Impairment of social behaviour in *MAPT* mutation carriers within the GENFI cohort

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INTRODUCTION

Early and progressive impairments in social behaviour underpin the core clinical features of FTD and may begin to manifest before clinical diagnosis[1]. However, social symptoms are understudied compared to language and executive function domains. The Social Impairment Rating Scale (SIRS) quantitatively measures six social symptoms as part of a clinical interview [lack of adherence to social norms, social withdrawal, socioemotional detachment, lack of response to social cues, inappropriate trusting behaviour, and person recognition difficulties][2] incorporated into the core Genetic FTD Initiative (GENFI) assessment.

AIMS

To explore the development of symptoms of social impairment and their neuroanatomical correlates in the GENFI cohort, including participants in both the presymptomatic and symptomatic stages of disease, with mutations in the *GRN* and *MAPT* genes and expansions in the *C9orf72* gene.

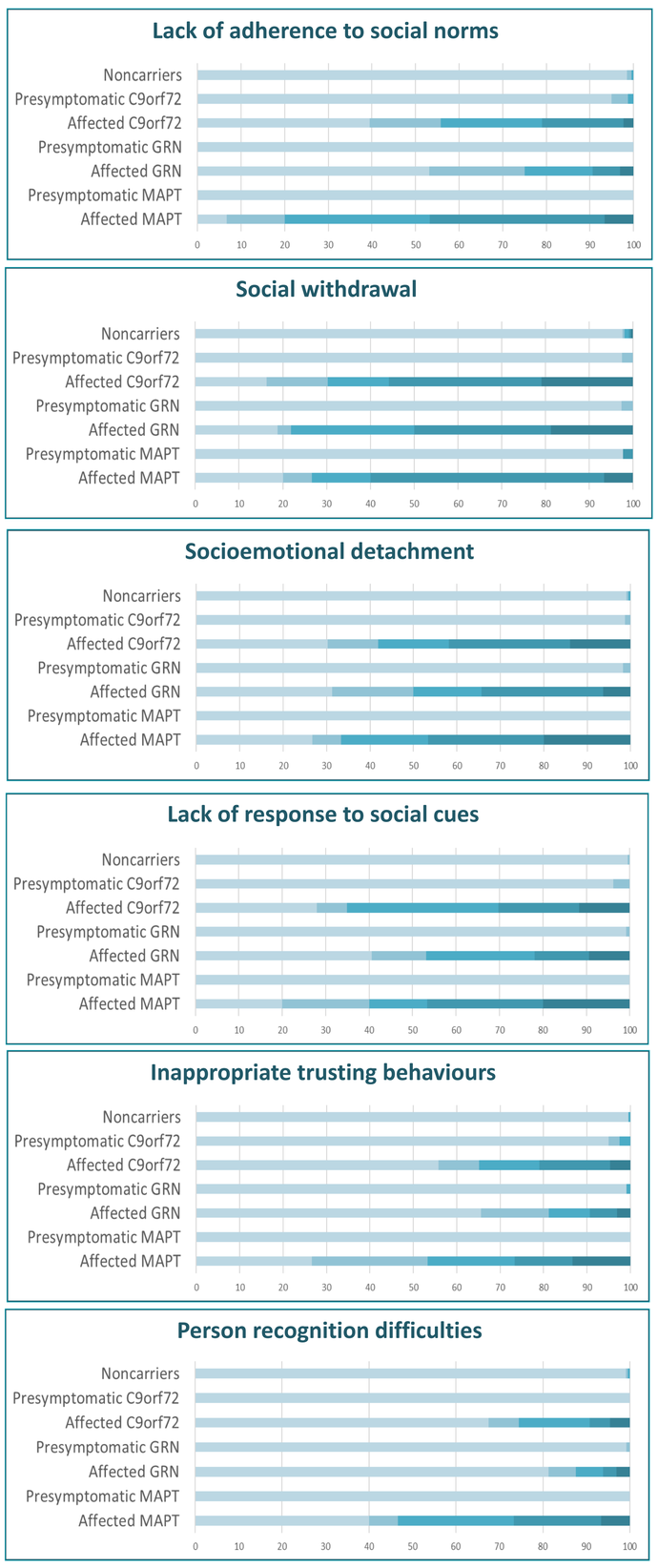

Figure 1. Frequency of participants affected by SIRS subscores in the GENFI cohort.

METHODS

Participants were recruited from the GENFI cohort: 204 mutation negative controls, 237 presymptomatic *C9orf72*, *GRN* and *MAPT* mutation carriers, and 90 symptomatic mutation carriers. Differences in the SIRS-sum of boxes (SIRS-SB) score and each individual SIRS subscore were analysed using a general linear model, controlling for age and gender. 282 of the mutation carriers had an available T1-weighted MRI scan of suitable quality for voxel-based morphometry (VBM) analysis. Using SPM12 we fit multiple regression models for each score in each mutation, including age, gender, scanner type and TIV as nuisance covariates. Statistical parametric maps were FWE-corrected ($p<0.05$) for multiple comparisons.

	Lack of adherence to social norms	Social withdrawal	Socioemotional detachment	Lack of response to social cues	Inappropriate trusting behaviours	Person recognition difficulties	SIRS-sum of boxes score
Controls vs Affected *C9orf72*	-0.715*	**-1.482***	-1.172*	-1.082*	-0.594*	-0.403*	-5.448*
Controls vs Affected *GRN*	-0.445*	-1.429*	-0.978*	-0.816*	-0.336*	-0.217*	-4.223*
Controls vs Affected *MAPT*	**-1.370***	-1.385*	**-1.348***	**-1.350***	**-0.961***	**-0.878***	**-7.291***

Table 1. *MAPT* mutation carriers experience severe social impairment in all SIRS subdomains compared to controls (*$p<0.001$).

RESULTS

Behavioural analyses. All symptomatic groups had a mean (SD) SIRS-SB score significantly greater than controls: *MAPT* 7.5 (4.5), *C9orf72* 5.7 (4.1) and *GRN* 4.5 (3.7), $p<0.001$. Comparing individual subscores of the SIRS in presymptomatic and affected groups, *MAPT* carriers were the most severely affected in five out of six SIRS subdomains (Table 1).

Brain-behaviour analyses. Whilst all genetic groups experienced grey matter (GM) volume loss associated with increasingly severe symptoms of lack of adherence to social norms, social withdrawal, and lack of response to social cues, only *MAPT* experienced GM atrophy associated with all SIRS subdomains (Fig. 2). Distinct patterns of GM atrophy associated with increasing SIRS-SB score was seen in all genetic groups (Fig. 3).

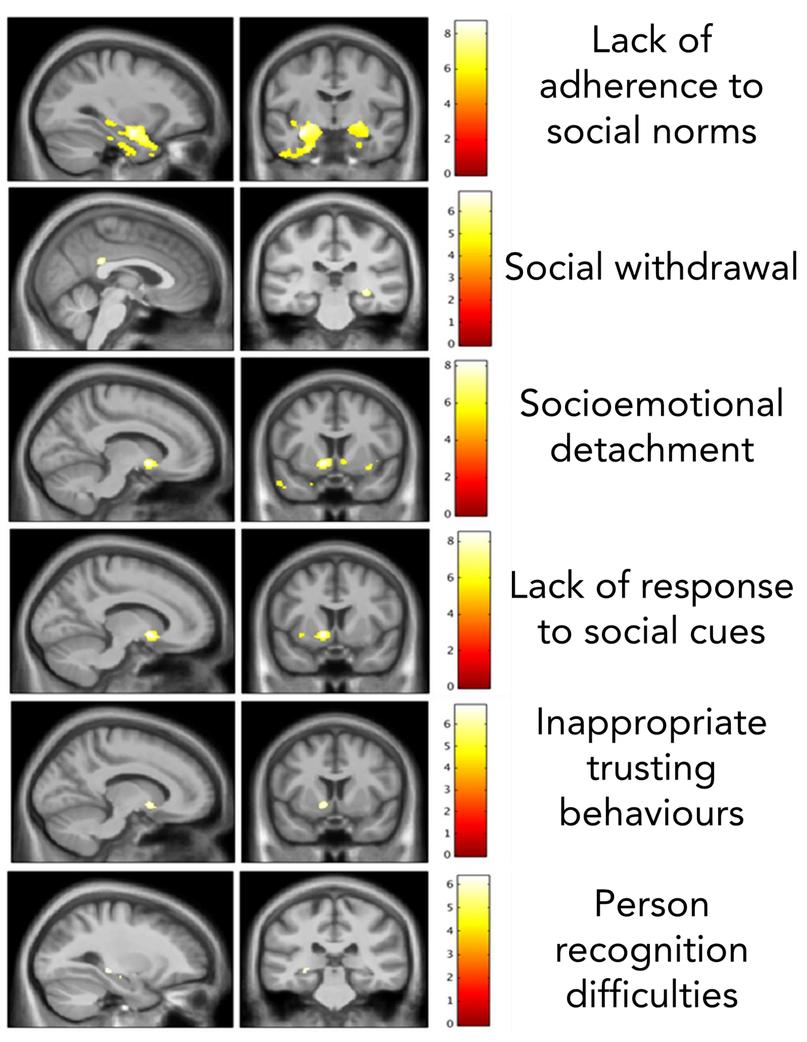

Figure 2. *MAPT* mutation carriers experience grey matter atrophy associated with all SIRS subdomains

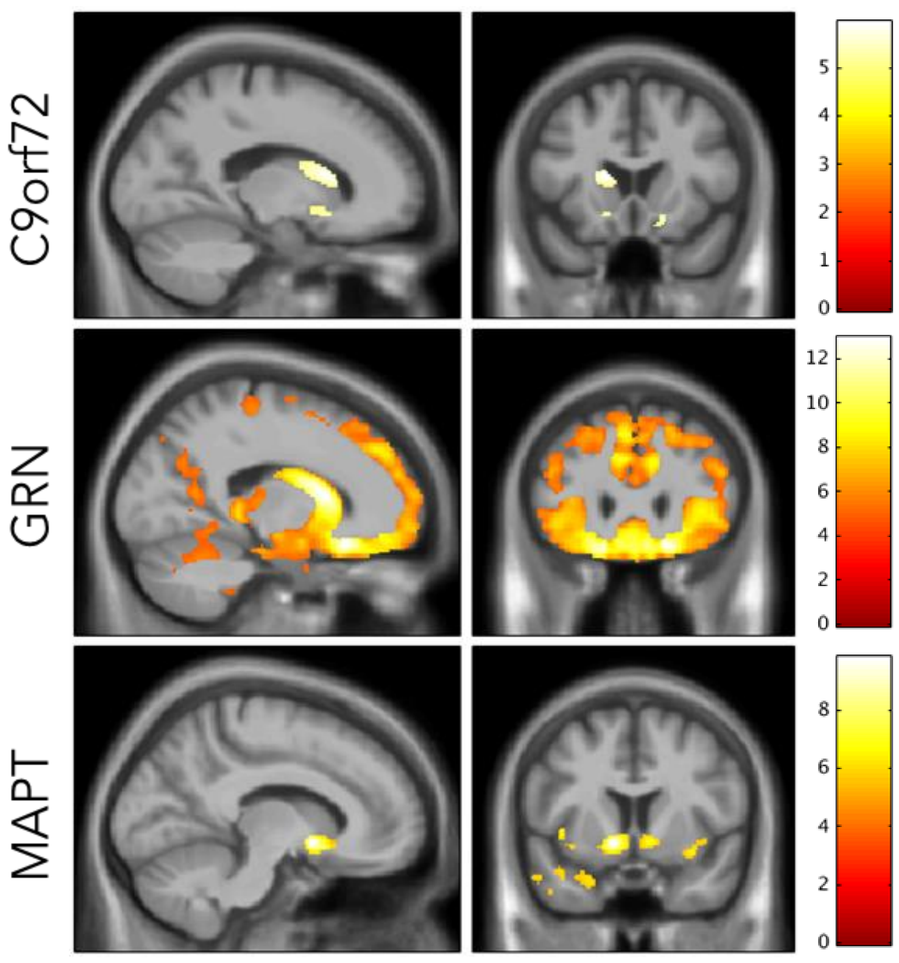

Figure 3. Mutation-specific patterns of grey matter atrophy were associated with the SIRS-sum of boxes score in all three mutation carrier groups.

CONCLUSION

MAPT mutation carriers exhibited more severe symptoms of social impairment (measured by SIRS), compared with the *GRN* and *C9orf72* groups. The SIRS provides a reliable measure of social impairment in multiple domains, and may improve characterisation of FTD by providing a longitudinal outcome measure to track disease progression.

REFERENCES

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