global CDR[®] plus NACC FTLD score. Error bars represent standard error of the mean.

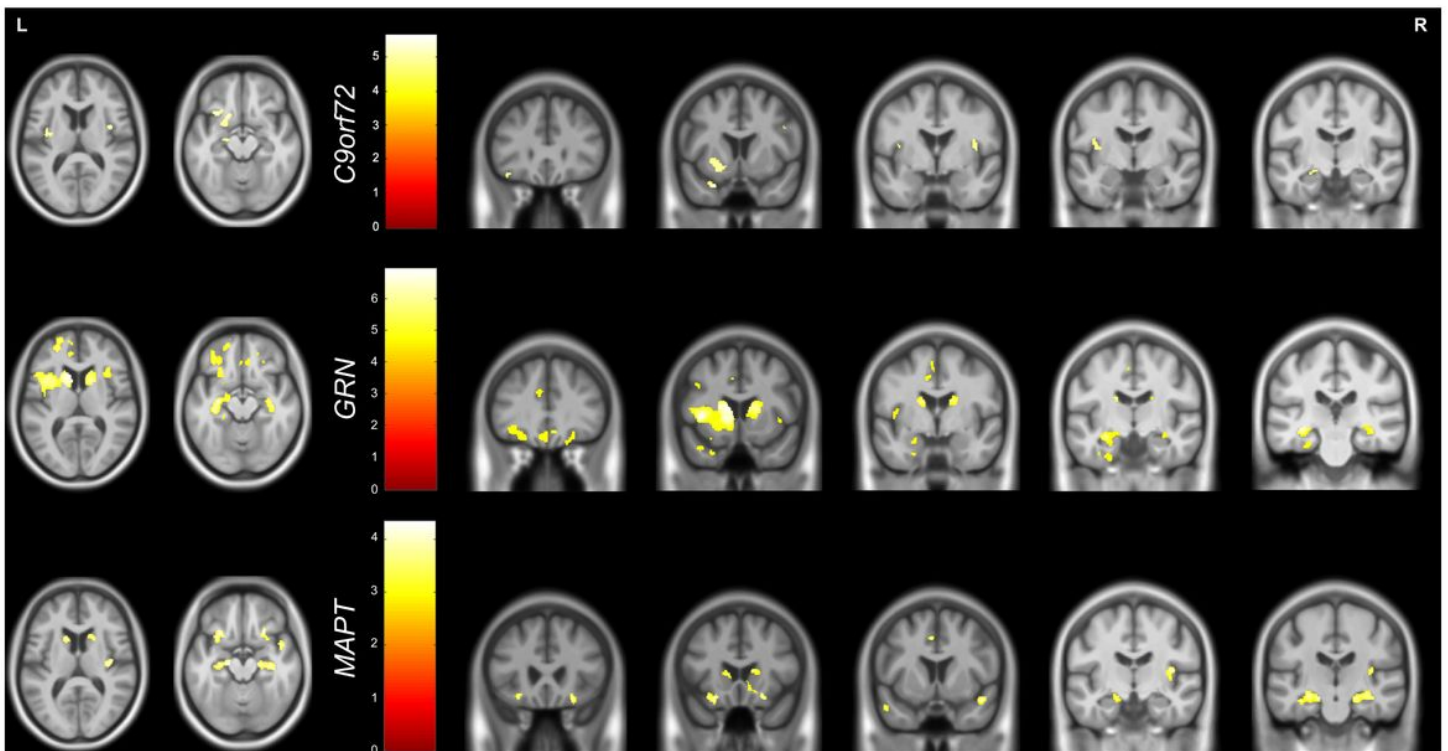


Figure 3

Neural correlates of RSMS Total score. Results for C9orf72 and GRN groups are shown corrected at $p < 0.05$, with results for the MAPT group shown at $p < 0.001$ uncorrected. Results are shown on a study-specific T1-weighted MRI template in MNI space.

Supplementary Files

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- [FranklinSupplementarydatafinal.docx](#)
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