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Prodromal language impairment in genetic frontotemporal dementia within the GENFI cohort

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ABSTRACT

Objective: To identify whether language impairment exists presymptomatically in genetic frontotemporal dementia (FTD), and if so, the key differences between the main genetic mutation groups.
Methods: 682 participants from the international multicentre Genetic FTD Initiative (GENFI) study were recruited: 290 asymptomatic and 82 prodromal mutation carriers (with *C9orf72, GRN,* and *MAPT* mutations) as well as 310 mutation-negative controls. Language was assessed using items from the Progressive Aphasia Severity Scale, as well as the Boston Naming Test (BNT), modified Camel and Cactus Test (mCCT) and a category fluency task. Participants also underwent a 3 T volumetric T1-weighted MRI from which regional brain volumes within the language network were derived and compared between the groups.
Results: 3% of asymptomatic (4% *C9orf72*, 4% *GRN*, 2% *MAPT*) and 48% of prodromal (46% *C9orf72*, 42% *GRN,* 64% *MAPT*) mutation carriers had impairment in at least one language symptom compared with 13% of controls. In prodromal mutation carriers significantly impaired word retrieval was seen in all three genetic groups whilst significantly impaired grammar/syntax and decreased fluency was seen only in *C9orf72* and *GRN* mutation carriers, and impaired articulation only in the *C9orf72* group. Prodromal *MAPT* mutation carriers had significant impairment on the category fluency task and the BNT whilst prodromal *C9orf72* mutation carriers were impaired on the category fluency task only. Atrophy in the dominant perisylvian language regions differed between groups, with earlier, more widespread volume loss in *C9orf72*, and later focal atrophy in the temporal lobe in *MAPT* mutation carriers.
Conclusions: Language deficits exist in the prodromal but not asymptomatic stages of genetic FTD across all three genetic groups. Improved understanding of the language phenotype prior to phenoconversion to fully symptomatic FTD will help develop outcome measures for future presymptomatic trials.

1. Introduction

Frontotemporal dementia (FTD) is a common cause of young onset dementia and leads to progressive behavioural, language, and motor dysfunction. It is autosomal dominantly inherited in around a third of individuals [33], with the main genetic causes being mutations in progranulin (*GRN*), microtubule-associated protein tau (*MAPT*) and chromosome 9 open reading frame 72 (*C9orf72*) [42]. The study of healthy 'at-risk' individuals who have a first-degree relative with a confirmed genetic mutation allows a window into the earliest stages of the disease. The Genetic FTD Initiative (GENFI) study has studied such individuals with the aim of improving the understanding of the presymptomatic period of FTD. A greater understanding of the stages that precede symptom onset within each mutation group will allow for better stratification and monitoring of disease progression in future prevention trials of disease-modifying therapies [35].

Although behavioural change is the commonest symptom in FTD, language problems are also seen very frequently [16]. If language is the first and predominant symptom, the diagnosis is primary progressive aphasia (PPA), with three subtypes described: non-fluent variant (nfvPPA), semantic variant (svPPA) and logopenic variant PPA (lvPPA). However, a substantial minority of patients do not fit criteria for any of the three and are called PPA-not otherwise specified (PPA-NOS). In genetic FTD, around 40% of symptomatic *GRN* mutation carriers have PPA, roughly split between those with a nfvPPA phenotype and those with PPA-NOS. In contrast, PPA is uncommon in people with *C9orf72* or *MAPT* mutations (≤5%) [44]. However, language symptoms are reported in all three mutation groups [5,31], and are also seen in people with behavioural variant FTD (bvFTD) [10,13] with 60–80% of mutation carriers in each genetic group having some linguistic difficulties [36]. It will therefore be important, independent of the subsequent phenotype, to identify what language features can be detected prior to phenoconversion to fully symptomatic status when considering development of outcome measures for presymptomatic clinical trials.

This study therefore aims to identify the salient linguistic features of presymptomatic mutation carriers and the key differences between the main genetic mutation groups (*C9orf72*, *GRN*, and *MAPT*). Based on previous literature, we hypothesise that the earliest changes will be seen in the *C9orf72* group [2,4,39,40], with more linguistic deficits in the *GRN* group (Samra et al., in press; [38], and more focal impairment, particularly in semantic knowledge, in the *MAPT* mutation carriers [5,19]. Neuroimaging analysis is hypothesized to show parallel findings, with early atrophy in the language brain regions in *C9orf72* [2,40], and more focal loss that may not be evident until prodromal or symptomatic stages in *GRN* and *MAPT* mutation carriers [4], with the medial temporal lobe particularly affected in the *MAPT* group [3,27,43].

2. Methods

2.1. Participants

Participants were recruited from the fifth data freeze of the GENFI study between 20 January 2012 and 30 May 2019, including sites in the UK, Canada, Belgium, France, Germany, Italy, the Netherlands, Portugal, Spain and Sweden. Languages spoken were of those countries i.e. English, French, German, Italian, Dutch, Portuguese, Spanish and Swedish. All aspects of the study were approved by local ethics committees, and written informed consent was obtained from all participants.

Participants underwent a standardised clinical assessment including a history, neurological examination, neuropsychometric assessment, the Mini-Mental State Examination (MMSE), and the CDR® plus NACC FTLD global score [26]. The CDR® plus NACC FTLD was used to classify mutation carriers as either presymptomatic (global score of 0, asymptomatic, or 0.5, prodromal) or fully symptomatic (score ≥ 1). In total there were 372 mutation carriers with a CDR® plus NACC FTLD global

score of 0 (asymptomatic, 290 participants) or 0.5 (prodromal, 82 participants): 148 *C9orf72* (111 asymptomatic, 37 prodromal), 161 *GRN* (130 asymptomatic, 31 prodromal), and 63 *MAPT* (49 asymptomatic, 14 prodromal) individuals. Controls in the study consisted of all mutation-negative family members with a CDR® plus NACC FTLD global score of 0 or 0.5, which was 310 participants in total. Demographics are shown in Table 1.

2.2. Language assessment

Language was assessed by a clinician using the GENFI clinical questionnaire, which is based on the Progressive Aphasia Severity Scale (PASS) [37]. This contains ten language symptoms scored as per a CDR scale i.e., 0 = asymptomatic, 0.5 = questionable/very mild, 1 = mild, 2 = moderate and 3 = severe: impaired articulation, decreased fluency, impaired grammar/syntax, impaired word retrieval, impaired speech repetition, impaired sentence comprehension, impaired single word comprehension, dyslexia (acquired impairment of reading), dysgraphia (acquired impairment of writing), and impaired functional communication. The assessment consists of a semi-structured interview with inclusion of both the participant and an informant to generate an overall clinician-judged score for each symptom. An overall PASS score can be generated from summing each of the individual language symptom scores.

2.3. Cognitive assessment

Within the GENFI neuropsychology battery, the 30-item version of the Boston Naming Test [12,23] (BNT), the modified Camel and Cactus Test [28] (mCCT) and category fluency (animals) were the linguistic measures used.

2.4. Imaging

630 participants had a 3 T volumetric T1-weighted magnetic resonance imaging (MRI) scan (205 Philips Achieva, 145 Siemens Prisma, 151 Siemens Trio, 119 Siemens Skyra, 10 GE Signa HD) of sufficient quality to be analysed: 281 controls and 349 presymptomatic mutation carriers (136 *C9orf72*, 154 *GRN*, and 59 *MAPT* mutation carriers) of whom 274 were asymptomatic (104 *C9orf72*, 124 *GRN*, and 46 *MAPT* mutation carriers) and 75 were prodromal (32 *C9orf72*, 30 *GRN*, and 13 *MAPT* mutation carriers).

Volumetric MRI scans were first bias field corrected and whole brain parcellated using the geodesic information flow (GIF) algorithm [6], which is based on atlas propagation and label fusion. We focused on key language regions, calculating grey matter volumes of the cortex for seven left hemisphere perisylvian regions (Fig. 1a): inferior frontal gyrus, insula, motor cortex, temporal pole, superior temporal gyrus, supratemporal region, and angular gyrus [8,15,41]. All measures were expressed as a percentage of total intracranial volume (TIV) computed

Table 1
Demographics, clinical scores, severity of linguistic symptoms, cognitive task data and regional brain volumes for asymptomatic and prodromal mutation carriers. Data are shown as mean (standard deviation). Bold items are significantly impaired compared to controls. For significant group differences: [a]compared to asymptomatic *C9orf72* mutation carriers, [b]compared to asymptomatic *GRN* mutation carriers, [c]compared to asymptomatic *MAPT* mutation carriers; [d]compared to prodromal *MAPT* mutation carriers. No comparisons were made between asymptomatic and prodromal mutation carriers. Abbreviations: bvFTD, behavioural variant frontotemporal dementia; TIV, total intracranial volume.

	Controls	Asymptomatic mutation carriers			Prodromal mutation carriers		
		C9orf72	*GRN*	*MAPT*	*C9orf72*	*GRN*	*MAPT*
Number of participants	310	111	130	49	37	31	14
% Male	44	41	34	39	41	48	29
% Right-handed	93	91	89	90	92	90	100
Age (years)	46.0 (12.7)	44.4 (11.8)	45.8 (12.2)	**39.2 (10.4)[ab]**	49.4 (11.2)	**51.8 (13.2)**	45.7 (12.6)
Education (years)	14.5 (3.3)	14.4 (3.0)	14.7 (3.4)	14.4 (3.3)	14.1 (2.6)	14.0 (4.0)	13.5 (2.4)
MMSE	29.3 (1.0)	29.2 (1.2)[bc]	29.4 (0.9)	29.5 (0.8)	**28.5 (2.1)**	28.5 (2.4)	28.2 (2.3)
CDR® plus NACC FTLD Global score	0.1 (0.2)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	**0.5 (0.0)**	**0.5 (0.0)**	**0.5 (0.0)**
CDR® plus NACC FTLD Sum of Boxes	0.2 (0.4)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	**1.1 (0.8)**	**1.0 (0.8)**	**1.0 (0.8)**
Progressive Aphasia Severity Scale	0.1 (0.5)	0.0 (0.2)	0.0 (0.1)	0.0 (0.1)	**0.9 (1.5)**	**1.2 (2.3)**	**0.6 (0.5)**
Linguistic symptoms							
Impaired articulation	0.01 (0.06)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	**0.11 (0.27)**	0.08 (0.23)	0.04 (0.13)
Decreased fluency	0.01 (0.08)	0.00 (0.05)	0.00 (0.00)	0.00 (0.00)	**0.08 (0.19)**	**0.15 (0.32)**	0.04 (0.13)
Impaired grammar/syntax	0.01 (0.10)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	**0.08 (0.19)[d]**	**0.23 (0.55)[d]**	0.00 (0.00)
Impaired word retrieval	0.06 (0.18)	0.01 (0.08)	0.02 (0.10)	0.01 (0.07)	**0.19 (0.32)**	**0.32 (0.63)**	**0.39 (0.35)**
Impaired speech repetition	0.00 (0.04)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.03 (0.11)	0.02 (0.09)	0.00 (0.00)
Impaired sentence comprehension	0.00 (0.03)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.08 (0.25)	0.06 (0.21)	0.00 (0.00)
Impaired single word comprehension	0.00 (0.03)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.04 (0.18)	0.05 (0.15)	0.04 (0.13)
Dyslexia	0.01 (0.13)	0.02 (0.19)	0.00 (0.00)	0.00 (0.00)	0.14 (0.47)	0.10 (0.24)	0.04 (0.13)
Dysgraphia	0.01 (0.13)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.11 (0.38)	**0.10 (0.20)**	0.04 (0.13)
Impaired functional communication	0.01 (0.14)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.05 (0.16)	0.13 (0.34)[d]	0.00 (0.00)
Cognitive tasks							
Boston Naming Test (/30)	27.9 (1.9)	27.3 (3.1)	27.9 (1.9)	27.6 (2.1)	27.5 (3.4)	26.7 (3.7)	**25.7 (3.9)**
Modified Camel and Cactus Test (/32)	30.3 (1.7)	29.9 (2.2)	30.4 (1.4)	30.0 (2.1)	29.4 (2.8)	29.4 (2.2)	29.5 (2.5)
Category Fluency (max in 60s)	24.4 (6.4)	23.6 (6.4)[b]	25.2 (5.4)	24.3 (5.8)	**21.6 (6.0)**	23.0 (6.3)	**22.1 (4.1)**
Regional left hemisphere brain volumes (as a % of TIV)							
Inferior frontal gyrus	0.57 (0.08)	**0.56 (0.07)[b]**	0.58 (0.06)	0.59 (0.07)	0.57 (0.08)	0.53 (0.07)	0.57 (0.05)
Insula	0.37 (0.04)	**0.36 (0.04)[b]**	0.37 (0.03)	0.38 (0.04)	**0.35 (0.05)**	0.35 (0.04)	0.35 (0.05)
Motor cortex	1.40 (0.16)	1.39 (0.11)[b]	1.44 (0.12)	1.38 (0.09)[b]	**1.33 (0.15)**	1.36 (0.13)	1.41 (0.07)
Temporal pole	0.49 (0.07)	0.49 (0.05)	0.49 (0.05)	0.49 (0.06)	**0.47 (0.06)**	0.48 (0.06)	0.46 (0.09)
Superior temporal gyrus	0.49 (0.06)	**0.48 (0.05)[b]**	0.49 (0.05)	0.48 (0.05)[b]	0.47 (0.05)	0.46 (0.06)	0.47 (0.05)
Supratemporal region	0.42 (0.06)	**0.41 (0.05)[bc]**	0.42 (0.05)	0.43 (0.05)	**0.39 (0.04)**	0.39 (0.05)	**0.39 (0.04)**
Angular gyrus	0.53 (0.08)	0.53 (0.07)	0.54 (0.08)	0.54 (0.07)	**0.50 (0.08)**	0.52 (0.09)	0.54 (0.08)

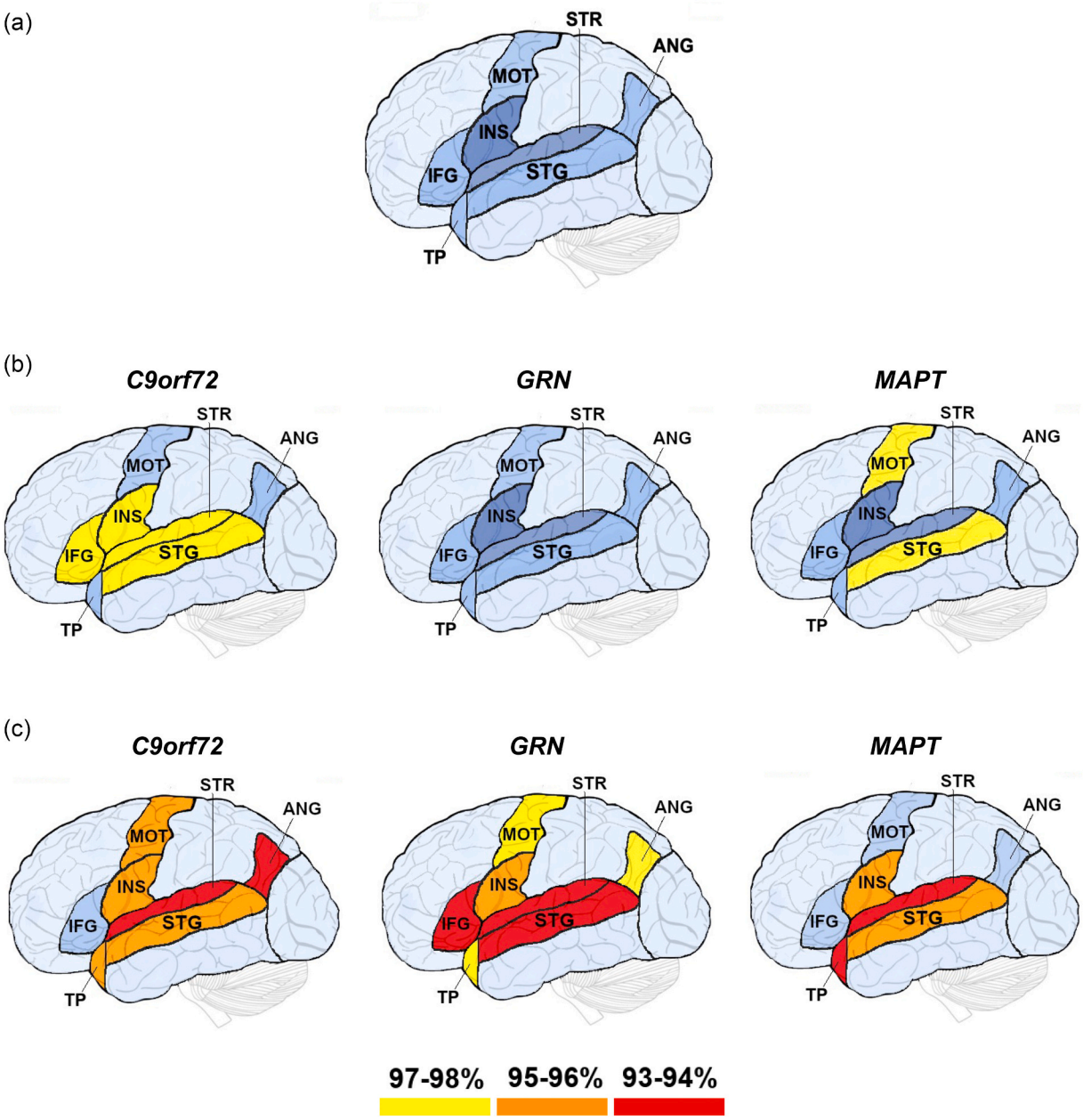

Fig. 1. (a) Left perisylvian regions included in the MR imaging analysis are shown in this artificial representation of the lateral surface of the brain, with the insula and supratemporal region shown in darker blue to represent that they are deeper structures within the sylvian fissure, and region of interest volumes in each (b) asymptomatic and (c) prodromal genetic group as a percentage of mean control volume: IFG, inferior frontal gyrus; INS, insula; MOT, motor cortex; TP, temporal pole; STG, superior temporal gyrus; STR, supratemporal region; ANG, angular gyrus. The darkest colours represent areas of lowest brain volume as per the key. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

with SPM12 v6470 (Statistical Parametric Mapping, Wellcome Trust Centre for Neuroimaging, London, UK) running under Matlab R2014b (Math Works, Natick, MA, USA) [24].

2.5. Statistical analysis

All statistical analyses were performed using Stata/MP 16.1. Statistical tests of normality were performed using the Shapiro-Wilk test. Demographics were compared between groups using either linear regression (age and education) or a chi-squared test (sex). Linear regressions adjusting for age and sex were used to compare the MMSE, CDR® plus NACC FTLD and PASS scores as well as the cognitive tasks and regional brain volumes between groups. Individual linguistic symptoms were compared in each disease group versus controls using linear regressions adjusting for age and sex, and 95% bias-corrected bootstrapped confidence intervals with 2000 repetitions (as there was minimal variation from zero in severity scores for the control group), and between genetic groups using an ordinal logistic regression adjusting for age and sex. As the same disease process is likely to be causing the linguistic deficits within each genetic group at the different stages, we combined the asymptomatic and prodromal mutation carriers into a single presymptomatic cohort for each genetic group in order to examine the strength of association between language-associated brain regions and both individual language symptoms and linguistic tasks. This was performed using Spearman rank correlations uncorrected for multiple comparisons.

3. Results

3.1. Demographics

There was no evidence for differences between the groups in terms of either years of education or sex. The asymptomatic *MAPT* mutation carriers were approximately five years younger than controls ($p < 0.001$, Table 1) and the other two asymptomatic mutation carrier groups ($p = 0.004$ when compared to *C9orf72*, $p < 0.001$ when compared to *GRN*); the prodromal *GRN* mutation carriers were older than controls ($p = 0.020$) (Table 1).

3.2. Disease severity

There was some evidence that the MMSE was lower in asymptomatic *C9orf72* mutation carriers compared to the other asymptomatic mutation carrier groups ($p = 0.034$ when compared to *GRN*, $p = 0.022$ when compared to *MAPT*) but no other asymptomatic groups were significantly different than controls. Prodromal *C9orf72* mutation carriers had a significantly lower MMSE compared with controls ($p = 0.017$) but there were no other prodromal group differences. In comparison the CDR® plus NACC FTLD was impaired in all three prodromal mutation carrier groups (but not asymptomatic mutation carriers) compared with controls (all $p < 0.001$). There was no evidence of differences in CDR® plus NACC FTLD between the disease groups.

3.3. Language symptoms

3% of the asymptomatic mutation carriers had impairment in at least one language symptom (4% of the *C9orf72* group, 4% of the *GRN* group and 2% of the *MAPT* group) whilst 48% of the prodromal mutation carriers had impairment in at least one language symptom (46% of the *C9orf72* group, 42% of the *GRN* group and 64% of the *MAPT* group) (Table 1, Fig. 2). In comparison, only 13% of the controls showed any impairment. The PASS score was significantly higher than controls in each of the prodromal groups (*C9orf72*: $p = 0.003$; *GRN*: $p = 0.008$; *MAPT*: $p = 0.002$), but not in the asymptomatic groups (Table 1).

None of the language symptoms were significantly abnormal in the asymptomatic mutation carriers compared with controls (Table 1, Fig. 2). However, impairment was seen in at least one symptom within each of the genetic groups in the prodromal mutation carriers. All three groups had impaired word retrieval compared with controls: severity mean 0.19 (standard deviation 0.32), frequency 30% in the *C9orf72* expansion carriers, 0.32 (0.63), 29% in the *GRN* mutation carriers, 0.39 (0.35), 64% in the *MAPT* mutation carriers, and 0.06 (0.18), 10% in controls. Both prodromal *C9orf72* and *GRN* groups had significantly impaired grammar/syntax and decreased fluency compared with controls: for grammar/syntax - severity mean 0.08 (0.19), frequency 16% in the *C9orf72* expansion carriers, 0.23 (0.55), 19% in the *GRN* mutation carriers and 0.01 (0.10), 2% in controls; for fluency - severity mean 0.08 (0.19), frequency 16% in the *C9orf72* expansion carriers, 0.15 (0.32), 19% in the *GRN* mutation carriers and 0.01 (0.08), 3% in controls. Lastly, *C9orf72* expansion carriers also had impaired articulation compared with controls: severity mean 0.11 (0.27), frequency 16% in the *C9orf72* expansion carriers, and 0.01 (0.06), 2% in controls, whilst *GRN* mutation carriers had significant dysgraphia compared with controls: severity mean 0.10 (0.20), frequency 19% in the *GRN* mutation carriers, and 0.01 (0.13), 2% in controls.

3.4. Cognitive assessment

No differences were seen in the linguistic tasks compared with controls in the asymptomatic genetic groups. However, prodromal *C9orf72* expansion carriers were significantly impaired in category fluency (21.6 (6.0)) compared with controls (24.4 (6.4), $p = 0.011$). Prodromal *MAPT* mutation carriers were also significantly impaired on the category fluency task (22.1 (4.1), $p = 0.027$) as well as the BNT (25.7 (3.9), compared with 27.9 (1.9) in controls, $p = 0.027$).

3.5. Imaging analysis

The asymptomatic *C9orf72* group had significantly reduced regional brain volumes compared with controls in a number of regions (Table 1, Fig. 1b): insula (97% of mean control volume, $p = 0.024$), inferior frontal gyrus (98%, $p = 0.036$), superior temporal gyrus (98%, $p = 0.036$) and supratemporal region (98%, $p = 0.018$). No significant differences were seen in the *GRN* or *MAPT* asymptomatic groups. Regional volumes were also significantly reduced in the prodromal *C9orf72* group: insula (95% of mean control volume, $p = 0.005$) and supratemporal region (93%, $p = 0.008$) as well as temporal pole (96%, $p = 0.047$), motor (95%, $p = 0.008$) and angular gyrus (94%, $p = 0.032$). In the prodromal *MAPT* mutation carriers, the supratemporal region was significantly reduced in volume (93%, $p = 0.001$), with the temporal pole also reduced to a similar extent (94%, but not significantly different to controls, $p = 0.274$). No volumes were significantly different to controls in the prodromal *GRN* group.

For linguistic symptoms, dysgraphia in *C9orf72* mutation carriers significantly negatively correlated with volume of the insula ($r = -0.20$, $p = 0.029$) and angular gyrus ($r = -0.19$, $p = 0.031$) (Supplementary Table 1). In the *GRN* mutation carriers decreased fluency negatively correlated with volumes of the inferior frontal gyrus ($r = -0.21$, $p = 0.013$), insula ($r = -0.18$, $p = 0.035$) and angular gyrus ($r = -0.17$, $p = 0.048$), impaired grammar/syntax negatively correlated with supratemporal region volume ($r = -0.19$, $p = 0.031$), impaired word comprehension negatively correlated with inferior frontal gyrus volume ($r = -0.18$, $p = 0.043$), and impaired functional communication negatively correlated with volumes of the inferior frontal gyrus ($r = -0.20$, $p = 0.022$), insula ($r = -0.19$, $p = 0.025$) and supratemporal region ($r = -0.18$, $p = 0.038$). No correlations were seen in the *MAPT* mutation group.

In the *C9orf72* group there were no correlations between scores on the linguistic cognitive tasks and brain volumes (Supplementary Table 2). In the *GRN* group, there was a significant positive correlation between category fluency score and insula volume: $r = 0.21$, $p = 0.017$. In *MAPT* mutation carriers a positive correlation was seen between mCCT score and insula volume ($r = 0.29$, $p = 0.031$).

4. Discussion

In this study we have shown that language impairment occurs in the prodromal period of all three major genetic forms of FTD, with overlapping but distinct features. Impaired word retrieval was seen in all three groups and both decreased fluency and impaired grammar/syntax were seen in the *C9orf72* and *GRN* groups, but impaired articulation was only seen in the *C9orf72* mutation carriers. Impairment on a category fluency task was seen in both *C9orf72* and *MAPT* mutation carriers but only the *MAPT* group performed significantly worse on a test of naming. Atrophy was seen in core language network areas as early as the asymptomatic stage in *C9orf72* expansion carriers with volume loss in temporal regions in *MAPT* mutation carriers prodromally.

All three groups had impaired word retrieval. Such deficits can be due to multiple different underlying linguistic difficulties including both semantic and lexical access impairment as well as problems in non-linguistic cognitive domains impacting on the language system. (Note should be made however that 10% of controls also had impaired word retrieval, representing the fact that this is a common symptom in the general population and in those presenting with subjective cognitive impairment, where the underlying causes are often unclear [21,25]). It is likely that different mechanisms underpin the difficulties in the three genetic groups, with semantic problems predominating in *MAPT* mutations [29], and impairment of lexical access (or mixed problems) in the other two genetic groups [34]. Such an impairment of lexical retrieval

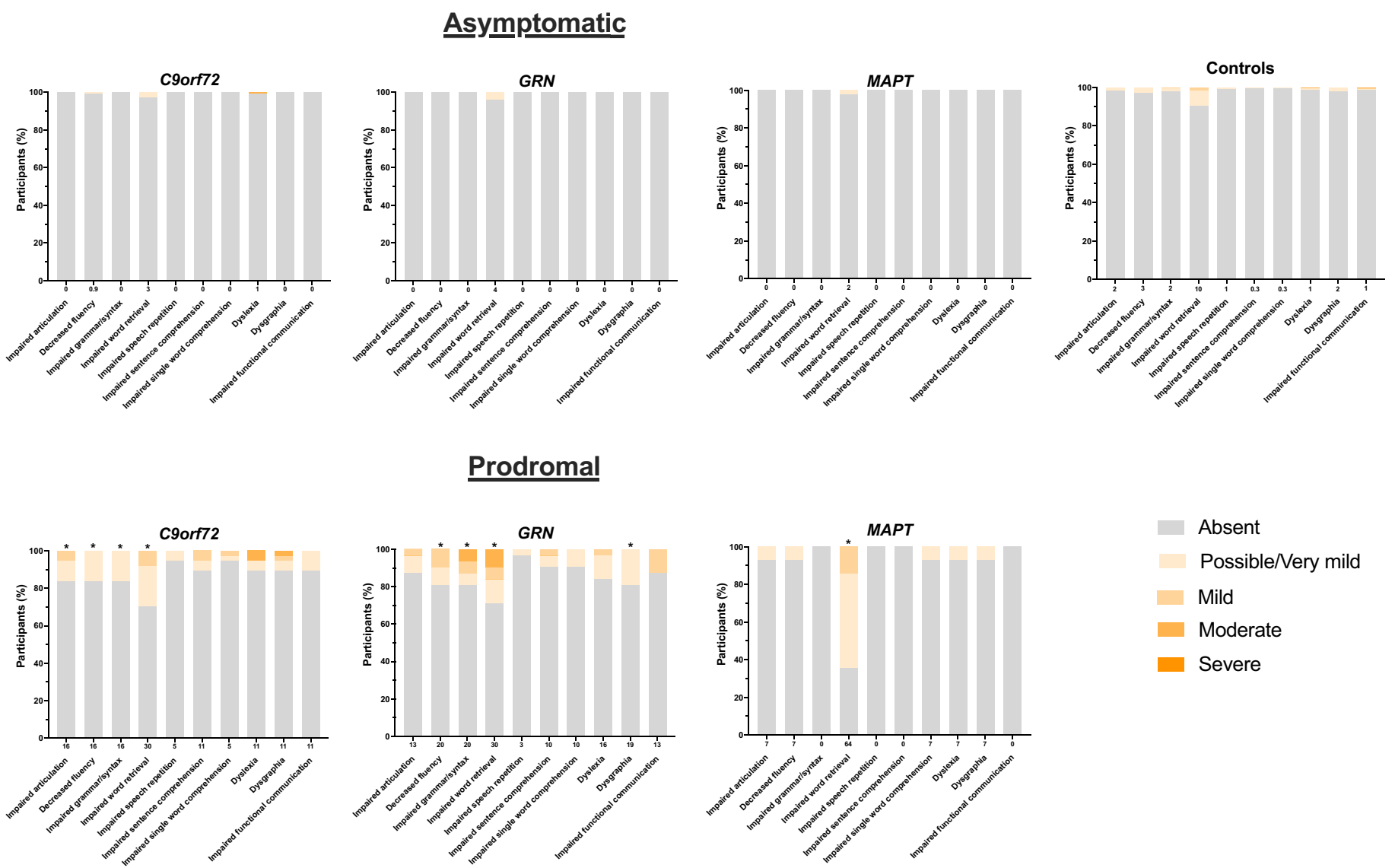

Fig. 2. The percentage of participants in each of the asymptomatic and prodromal groups and controls who score 0 = absent, 0.5 = very mild/questionable, 1 = mild, 2 = moderate, or 3 = severe for each linguistic symptom: y-axis shows all participants in each group (100%), x-axis shows the different linguistic symptoms. Values along the bottom of x-axis represent the frequency (%) with which the symptom is present in any category above zero (i.e. 0.5 to 3). An asterisk above the bar indicates that the symptom severity is significantly greater than controls.

can lead to decreased fluency, which was seen here in *C9orf72* and *GRN* mutation carriers, although nonfluency can also occur due to other underlying linguistic deficits including problems with grammar (also seen in both *C9orf72* and *GRN* mutation carriers), or impaired articulation (seen in the *C9orf72* mutation carriers alone). The presence of significant linguistic deficits occurring prodromally in all three groups highlights the importance of including a language component in any clinical rating scale of genetic FTD.

Nearly half of the *C9orf72* expansions had language difficulties, with this group showing significant impairment of word retrieval, grammar/syntax, fluency and articulation as well as poor performance on the category fluency task. Whilst these features are often seen in people with nonfluent variant PPA (and therefore may be thought to herald such a diagnosis), such a presentation in symptomatic *C9orf72* mutation carriers is uncommon [11]. In fact, these features are also seen alongside prominent behavioural change in those with a symptomatic diagnosis of bvFTD [36], and are not necessarily the initial symptom at phenoconversion. Furthermore, impaired articulation can be related to non-linguistic impairments such as dysarthria which is a feature of the bulbar presentation of amyotrophic lateral sclerosis, another phenotype of *C9orf72* expansions [17]. Interestingly, atrophy of quite a number of the language network regions was seen even at the asymptomatic stage, with further atrophy prodromally. This is consistent with previous studies showing widespread atrophy in presymptomatic *C9orf72* mutation carriers [2,40], including early involvement of more posterior regions, as seen here in the angular gyrus, where atrophy correlated with impairment of writing in this group.

Similar to the *C9orf72* group, just under half of the prodromal *GRN* mutation carriers had language symptoms with significant difficulties in word retrieval, fluency, grammar/syntax and dysgraphia. In contrast, however, in a previous GENFI study (Samra et al., in press) over 40% of symptomatic *GRN* mutation carriers had a PPA phenotype, either nfvPPA or PPA-NOS. It may well be therefore that some of the prodromal mutation carriers in this study are destined to develop PPA, but it is important to note that other studies (Le [22,36]) have shown that over 50% of people with *GRN*-associated bvFTD also have linguistic deficits (as secondary features to the behavioural change): at present it is not possible to predict exactly who will develop which phenotype. Unlike the other two groups none of the language network regional volumes were significantly lower than controls. This is consistent with previous studies [2] showing that atrophy occurs quite late in the presymptomatic period. However, a number of symptoms (including decreased fluency and impairment on the category fluency task) correlated with atrophy in the inferior frontal gyrus and insula, regions both known to be affected in *GRN*-associated PPA and bvFTD (Samra et al., in press; [36]).

Although only one linguistic symptom was significantly abnormal in the prodromal *MAPT* mutation group, impaired word retrieval occurred in 64% of carriers. Consistent with this impairment, the prodromal *MAPT* group also had significant difficulties on both the naming and category fluency task. As mentioned above, this is likely to be due to semantic impairment, a feature previously described in *MAPT* mutations ((Samra et al., in press; [5,28–30]). Whilst anomia can rarely be the presenting symptom leading to a diagnosis of svPPA in people with *MAPT* mutations, it is more commonly a secondary (albeit prominent) feature in those presenting with personality change and diagnosed with bvFTD [1,7,19,32,36]. The imaging analysis here showed the largest percentage volume loss compared with controls prodromally was in the left supratemporal region and temporal pole. The anterior temporal lobe is an important part of the semantic network [18,20] although a correlation of mCCT score and insula volume suggests other areas are likely to be important in language function in *MAPT* mutation carriers.

4.1. Limitations

Although the GENFI study is one of the largest genetic FTD cohorts worldwide, there were modest numbers in each group after stratification and further studies aiming to replicate this data will be helpful. Another limitation was the limited availability of language cognitive tests within the GENFI battery. With a lack of validated cross-language verbal linguistic tasks the multilingual GENFI study has focused on non-verbal or already validated tasks in its cognitive battery. Moreover, non-linguistic deficits may impact performance on tasks such as category fluency or the mCCT, where executive dysfunction can lead to impairments [9,14]. Lastly, it is currently impossible to predict whether a presymptomatic mutation carrier with language features will go on to develop bvFTD, PPA or another clinical syndrome. Future longitudinal studies in GENFI and other familial FTD cohorts will be important to better understand phenoconversion and to establish which features predict particular FTD phenotypes during the prodromal period.

4.2. Conclusions

In summary, linguistic deficits seem to occur when individuals with genetic FTD enter the prodromal phase, with important differences being shown between the three genetic groups both in terms of clinical features and the pattern of atrophy in the key language network regions. The study highlights the importance of including language symptoms in any clinical rating scale for genetic FTD, particularly when considering staging of the disease and for monitoring disease progression.

Ethics approval and consent to participate

All GENFI sites had local ethical approval for the study, and all participants gave written informed consent.

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Declaration of Competing Interest

The authors declare that they have no competing interests.

Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Appendix A. Supplementary data

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