Anomia is present pre-symptomatically in frontotemporal dementia due to MAPT mutations

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Abstract

Introduction

A third of frontotemporal dementia (FTD) is caused by an autosomal-dominant genetic mutation in one of three genes: microtubule-associated protein tau (MAPT), chromosome 9 open reading frame 72 (C9orf72) and progranulin (GRN). Prior studies of prodromal FTD have identified impaired executive function and social cognition early in the disease but few have studied naming in detail.

Methods

We investigated performance on the Boston Naming Test (BNT) in the GENetic Frontotemporal dementia Initiative cohort of 499 mutation carriers and 248 mutation-negative controls divided across three genetic groups: C9orf72, MAPT and GRN. Mutation carriers were further divided into 3 groups according to their global CDR plus NACC FTLD score: 0 (asymptomatic), 0.5 (prodromal) and 1+ (fully symptomatic). Groups were compared using a bootstrapped linear regression model, adjusting for age, sex, language and education. Finally, we identified neural correlates of anomia within carriers of each genetic group using a voxel-based morphometry analysis.

Results

All symptomatic groups performed worse on the BNT than controls with the MAPT symptomatic group scoring the worst. Furthermore, MAPT asymptomatic and prodromal groups performed significantly worse than controls. Correlates of anomia in MAPT mutation carriers included bilateral anterior temporal lobe regions and the anterior insula. Similar bilateral anterior temporal lobe involvement was seen in C9orf72 mutation carriers as well as more widespread left frontal atrophy. In GRN mutation carriers, neural correlates were limited to the left hemisphere, and involved frontal, temporal, insula and striatal regions.

Conclusion

This study suggests the development of early anomia in MAPT mutation carriers, likely to be associated with impaired semantic knowledge. Clinical trials focused on the prodromal period within individuals with MAPT mutations should use language tasks, such as the BNT for patient stratification and as outcome measures.

Keywords

Frontotemporal dementia · Tau · Progranulin · C9orf72 · Naming · Cognition

Introduction

Frontotemporal dementia (FTD) is a heterogeneous neurodegenerative disorder presenting with distinct changes in behaviour, language and motor function [1]. A third of cases are caused by an autosomal-dominant genetic mutation in one of three genes: microtubule-associated protein tau (MAPT), chromosome 9 open reading frame 72 (C9orf72)
and progranulin (GRN) [2]. Although mutations in any of these genes can lead to impaired naming ability (anomia), MAPT mutation carriers tend to show the most pronounced deficit with previous studies showing that such difficulties can even be detected before symptom onset [3–5]. Importantly, whilst anomia is one of the key manifestations of people with the language variant of FTD [6], a similar pattern of naming deficits, albeit often less severe, has been found in the early stages of people presenting with both behavioural and motor symptoms [7–9], suggesting that impairment could potentially be seen in all of the phenotypes of genetic FTD.

Neuroanatomical correlates of naming deficits in FTD have implicated a widespread network of brain regions focused on the left hemisphere [10], which reflects the different components of the language pathway that contribute to naming [11]. In FTD due to C9orf72, GRN or MAPT mutations, there are both shared and distinct networks of atrophy across genetic groups, observable even at the pre-symptomatic stage [12]. This raised our hypothesis that the neuroanatomical correlates underlying naming differ according to the genetic aetiology of FTD.

The current study assessed naming deficits using the short 30-item version of the Boston Naming Test (BNT) [13] in a large cohort of C9orf72, MAPT and GRN mutation carriers. We expected all symptomatic mutation carriers to be impaired compared to mutation-negative controls on the BNT, but that MAPT mutation carriers would be the most impaired, potentially even in pre-symptomatic stages [4]. We also aimed to investigate the neural correlates of the BNT within each genetic group using voxel-based morphometric analyses of grey matter volume derived from structural Magnetic Resonance Imaging (MRI). We expected regions of the left-lateralised language network to be implicated in naming deficits across the groups, with potentially more focal anterior medial temporal structures in MAPT mutation carriers and a wider network in the C9orf72 and GRN groups.

Methods

Participants

Participants were recruited from the fifth data freeze of the GENFI study including sites in the UK, Canada, Sweden, Netherlands, Belgium, Spain, France, Portugal, Italy and Germany with eight different languages. Ethical approval was obtained for the study and all participants provided informed written consent. As well as the 30-item version of the Boston Naming Test in their preferred language [14], all participants underwent a standardised GENFI clinical assessment including a medical history, physical examination, the Mini-Mental State Examination (MMSE), and the Clinical Dementia Rating Scale (CDR) with National Alzheimer’s Coordinating Centre (NACC) FTD-specific modules (CDR plus NACC FTLD). The CDR plus NACC FTLD provides both a summed score (CDR plus NACC FTLD sum of boxes) and a global score, where 0 is asymptomatic, 0.5 is prodromal, 1 is mildly symptomatic, 2 is moderately symptomatic and 3 is severely symptomatic, with the last three scores also being combined to create a 1 + or ‘fully symptomatic’ group [15].

747 GENFI participants completed the BNT and were included in the present study: 248 mutation-negative carriers (controls), 212 C9orf72 expansion carriers, 201 GRN mutation carriers, and 86 MAPT mutation carriers. Mutation carriers were further divided into three groups according to their CDR plus NACC FTLD global score. Within the symptomatic mutation carrier groups, 101 met the diagnostic criteria for behavioural variant FTD (bvFTD: 54 C9orf72, 26 GRN and 21 MAPT), 20 primary progressive aphasia (PPA: 3 C9orf72, 16 GRN and 1 MAPT) and 14 amyotrophic lateral sclerosis with or without FTD (14 C9orf72). Demographic data for the groups are described in Table 1.

Magnetic Resonance Imaging (MRI)

Participants underwent volumetric T1-weighted magnetic resonance imaging (MRI) according to the harmonized GENFI imaging protocol on a 3T scanner, with only mutation carriers included in the neural correlate imaging analysis. From a total of 499 mutation carriers included in the naming study, 94 were excluded from the imaging analysis due to either imaging not being performed or not passing quality control. 405 scans were included: Siemens Trio 3T (n = 111), Siemens Skyra 3T (n = 64), Siemens Prisma 3T (n = 91), Philips Achieva 3T (n = 135) and GE 3T (n = 4).

BNT statistical analysis

Statistical analyses were performed using STATA version 16.0 (Texas, USA). The significance level was set at p < 0.05 across all comparisons. We compared group demographic data with linear regression except for sex which was compared using chi-square tests.

BNT scores in controls were assessed by calculating cumulative frequency (and therefore percentile scores), as well as investigating the effect of sex (Mann–Whitney U test), age (Spearman’s rank correlation), and education (Spearman’s rank correlation).

BNT scores in the mutation carrier groups were compared to each other and to controls using a bootstrapped linear mixed effects model (2000 repetitions) (due to non-normality). The model was adjusted for age, sex, education, language and family clustering with 95% bootstrapped confidence intervals.
confidence intervals. Post hoc pairwise comparisons were used to assess differences in group performance.

### Structural brain imaging analysis

Voxel-based morphometric (VBM) analysis was performed using Statistical Parametric Mapping (SPM) 12 software, version 7219 (www.fil.ion.ucl.ac.uk/spm), running under Matlab R2014b (Mathworks, USA). The T1-weighted images were normalized and segmented into grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF) probability maps, using standard procedures and the fast-diffeomorphic image registration algorithm (DARTEL) [16]. GM segmentations were affine-transformed into the Montreal Neurological Institute (MNI) space, modulated and smoothed using a Gaussian kernel with 6 mm full width, at half maximum, before analysis. Finally, a customised explicit brain mask was applied based on an optimised voxel threshold intensity criterion [17]. All segmentations were visually checked at each stage. Total intracranial volume was calculated using SPM [18].

The relationship of BNT score with GM density in the three mutation carrier groups was explored using a flexible factorial regression model. A main effect of BNT was included in the model and genetic group was included as an interaction. Age, sex, TIV and scanner type were included as covariates in the initial model with a further model additionally including disease severity as measured by the CDR plus NACC FTLD sum of boxes. All comparisons were adjusted for multiple comparisons. An empirically determined cluster size threshold was also applied (23 for the initial model, and 62 for the further model).

### Results

#### Demographic data

Differences between groups were seen in age, sex and years of education (Table 1). Compared with controls, all symptomatic groups \((p < 0.001)\) as well as prodromal C9orf72 \((p = 0.033)\) and GRN \((p = 0.010)\) mutation carriers were significantly older, whilst asymptomatic MAPT mutation carriers were significantly younger than controls \((p = 0.001)\). Within each genetic group, all symptomatic groups were significantly older than the prodromal groups \((p < 0.003)\) who were significantly older than the asymptomatic groups \((p < 0.033)\) apart from in MAPT mutations carriers where no difference in age was observed between prodromal and asymptomatic groups. There were significantly more males than females in the symptomatic C9orf72 \((p = 0.001)\) and MAPT \((p = 0.027)\) mutation carriers compared with the control group. With genetic groups, there were significantly more males than females in the symptomatic C9orf72 mutation carriers compared with the prodromal \((p = 0.011)\) and asymptomatic \((p = 0.003)\) groups. There were also more males than females in the symptomatic MAPT mutation carriers compared to the prodromal \((p = 0.023)\) and asymptomatic \((p = 0.030)\) groups. In terms of years of education, symptomatic GRN and C9orf72 mutation carriers had significantly fewer years of education than controls \((p < 0.001)\).

|               | \(N\) | Age (years) | % Male | Education (years) | CDR plus NACC FTLD sum | MMSE | BNT |
|---------------|------|-------------|--------|-------------------|------------------------|------|-----|
| Controls      | 248  | 44.9 (12.7) | 43.2   | 14.4 (3.2)        | 0.0 (0.0)              | 29.3 (1.1) | 27.8 (1.9) |
| C9orf72 0    | 110  | 44.2 (11.7) | 41.8   | 14.3 (3.0)        | 0.0 (0.0)              | 29.2 (1.1) | 27.3 (3.1) |
| C9orf72 0.5  | 36   | 49.3 (11.4) | 38.9   | 14.1 (2.5)        | 1.2 (0.8)              | 28.6 (2.0) | 27.5 (3.4) |
| C9orf72 1+   | 66   | 62.1 (8.6)  | 65.2   | 13.2 (3.7)        | 10.7 (5.4)             | 24.0 (5.8) | 20.6 (7.6) |
| GRN 0        | 128  | 45.8 (12.2) | 35.2   | 14.7 (3.4)        | 0.0 (0.0)              | 29.4 (0.9) | 27.9 (1.9) |
| GRN 0.5      | 30   | 51.7 (13.4) | 50.0   | 14.0 (4.0)        | 1.0 (0.8)              | 28.4 (2.4) | 26.7 (3.7) |
| GRN 1+       | 43   | 63.5 (7.9)  | 51.2   | 11.9 (3.3)        | 8.6 (5.4)              | 21.3 (6.1) | 21.2 (6.5) |
| MAPT 0       | 48   | 39.3 (10.5) | 39.6   | 14.4 (3.6)        | 0.0 (0.0)              | 29.5 (0.8) | 27.6 (2.1) |
| MAPT 0.5     | 14   | 45.7 (12.6) | 28.6   | 13.5 (2.4)        | 1.1 (0.8)              | 28.2 (2.3) | 25.7 (3.9) |
| MAPT 1+      | 24   | 57.3 (10.2) | 66.7   | 13.7 (3.9)        | 9.3 (5.5)              | 23.7 (6.7) | 17.0 (8.0) |

CDR plus NACC FTLD sum of boxes (SOB) score is shown as well as the Mini-Mental State Examination (MMSE) and Boston Naming Test. Scores are shown as means (standard deviations).
Within genetic groups, symptomatic GRN mutation carriers had fewer years of education compared with the other two groups \( (p < 0.05) \) and symptomatic C9orf72 mutation carriers had significantly fewer years of education than the asymptomatic group \( (p < 0.05) \).

**BNT scores in controls**

Calculation of cumulative frequency in controls revealed a 5th percentile cut-off score at 24 (Supplementary Table S1). BNT scores did not correlate with age \( (\rho = -0.04, p = 0.53) \), and there was no significant effect of sex on BNT score \( (U = -10,590, p = 0.72) \) (Supplementary Table S2). However, there was a weak positive correlation with education \( (\rho = 0.28, p < 0.001) \).

**BNT scores in genetic groups**

All three fully symptomatic mutation carrier groups performed significantly worse than controls on the BNT \( (p = <0.001) \) (Fig. 1, Table 1, Supplementary Table S3). Asymptomatic and prodromal MAPT mutation carriers also performed significantly worse than controls \( (p = 0.012 \text{ and } 0.011 \text{ respectively}) \) but neither of the GRN or C9orf72 pre-symptomatic groups performed significantly worse than controls on the task.

Within genetic groups, the fully symptomatic groups performed worse than both the prodromal and asymptomatic groups in MAPT, GRN and C9orf72 mutation carriers \( (p = <0.001) \). Additionally, the GRN prodromal group scored significantly worse than the asymptomatic group \( (p = 0.018) \).

Between genetic groups at the same disease stage, symptomatic MAPT mutation carriers performed significantly worse than symptomatic GRN and C9orf72 mutation carriers \( (p = 0.007 \text{ and } 0.034 \text{ respectively}) \). Prodromal MAPT mutation carriers performed significantly worse than prodromal C9orf72 mutation carriers \( (p = 0.020) \), whilst both asymptomatic MAPT and C9orf72 mutation carriers performed significantly worse than asymptomatic GRN carriers \( (p = 0.003, p = 0.048 \text{ respectively}) \).

**Neuroanatomical correlates of BNT score**

The initial VBM analysis model revealed partially overlapping neural correlates of naming in the three genetic groups (Figs. 2, 3, Supplementary Table S4). In MAPT mutation carriers, the anterior and medial temporal regions were implicated bilaterally as were the bilateral anterior insular cortices. In C9orf72 mutation carriers, the anterior temporal structures were also bilaterally involved. However, more widespread correlates of naming were seen in this group, particularly affecting the left hemisphere, in frontal (inferior, middle and superior) and insular cortices as well as the caudate. In GRN mutation carriers, correlates were only found within the left hemisphere, but were more distributed than the other two groups, affecting frontal (including premotor and supplementary motor cortices), anterior and lateral temporal, anterior parietal and striatal regions.

Adjusting for disease severity found very similar results in the additional VBM analysis model, although at an uncorrected \( p < 0.001 \) threshold, with no results found.
when correcting for multiple comparisons (Supplementary Fig. S1 and Supplementary Table S5): similar neural correlates were seen in each group although with more focal left anterior temporal lobe involvement for the C9orf72 mutation carriers in this analysis.

Discussion

In this study, we found that all genetic groups performed significantly worse on the BNT than controls when people were fully symptomatic, but only in the MAPT mutation group was naming ability impaired presymptomatically, being abnormal in both prodromal and asymptomatic mutation carriers. This highlights that naming performance is significantly impaired in people with genetic FTD, particularly in those with MAPT mutations, consistent with the previous literature [3–5, 11]. However, here we demonstrate very early naming change in the MAPT genetic group, and with overlapping but distinct neural correlates across the genetic groups: bilateral anterior temporal and anterior insula regions in MAPT mutation carriers, with similar temporal lobe involvement as well as more widespread left hemisphere atrophy in C9orf72 mutation carriers, and only distributed left hemisphere correlates in GRN mutation carriers.

The results in MAPT mutation carriers are consistent with previous work, where more severe deficits are seen on naming tasks cross-sectionally and the most decline over time is seen compared with both C9orf72 and GRN mutation carriers [4, 19]. We also found that both MAPT asymptomatic and prodromal groups performed significantly worse than controls. This finding has not been reported in the literature.
but is in keeping with previous work showing that MAPT mutation carriers have naming deficits before a formal diagnosis of FTD [4, 20]. Our study provides further evidence for subtle cognitive changes at a pre-symptomatic stage. Clinical trials for MAPT mutation carriers should consider using naming tasks such as the BNT as a marker for patient selection and outcome measure.

In MAPT mutation carriers, focal atrophy within the bilateral anterior and medial temporal lobes was associated with BNT score. The anterior temporal lobe has often been associated with semantic memory, particularly in studies which show that this region is specifically atrophied and hypometabolic in people with the semantic variant of PPA compared with those with Alzheimer’s disease [21]. Symptomatic and late pre-symptomatic MAPT mutation carriers are significantly impaired compared to controls on semantic memory tasks, with performance correlating strongly with bilateral temporal lobe volume [22]. Moreover, semantic deficits are suggested to occur with greater frequency in MAPT mutation carriers than in GRN or C9orf72 mutation carriers [3–5]. Thus, a core semantic deficit has been put forward as the defective mechanism underlying MAPT mutation carriers’ anomia, and our imaging results appear in line with such claims. Moreover, in view of the extremely symmetrical neuroanatomical correlates with the BNT, it appears that both verbal and visual semantics are equally likely to be related to MAPT mutation carriers’ poor BNT score.

In C9orf72 and GRN mutation carriers, reduced grey matter volume in the anterior temporal structures was also related to BNT performance. In the C9orf72 group, these extended to include bilateral hippocampi, whilst in the GRN group, these were left hemisphere only. In a recent study of a large cohort of patients, semantic deficits were also found in both C9orf72 and GRN mutation carriers [22].

The strength of this study’s results comes from the use of a large cohort of people with genetic FTD, which enabled gene-specific analyses, compared to control group of mutation-negative family members. We were therefore able to find pre-symptomatic naming deficits in MAPT mutation carriers and reveal different levels of performance in naming, between the three genetic groups. Different processes underlying naming in each genetic group are suggested by the diverse brain regions which appeared related to naming performance.

Conclusion

Overall, our findings are consistent with the hypothesis that large-scale neural network degeneration underlies the impairment of naming ability in genetic FTD, but with different contributory regions in each genetic form. This study highlights the potential use of a simple naming task as an
outcome measure for international clinical trials in presymptomatic MAPT mutation carriers, and in helping differential diagnosis and severity staging by understanding the sources of naming difficulty.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s00415-022-11068-0.

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