Social cognitive impairment in familial frontotemporal dementia: results from the GENFI study

Russell LL[1], Moore KM[1], Bocchetta M[1], Convery RS[1], Woollacott IOC[1], Shafei R[1], Nicholas J[2,] van Swieten J[3], Borroni B[4], Galimberti D[5], Sanchez-Valle R[6], Laforce R[7], Moreno F[8], Synofzik M[9], Graff C[10,] Masellis M[11], Tartaglia C[12], Rowe J[13], Vandenberghe R[14,] Finger E[15], Tagliavini F[16], de Mendonça A[17,] Santana I[18], Butler C[19], Ducharme S[20], Gerhard A[21], Danek A[22], Levin J[22], Otto M[23], Rohrer JD[1] on behalf of GENFI

[1]Dementia Research Centre, Department of Neurodegenerative Disease, UCL Queen Square Institute of Neurology, United Kingdom [2-23] Principal investigators of the GENFI study

INTRODUCTION

Impairment of social cognition is one of the most prominent symptoms in behavioural variant frontotemporal dementia (bvFTD). However, the current literature has focused on investigating such problems in sporadic FTD, with very few studies in familial FTD. This study investigates differences between mutation carriers and non-mutation carriers to look at differences in social cognition in three genes most commonly associated with FTD: chromosome 9 open reading frame 72 (*C9orf72*), progranulin (*GRN*) and microtubule-associated protein tau (*MAPT*).

Table 1: Demographic information for the GENFI cohort

	Controls	Presymptomatic carriers			Symptomatic carriers		
		C9orf72	GRN	MAPT	C9orf72	GRN	MAPT
N	205	79	114	44	43	32	15
Gender (F:M)	115 : 90	51 : 28	73 : 41	28 : 16	15 : 28	18 : 14	7 : 8
Handedness (R:L:A)	189 : 14 : 2	72 : 7	98 : 13 : 3	40 : 4	38 : 3 : 2	32 : 0	13 : 2
Age	46.6 (12.9)	45.8 (11.9)	46.7 (12.2)	41.1 (10.4)	64.2 (8.2)	62.5 (9.9)	58.0 (6.6)
Education	14.3 (3.3)	14.4 (2.6)	14.7 (3.5)	14.2 (3.3)	13.1 (4.0)	11.0 (3.4)	14.5 (3.8)
MMSE	29.4 (1.0)	29.2 (1.2)	29.4 (1.0)	29.5 (0.8)	23.3 (7.1)	19.6 (8.3)	23.4 (8.1)
Estimated years to onset	-13.0 (13.7)	-14.8 (10.5)	-13.2 (12.1)	-12.0 (10.5)	4.4 (6.5)	1.7 (9.2)	5.5 (5.0)

METHODS

237 presymptomatic mutation carriers (79 *C9orf72*, 114 *GRN* and 44 *MAPT*), 90 symptomatic mutation carriers (43 *C9orf72*, 32 *GRN* and 15 *MAPT*) and 205 non-mutation carriers (controls) were recruited from the Genetic FTD Initiative (GENFI). Participants completed the Mini-SEA, consisting of the Faux-pas test (a measure of Theory of Mind) and the Ekman Facial Recognition task (a measure of emotion processing) and their informants completed two questionnaires assessing various aspects of empathy, the modified Interpersonal Reactivity Index (mIRI) and the Revised Self-Monitoring Scale (RSMS). Each of these questionnaires is made up of two subscales (mIRI: perspective taking (PT) and empathic concern (EC); RSMS: sensitivity to expressive behaviour (EX) and the ability to monitor self-presentation (SP)). Linear mixed modelling was performed to assess differences between all groups, as well as investigating differences in performance between the mutation carriers and non-carriers across years to estimated onset. A VBM analysis assessed the neuroanatomical correlates of performance on each of the tests for the mutation carriers in each genetic group.

RESULTS

On all tasks, the symptomatic mutation carriers performed significantly lower than the presymptomatic mutation carriers and control group (all p<0.001). Differences were observed between the symptomatic mutation carriers on the Faux-pas test (*C9orf72*<*MAPT*, $p = 0.038$), RSMS Total (*C9orf72/MAPT*<*GRN*, $p = 0.047$, $p = 0.002$ respectively), RSMS EX (*C9orf72/MAPT*<*GRN*, $p = 0.027$, $p = 0.001$ respectively) and RSMS SP (*MAPT*<*GRN*, $p = 0.018$). When looking at the presymptomatic mutation carriers, differences were observed on the Mini-SEA (*MAPT*<*GRN*, $p = 0.048$), the Faux-pas (*C9orf72/MAPT*<*GRN*, p = 0.004, $p = 0.020$ respectively), mIRI PT (*MAPT*<*GRN*, $p = 0.029$) and the RSMS EX (*C9orf72*<*GRN*, $p = 0.034$). When looking at performance stratified over years to estimated onset, a different pattern of performance was seen in the different genetic groups. The *C9orf72* mutation carriers showed a significantly different performance compared to controls between 11 and 21 years prior to estimated onset on all tasks. In comparison, the *MAPT* group showed differences between 1 and 7 years before estimated onset (except on the Ekman), and the *GRN* group showed the least presymptomatic change, occurring around 3 years after estimated onset to 4 years prior to onset (except on the Faux-pas). The VBM analysis was performed on each of the mutation carrier groups and their performance on each of the tests. Different patterns of atrophy were observed for each of the genetic mutations and each of the tests (see *Figure 3*) although with a frontal-temporal-striatal network commonly implicated.

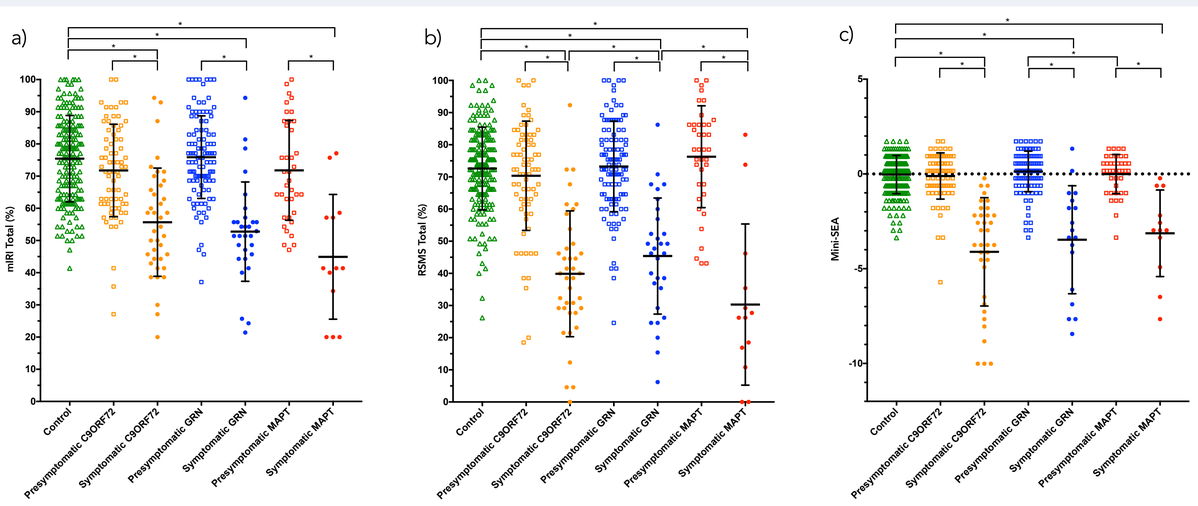

Figure 1: Scores for a) mIRI Total, b) RSMS Total and c) Mini-SEA in controls, presymptomatic mutation carriers and symptomatic mutation carriers for the three genetic groups. *represents a significant difference between groups

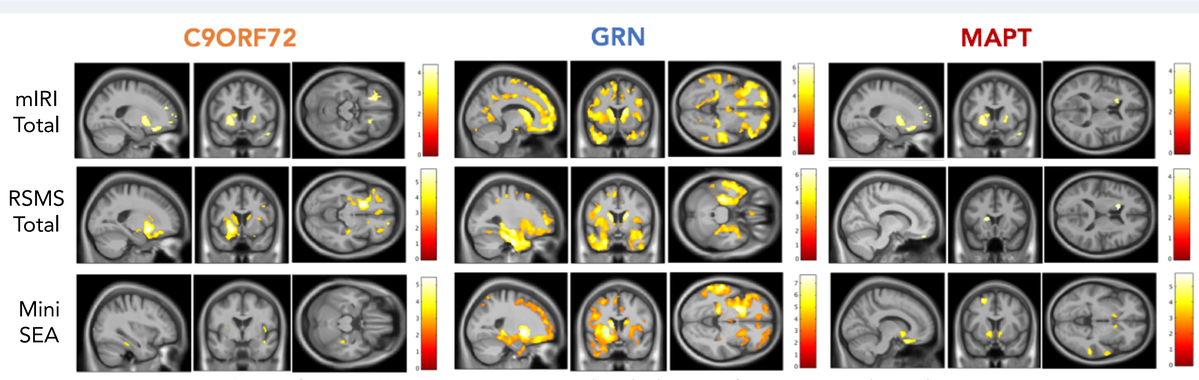

Figure 3: VBM analysis on GM regions associated with the social cognitive tasks in the mutation carrier groups. Analysis were adjusted for age, gender and TIV. The colour bar indicates the T values.

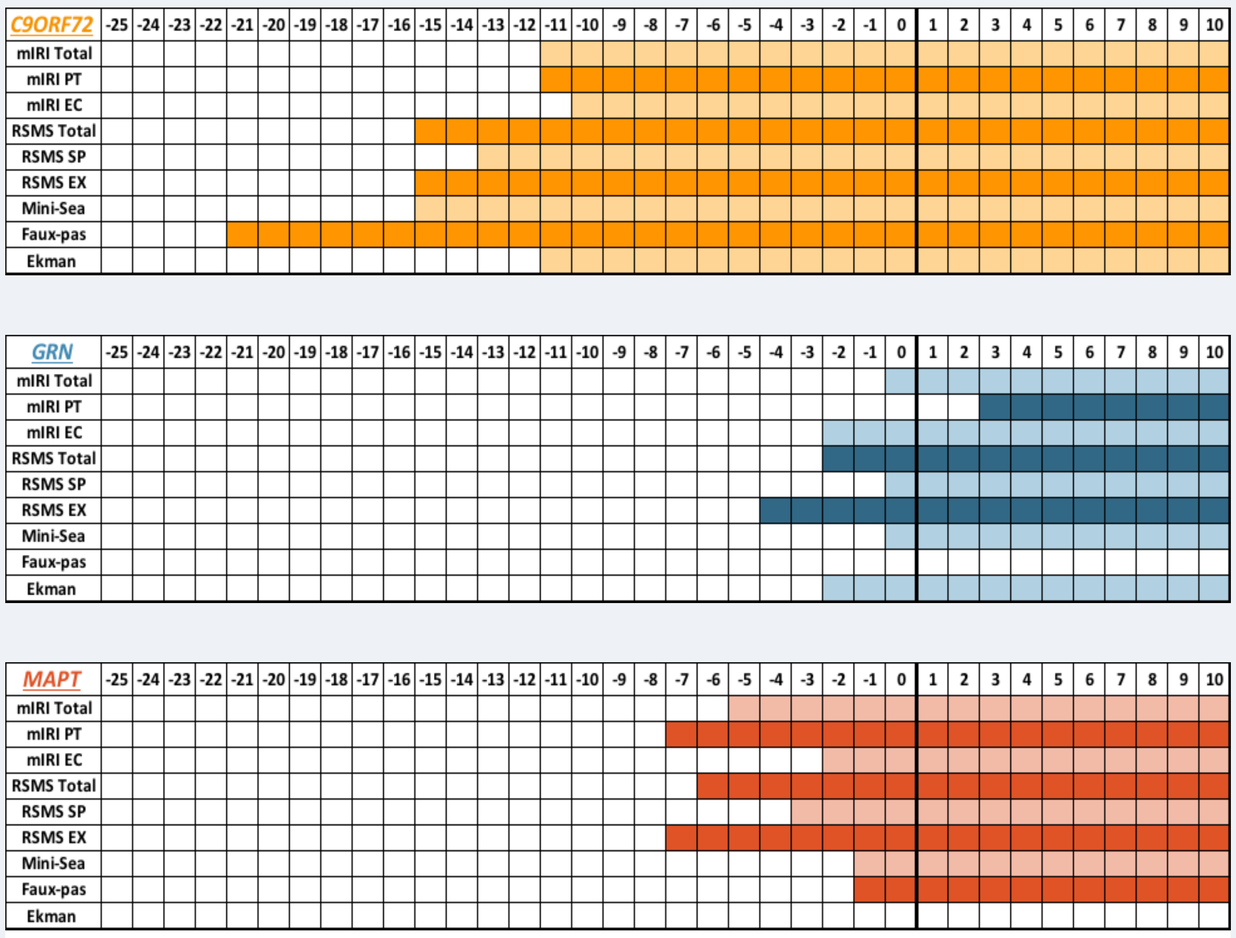

Figure 2: Timepoint (by years to estimated onset) that there is a significant difference between non-carriers and mutation carriers in each of the tests across the three genes (*C9orf72* in orange, *GRN* in blue and *MAPT* in red).

CONCLUSIONS

This is one of the first studies to comprehensively evaluate social cognitive performance in individuals with familial FTD and provides an insight into differences in social functioning between the genetic groups, and the different neuroanatomical correlates.

Acknowledgements: LLR, KM, MB, RC, IW, RS, and JDR acknowledge the support of the NIHR Queen Square Dementia Biomedical Research Unit and the Leonard Wolfson Experimental Neurology Centre. The Dementia Research Centre at UCL is an Alzheimer's Research UK coordinating centre and received equipment funded by Alzheimer's Research UK and the Brain Research Trust. JDR is an MRC Clinician Scientist and has received funding from the NIHR Rare Diseases Translational Research Collaboration.