Brain atrophy over time in genetic and sporadic frontotemporal dementia: a study of 198 serial magnetic resonance images

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Background and purpose: The aim of our study was to determine the utility of longitudinal magnetic resonance imaging (MRI) measurements as potential biomarkers in the main genetic variants of frontotemporal dementia (FTD), including microtubule-associated protein tau (\textit{MAPT}) and progranulin (\textit{GRN}) mutations and \textit{C9ORF72} repeat expansions, as well as sporadic FTD.

Methods: In this longitudinal study, 58 subjects were identified who had at least two MRI and \textit{MAPT} mutations (n = 21), \textit{GRN} mutations (n = 11), \textit{C9ORF72} repeat expansions (n = 11) or sporadic FTD (n = 15). A total of 198 serial MRI measurements were analyzed. Rates of whole brain atrophy were calculated using the boundary shift integral. Regional rates of atrophy were calculated using tensor-based morphometry. Sample size estimates were calculated.

Results: Progressive brain atrophy was observed in all groups, with fastest rates of whole brain atrophy in \textit{GRN}, followed by sporadic FTD, \textit{C9ORF72} and \textit{MAPT}. All variants showed greatest rates in the frontal and temporal lobes, with parietal lobes also strikingly affected in \textit{GRN}. Regional rates of atrophy across all lobes were greater in \textit{GRN} compared to the other groups. \textit{C9ORF72} showed greater rates of atrophy in the left cerebellum and right occipital lobe than \textit{MAPT}, and sporadic FTD showed greater rates in the anterior cingulate than \textit{C9ORF72} and \textit{MAPT}. Sample size estimates were lowest using temporal lobe rates in \textit{GRN}, ventricular rates in \textit{MAPT} and \textit{C9ORF72}, and whole brain rates in sporadic FTD.

Conclusion: These data support the utility of using rates of atrophy as outcome measures in future drug trials in FTD and show that different imaging biomarkers may offer advantages in the different variants of FTD.

Introduction

Familial frontotemporal dementia (FTD) has become increasingly important as a number of major gene mutations have been discovered, including mutations in the microtubule-associated protein tau (\textit{MAPT}) [1] and progranulin (\textit{GRN}) [2,3] genes, and repeat expansions in the \textit{C9ORF72} gene [4,5]. These mutations are associated with specific pathologies making them ideal targets for future therapeutic trials in FTD [6]. Families with these genetic mutations can also be prospectively followed providing invaluable opportunities to assess, and potentially treat, the very earliest stages of the disease. However, if these subjects are to be included in treatment trials, outcome measures will be needed that provide biomarkers of disease progression. Longitudinal magnetic resonance imaging (MRI) measures can serve as excellent disease biomarkers,
although little is known about how atrophy progresses over time in these genetic variants of FTD. Cross-sectional studies have shown that the different genetic mutations have specific focal neuroimaging signatures [7–11], suggesting that regional longitudinal MRI may prove to be the most useful biomarker.

The aim of the study was to assess whole brain and regional rates of atrophy in MAPT, GRN and C9ORF72, as well as sporadic FTD, using large cohorts of subjects with multiple longitudinal MRI measurements. It was hypothesized that regional MRI measures may provide smaller sample size estimates for treatment trials compared to global measures of atrophy. These findings will help characterize progression in these variants and determine whether longitudinal MRI measures could have utility as potential biomarkers in FTD. This study furthers our previous work on genetic FTD [10–12] by assessing for the first time regional rates of atrophy over time in MAPT, GRN, C9ORF72 and sporadic FTD, and providing sample size estimates.

Methods

Subjects

All subjects who had been seen at Mayo Clinic, Rochester, MN, who had screened positive for mutations in MAPT, GRN or C9ORF72, as well as sporadic FTD, were symptomatic and who had two or more volumetric MRI measurements (n = 43) between January 1993 and December 2012 were identified. Genetic analyses were performed as previously described [1,2,4,13]. Twenty-one subjects were identified with MAPT mutations, representing 10 families and nine different mutations (P301L, IVS10+16, IVS10+3, N279K, V337M, S305N, G389R, R406W, Q336H). Eleven subjects were identified with GRN mutations, representing seven families and seven different mutations. The remaining 11 subjects had repeat expansions in C9ORF72.

All subjects with behavioral variant FTD (bvFTD) [14], with or without amyotrophic lateral sclerosis (ALS), who did not have a family history of either FTD or ALS in a first or second degree relative, screened negative for MAPT, GRN and C9ORF72 mutations, and had two or more serial MRI measurements were also identified (n = 15). All 15 were considered to have sporadic FTD.

All subjects had been prospectively recruited and longitudinally followed in our Alzheimer’s Disease Research Center with volumetric MRI performed annually. Clinical diagnoses were made according to consensus criteria for bvFTD [14], FTD with ALS [15], primary progressive aphasia [16] or Alzheimer’s disease [17].

Informed consent was obtained from all subjects and/or their proxies for participation in the study, which was approved by the Mayo Clinic Institutional Review Board.

Magnetic resonance imaging analysis

All subjects underwent a standardized protocol head MRI that included a T1-weighted three-dimensional volumetric sequence [18]. Whilst some subjects had been scanned at 1.5 T and some at 3 T, longitudinal scans for each subject were limited to those performed at the same field strength. A total of 198 serial MRI measurements were analyzed. All images underwent pre-processing corrections for gradient non-linearity and intensity inhomogeneity. All scan pairs for each subject underwent 9 degree-of-freedom rigid-body registration and differential bias correction [19].

Rates of atrophy were calculated at the global, lobar, regional and voxel level. For the global analysis, rates of whole brain atrophy and ventricular expansion were calculated from all scan pairs registered to baseline using the brain boundary shift integral [20,21]. Rates of lobar and regional atrophy were assessed using all scan pairs and an in-house modified version of tensor-based morphometry using symmetric normalization [22] (TBM-SyN) in SPM5 [23]. The AAL [24] atlas was used to obtain regional volume estimates for every scan pair. Specific regions of interest analyzed were based on cross-sectional findings in each mutation, and covered frontal, temporal, parietal and occipital lobes, and insula, cerebellum, thalamus, striatum and sensorimotor cortex. Left and right hemispheres were assessed separately. Voxel-level comparisons of annualized log Jacobians from TBM-SyN were performed across groups using SPM5 to allow visualization of group differences. t tests were used to compare across the groups with results assessed at P < 0.001 with an extent threshold of 200 voxels.

Statistical analysis

Linear mixed effects models with subject-specific random intercepts and slopes to fit longitudinal models of log(volume) over time were used [25]. The timescale was time from baseline scan. A time-by-group interaction was specified to obtain group-specific slope coefficients. By estimating approximate percentage change via the log transformation, a reasonable assumption is made of a constant rate of decay, i.e. x%/year, which is non-linear on the volume scale. On inspecting the data at the subject level, trajectories tended to be approximately linear over the period of follow-up,
providing empirical support for the model. Whilst age differed across groups, no adjustment for age was made because of intrinsic age differences across groups. To adjust our models for age, ignoring technical difficulties due to imbalance in the age distributions across the groups would essentially be ‘anchoring’ groups at a common age. This would have the unintended consequence of comparing late-stage MAPT cases versus early stage cases from other groups. In order to assess the influence of field strength the models were re-run including a field-strength-by-time interaction. The interactions were not significant (P > 0.12) and the interaction coefficient estimates were small and ambiguous in terms of the direction of the effect across regions indicating that field strength was not associated with rates in our cohort.

Sample sizes needed per arm were estimated to conduct a hypothetical 12-month parallel design two-arm clinical trial designed to detect a slowing of atrophy by 20% with 80% power and two-sided alpha of 5%. The rate of change for each subject was first estimated based on a least squares fit using all scans and treating log volume as the response with time in years as the predictor. The placebo rate was assumed to be equal to the observed mean whilst the treated rate was assumed to be 20% less. The effect size was calculated as the difference between the two rates divided by the observed standard deviation and this was plugged into the standard two-sample, two-sided t test formula.

Our analyses were performed using all available subjects with the rationale that a clinical treatment trial will probably recruit all subjects with these mutations, regardless of clinical phenotype. A secondary analysis was also performed, however, limited to subjects with bvFTD (n = 46, 154 scans).

**Results**

**Subject demographics**

Subject groups did not differ in demographics, cognitive or functional performance, or follow-up time, but did differ in age, with the MAPT group younger than the other groups (Table 1).

**Global rates of atrophy**

Annualized rates of whole brain atrophy were greatest in GRN, followed by sporadic FTD, C9ORF72, and lastly MAPT, with a trend for differences across groups (P = 0.06) (Table 2). Similarly, rates of ventricular expansion were greatest in GRN, followed by sporadic FTD, and then C9ORF72 and MAPT, with no difference observed across groups (Table 2).

**Lobar rates of atrophy**

Lobar rates of atrophy were greatest in the frontal lobe, followed by the temporal lobe, in MAPT, C9ORF72 and sporadic FTD (Table 2). In contrast, GRN showed greatest rates in the parietal lobe. Lobar rates were highly asymmetric in GRN, with greatest rates in the left hemisphere, whilst rates in the other three groups were more symmetric. Rates of atrophy across all four lobes were greatest in GRN. Specifically, GRN showed greater rates of atrophy than all three other groups in the total temporal, total parietal, left parietal and left occipital lobe. Rates of left frontal and right parietal atrophy were greater in GRN compared to both MAPT and C9ORF72, but not sporadic FTD. Rates of total and right occipital atrophy in GRN were only greater than MAPT. In addition, rates of right occipital atrophy were greater in C9ORF72 compared to MAPT. The results remained largely the same when the analysis was limited to subjects with bvFTD (Table S1), except that rates in GRN were more symmetric.

**Regional rates of atrophy**

Regional rates of atrophy within each group are shown in Fig. 1. Similar to the lobar-level analysis, rates of atrophy were asymmetric in GRN, with greater involvement of the left hemisphere, and GRN showed faster rates than the other groups across most regions of interest. Some group differences were also observed between MAPT, C9ORF72 and sporadic FTD. First, sporadic FTD showed greater rates of left and right anterior cingulum atrophy compared to both MAPT and C9ORF72, and showed greater rates of left thalamic atrophy than MAPT. Secondly, C9ORF72 and sporadic FTD both showed greater rates of atrophy in the left cerebellum compared to MAPT. Regional rates of atrophy for the secondary analysis limited to bvFTD are shown in Fig. S1.

In the voxel-level comparisons, GRN showed greater rates of atrophy than C9ORF72, MAPT and sporadic FTD in precuneus, posterior cingulate, inferior parietal lobe and lateral temporal lobe, as well as prefrontal cortex (Fig. 2). No other voxel-level differences in rates of atrophy were observed across groups.

**Sample size estimates**

The smallest sample size estimates were obtained with rate of temporal lobe atrophy in GRN, followed by
rate of ventricular expansion, where 51 and 61 subjects respectively would be required per treatment arm to detect a 20% treatment effect (Table 3). Rate of ventricular expansion provided the smallest sample size estimates in both MAPT and C9ORF72 groups providing sample size estimates of 191 subjects in MAPT and 56 subjects in C9ORF72. Rate of whole brain atrophy provided the smallest sample size in sporadic FTD, with 87 subjects required per treatment arm to detect a 20% treatment effect.

Discussion

In this detailed longitudinal study utilizing 198 serial MRI measures, it was demonstrated that regional rates of atrophy differ across genetic and sporadic...
variants of FTD and that different imaging biomarkers may offer advantages in the different variants of FTD.

Subjects with GRN mutations showed the fastest rates of atrophy, with particularly fast rates in parietal lobes. These results concur with previous studies that have found fast rates of whole brain atrophy [8,12] and parietal loss on cross-sectional MRI [8,10] in GRN, suggesting that change over time is occurring in the same set of regions that are affected cross-sectionally. Striking asymmetry is also a common finding in GRN [8,11], and asymmetric rates of atrophy in this group were indeed observed. The preference for the left hemisphere probably explains why a number of GRN subjects presented with primary progressive aphasia. However, when the analysis was limited to bvFTD, asymmetric rates were no longer observed, which is at odds with our cross-sectional findings [11]. It is possible that whilst some asymmetry may exist early in these subjects, atrophy later in the disease occurs in a more symmetric fashion over time.

Figure 1 Estimated annual percentage change (95% confidence interval) in regional volumes within each group. L, left; R, right; ant, anterior; post, posterior; dorsolat, dorsolateral; cing, cingulate. *Significant difference observed across the four groups at $P < 0.05$. Significant ($P < 0.05$) pairwise $P$ values are shown as circles in the far right panel.
MAPT and C9ORF72 showed the slowest overall rates of atrophy, suggesting that these are relatively slowly progressive variants of FTD. Both groups showed the fastest rates of atrophy in the frontotemporal lobes. Repeat expansions in C9ORF72 have previously been associated with small volumes of cerebellum and occipital lobe on a cross-sectional study [11], and increased rates of atrophy were similarly found in these regions compared to MAPT. However, no evidence was found that C9ORF72 was associated with increased rates of atrophy in the thalamus or sensorimotor cortex compared to the other FTD groups, even though small volumes have been reported in these structures in cross-sectional studies [7,9]. The findings in MAPT concur with the fact that the frontal and temporal lobes are typically atrophic in subjects with MAPT. Cross-sectional data, however, identified the temporal lobes as having the greatest amount of atrophy [8,26]. This discordance could suggest that the temporal lobes are already so atrophic at baseline in MAPT subjects that rates of atrophy have started to slow, with little tissue left to lose. Alternatively, temporal lobe atrophy could be an early feature of MAPT subjects, with the frontal lobes starting to become more involved as the disease progresses.

The sporadic FTD group showed disproportionately fast rates of atrophy in the frontal lobes, particularly the anterior cingulate gyrus. Whilst these findings concord with the fact that the majority of these subjects presented with bvFTD, the findings were not confounded by clinical syndrome. Greater rates of anterior cingulate atrophy in sporadic FTD compared to MAPT and C9ORF72 were still observed when the cohort was limited to bvFTD. Involvement of the anterior cingulate therefore seems to be particularly associated with sporadic forms of bvFTD and FTD with ALS.

Importantly, the sample size analysis allowed us to assess the potential utility of these MRI measures for clinical treatment trials. Regional rates of atrophy provided larger sample size estimates compared to whole brain and ventricular rates across all groups, except for GRN in which the rate of temporal atrophy provided the smallest sample size estimates. The rate of temporal atrophy outperformed the rate of parietal atrophy in GRN due to a smaller degree of variance in this measure (standard deviation 0.019 vs. 0.033). Temporal rates of atrophy may therefore have utility for clinical treatment trials including subjects with GRN mutations. In general, however, rates of ventricular expansion appear to hold the most promise as a potential outcome measure across all variants of FTD, and hence should be the outcome measure of choice if a single metric is required. This may, in part, be driven by reduced disease-related variability and measurement error for ventricular volume which can

<table>
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<tr>
<th>Outcome measure</th>
<th>GRN</th>
<th>MAPT</th>
<th>C9ORF72</th>
<th>Sporadic FTD</th>
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<tbody>
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<td>238</td>
<td>135</td>
<td>87</td>
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<tr>
<td>Ventricular BSI</td>
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<td>Occipital lobe</td>
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<td>3144</td>
<td>258</td>
<td>668</td>
</tr>
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</table>

BSI, boundary shift integral. Smallest sample size estimates for each group have been bolded.

Figure 2 Voxel-level maps showing regions of increased rates of atrophy in the GRN group compared to the MAPT, C9ORF72 and sporadic FTD groups. Results are shown on medial and lateral renderings of the brain at $P < 0.001$ with an extent threshold of 200 voxels.

Table 3 Estimated sample size per arm needed to detect a 20% improvement in atrophy rate with 80% power assuming a two-sided alpha of 5% in a 12-month trial

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be measured with a high degree of accuracy and may be less affected by variability in lobar patterns of atrophy.

One major advantage of our study was the fact that a large number of serial MRI measurements that had been collected over 20 years were analyzed; reflecting a highly rare and valuable cohort. Whilst variability may exist across specific mutations within the GRN and MAPT groups, cross-sectional studies have found relatively consistent imaging patterns across mutations [26]. The majority of our findings were also confirmed in the analysis limited to only bvFTD. Given the duration of study, the MRI measures were inevitably performed on a number of different scanners. However, all MRI was performed on GE Signa scanners with identical gradients and head coils and all scanners underwent a standardized quality control calibration procedure daily. A limitation of the study was the limited length of follow-up and the relatively small number of subjects in each mutation group.

In summary, our data show that regional rates of atrophy differ subtly across genetic and sporadic FTD. Our findings support the utility of using regional and global volume measurements as longitudinal outcome measures in future experimental drug trials in sporadic and familial FTD. Future studies will be needed to determine whether they may also be good pre-symptomatic biomarkers of disease.

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Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Estimated annual percentage change (95% confidence interval) in regional volumes by group with pairwise P values for the secondary analysis including only subjects with behavioral variant frontotemporal dementia.

Table S1. Estimated annual percentage change (95% confidence interval) in global and lobar volumes by group using only behavioral variant frontotemporal dementia subjects.

References


