

TITLE PAGE

Title: Faster Cortical Thinning and Surface Area Loss in Presymptomatic and Symptomatic *C9orf72* Repeat Expansion Adult Carriers

Running head: Cortical thinning in *C9orf72* expansion carriers

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ABSTRACT

Objective: *C9orf72* expansion is the most common genetic cause of frontotemporal dementia (FTD). We examined aging trajectories of cortical thickness (CTh) and surface area in *C9orf72* expansion adult carriers compared to healthy controls to characterize preclinical cerebral changes leading to symptoms.

Methods: Data were obtained from the Genetic Frontotemporal Dementia Initiative. T1-weighted MRI scans were processed with CIVET 2.1 to extract vertex-wide CTh and CSA. Symptomatic

and presymptomatic subjects were compared to age-matched controls using mixed-effects models, controlling for demographic variables. Aging trajectories were compared between carriers and non-carriers by testing the ‘age by genetic status’ interaction. False-discovery rate corrections were applied to all vertex-wide analyses.

Results: The sample included 640 scans from 386 subjects, including 54 symptomatic *C9orf72* carriers (72.2% behavioral variant FTD), 83 asymptomatic carriers and 249 controls (age range 18-86). Symptomatic carriers showed fairly symmetric reduction in CTh/CSA in most of the frontal lobes, in addition to large temporo-parietal areas. Presymptomatic subjects had reduced CTh/CSA in more restricted areas of the medial fronto-parietal lobes, in addition to scattered lateral fronto-parieto-temporal areas. These differences were explained by faster cortical thinning linearly throughout adulthood in a similar anatomical distribution, with differences emerging in the early 30s. CSA reduction was also faster in mutation carriers predominantly in the ventro-frontal regions.

Interpretation: *C9orf72* mutation carriers have faster cortical thinning and surface loss throughout adulthood in regions that show atrophy in symptomatic subjects. This suggests that the pathogenic effects of the mutation lead to structural cerebral changes decades prior to symptoms.

MANUSCRIPT

Introduction

About 40% of patients suffering from frontotemporal dementia (FTD) have family history of dementia, and around 20% have a clear autosomal dominant history.¹ Among these familial cases,

about 50 to 60% are caused by identified genes.^{2, 3} The most common mutation is the hexanucleotide expansion in the *chromosome 9 open reading 72 gene (C9orf72)*,⁴ which causes behavioral variant FTD (bvFTD), amyotrophic lateral sclerosis (ALS), or FTD-ALS as common phenotypes.⁵ The *C9orf72* repeat expansion (referred to as ‘mutation’ for simplicity in the article) is autosomal dominant with almost full penetrance, leading to disease onset in average between ages 40-70, although cases with later onset have been described.^{1, 5}

C9orf72 mutations are known for their frequent predominantly psychiatric prodromes, often preceding more typical bvFTD symptoms by several years.⁶ This suggests that the negative cerebral and neuronal effects of the mutation are present many years prior to the onset of FTD or ALS symptoms. Results from the Genetic Frontotemporal Dementia Initiative (GENFI) using voxel-based morphometry (VBM) have suggested that the negative impact from the mutation is reflected by subtle gray matter volume loss that can be observed up to 10-15 years prior to the estimated age at symptom onset in FTD mutation carriers.⁷ In more recent analyses, presymptomatic carriers were found to have significant volume reduction in restricted areas of the inferior frontal and superior temporal lobe (in addition to a trend for broader regions including the parietal areas and anterior insula).⁸ Presymptomatic central nervous system changes have also been documented in the spinal cord.⁹

Cortical thickness (CTh) and cortical surface area (CSA) are two partially genetically independent surface-based cortical measures contributing to the volume of the human cortex.¹⁰ CTh is known to increase in early childhood, followed by a gradual thinning in adolescence and a slower thinning phase in adulthood.^{11, 12} CTh is influenced by disease processes including neurodevelopmental and neurodegenerative diseases, and therefore potentially constitutes a sensitive marker for the presymptomatic and early symptomatic impact of *C9orf72* mutations. There is limited literature on the topic of presymptomatic CTh changes in *C9orf72*, with most studies having very small sample sizes (≤ 15 carriers) and, unsurprisingly, finding divergent results. Three out of four studies found scattered cross-sectional thinning¹³⁻¹⁵, while two did not find differences in the rate of thinning versus non-carriers over time.^{13, 15} One study reported no differences in CTh, but a lower gyrification index in presymptomatic carriers that did not change over time, suggesting an early developmental effect.¹⁵ To our knowledge no study has explored the impact of the *C9orf72* mutation on CSA.

Using a much larger sample size than all previous published articles on CTh, our study aims to clarify what are the differences in cortical developmental and aging trajectories for both CTh and CSA between carriers and non-carriers, in order to determine when atrophic changes start in relation to the onset of the disease. Our hypothesis was that mutation carriers would show significant cortical loss more than 10 years before the onset of clinical symptoms.

2. Material and Methods

2.1 Clinical Sample

GENFI is a multisite longitudinal study of familial FTD with 23 research centres in Europe and Canada (<http://genfi.org.uk/>). Data from asymptomatic gene carriers is collected to aid in developing clinical markers to identify the disease at its early stages and predict symptom onset in mutation carriers. The second iteration (GENFI2) is a continuation phase which greatly expands the sample size and aims to widen the breadth of the data explored. We retrieved data from data release 3 of GENFI2 (12/2017) including demographic information, genetic status, disease status, neuropsychological testing, and structural T1 magnetic resonance imaging scans at repeated visits. We selected data from all *C9orf72* mutation carriers (both symptomatic and presymptomatic) and controls belonging to any genetic group (i.e., non-carriers in families with *C9orf72*, *GRN* and *MAPT* mutations), with an age range from 18 to 86-year-old. All participants provided informed consent for participation to GENFI2, and this study was conducted with approval from the McGill University Health Centre ethics board.

2.1 MRI Image Processing

3D-T1 structural MRI scans were acquired for all subjects (3T MPRAGE, 1.1mm isometric slice thickness). All scans were visually inspected for a first line of quality control by the data coordinating site (University College London). Using the CBRAIN platform,¹⁶ T1 scans were processed with CIVET 2.1 (<http://www.bic.mni.mcgill.ca/ServicesSoftware/CIVET-2-1-0-Table->

of-Contents) to extract vertex-wide CTh and CSA (81,924 vertices). A summary of methodological steps can be found in Ducharme et al. 2016.¹² CIVET 2.1 outputs were visually inspected by two investigators (VJP and SD) for post-processing quality control to eliminate scans with truncated regions or inadequate gray-white matter identification.¹² From a total of 680 scans, 40 failed the post processing QC. The final sample after quality control was 640 scans from 386 subjects including 54 symptomatic mutation carriers (all clinical phenotypes included, see distribution in Table 1), 83 asymptomatic mutation carriers and 249 healthy controls. There were 226 subjects with one visit, 93 with two, 45 with three, 17 with four and 5 with five.

2.2 Statistical Analyses

Demographics

Basic characteristics including demographics and clinical measures of the three clinical groups were compared at their baseline visits using a one-way ANOVA with Tukey post-hoc tests for continuous variables and chi-square for categorical variables (using $p < 0.05$ uncorrected as the significance threshold). Prevalence of medical comorbidities known to have an impact on CTh including hypertension, cerebrovascular disease, diabetes, hypercholesterolemia, traumatic brain injury, smoking and alcohol abuse were also compared across groups.

Group Contrasts

All statistical analyses on vertex-wide CTh and CSA were performed in Matlab using SurfStat (<http://www.math.mcgill.ca/keith/surfstat/>). First, using mixed-effect models to account for the imbalanced number of study visits between subjects, we compared vertex-wide CTh and CSA (in two separate models) by contrasting symptomatic subjects and healthy non-carriers, controlling for age, scanner site, and sex using the following model:

$$CTh \text{ (or CSA)} = 1 + b_1Sex + b_2ScannerSite + b_3Age + b_4GeneStatus + random(Subject ID) + error$$

Given that GENFI2 controls include subjects as young as 18 years of age, we restricted controls to keep only those as young as the youngest symptomatic subject which was 46.5-year-old (number of scans: n=80 carriers and n=211 controls). Analyses were performed with and without total brain volume (TBV) as a control variable. Analyses with TBV provide absolute differences in terms of cortical surface, while results with TBV tend to over-control for gray matter changes (particularly for CSA)¹⁷ but provide results that are more specific to the cortex for CTh. In this context, both analyses provide valuable information and therefore results with and without TBV are provided for all analyses below. Results from these vertex-wide analyses and all the following ones were corrected for multiple comparisons using false discovery rate (FDR) $p < 0.05$.

Aging Trajectories

To determine if there are differences in the rate or trajectory of cortical changes across time, we performed mixed-effect models including all subjects (symptomatic carriers, asymptomatic carriers, and controls) using the following equation:

$$CTh \text{ (or CSA)} = I + b_1Sex + b_2ScannerSite + b_3Age + b_4GeneStatus + b_5Age*GeneStatus + random(Subject ID) + error$$

The 'age*gene' interaction while controlling for age represents the added effect of being a mutation carrier over the normal thinning that occurs with aging. In order to determine if differences are best explained by an acceleration of thinning near the onset of the disease, we first tested a quadratic model ('age*age*gene') before moving to the simple linear model above, if quadratic results were negative. Analyses were performed with and without TBV as a control variable. In a second step, the mean thickness of significant areas was extracted to perform additional analyses in SPSS version 25. The optimal cortical aging trajectory (linear versus quadratic) was confirmed with mixed effect models (AR(1) covariance structure) as above using mean CTh/CSA of significant areas as the variable of interest and applying the Akaike's Information Criterion (AIC), factoring the goodness of fit and tradeoff of increasing the complexity of the model by adding terms. In a following step, we included medical comorbidities that are known to be associated with cortical thinning and were found to be slightly different between groups (see Table 1) as control variables in the model. Finally, we repeated analysis with

Estimated Years to Onset (EYO – i.e., difference between the chronological age of the subjects and the mean age at onset in the subject’s family) to determine if results were stronger than with age alone.

Presymptomatic carriers only

We repeated the above analyses of group contrasts and trajectories excluding all symptomatic subjects. Given that healthy controls included subjects that were almost 20 years older than the oldest presymptomatic carrier, only controls that were as old or younger as the oldest presymptomatic carrier (68.5-year-old and below) were kept for analyses (number of scans n=135 mutation carriers and n=400 controls) in order to maintain similar age distributions.

Association with clinical variables

Mean CTh and mean CSA of statistically significant areas from the linear model were extracted for each subject. As exploratory secondary analyses, using mixed-effects models in SPSS (AR(1) covariance structure) we analyzed the association between the cerebral variables, performance on the Mini-Mental State Examination (MMSE) and the total Cambridge Behavioural Inventory (CBI)¹⁸ score to determine if cortical changes are related to major measures of cognitive/behavioral changes in gene carriers (n=215 scans). Age and sex were controlled for. Of note, only 194 of the 215 patient-visits had CBI values because this was not collected in the early phase of GENFI.

3. Results

Demographics

Table 1 shows the detailed distribution of basic demographics and clinical variables across the three subject groups. As expected, symptomatic subjects were in average older, had lower MMSE and higher CBI scores. Presymptomatic subjects were slightly younger than controls, but not significantly. Symptomatic subjects were also found to have a higher proportion of males and have lower education level. Of note, there was a higher prevalence of cardiovascular comorbidities including hypertension, hypercholesterolemia and stroke in the symptomatic subjects (who are on average older).

Symptomatic group contrasts

Compared to age-matched controls, when controlling for TBV, symptomatic subjects showed cortical thinning in almost all of the frontal lobes and lateral and anterior medial temporal lobes with some sparing of the right temporal pole, as well as large sections of the medial and dorsal parietal lobe sparing the primary sensory areas ([Figure 1A](#)). The Cohen's d for the effect of genetic status within areas of significance was -0.76 (95% CI -0.92 to -0.61), corresponding to a large effect size. The CTh contrast without controlling for TBV showed significance across almost the entire brain. The similar contrast for CSA was not significant when controlling for TBV. However, when not controlling for TBV subjects showed more restricted surface area in a fairly similar

pattern to CTh, with slightly less frontal involvement but including broader zones of the temporal poles ([Figure 1B](#)). Within areas of significance, the Cohen's d for the effect of genetic status was -0.54 (95% CI -0.7 to -0.38), corresponding to a medium effect size.

Aging trajectories

Including all subjects (i.e., both presymptomatic and symptomatic *C9orf72* carriers compared to all controls), analyses of the quadratic interaction ('age*age*gene status') were not significant for both CTh and CSA. There was a significant first-degree linear 'age*gene' interaction on CTh controlling for TBV that was explained by faster thinning in the mutation carrier group ([Figure 2A](#)). Within areas of significance, the partial Pearson correlation values ranged from -0.21 to -0.09 (mean -0.123; 95% CI -0.125 to -0.121). The anatomical distribution was essentially similar to results observed in the group contrast above. The model without controlling for TBV showed more widespread significance. The first-degree 'age*gene' interaction on CSA without controlling for TBV demonstrated accelerated loss of surface area in mutation carriers predominantly in the ventral frontal areas, in addition to small parts of the left lateral frontal lobe ([Figure 2B](#)). Within areas of significance, the partial Pearson correlation values ranged from -0.18 to -0.11 (mean -0.132, 95% CI -0.133 to -0.131). The model controlling for TBV was not significant. Of note, including cardiovascular comorbidities (hypertension, hypercholesterolemia, stroke) as control variables did not change results. Similar analyses with EYO instead of age showed similar results with a slightly reduced anatomical distribution.

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Mean CTh of the significant areas from figure 2A was extracted for each subject. In order to confirm the best fitting aging trajectory, we performed mixed-effect models in SPSS for quadratic and linear equations to obtain the AIC values (lower values corresponding to a more efficient model). The AIC for the quadratic model was -1122.5, compared to -1135.3 for the first-order linear model (therefore confirming that the quadratic model does not have a more efficient fit). Figure 3 depicts scatterplots for both models. *C9orf72* mutation carriers show a steadily faster thinning over time without a significant acceleration near the older ages, with differences emerging in the early 30s. Similarly, there was a better first order linear fit for CSA (mean values from significant areas in Figure 2B) compared to quadratic (AIC -1093.4 compared to -1080.4 respectively). This suggests that group differences demonstrated in Figure 1A are caused by faster cortical loss in the presymptomatic phase, rather than normal aging trajectories followed by rapid atrophy only around clinical disease onset.

Presymptomatic Carriers Only

For analyses including only presymptomatic carriers, only the controls that were of equal age or younger than the oldest presymptomatic subject (68.5 year-old) were included. The group contrast showed thinner cortex predominantly in the medial frontal and parietal regions, with a few scattered lateral fronto-parietal and temporal areas (Figure 4A). The Cohen's *d* for the effect of genetic status within areas of significance was -0.23 (95% CI -0.42 to -0.03), corresponding to a

small to moderate effect size. As expected, there were slightly broader areas of significance when not controlling for TBV. Presymptomatic carriers showed smaller CSA predominantly in the ventral, medial and inferior frontal lobes (Figure 4B) when not controlling for TBV, while there were no significant differences when controlling for TBV. Within areas of significance, the Cohen's *d* for the effect of genetic status was -0.25 (95% CI -0.45 to -0.06), corresponding to a small to medium effect size. The 'age*gene' interaction in presymptomatic subjects showed a trend for faster cortical thinning that did not reach significance after FDR correction (Figure 5).

Clinical associations

In secondary exploratory analyses of gene mutation carriers (n=215), mean CTh and CSA of the significant areas (Figure 2A and 2B) were found to be both significantly associated with MMSE (F=10.1, p=0.002 and F=5.5, p=0.022 respectively). Both cortical measures were also inversely associated with CBI (F=5.4, p=0.02 and F=9.6, p=0.002 respectively).

Discussion

This is the largest study of cortical changes in *C9orf72* mutation adult carriers. At the group contrast level, symptomatic carriers showed an expected cortical thinning of almost all of the frontal lobes, lateral and anterior medial temporal lobes, and several medial and dorsal parietal areas in a fairly symmetric pattern, sparing primary sensory cortices and most of the occipital lobes. Surface area was reduced in most of the same areas and included more of the temporal poles.

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Compared to age matched controls, presymptomatic gene carriers also showed reduced CTh and CSA particularly in the medial frontal and parietal regions, although less diffusely than for the symptomatic subjects. Analyses of aging CTh and CSA trajectories were determined by testing the ‘age*gene status’ interaction. In normal aging, during adulthood there is a slow progressive loss of cortical gray matter with a slight acceleration in elderly subjects.¹⁹ The *C9orf72* mutation carriers group showed faster cortical thinning starting early in adulthood that continued at a steady pace, without an acceleration around the typical age of symptom onset. There was also faster surface area loss but restricted to ventral frontal areas, therefore CTh appears to be a more sensitive marker of the impact of the mutation on the brain than CSA. Exploratory analyses suggested that the loss of CTh and CSA were both associated with impaired cognitive performance and behavioral symptoms in gene carriers.

Our results are in line with published studies on cortical gray matter volume showing relatively diffuse and symmetric loss in symptomatic subjects,²⁰ in addition to presymptomatic loss in several areas of the frontal, temporal and parietal lobes up to 25 years prior to symptom onset.^{8, 21} In contrast to previous studies of CTh in *C9orf72* mutation carriers that had not demonstrated accelerated thinning in presymptomatic subjects,^{13, 15} we are able to demonstrate that the differences in CTh and CSA observed in clinical subjects appear to be the result of faster decline in thickness and surface starting in early adulthood (compared to normative CTh and CSA loss over time with atrophy only around disease onset). Those differences with previous studies are

probably explained by our larger sample size and wider age range of subjects. As opposed to what has been observed in Alzheimer's disease²² and suggested in a small study of converters with *MAPT* and *GRN* mutations,²³ we did not observe an acceleration in cortical thinning or loss of surface area in the usual symptomatic age range.

Repeat expansion in the *C9orf72* gene causes the abnormal accumulation of transactive response DNA binding protein 43 kDa (TDP-43) and dipeptides repeats (DPRs) inclusions that are widely distributed in the brain, including the neocortex.^{5, 24} The distribution of pathology tends to match the distribution of neurodegeneration, with more neocortical accumulation in patients with FTD than with ALS.^{5, 25} While it is not possible to determine the cause of faster cortical thinning and surface area loss with our study design, the anatomical distribution of thinning in line with pathological processes supports the theory that the detrimental effect of the mutation sets in decades before symptoms and that the neurodegenerative phase is not restricted to the symptomatic period. Concretely, this evidence indirectly suggests that future disease modifying treatments will have to be delivered early in the course of the disease and potentially presymptomatically to have the maximal impact.

The strengths of this study include the larger sample size compared to previous publications, the well validated method of CTh and CSA measurements²⁶ with stringent post-processing quality control,¹² and the anatomical distribution of findings in line with the current knowledge of *C9orf72*

related FTD.^{5, 8} Of note, a previous GENFI study showed that atrophy patterns identified by automated morphometric analyses were found to be strongly correlated with atrophy as detected by structured visual rating scales (although those scales could not detect preclinical atrophy in *C9orf72* asymptomatic carriers).²⁷ Several weaknesses have to be acknowledged. First, given its correlational design it is not possible to determine the direct causality between the mutation and faster thinning. However, the association remained while controlling for key demographic variables and medical comorbidities, and it is highly biologically plausible that the negative effects of the mutation are present throughout the development and aging of the brain. Second, given the unbalanced sample, longitudinal results were modeled with mixed-effects models, therefore we cannot completely exclude the possibility of a cohort effect. Results will therefore have to be confirmed with a true longitudinal design. Third, the interaction between age and mutation status did not reach significance in the restricted sample with only presymptomatic subjects, probably due to the smaller sample size and more restricted age distribution. However, results with all subjects clearly showed a first-order linear decline across the entire aging process that is not restricted to the symptomatic phase, as visualized on Figure 5. We hypothesize that a larger sample size will confirm the finding in presymptomatic subjects.

In conclusion, our study demonstrates that *C9orf72* repeat expansion carriers have faster cortical thinning throughout aging in adulthood in regions that show atrophy in clinically symptomatic subjects. We further provide the first demonstration of faster loss of CSA in more restricted

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anatomical areas. Reductions in CTh and CSA were both associated with decline in global cognitive performance and increased behavioral symptoms. With longitudinal follow-up of the GENFI2 cohort, future studies will be able to determine what happens to CTh and CSA on an individual level when subjects transition from the presymptomatic to the symptomatic phase. It will further be of key importance to identify factors, such as medical comorbidities and cognitive reserve, that may delay the symptomatic impact of the progressive cortical volume loss.²⁸

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Contribution of Authors

GL, SD, BB, JVS, DG, RS, RL, FM, MS, CG, CT, JR, RV, EF, FT, IS, CB, AG, AD, JL, MO, GF, SS, and JR contributed to study concept and design as well as data collection.

GL, SD, VJP, and JM contributed to data analysis.

GL and SD drafted the manuscript and figures.

The members of the GENFI Consortium and their institutional affiliations are listed in the Supplementary Online Table.

Potential Conflict of Interests

No conflict of interest to report.

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FIGURE LEGENDS

Figure 1. Figure 1A (left) depicts areas that are significantly thinner in symptomatic *C9orf72* mutation carriers compared to controls, controlling for age, sex, total brain volume and scanner site. Figure 1B (right) shows cortical regions with smaller surface areas in symptomatic *C9orf72* mutation carriers compared to controls, controlling for age, sex, and scanner site (not controlled for total brain volume). Results are at $p < 0.05$ with false discovery rate correction.

Figure 2. Figure 2A (left) depicts areas that have significantly faster cortical thinning in *C9orf72* mutation carriers (asymptomatic and symptomatic) compared to controls, controlling for age, sex, total brain volume and scanner site. Figure 2B (right) shows cortical regions with faster surface area loss over time in symptomatic *C9orf72* mutation carriers compared to controls, controlling for age, sex, and scanner site (not controlled for total brain volume). Results are at $p < 0.05$ with false discovery rate correction.

Figure 3. Scatterplots of mean cortical thickness (mm) of significant areas from the age*gene status interaction (Figure 2A) against age in years. *C9orf72* mutation carriers are in gray, and non-carriers are in black. For visualization purpose, the left scatterplot shows first-order linear curves, while the figure on the right depicts quadratic model curves that had a less efficient fit as per the Akaike information criterion.

Figure 4. Figure 4A (left) depicts areas that are significantly thinner in asymptomatic *C9orf72* mutation carriers compared to non-carriers, controlling for age, sex, total brain volume and scanner site. Figure 4B (right) shows cortical regions with reduced surface area in asymptomatic

C9orf72 mutation carriers compared to non-carriers, controlling for age, sex, and scanner site. Results are at $p < 0.05$ with false discovery rate correction.

Figure 5. Scatterplot of mean cortical thickness (mm) of significant areas from the 'age*gene status' interaction (Figure 2A) against age in years in presymptomatic subjects only. *C9orf72* mutation carriers are in gray, and non-carriers are in black. Figure provided for visualization purpose.

Table 1. Basic Demographic, Clinical Characteristics and Medical Comorbidities of the Three Clinical Groups

	Symptomatic Carriers	Presymptomatic Carriers	Controls
Number of subjects	54	83	249
Number of scans	80	135	425
Age in Years**	65.0±7.4 ⁺⁺ (46.5-75.7)	44.6±11.8 (21.4-67.5)	47.3±13.8 (18.6-85.6)
Sex[#]	Female = 19 (35.2%) Male = 35 (64.8%)	Female = 53 (63.9%) Male = 30 (36.1%)	Female = 140 (56.2%) Male = 109 (33.8%)
Clinical Disease Subtype	bvFTD = 39 (72.2%) ALS = 4 (7.4%) FTD-ALS = 5 (9.3%) PPAnfv = 2 (3.7%) PPAsv = 1 (1.8%) Dementia NOS = 2 (3.7%) PSP = 1 (1.8%)	N/A	N/A
Education*	12.7±3.9 ⁺	14.2±2.9	14.0±3.6
Mini-Mental State Examination**	23.8±5.4 ⁺⁺	29.1±1.3	29.3±1.1
Cambridge Behavioral Inventory**	62.7±31.8 ⁺⁺	5.4±6.8	3.8±6.3
Traumatic Brain Injury	R/A = 1 (1.9%) R/I = 5 (9.3%)	R/A = 1 (1.2%) R/I = 8 (9.6%)	R/A = 0 (0%) R/I = 29 (11.6%)
Hypertension^{##}	R/A = 16 (29.6%) R/I = 3 (5.6%)	R/A = 10 (12.0%) R/I = 1 (1.2%)	R/A = 20 (8.0%) R/I = 8 (3.2%)
Stroke[#]	R/A = 1 (1.9%) R/I = 2 (3.7%)	R/A = 0 (0%) R/I = 0 (0%)	R/A = 0 (0%) R/I = 1 (0.4%)
Hypercholesterolemia[#]	R/A = 13 (24.1%) R/I = 3 (5.6%)	R/A = 6 (7.2%) R/I = 3 (3.6%)	R/A = 23 (9.2%) R/I = 7 (2.8%)
Diabetes	R/A = 4 (7.4%) R/I = 0 (0%)	R/A = 1 (1.2%) R/I = 0 (0%)	R/A = 5 (2.0%) R/I = 1 (0.4%)
Smoking^τ	R/A = 3 (12.5%) R/I = 8 (33.3%)	R/A = 4 (9.3%) R/I = 7 (16.3%)	R/A = 15 (14.6%) R/I = 19 (18.4%)
Alcohol use disorder^τ	R/A = 1 (4.2%) R/I = 0 (0%)	R/A = 1 (2.3%) R/I = 1 (2.3%)	R/A = 2 (1.9%) R/I = 1 (1.0%)

* p<0.05 One-way ANOVA

**p<0.001 One-way ANOVA

+ p<0.05 post-hoc Tukey versus controls

++p<0.001 post-hoc Tukey versus controls

p<0.05 difference in distribution across groups (chi-square)

p<0.001 difference in distribution across groups (chi-square)

τ: only subjects from GENFI2 were evaluated for smoking and alcohol use disorder (170/386)

ALS = amyotrophic lateral sclerosis

bvFTD = behavioral variant frontotemporal dementia

Nfv = non-fluent variant

NOS = Not otherwise specified

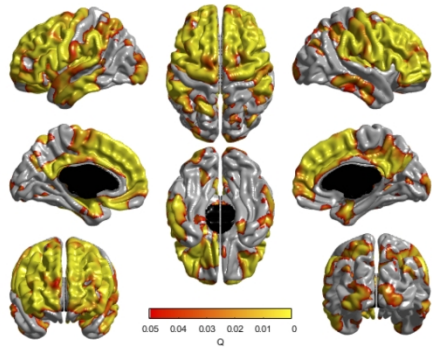
PPA = Primary Progressive Aphasia

PSP = Progressive supranuclear palsy

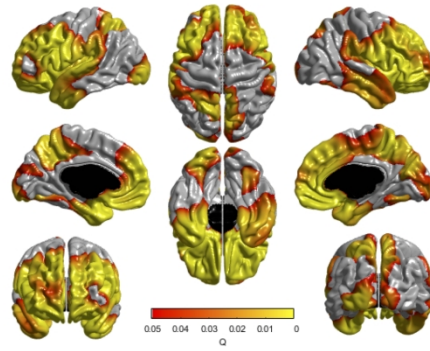
R/A = Recent/Active

R/I = Remote/Inactive

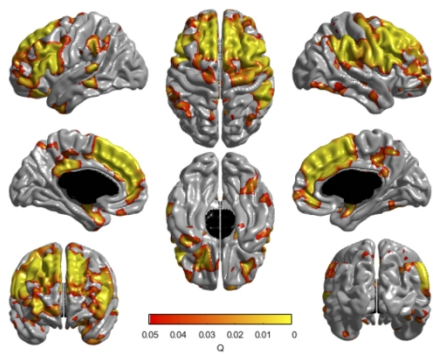
Sv = semantic variant



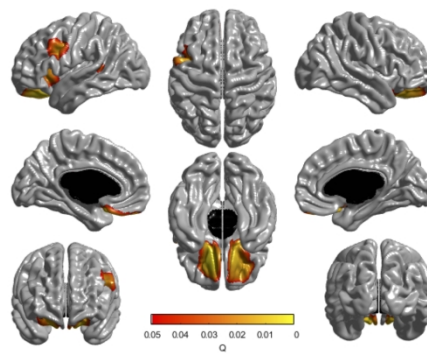
1A. Cortical Thickness



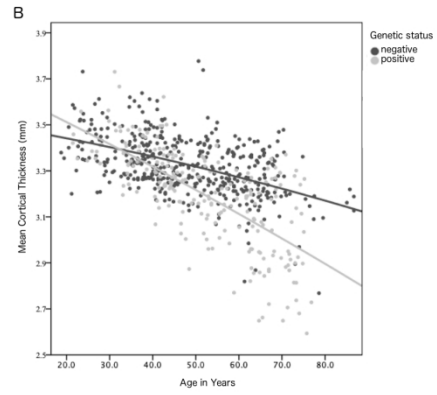
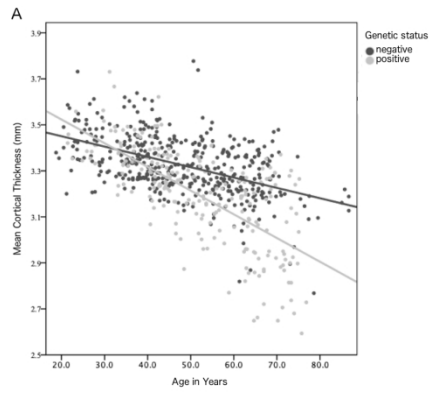
1B. Cortical Surface Area

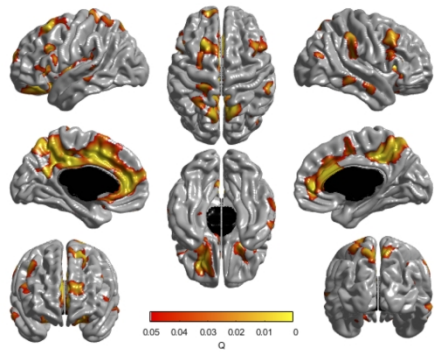


2A. Cortical Thickness

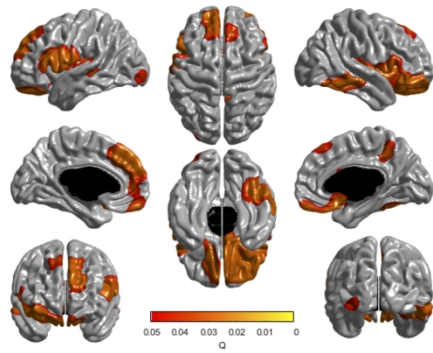


2B. Cortical Surface Area





4A. Cortical Thickness



4B. Cortical Surface Area

