Role of Brain Structure in Neuropsychiatric and Behavioural Symptomatology in Genetic Frontotemporal Dementia

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Abstract

Frontotemporal dementia (FTD) is a heterogeneous neurodegenerative brain disorder characterized by progressive impairments in behaviour or language. Approximately 30% of FTD cases are caused by autosomal dominant mutations in one of three genes: chromosome 9 open reading frame 72 (*C9orf72*), progranulin (*GRN*), and microtubule-associated protein tau (*MAPT*). Neuropsychiatric symptoms (e.g., hallucinations, delusions, anxiety) and sleep disturbances (e.g., insomnia, hypersomnia) are common features among carriers of FTD-related mutations and have been observed prior to the onset of more typical FTD symptoms. The underlying neural correlates for these symptoms, however, remain unclear. To better characterize how brain structure may play a role in this symptomatology, this thesis used MRI-based imaging data from a large cohort of presymptomatic and symptomatic FTD-related mutation carriers. To achieve this, the thesis is divided into two projects that investigate 1) the relationship between mutation-specific longitudinal changes in brain structure and neuropsychiatric symptomatology; and 2) we examined sleep dysfunction in FTD-related mutation carriers and how it relates to changes in the hypothalamus, a structure integral to the regulation of sleep and wakefulness. In project 1, we characterized mutation-specific neuroanatomical trajectories and patterns of covariance relating anatomy and symptoms using partial least squares correlation. We found mutation specific spatial and temporal patterns of brain atrophy. Moreover, we found distinct patterns of covariance between changes in brain structure that reflected worsening in neuropsychiatric symptoms, including a previously established link between *C9orf72* mutations and psychosis. In project 2, we examined differences in sleep dysfunction, volumetric changes in hypothalamic structure, vertex-wise changes in cortical thickness in mutation carriers relative to controls, and associations between cortical and hypothalamic atrophy and changes in sleep dysfunction. We

found significant sleep dysfunction across all mutation, with greatest severity in *MAPT* carriers who also showed consistently significant hypothalamic volume loss across the lifespan which was related to increased sleep dysfunction. Taken together, this thesis contributes to our understanding of the neural mechanisms underlying neuropsychiatric and sleep disturbances in genetic FTD, which may in turn inform the neurobiology of atypical adverse symptoms in other related neurodegenerative disorders.

Résumé

La démence frontotemporale (DFT) est un trouble cérébral neurodégénératif hétérogène caractérisé par des troubles progressifs du comportement ou du langage. Les variantes génétiques de la DFT représentent environ 30 % des cas de DFT, dont la majorité sont causées par des mutations autosomales dominantes dans l'un des trois gènes suivant: le cadre de lecture ouvert 72 du chromosome 9 (C9orf72), la progranuline (GRN) et la protéine associée aux microtubules tau (MAPT). Les symptômes neuropsychiatriques (par exemple, les hallucinations, les délires, l'anxiété, etc.) et les troubles du sommeil (comme l'insomnie, l'hypersomnie, etc.) sont particulièrement fréquents chez les porteurs de mutations liées à la DFT et ont été observés avant l'apparition des symptômes plus typiques de la DFT. Les corrélats neuronaux sous-jacents à ces symptômes demeurent toutefois incertains. Dans cette thèse, nous avons utilisé des données d'imagerie par résonance magnétique (IRM) d'une grande cohorte de porteurs de mutations liées à la DFT présymptomatiques et symptomatiques pour étudier la relation entre les structures cérébrale et la symptomatologie neuropsychiatrique dans la DFT génétique. Pour y parvenir, la thèse est divisée en deux projets, décrit dans les Chapitres 3 et 4. Dans le projet 1, nous avons examiné les changements longitudinaux de la structure cérébrale et la façon dont ces changements sont liés à la symptomatologie neuropsychiatrique. Plus précisément, nous avons examiné les trajectoires longitudinales de l'atrophie cérébrale par voxel du cerveau entier chez les porteurs de mutations liées à la DFT à l'aide d'une modélisation linéaire à effets mixtes. De plus, nous avons utilisé la régression des moindres carrés partiels pour vérifier si ces changements secondaires à la mutation dans la structure cérébrale seraient liés à des changements différentiels dans les symptômes comportementaux et neuropsychiatriques. Nous avons découvert des modèles spatiaux et temporels spécifiques de l'atrophie cérébrale

spécifiques aux mutations individuelles. Nous avons aussi trouvé des modèles distincts de covariance entre les changements dans la structure cérébrale qui reflétaient des changements différentiels dans les symptômes neuropsychiatriques, y compris un lien précédemment établi entre les mutations C9orf72 et la psychose. Dans le projet 2, nous avons examiné les problèmes de sommeil chez les porteurs de mutations liées à la DFT et son lien avec les modifications de l'hypothalamus, une structure faisant partie intégrante de la régulation du sommeil et de l'éveil. À l'aide de modèles linéaires à effets mixtes, nous avons examiné les différences de dysfonctionnement du sommeil, les modifications volumétriques de la structure hypothalamique et les modifications de l'épaisseur corticale des porteurs de mutation par rapport aux témoins. Nous avons également examiné les associations entre les changements dans le dysfonctionnement du sommeil et l'atrophie corticale, puis l'hypothalamus. Bien que nous ayons trouvé un dysfonctionnement du sommeil significatif pour toutes les mutations, les sujets porteurs de MAPT démontrent des symptômes plus sévères. De plus, les sujets porteurs de MAPT ont montré une perte de volume hypothalamique significative et constante tout au long de leur vie, ainsi que des volumes hypothalamiques réduits qui étaient liés à un dysfonctionnement accru du sommeil. Dans l'ensemble, cette thèse contribue à notre compréhension des mécanismes neuronaux sous-jacents aux troubles neuropsychiatriques et du sommeil dans la DFT génétique. Ces travaux contribuent à éclairer la neurobiologie des symptômes neuropsychiatriques dans d'autres troubles neurodégénératifs apparentés.

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Contributions of the Authors

All data used in the analyses presented in Chapters 3 and 4 were obtained from the Genetic Frontotemporal Dementia Initiative (GENFI). The DBM pipeline as well as the within-subjects pipeline used in Chapter 3 were developed by Dr. Gabriel Devenyi. Dr. Martina Bocchetta assisted with the hypothalamus segmentation used in chapter 4. I conducted all image processing and quality control assessments, conducted the statistical analyses, visualized, and interpreted the results, created all the tables and figures, and wrote the chapters.

Co-author contributions:

Simon Ducharme: Data collection (GENFI), study design and supervision, review and editing of manuscripts.

Mallar Chakravarty: Study design and supervision, review and editing of the manuscripts.

Gabriel Devenyi: Technical support and assistance with processing imaging data.

Aurelie Bussy: Assistance with image processing and methodology in Chapter 3.

Martina Bocchetta: Assistance with volumetric analyses in Chapter 5.

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Chapter 1 - Introduction

1.1 Statement of the problem – general context

In 2019, dementia was estimated to affect roughly 57 million people worldwide, with that number projected to increase to over 150 million by 2050 (Nichols et al., 2022). Early-onset dementia refers to the onset of dementia before the age of 65, which can be particularly devastating due to its effects on parenthood, occupational functioning, caregiver burden, and potential for misdiagnosis (Draper et al., 2016; Galvin et al., 2017; van Vliet et al., 2010). Although relatively rare, frontotemporal dementia (FTD) is the second most common cause of early onset dementia after Alzheimer's Disease (AD) and has a particularly early age-of-onset for clinical symptoms (between 40 and 65) (Seo et al., 2018). FTD causes progressive and deleterious changes in behaviour and personality or, more rarely, in one's ability to produce or understand language (Galimberti et al., 2015). There are several fully penetrant autosomal dominant mutations that cause FTD, the most common of which are estimated to account for up to a third of FTD cases (Takada, 2015). These mutations cause overlapping but characteristic patterns of brain atrophy that begin long before the onset of typical FTD symptoms (Greaves & Rohrer, 2019).

Neuropsychiatric and adverse behavioural symptomatology, e.g., hallucinations, depression, sleep disturbances, are common in genetic FTD (Ducharme et al., 2017; Sani et al., 2019). Many of these adverse symptoms have been observed prior to the onset of more typical FTD symptoms and may constitute the prodrome of genetic FTD (Ducharme et al., 2017; Hwang et al., 2020; Tavares et al., 2020). These symptoms have the capacity to not only impact daily living for the patient and contribute to distress in caregivers (Merrilees et al., 2014). In the case

of psychiatric-related symptoms, these symptoms may also overlap with many primary psychiatric disorders (Woolley et al., 2011). Ultimately, this may lead to an erroneous diagnosis which may have major implications for prognostics and treatment (Woolley et al., 2011). However, the neuroanatomical changes underlying psychiatric symptoms and common behavioural symptoms, such as sleep dysfunction, in genetic FTD are poorly understood.

Previous work has largely examined the relationships between cortical atrophy caused by FTD to cognitive and behavioural impairment (Borrego-Écija et al., 2021; Le Blanc et al., 2020; Ratti et al., 2021). However, a growing body of literature is emphasizing the importance of subcortical structures, e.g., the thalamus, amygdala, and hypothalamus, and the cerebellum in various neuropsychiatric and behavioural symptomatologies in genetic FTD (Bocchetta, Malpetti, et al., 2021; Ducharme et al., 2017; Hwang et al., 2020). It is therefore critical to obtain a better understanding of how neurobiological changes, not only in the cortex but also in the subcortex and cerebellum relate to adverse neuropsychiatric and behavioural symptomatology in genetic FTD. Studying preclinical mutation carriers may provide insight into the array of neuroanatomical and behavioural changes that precede the onset of frank FTD symptoms. To achieve this, the thesis is divided into two projects.

Project 1 - We will examine the progression of cortical and subcortical atrophy across mutation carrier groups in a longitudinal sample of presymptomatic and symptomatic subjects with mutations causative of FTD and related them to severity of neuropsychiatric symptoms such as hallucinations, abnormal beliefs and behaviours, anxiety, and depression.

Project 2 – We will examine the progression of sleep disturbances across the lifespan in a large cohort of presymptomatic and symptomatic FTD-related mutation carriers and these

symptoms to changes in cortical structure and the hypothalamus, a subcortical structure thought to be important for the maintenance and regulation of sleep and wakefulness.

Chapter 2 - Background Information

2.1 Overview of Frontotemporal Dementia

Frontotemporal dementia (FTD) is a heterogeneous neurodegenerative brain disorder that presents with various clinical, pathological, and genetic features (Bang et al., 2015). FTD is an early onset form of dementia and the second most common cause of dementia under the age of 65 (Coyle-Gilchrist et al., 2016; Ratnavalli et al., 2002). FTD is an incredibly devastating disease with life expectancy, post-diagnosis, ranging between 3 and 14 years, with the tempo of the decline being dependent on clinical phenotype (Onyike, 2011). Estimates regarding the prevalence of FTD are varied. The point prevalence of FTD, the estimate of the population currently suffering from disorder at a given time, ranges from 0.1 per 1000 to 4.61 per 1000 individuals (Hogan et al., 2016). Roughly half of FTD patients present with profound and progressive changes in executive function and behaviour based on observation or history provided by a knowledgeable informant (this is the behaviour variant FTD; bvFTD) (Bang et al., 2015; Galimberti et al., 2015; Young et al., 2018). Alternatively, patients may also present with primarily language deficits, either progressive agrammatism in language production or apraxia of speech (non-fluent/agrammatic variant primary progressive aphasia; nfvPPA), progressive changes in semantic knowledge and naming (semantic variant primary progressive aphasia; svPPA), or with impaired single-word retrieval or repetition of sentences and phrases (logopenic variant primary progressive aphasia; lvPPA) (Bang et al., 2015). Further, FTD is associated with progressive motor impairment, typically Amyotrophic Lateral Sclerosis (FTD-ALS) (Strong et al., 2017) or various forms of atypical parkinsonism such as corticobasal syndrome (CBS)

(Armstrong et al., 2013) or progressive supranuclear palsy (PSP) (Höglinger et al., 2017). Given time, no matter the presenting phenotype, FTD will evolve into a global dementia (Kertesz et al., 2005).

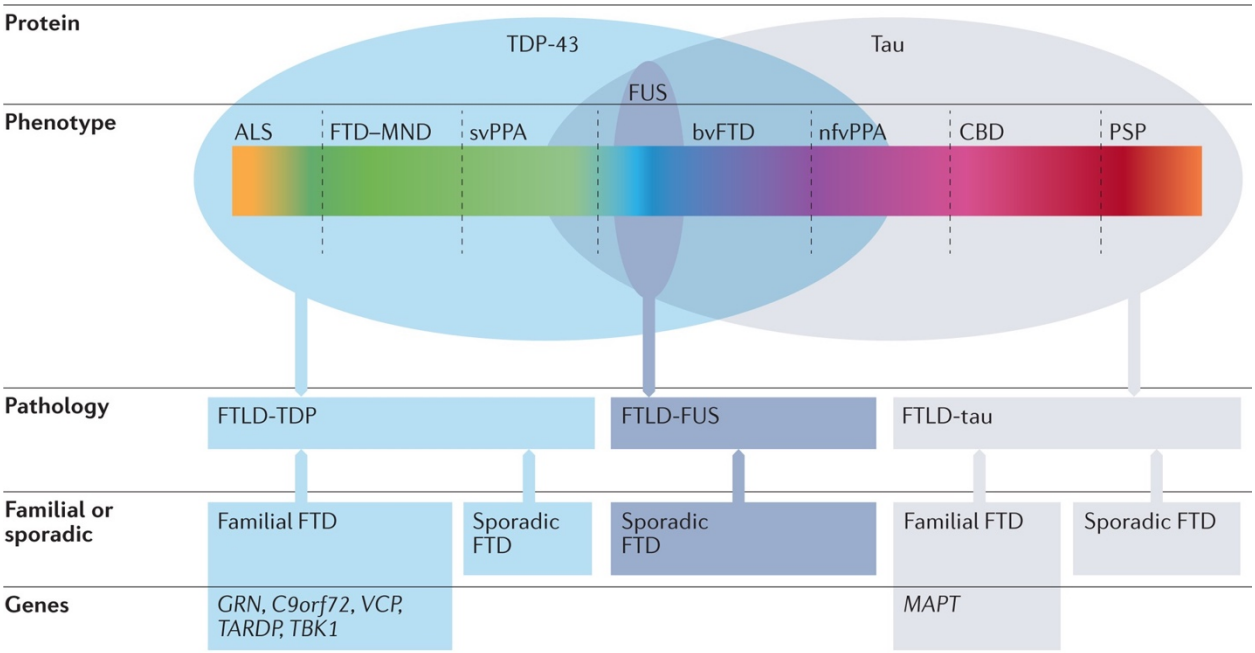

Figure 2.1 Genetic forms of frontotemporal dementia (FTD) have predictable pathology: GRN mutations and C9orf72 repeat expansions result in TDP-43 pathology, whereas MAPT mutations result in tau pathology. By contrast, variable underlying pathologies and genetic forms are found across the clinical spectrum of FTD. CBD, corticobasal degeneration; FUS, RNA-binding protein FUS; nfvPPA, nonfluent variant primary progressive aphasia; PSP, progressive supranuclear palsy; svPPA, semantic variant primary progressive aphasia; TDP-43, transactive response DNA-binding protein 43. Figure and caption adapted from (Meeter et al. 2016).

FTD has a strong familial component with up to 30% of FTD patients have a strong family history (Rohrer et al., 2009). The majority of the heritability of this disease is derived from a fully penetrant autosomal dominant mutation in one of three genes: Chromosome 9 open reading frame 72 (*C9orf72*), Progranulin (*GRN*), or microtubule-associated protein tau (*MAPT*) (Greaves & Rohrer, 2019; Takada, 2015). There are other mutations known to cause FTD, such as *Valosin-Containing Protein* (*VCP*) and *TANK-binding kinase 1* (*TBK-1*), however cumulatively these mutations account for less than 5% of all FTD cases (Greaves & Rohrer,

2019). Globally, *C9orf72* expansions appear to be the most common mutation accounting for between 7-12% of FTD patients (Jonathan D Rohrer et al., 2015), however, the incidence of genetic mutation varies geographically, e.g., *GRN* being the most common mutation in Italy (Jonathan D. Rohrer et al., 2015). FTD caused by genetic mutations, unlike sporadic FTD, have clear underlying pathology, with MAPT mutations being associated with tau pathology, while *GRN* mutations and *C9orf72* expansions are associated with TAR-DNA binding protein-43 (TDP-43) pathology (Takada, 2015). Pathogenicity derived from these mutations drives neuronal cell death, causing highly overlapping, but characteristic patterns of both cortical and subcortical atrophy (Greaves & Rohrer, 2019). Of relevance to this thesis, there is increasing evidence that FTD-related pathophysiological changes can begin decades before the onset of typical FTD symptoms and underly the patterns of atrophy underly the clinical presentations of this disorder (Bertrand et al., 2018; Le Blanc et al., 2020; Jonathan D. Rohrer et al., 2015). Although there are associations between the type of mutation and clinical phenotype, such as FTD-ALS only being associated with *C9orf72* expansions, the correlation between the underlying genotype and presenting phenotype is poor (Lashley et al., 2015). The most common clinical presentation across all mutation carrier groups is bvFTD, however, all phenotypes can occur (Lashley et al., 2015). Currently there are no treatments for FTD, although a number of gene therapy treatment studies are underway to treat genetic variants of FTD (Liscic et al., 2020; Riboldi et al., 2014; Schludi & Edbauer, 2018).

2.2 Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is a non-invasive, safe, and widely available medical imaging technique that is used to image soft tissue, including the brain. MRI is commonly used in both clinical and research contexts as it offers 3 dimensional images with high spatial

resolution. Though changes in MR image is acquisition parameters can allow one to acquire data sensitive to a variety of physiological processes, including neuroanatomical structure, blood oxygen levels, or diffusion (Plewes & Kucharczyk, 2012).

An MRI scanner is comprised of 4 main pieces of hardware, the main magnetic coil, gradient coils, the radiofrequency (RF) coils, either the head or integral RF coil, and the shim coil. The main magnet coils of the MRI generate a strong, constant magnetic field (B_0), which is measured in Tesla (T) (Currie et al., 2013). The majority of MRI systems in research are 1.5 or 3T, however, 7T scanners are becoming more common (McKiernan & O'Brien, 2017). This magnetic field, is used to magnetize protons, specifically found in hydrogen nuclei, in the tissue(Currie et al., 2013). There are three sets of gradient coils, which represent the three orthogonal directions (x, y, and z), with the B_0 signal applied in the z direction. These coils are used to localize the MR signal in tissues and space (Currie et al., 2013; Grover et al., 2015). The RF coils serve two purposes. First, to transmit RF energy to the tissue of interest, the body for the integral RF coil or the head for the RF head coil, and second, to receive the induced signal back from the tissue (Currie et al., 2013). Lastly, the shim coils are used to reduce inhomogeneities in the MRI signal (Currie et al., 2013).

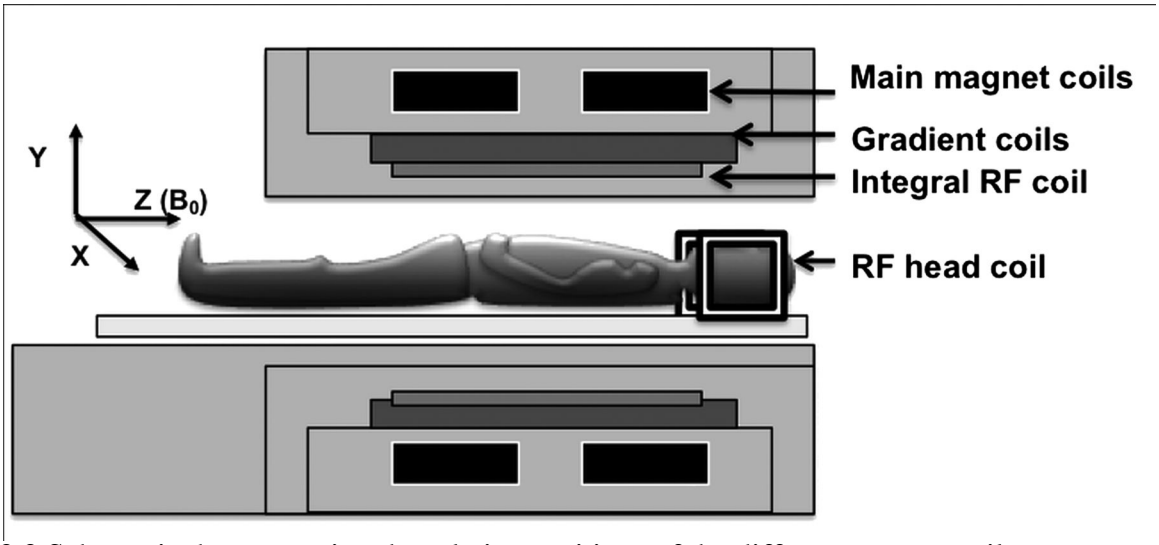

Figure 2.2 Schematic demonstrating the relative positions of the different magnet coils comprising the MR machine. The patient is positioned within the bore of the machine and is surrounded by coils that lie concentric to each other and in the following order (from furthest to closest to the patient): main magnet coils, gradient coils and radiofrequency (RF) coils. For neuroimaging, a further RF coil is placed around the patient's head to improve signal to noise ratio. Figure and caption adapted from (Currie et al., 2013).

The origin of most MR signals used to generate images are derived from the single proton found in the hydrogen nucleus. The proton is constantly spinning and the positive charge spins with it, generating a magnetic field called a magnetic moment. The magnetic moments typically are randomly oriented, however, in the presence of a strong magnetic field, such as B_0, will align either parallel or antiparallel with the magnetic field. The preferred state, the alignment requiring the least amount of energy, will be parallel to B_0, and is called longitudinal magnetization. The difference between the number of parallel and antiparallel alignments is very small, however, will vary based on the field strength of B_0 and the temperature of the tissue. The frequency of the procession of the protons (also called the Larmor frequency and measured in MHz) in the magnetic field can be described by the Larmor equation: $\omega_0 = \gamma B_0$, where γ is a constant called the gyromagnetic ratio that is dependent on the type of nucleus, and in the case of hydrogen it is 42.6 MHz/T. This equation describes that the frequency of progression is dependent on the strength of B_0.

To obtain a MR signal from the tissue, a sequence of RF pulses, produced by the RF coil, is directed toward the tissue. The RF pulse, transfers some of its energy into the protons, disturbing their precession, and causing them to fall out of alignment with the B_0 magnetic field process in the transverse plane, along the x-y axis. Importantly, this can only occur if the RF pulse is at the same frequency as the processional frequency of the proton, also known as resonance and, as such, the RF pulses are set at the Larmor frequency. As the RF pulse is turned off, the protons begin to "relax", where they fall out of the higher energy state, along the B_0 axis. This relaxation occurs in two separate ways. First, the longitudinal magnetization returns to its original value, called longitudinal, or T1 relaxation. T1 relaxation is the processes where the proton exchanges energy with its environment to return to their lower energy state. The rate at which this occurs, varies by the types of tissues the protons are bound in, such that differing tissue types have differing T1 relaxation times. It is these differences in relaxation times that allow for the visualization of the contrast of differing tissue types in MRI images. Alternatively, transverse, or T2 relaxation occurs when protons fall of phase and transverse magnetization disappears. Akin to T1 relaxation, T2 relaxation time is dependent on tissue type.

As the RF pulse is removed, the T1 and T2 relaxations occur independently, albeit simultaneously. Gradient coils are used to obtain spatial information of the signal emitted by the relaxation of the protons. Field gradients are then used to localize and encode the MR signal. This information is digitized and stored in k-space, where datapoints represent the spatial frequencies of an MRI. This data can then be converted into an image and visualized using the Fourier transform.

2.3 MRI Image processing

2.3.1 Deformation based morphometry

Deformation based morphometry (DBM) is an MRI imaging processing technique that allows for the characterization of differences in macrostructural neuroanatomy across the whole brain using T1-weighted structural MRI images (Ashburner et al., 1998). In principle, MRI images from individual subjects are spatially normalized and registered in an iterative group-wise fashion to create a template image (Chung et al., 2001) using linear and non-linear registration techniques (Avants et al., 2009). The resulting deformation field for each subject represents the minimum deformation required to warp that brain to the template brain. These deformation fields, in turn, can be used to compare the volumetric change that a subject's brain must undergo through this mapping procedure (Ashburner & Friston, 2000). The deformations can ultimately be used to calculate volume changes at the voxel level by way of the Jacobian determinant (Mietchen & Gaser, 2009). The absolute Jacobian determinants represent all the linear and non-linear transformations required to warp the subject-scan to the study average. In contrast, the relative Jacobian determinant only models the non-linear deformations, explicitly omitting the linear transformations which are attributable to differences in total brain size (Chung et al., 2001).

There are several advantages to using DBM over other similar image processing metrics such as voxel-based morphometry (VBM). While both VBM and DBM can be used to measure whole brain morphometric changes in brain structure at the voxel scale, DBM does not require tissue segmentation, allowing for the use of information across the full brain in the analysis (Scanlon et al., 2011; Yang et al.). Second, the high-dimensional nature of the registration in

DBM allows for the detection of subtle changes that may not be detectable using VBM (Scanlon et al., 2011).

2.3.2 Volumetric analysis

Volumetric analysis is the estimation of the volumes of brain structures based on MRI imaging, usually based on segmentation. Volumes are based on the number of voxels, or volume pixels, in a given segmented region and the resolution therein. There are several ways to segment neuroanatomical structures. Although manual segmentation, performed by an expert rater, is the gold standard for image segmentation, this method has several shortcomings (González-Villà et al., 2016). Principle among them, is that this is a very time-consuming task. Moreover, manual segmentations are subject to intra- and inter-rater variability, limiting the reproducibility of these segmentations (González-Villà et al., 2016). As such, this method is not suitable to large scale examinations, highlighting the need for automated segmentation methods. Therefore, there have been several different automatic segmentation algorithms that have been developed, using several different strategies.

Atlas-based segmentation algorithms have frequently been used and provide a useful alternative to manual segmentation. Propagation-based algorithms make use of an MRI scan and a corresponding manual segmentation in the regions of interest called an atlas (Aljabar et al., 2009; Cabezas et al., 2011). In essence, the atlas image will be registered to the target image using a transformation based on image registration using, tissue classification, and related image features. This transformation can then be backpropagated to the target image to obtain the final segmentation (González-Villà et al., 2016; Lerch et al., 2017). The accuracy of these techniques however, may be limited due to misregistration, biases in the original atlas, or resampling errors

(Chakravarty et al., 2013). More recent advancements using multi-atlas approaches, however, have improved the accuracy of this approach (Chakravarty et al., 2013).

Alternatively, recent advancements in machine learning have brought forth the development of learning-based algorithms. In essence, the goal of these algorithms is to predict the segmentation label given the input of sufficient features, often derived from a training set of labeled images (González-Villà et al., 2016). In recent years, machine learning-based algorithms have allowed for the segmentation of structures that have historically been difficult to segment, such as the olfactory bulb (Estrada et al., 2021) and hypothalamus (Billot et al., 2020).

2.3.3 Cortical thickness analysis

The human cerebral cortex is a highly folded, multilayered structure, that is, on average, 2.5 mm thick, though thickness can vary from 1 to 4.5 mm (Fischl & Dale, 2000). Cortical thickness represents the space between the pial surface and the white-grey matter interface. Measurement of the thickness of the cortex remains challenging due to the highly folded nature of the cortex and the limited resolution of most MRI images, which is typically $1mm^3$ (Wagstyl & Lerch, 2018). There are, however, several differing methodologies that are used to measure cortical thickness in structural MRI images, including manual, surface-based, and voxel-based measures. Currently, surfaced-based measures are the most common approaches, with FreeSurfer (Fischl, 2012) and CIVET (Kim et al., 2005; MacDonald et al., 2000) being the dominant packages. Both of these surface-based measures, follow a similar processing pipeline, however, the CIVET pipeline will only be detailed as that is the measure used in this thesis. In brief, MRI images are registered to MNI space and intensity inhomogeneities are corrected (Wagstyl & Lerch, 2018). Using a brain extraction toolkit, the cerebrum is separated from the dura, skull, cerebellum, brainstem, and background. Tissues are then classified as either white matter, grey

matter, and cerebrospinal fluid. The inner (white/grey boundary) and outer (grey matter/pial surface) cortical surfaces are extracted. Cortical thickness is then computed and represents the distance between the inner and outer cortical surface. Finally, surfaces are smoothed to reduce noise and are aligned.

Although, surfaced-based cortical thickness measures are a powerful tool to measured subtle neuroanatomical changes, there are limitations. These tools remain computationally expensive (Wagstyl & Lerch, 2018) and are susceptible to common imaging artifacts such as motion (Ducharme et al., 2016). As such, quality control to ensure grey and white matter tissue classification and surface extraction are successful, is integral.

2.4 Neuroimaging features of genetic FTD

The majority of neuroimaging studies of genetic FTD have used magnetic resonance imaging to examine neuroanatomical changes in FTD, however, studies have also used positron emission tomography (PET) or single-proton emission computed tomography (SPECT) (Gordon et al., 2016). Neuroimaging studies in genetic FTD have revealed highly overlapping but characteristic patterns of atrophy within the different genetic mutations (Cash et al., 2018).

Early examinations of the neuroimaging features associated with *C9orf72* expansions report patterns of bilateral atrophy in regions associated with FTD, such as frontal, temporal, and insular cortex (Colin J. Mahoney et al., 2012; Prado et al., 2015; Whitwell et al., 2012; Yokoyama & Rosen, 2012). The canonical cortical atrophy pattern associated with *C9orf72*-related FTD, has been shown to be widespread bilateral atrophy in frontal, temporal, insular, and cingulate cortex, alongside atrophy in the precuneus, posterior and occipital lobes (Li Hi Shing et al., 2021). Severe subcortical atrophy has been consistently reported. Notably, atrophy in the amygdala, striatum, hippocampus, hypothalamus, and basal ganglia are common occurrences,

with thalamic atrophy perhaps being particularly pronounced (Bocchetta et al., 2020; Bocchetta Todd, et al., 2021; Cash et al., 2018).

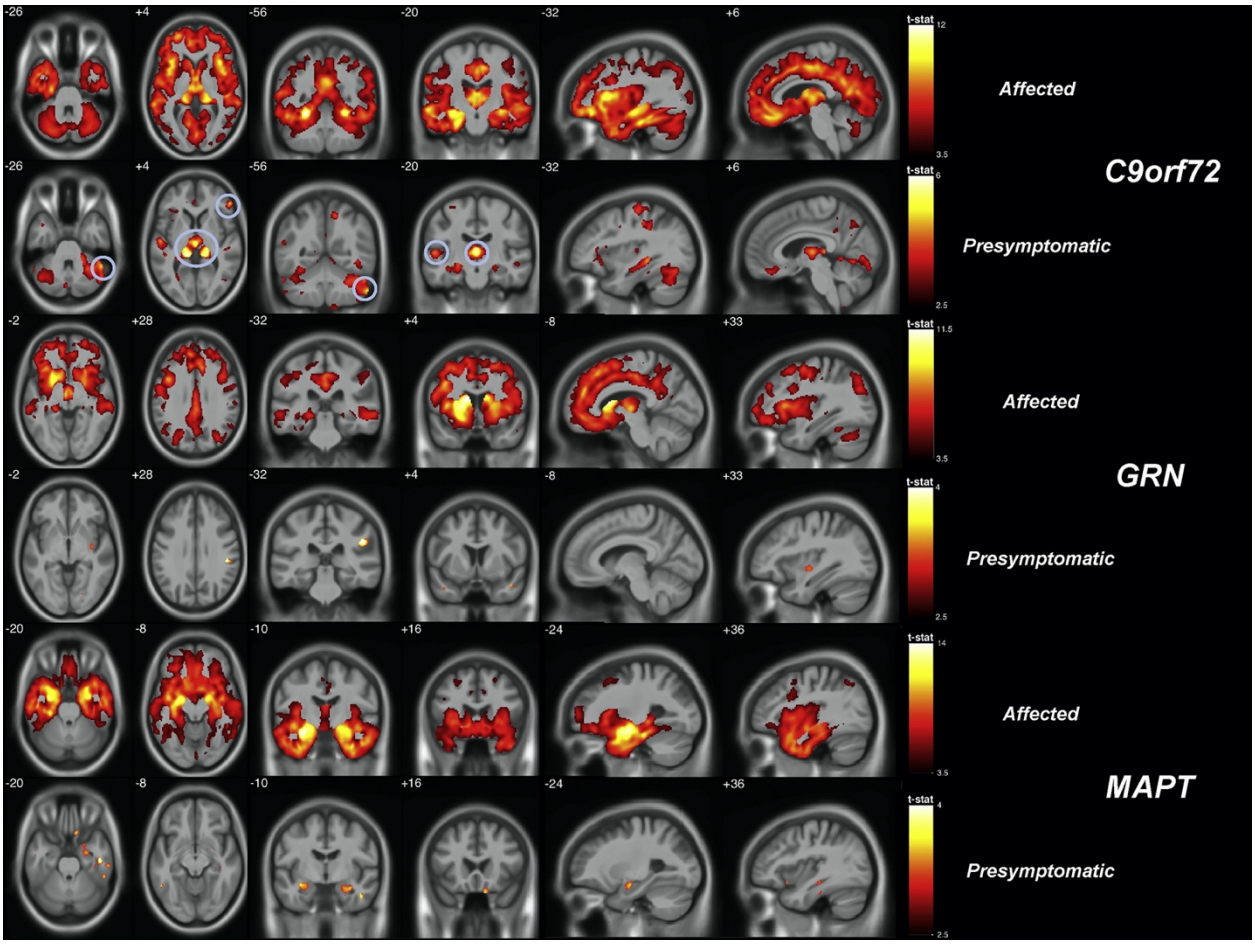

Figure 2.3 Gray-matter (GM) differences by mutation and clinical status. GM differences in affected (odd rows) and presymptomatic (even rows) carriers compared to noncarriers. Comparisons to the C9orf72 carriers are in the top 2 rows, the GRN carriers in the middle 2 rows, and MAPT carriers in the bottom 2 rows. Figure and caption adapted from (Cash et al., 2018).

Lastly, and perhaps unique to *C9orf72* carriers, there appears to be considerable cerebellar atrophy associated with *C9orf72* expansion related FTD. Consistent findings relating cerebellar atrophy have been found and *C9orf72* expansions have been associated to having smaller cerebellar volumes than either sporadic FTD patients or in FTD caused by other pathogenic mutations (Bocchetta et al., 2016; Bocchetta Todd, et al., 2021; Cash et al., 2018).

Conversely, *GRN* mutation related FTD is associated with strongly asymmetrical patterns of atrophy, predominantly affecting either the left or right hemispheres and affecting inferior frontal, temporal, and inferior parietal lobes as well as anterior cingulate and insular cortex (Cash et al., 2018; C. J. Mahoney et al., 2012). *GRN*-related FTD is associated with considerable subcortical atrophy. Atrophy has also been observed in the amygdala, hippocampus, basal ganglia, thalamus, hypothalamus (Bocchetta Todd, et al., 2021; Premi et al., 2014). Findings regarding the involvement of the cerebellum in *GRN*-related FTD are mixed, with one study showing relative sparing of the cerebellum (Bocchetta et al., 2016) while another has shown limited cerebellar involvement in associative regions, albeit later in the disease course (Bocchetta Todd, et al., 2021).

Lastly, *MAPT* mutation related FTD is associated with symmetrical, although more focal atrophy as compared to mutation carrier groups, primarily affecting anterior temporal lobes and orbitofrontal cortex (Cash et al., 2018; Rohrer & Rosen, 2013). Like other mutation carrier groups of atrophy in the thalamus, hypothalamus, amygdala, hippocampus and caudate in *MAPT* related FTD is common (Bocchetta Todd, et al., 2021; Cash et al., 2018). Atrophy in the amygdala and hypothalamus may be particularly pronounced among *MAPT* carriers, with studies showing greatly reduced volumes in these structures in *MAPT* carriers as compared to controls and other mutation carrier groups (Bocchetta et al., 2015; Bocchetta et al., 2019). Previous findings would suggest minimal cerebellar structure changes in *MAPT* related FTD (Bocchetta Todd, et al., 2021; Cash et al., 2018), however at least one study has found some medial cerebellar involvement, primarily in the vermis (Bocchetta et al., 2016).

Many of the neuroanatomical changes described above have been detected up to two decades before the expected onset of typical FTD symptoms (Jonathan D. Rohrer et al., 2015).

C9orf72 expansion carriers, showed the earliest and most extensive preclinical neuroanatomical changes, with structural changes observed over 20 years before the expected onset of clinical symptoms and with the thalamus and posterior cortical structures being the first impacted (Bocchetta Todd, et al., 2021; Cash et al., 2018; Jonathan D. Rohrer et al., 2015). There is evidence of significant cortical and subcortical atrophy, including the thalamus, hypothalamus, hippocampus, and amygdala, alongside atrophy in associative lobes in the cerebellum, namely lobules VIIA-Crus I and VIIB, prior to the expected onset of symptoms (Bocchetta Todd, et al., 2021; Cash et al., 2018). In *GRN* carriers, the insula, followed by frontal, temporal and parietal lobes are the earliest structures to deteriorate, up to 15 years prior to expected onset of clinical symptoms (Bocchetta Todd, et al., 2021; Cash et al., 2018; Jonathan D. Rohrer et al., 2015). Lastly, in *MAPT* carriers, temporal lobes alongside medial temporal subcortical structures, i.e., the amygdala and hippocampus, are the structures that were impacted initially, up to 15 years before the estimated onset of clinical symptoms (Bocchetta Todd, et al., 2021; Cash et al., 2018; Jonathan D. Rohrer et al., 2015).

Few studies, to date, however, have examined longitudinal changes in preclinical and clinical genetic FTD. As such, rates of cerebral atrophy in genetic FTD are poorly understood. Previous work has suggested that symptomatic GRN carriers see the fastest rates of atrophy, while *MAPT* and *C9orf72* carriers progress more slowly (Staffaroni et al., 2020; Whitwell et al., 2015). In preclinical mutation carriers, one study has found grey and white matter changes at two year follow-up, however this was limited to temporal poles in *MAPT* mutation and some dorsal parietal atrophy *C9orf72* expansion carriers (Panman et al., 2019). These findings, taken together, may suggest longer lasting, albeit slower atrophy rates in *MAPT* and *C9orf72* carriers, as compared to later onset with more rapid rates of atrophy in *GRN* mutation carriers.

Chapter 3 - Longitudinal cerebellar and subcortical involvement in neuropsychiatric symptoms in Genetic FTD.

3.1 Preface

Genetic variants of frontotemporal dementia (FTD), though typified by profound and progressive changes in the domains of language or behaviour and personality, has frequent atypical symptomatology, such as neuropsychiatric symptoms (e.g., hallucinations, delusions, and anxiety) that can impact not only the well-being of those with the mutations but also their caregivers and loved ones (Caga et al., 2021; Mourik et al., 2004). The character, frequency, and severity of these symptoms, however, has been shown to differ between mutations causative of FTD (Benussi et al., 2021). This work sought to better understand the spatial features and temporal progression of mutation specific atrophy in genetic FTD and how these progressive neurodegenerative changes might relate to diverging behavioural and neuropsychiatric characteristics. As such, this chapter includes a longitudinal examination, using magnetic resonance imaging (MRI), of the mutation specific progression of brain atrophy genetic variants of FTD. Moreover, we sought to relate these changes, using a novel longitudinal multivariate statistical technique, to changes in behavioural and neuropsychiatric symptoms, with a particular interest in psychotic features.

Longitudinal cerebellar and subcortical involvement in neuropsychiatric symptoms in Genetic FTD.

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List of Figures & Tables: Table 3.1: Baseline demographic and clinical characteristics in mutation carriers and healthy controls; Table 3.2: Demographic characteristics in mutation carriers and healthy controls used in partial least squares analyses; Figure 3.1 Brain slices highlighting significant voxels in *C9orf72;* Figure 3.2 Brain slices highlighting significant voxels in *GRN* carriers; Figure 3.3 Brain slices highlighting significant voxels in *MAPT;* Figure 3.4 Brain slices highlighting significant voxels in *C9irf72* carriers; Figure 3.5 PLS analyses between voxel-wise 2 year within-subject changes; Figure 3.6. Plots describing the relationship of the brain and behaviour scores.

List of Abbreviations: FTD: Frontotemporal Dementia; *C9orf72*: chromosome 9 open reading frame 72; *GRN*: progranulin; *MAPT*: microtubule associated protein tau; AD: Alzheimer's Disease; GENFI: Genetic Frontotemporal Dementia Initiative; CBI-R: Cambridge Behavioural Inventory - Revised ; T1-w: T1-weighted; DBM: Deformation-based morphometry; FDR: False Discovery Rate; AIC: Akaike information criterion; *VCP*: Valosin-Containing Protein ; TBK-1: *TANK-binding kinase 1*; PLS: Partial least squares; BSR: Bootstrap ratio; EYO: estimated years to onset; FLAIR: Fluid attenuated inversion recovery.

3.2 Rationale, Hypotheses, and Aim

Frontotemporal Dementia (FTD) is a heterogeneous neurodegenerative brain disorder, presenting with various clinical, neuropathological, and genetic features (Boxer et al., 2011; Boxer & Miller, 2005; Olszewska et al., 2016). Though the majority of FTD cases are sporadic in nature, FTD is also highly heritable, with up to 30% of cases presenting with a strong family history (Greaves & Rohrer, 2019). Of those with a familial history of the disorder, the majority of the heritability is derived from a fully penetrant autosomal dominant mutation in one of three genes: chromosome 9 open reading frame 72 (*C9orf72*), progranulin (*GRN*), or microtubule associated protein tau (*MAPT*) (Greaves & Rohrer, 2019).

Psychiatric symptoms, such as depression, anxiety, and delusions, are common in neurodegenerative disorders such as AD, and perhaps more prevalent in FTD (Woolley et al., 2011). Patients with FTD often receive a diagnosis of a primary psychiatric disorder, such as major depressive disorder, bipolar affective disorder, or schizophrenia, prior to their FTD diagnosis (Blass & Rabins, 2009; Gálvez-Andres et al., 2007; Velakoulis et al., 2009). Of particular concern is unusually large proportion of FTD patients with *C9orf72* expansions have psychiatric disorders as the initial presentation (Dobson-Stone et al., 2012; Ducharme et al., 2017; Snowden et al., 2012). Several studies emerged shortly after the discovery that *C9orf72* mutations caused FTD indicated an unusually high prevalence of psychotic symptoms directly preceding or closely following the onset of more typical FTD symptoms (Galimberti et al., 2015; Kertesz et al., 2013; Snowden et al., 2012; Solje et al., 2015). There is emerging evidence that presymptomatic mutation carriers may have subtle increases in these features (Jonathan D. Rohrer et al., 2015; Tavares et al., 2020). More recent work has indicated differential frequencies and severities of neuropsychiatric symptoms between mutation carrier groups following the

onset of FTD (Benussi et al., 2021). While *C9orf72* carriers presented with frequent and severe psychotic symptoms *MAPT* and *GRN* carriers presented with frequent and severe mood symptoms. The increased prevalence and severity of psychiatric symptoms in *C9orf72* carriers may be related to atrophy in the cerebellum and thalamus.

The cerebellum, up until the past few decades, has traditionally been thought to be solely important for the regulation and timing of motor control and learning (Schmahmann et al., 2019). There is a growing body of literature showing that the cerebellum is crucial to a variety of cognitive processes, including the modulation of thoughts, behaviours, and affect (Klein et al., 2016; Schmahmann et al., 2019). The modulation of these processes is driven by reciprocal connections to the cortex from associative regions of the cerebellum, that feed through the thalamus (Klein et al., 2016; Palesi et al., 2015; Schmahmann et al., 2019). Importantly in the context of this study the contralateral cerebello-thalamo-cortical circuit has been shown to be implicated in a variety of psychiatric disorders (Schmahmann et al., 2019). This circuit, has been associated with psychiatric symptoms in schizophrenia (Gupta et al., 2015; Moberget et al., 2018) and bipolar disorder (Shinn et al., 2017). Furthermore, and perhaps unique to *C9orf72* expansion carriers, is marked atrophy of associative regions of the cerebellum as well as significant thalamic involvement, which begins long before the onset of clinical symptoms (Bocchetta Todd, et al., 2021; Cash et al., 2018). This is supported by recent work from our laboratory (Bussy et al., 2021), where we observed ubiquitous atrophy across mutation carrier groups within several subcortical structures, including the thalamus, striatum, and globus pallidus. We observed however, that cerebellar atrophy was differentially impacted across mutation carrier groups, with *C9orf72* carriers showing the greatest atrophy and *MAPT* carriers showing a relative preservation of cerebellar structure. Lastly, it was noted that these changes in

brain structure, were reflective of deficits in, largely overlapping, behavioural and neuropsychiatric symptoms, with the exception of psychotic symptoms in *MAPT* carriers, suggesting that cerebellar atrophy may be related to emergence and severity of psychotic symptoms. In this project we sought to build upon this work, using a longitudinal approach to examine if true longitudinal change in brain structure would relate to changes in behavioural and psychiatric symptoms. Previous work on this topic has largely been cross-sectional, contained small sample sizes, and none have examined the rate of atrophy in cortical, cerebellar, and subcortical structures in genetic FTD, and how they relate to the presence and severity of neuropsychiatric features. As such, the present study aims to improve our understanding of the neuroanatomical correlates of psychiatric symptoms in individuals with mutations causative of FTD. We are seeking to address this aim through analysing a large longitudinal cohort of 473 participants, including presymptomatic and symptomatic subjects with mutations causative of FTD. The objectives of this project are two-fold:

1) We will characterize the longitudinal trajectory of neuroanatomical changes related to genetic FTD across time and across the lifespan and the magnitude and rates of atrophy in presymptomatic and symptomatic mutation carriers. We expect differential patterns and rates of atrophy across mutation carrier groups, with greater overall atrophy in *C9orf72* carriers as compared to controls, however greater rates of atrophy in *GRN* carriers relative to other groups.

2) We will evaluate whether there is an association between behavioural and neuropsychiatric symptoms and regional brain atrophy. We expect increased brain atrophy, will be associated with increased behavioural and neuropsychiatric symptoms. Further, we expect cerebellar and thalamic atrophy to correlate with increasing psychotic symptoms in *C9orf72* expansion carriers.

3.3 Methods

3.3.1 Participants

All data were acquired from data freeze 5 of the Genetic Frontotemporal dementia Initiative (GENFI) study (https://www.genfi.org), which includes participants tested between January 30, 2012, and May 31st, 2019. 1108 participants have been recruited across 25 sites across the UK, Canada, the Netherlands, Belgium, France, Spain, Portugal, Italy, Germany, Sweden, and Finland. All aspects of this study were approved by institutional review boards at each of the GENFI sites and all participants provided written informed consent.

3.3.2 Symptom assessment and Cambridge Behavioural Inventory

All participants underwent a standardized clinical and neuropsychological assessment as described by Rohrer and colleagues (Jonathan D. Rohrer et al., 2015). A binary variable of symptomatic vs. non-symptomatic was defined, based on clinician judgement, by clinicians at each visit. Individuals were deemed "non-symptomatic" should they not exhibit typical FTD symptoms or "symptomatic" should they exhibit these symptoms. Of interest to this project is the Cambridge Behavioural Inventory Revised (CBI-R) (Wear et al., 2008). The CBI-R is a validated, informant-based questionnaire designed to assess and quantify behavioural and psychiatric symptoms common in neurodegenerative disorders within the previous 4 weeks (Wear et al., 2008). Cognitively normal informants who know the participant well completed the CBI-R. Items are evaluated on a 5-point scale, from 0 to 4. A score of 0 suggests that there is no impairment, a score of 1 suggests that there is an occasional occurrence, i.e., a few times a month, 2 a repeated occurrence, where the symptom was present several times per week, 3 a daily occurrence, and 4 represents a constant occurrence. A score of 3 or 4 would denote a severe behavioral deficit (Wear et al., 2008). This assessment evaluated several domains, of interest to

the present study are memory (memory, attention, and orientation), abnormal behaviour (challenging behaviour and disinhibition), mood (depression and anxiety), beliefs (delusions, auditory, and visual hallucinations), stereotypic motor behaviours (repetitive and motor behaviours), and motivation. A composite score derived from the sum of the scores from individual items were obtained for each domain. Memory was rated on a 32-point scale, abnormal behaviour on a 24-point scale, motivation on 20 points, mood, and stereotypic behaviour on 16 points, and finally, beliefs on 12 points.

3.3.3 Image Acquisition

All participants were recruited and scanned at a GENFI site. Participants underwent whole-brain 1.1-mm isotropic resolution volumetric T1-weighted (T1-w) magnetic resonance imaging. MRI scans were acquired using a 3T scanner, or should one not be available, 1.5T. Protocols were designed to harmonize across scanners and imaging sites as much as possible (Jonathan D. Rohrer et al., 2015). Volumetric T1-w MRI were acquired for 983 subjects. Acquisition parameters were as follows: slice thickness 1.1mm (1 to 1.2 mm), repetition time of 2000 ms (6.6 to 2400), echo time 2.9ms (2.2 to 9 ms), flip angle 8 deg. (8 to 11), number of slices 208 (140 to 208).

3.3.4 Raw Image Quality Control

Involuntary subject motion during MRI acquisition such as blinking, swallowing, respiratory or cardiac movement can cause imaging artifacts, such as blurring or ringing, that can negatively impact the quality of the data (Bellon et al., 1986; Reuter et al., 2015; Zaitsev et al., 2015). Reduced image quality can bias derived bias derived morphometric estimates and reduce the reliability of these measures (Ducharme et al., 2016; Reuter et al., 2015). To control for these imaging artifacts, quality control of the raw images were assessed using the guidelines developed

in the Computational Brain Anatomy (CoBrA) Laboratory (Bedford et al., 2020) (https://github.com/CoBrALab/documentation/wiki/Motion-Quality-Control-(QC)-Manual).

3.3.5 Preprocessing

Preprocessing of the raw T1-w images was completed using the minc-bpipe-library pipeline (https://github.com/CoBrALab/minc-bpipe-library) to improve image quality and standardize the images that were used as inputs to the morphometric analyses. The minc-bpipe-pipeline allows for supervision at each step of the pipeline through providing quality control images at several preprocessing stages. The minc-bpipe-pipeline performed the following four steps: (1) N4 bias field correction (Tustison et al., 2010), (2) registration of the image into Montreal Neurological Institute (MNI) space using bestlinereg (Collins et al., 1994; Dadar et al., 2018), (3) field-of-view standardization and brain orientation into MNI space using an inverse-affine transformation of an MNI space head mask, and (4) extraction of the brain using the BEaST technique (Eskildsen et al., 2012).

3.3.6 Deformation Based Morphometry

To assess longitudinal voxel-wise morphometric changes in brain structure, we used the two-level deformation-based morphometry (DBM) pipeline, developed in the CoBrA Lab (https://github.com/CoBrALab/twolevel_ants_dbm), was used to investigate voxel-wise morphometry. In brief, skull-stripped preprocessed brains derived from the minc-bpipe-library were used as inputs. At the first level, images from each timepoint were warped using affine and non-linear registration to create an unbiased within-subject average image using the ANTs toolkit using a group-wise registration strategy (Avants et al., 2011). At the second level, using the within-subject averages another unbiased population level average image was built using the unbiased subject-level averages from the first level as the input. Relative voxel-wise volumetric

changes were estimated from the deformation fields through estimating the Jacobian determinant at each voxel. This measure represents the relative difference at each voxel as a proportion relative to the group average. This transformation allows for easier statistical analysis and interpretation whereby positive values indicate that the voxel in template space must be expanded to get to the subject space, and negative values indicate that the voxel in template space must be reduced. The relative Jacobians were then blurred with a 2 mm full-width-at-half-maximum 3D Gaussian to approximate the Gaussian assumptions required for the statistical field.

To assess voxel-wise morphometric change from baseline at two-year follow-up we assessed the difference of the Jacobians between these two timepoints (https://github.com/CoBrALab/documentation/wiki/Create-a-nifti-of-within-subject-change-(2-timepoints,-output-from-dbm)), which allowed the study of longitudinal changes at the single subject level rather than by modeling it through a pseudo-longitudinal design.

3.3.7 Longitudinal DBM analyses

Voxel-wise linear mixed-effects models (*mincLmer* from the *RMINC_1.5.2.2* package in R 3.6.3) were used to test the significance of longitudinal whole brain structural changes across time and the lifespan in mutation carriers relative to controls. To examine neuroanatomical differences between mutation carriers and controls, across time we used a model (eq. 1) that included, genetic mutation status (*non-carrier, C9orf72, GRN,* or *MAPT),* time, measured in months, from baseline scan, as well as the interaction between these measures, the participant's baseline age, and sex as fixed effects. Participant ID and the scanning site were included in this model as random effects to account for scanning site specific effects. The resulting maps were corrected for multiple comparisons using a $q \leq 0.05$ False Discovery Rate (FDR) to control for

the expected proportion of discoveries that are falsely rejected (Benjamini et al., 2001; Benjamini & Hochberg, 1995).

To examine neuroanatomical differences across the lifespan in mutation carriers relative to controls, we used a model (eq. 2) that included, genetic mutation status, the participants age at visit, as well as the interaction between these terms, and sex as fixed effects. Age was modeled as linear, second, and third order using (*poly* from the stats R package, version 3.6.2) and Akaike information criterion (AIC) was used to select the most appropriate longitudinal model (Akaike, 1974). The model with the lowest AIC, in this case the second order relationship, was considered to have the best fit (Portet, 2020) with the data and was subsequently used for the analysis over the lifespan. Participant ID, as well as scanning site were included in this model as random effects. These maps were corrected for multiple comparisons using FDR.

*Relative Jacobians ~ Genetic mutation status * Time + Baseline age + sex + (1|ID) + (1|Scanning Site) (eq. 1)*

*Relative Jacobians ~ Genetic mutation status * poly(Age at Visit, 2) + Sex + (1|ID) + (1|Scanning Site)* (eq. 2).

3.3.8 Two-year within-subjects DBM analyses

To test whether neuroanatomical change over a two-year period reflects changes in behavioural and psychiatric symptoms, as measured by scores on the CBI-R, within the same timeframe, we used Partial Least squares (PLS) correlation. PLSC is a multivariate statistical technique used to detect patterns of covariance across two matrices via single value decomposition (Abdi & Williams, 2013; Krishnan et al., 2011). This technique aims to identify a set of latent variables that explain patterns of covariance between brain and behavioural data, in this case relative Jacobians and CBI-R scores alongside the participants symptomatic status.

Each latent variable depicts a linear combination of structural abnormalities that maximally covary with a linear combination of symptoms. PLS analyses were run separately for each mutation carrier group to examine whether each mutation carrier group would be associated with distinct brain and behaviour patterns. The neuroanatomical data consisted of the 2-year within-subject relative Jacobians derived from our DBM analyses at each voxel for each subject (matrix size 8,675,289x39 for *C9orf72*; 8,675,289x39 x66 for *GRN*; 8,675,289x39 x35 for *MAPT*; and 8,675,289x101 for controls). The behavioural data consisted of the z-scored difference between CBI-R scores from baseline to the two-year assessment, as well as the participants symptomatic status (pre-symptomatic vs. symptomatic) for mutation carriers (7x39 for *C9orf72*; 7x66 for *GRN*; 7x35 for *MAPT*; and 6x101 for controls). Of note, this matrix does not contain information regarding the participant's sex, age at visit, or estimated years to symptom onset.

Each latent variable was tested statistically using permutation testing with 5,000 permutations, following a similar protocol as outlined in previous studies (Bussy et al., 2021; Krishnan et al., 2011; McIntosh & Lobaugh, 2004; McIntosh & Mišić, 2013; Zeighami et al., 2019). In brief, the ordering of observations in the neuroanatomical matrix was randomly permuted (N = 5,000 repetitions) and a set of null brain-behaviour correlations matrices, where the brain matrix was permuted and the behaviour matrix was not, were computed. In turn, these matrices were subjected to single value decomposition creating a distribution of singular values. From this testing, a non-parametric p-value was estimated for each latent variable to describe the likelihood that the original singular value was obtained by chance. A p-value threshold of 0.05 was selected to highlight the LVs which had at least a 95% chance of not being association with a random correlation in the original matrices.

The degree to which each brain and behaviour variable contributed to the latent variable was tested using bootstrap resampling (BSR). Both the rows of the brain and behavioural matrices were randomly sampled (N = 5,000), with replacement, to generate a set of 5,000 resampled correlation matrices where, in contrast with the permutation testing described above, the objective was to maintain the initial brain and behaviour relationship. These resampled correlation matrices were then subjected to single value decomposition in order to create a distribution of single value weights for each variable. A bootstrap ratio, which is simply the ratio of the single value weight over the standard error of the weigh is then calculated for each voxel to assess the contribution and the reliability of the brain variable (Zeighami et al., 2019). For the present study, we selected a BSR threshold of 2.58, which is analogous to a p-value of 0.01 (Abdi & Williams, 2013; Krishnan et al., 2011).

To examine the extent to which individual subjects loaded onto the atrophy and behavioural pattern derived from our PLS analyses we projected the weighted patterns of the matrices of the left and right singular vectors onto the individual subject data to receive a scalar brain and behaviour score for each participant (Zeighami et al., 2019).

Finally, post-hoc analyses of the latent variables derived from the PLSC analyses were conducted by testing patterns of brain and behaviour change specific to key demographic variables, such as age, sex, estimated years until onset of symptoms (EYO), and scanning site. Using general linear models, where the models (eq. 3 – 6) included brain and behaviour scores derived from each latent variable as the dependent variable, and either age at the time of visit, estimated age of onset, sex, or scanning site as predictor variables. Finally, we used an omnibus FDR correction across these statistical models to correct for multiple comparisons. As such, q-values will be reported.

Brain/Behaviour Score ~ Age at visit (eq. 3)

Brain/Behaviour Score ~ Sex (eq. 4)

Brain/Behaviour Score ~ EYO (eq. 5)

Brain/Behaviour Score ~ Scanning site (eq. 6)

3.4 Results

3.4.1 Participants

983 participants had at least one and up to 7 T1-weighted structural magnetic resonance images (MRI) acquired on a 1.5T or 3T scanner. The average interval between scans was 1.37 (SD = 0.62) years. Participants were known carriers of pathogenic mutations in *MAPT*, *GRN*, *Valosin-Containing Protein* (VCP), or *TANK-binding kinase 1* (TBK-1) genes or with a pathogenic expansion in the *C9orf72* gene (> 30 repeats). First-degree relatives who did not carry pathogenic mutations acted as controls. From the 983 subjects with at least 1 T1-weighted MR image, scans from 130 participants were discarded due to poor image quality. A further 11 subjects were excluded as they had a rarer mutation causative of FTD (i.e., VCP or TBK-1), 14 participants were excluded due to MR image preprocessing failure, and all participants with fewer than 2 scans were excluded (n = 355), thus leaving 473 subjects (scans = 1464) for longitudinal DBM analyses. Details regarding participants can be found in table 1.1. Given, that we used participants with a scan at baseline and two-year follow-up for the PLS analyses, we removed a further 232 participants who did not fit that criterion, thus leaving 241 participants for PLS analyses. Details regarding participant characteristics can be found in table 1.2.

Table 3.2. Baseline demographic and clinical characteristics in mutation carriers and healthy controls.

Characteristic	Controls *N* = 206	*C9orf72* *N* = 96	*GRN* *N* = 116	*MAPT* *N* = 55

Symptomatic, No (%)	-	22 (22.9%)	14 (12.1%)	11 (20%)
Female Sex, No (%)	123 (59.7)	50 (52.1)	72 (62.1)	30 (54.5)
Age, y	46.3 (12.9)	48.6 (14.0)	49.3 (11.9)	43.1 (11.6)
Education, y	14.3 (3.42)	14.4 (2.93)	14.4 (3.64)	14.4 (3.23)
MMSE, M	29.5 (0.95)	28.2 (2.69)	28.5 (3.30)	28.6 (3.49)
Interscan interval, y	1.35 (0.536)	1.30 (0.457)	1.33 (0.557)	1.30 (0.536)
CBI Memory	1.00 (1.93)	4.87 (6.99)	2.30 (4.74)	4.16 (7.17)
CBI Beliefs	0 (0)	0.36 (1.52)	0.06 (0.37)	0.10 (0.58)
CBI Abnormal Behaviour	0.46 (1.19)	2.69 (4.29)	0.88 (2.08)	2.08 (3.77)
CBI Mood	0.89 (1.51)	2.21 (2.92)	1.09 (2.07)	2.06 (2.80)
CBI Stereotypic Behaviours	0.45 (1.19)	2.24 (3.59)	0.82 (1.93)	1.98 (3.81)
CBI Motivation	0.39 (1.23)	2.85 (4.82)	1.31 (3.55)	2.80 (4.92)

Values listed as means (standard deviations) unless otherwise specified.

Table 3.3. Demographic characteristics in mutation carriers and healthy controls used in partial least squares analyses.

Characteristic	*Controls* *N* = 101	*C9orf72* *N* = 39	*GRN* *N* = 66	*MAPT* *N* = 35
Symptomatic, No (%)	-	9 (23.1)	7 (10.6)	10 (28.6)
Female Sex, No (%)	25 (64.1)	62 (61.4)	43 (65.2)	23 (65.7)
Age, y	50.4 (12.7)	52.4 (12.7)	51.2 (11.7)	47.4 (11.3)
Education, y	14.8 (3.46)	15.1 (2.54)	14.6 (3.86)	14.7 (3.42)

Values listed as means (standard deviations) unless otherwise specified.

3.4.2 Longitudinal DBM results

Group comparisons of whole brain structural changes over time revealed significant mutation specific patterns and rates of brain atrophy over time relative to controls (figure 3.1-3). In *C9orf72* expansion carriers (figure 3.1), atrophy was observed across the brain relative to controls, including extensive atrophy in medial and lateral prefrontal cortex as well as atrophy in

the posterior insular cortices. Further, we observed sporadic atrophy in the temporal and parietal lobes. Furthermore, we observed significant subcortical atrophy, most notably in the bilateral thalamus, and the cerebellum, in both associative regions and the vermis. Interestingly, we observed regions of significant enlargement, particularly in the caudal left hemisphere. Lastly, in a pattern we saw across all mutation carrier groups, we observed significant bilateral increases in the volume of the ventricles over time. In *GRN* mutation carriers (figure 3.2), we observed a pattern of sporadic atrophy largely in frontal, parietal, and temporal cortex, as well as the posterior insular cortex. Notably, and unlike either *C9orf72* or *MAPT* carriers, much of the atrophy is localized in white matter structures including the corpus collosum. Akin to *C9orf72* expansion carriers, there were significant bilateral increases in the volume of the ventricles. Lastly, in *MAPT* carriers (figure 3.3), we observe significant atrophy largely localized in bilateral temporal lobes, alongside some atrophy in the frontal cortex and limited atrophy in the thalamus and cerebellum. Again, we observed significant bilateral increases in the volume of the ventricles.

Group comparisons of whole brain structural changes modeled across the lifespan (as opposed to measured change over time) revealed significant differences from controls only in the *C9orf72* group (figure 3.4). *C9orf72* expansion carriers showed scattered atrophy, relative to controls across the cortex and subcortex, mainly in the thalamus and posterior lobes of the cerebellum. There were no significant associations between atrophy and age in *MAPT* or *GRN* mutation carriers that survived correction for multiple comparisons.

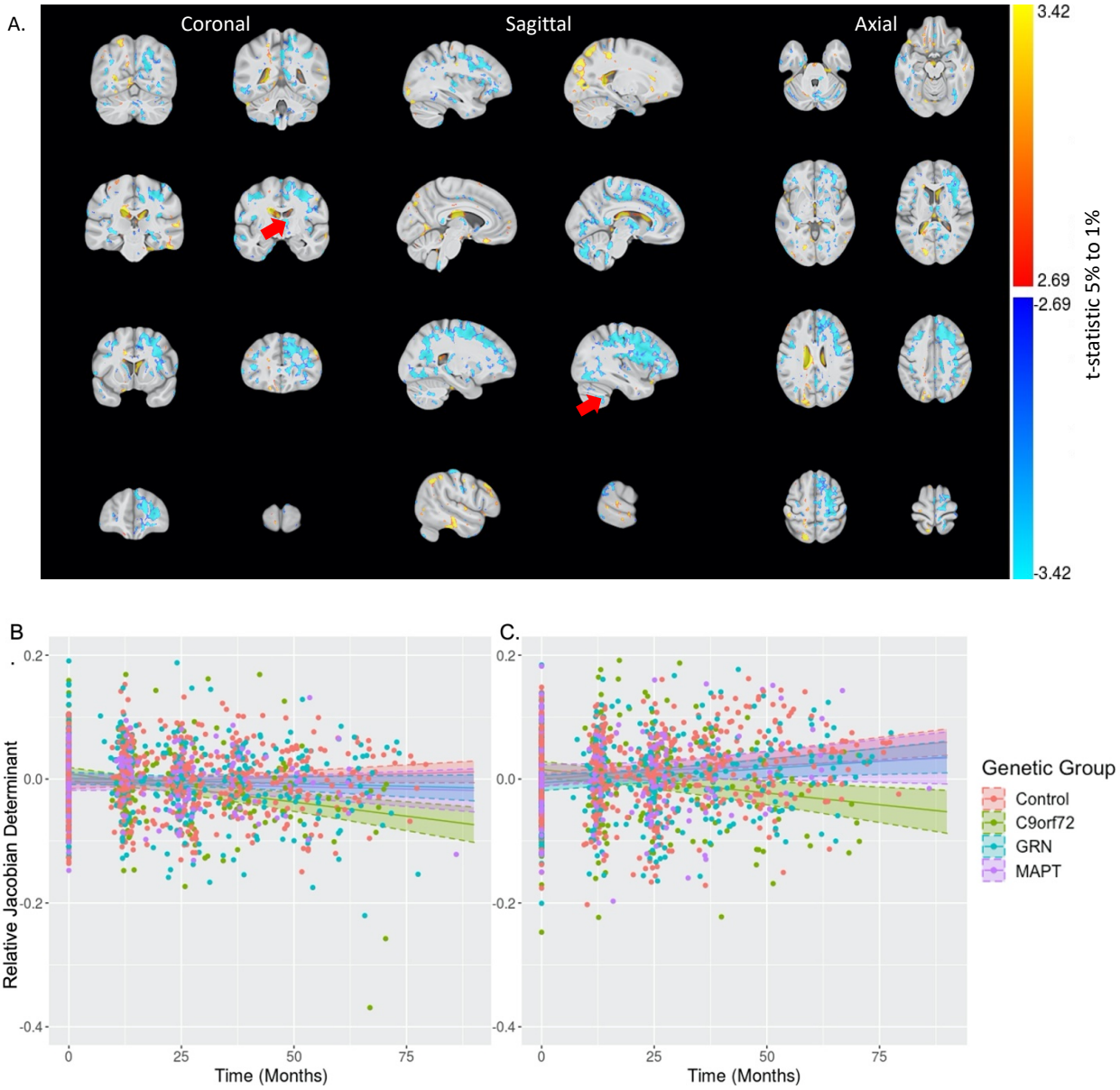


Figure 3.1 Brain slices highlighting significant voxels in *C9orf72* carriers from the longitudinal DBM analyses. t-value maps represent significant p-values between 1% and 5% post-FDR correction. B. Peak Voxels highlighting the relationship between relative Jacobians and time in month in left thalamus C. Peak Voxels highlighting the relationship between relative Jacobians and time in months in right cerebellum.

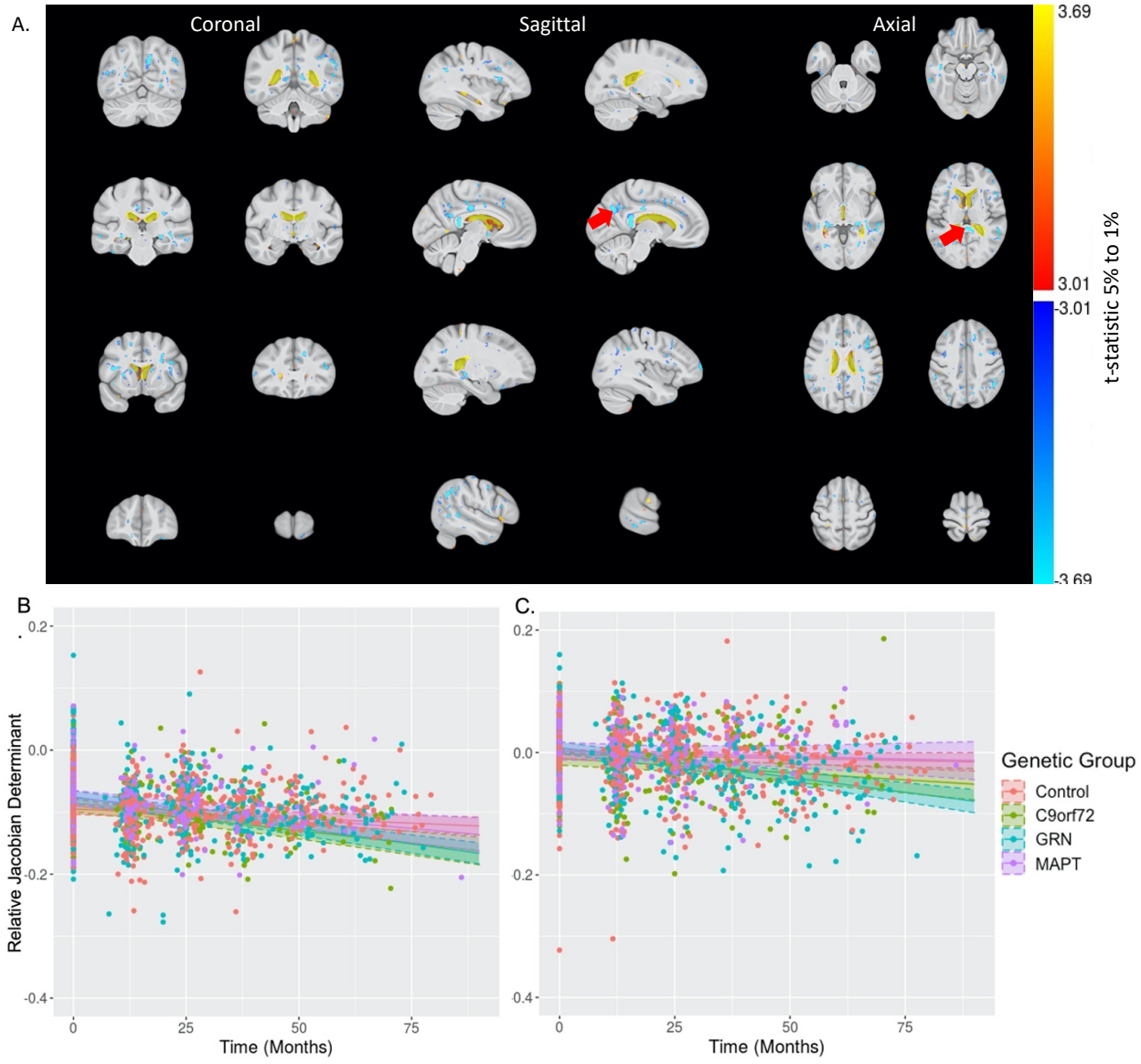


Figure 3.2 Brain slices highlighting significant voxels in *GRN* carriers from the longitudinal DBM analyses. t-value maps represent significant p-values between 1% and 5% post-FDR correction. B. Peak Voxels highlighting the relationship between relative Jacobians and time in month in the corpus collosum C. Peak Voxels highlighting the relationship between relative Jacobians and time in months in medial parietal cortex.

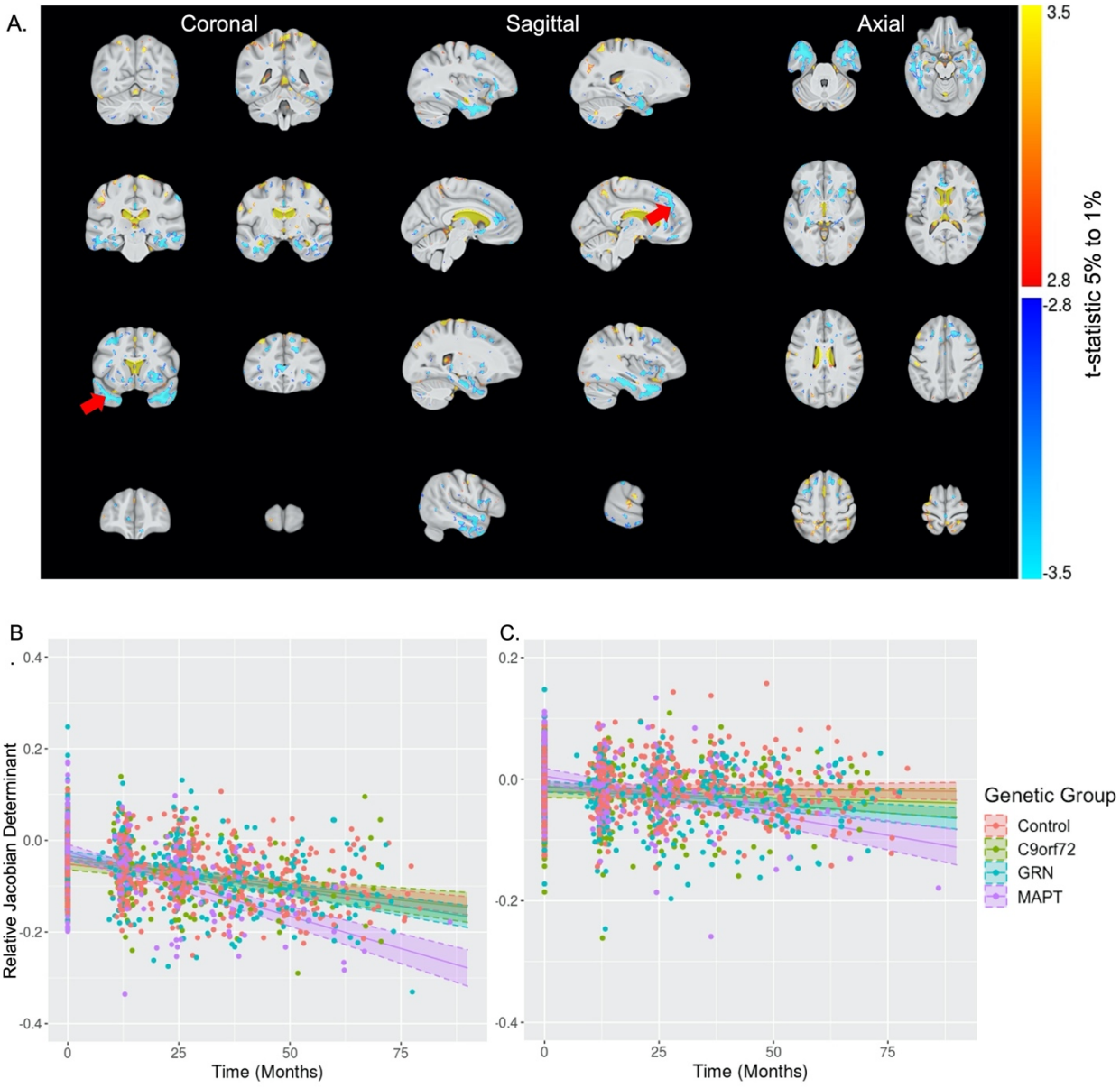


Figure 3.3 Brain slices highlighting significant voxels in *MAPT* carriers from the longitudinal DBM analyses. t-value maps represent significant p-values between 1% and 5% post-FDR correction. B. Peak Voxels highlighting the relationship between relative Jacobians and time in month in the left temporal lobe C. Peak Voxels highlighting the relationship between relative Jacobians and time in months in medial prefrontal cortex.

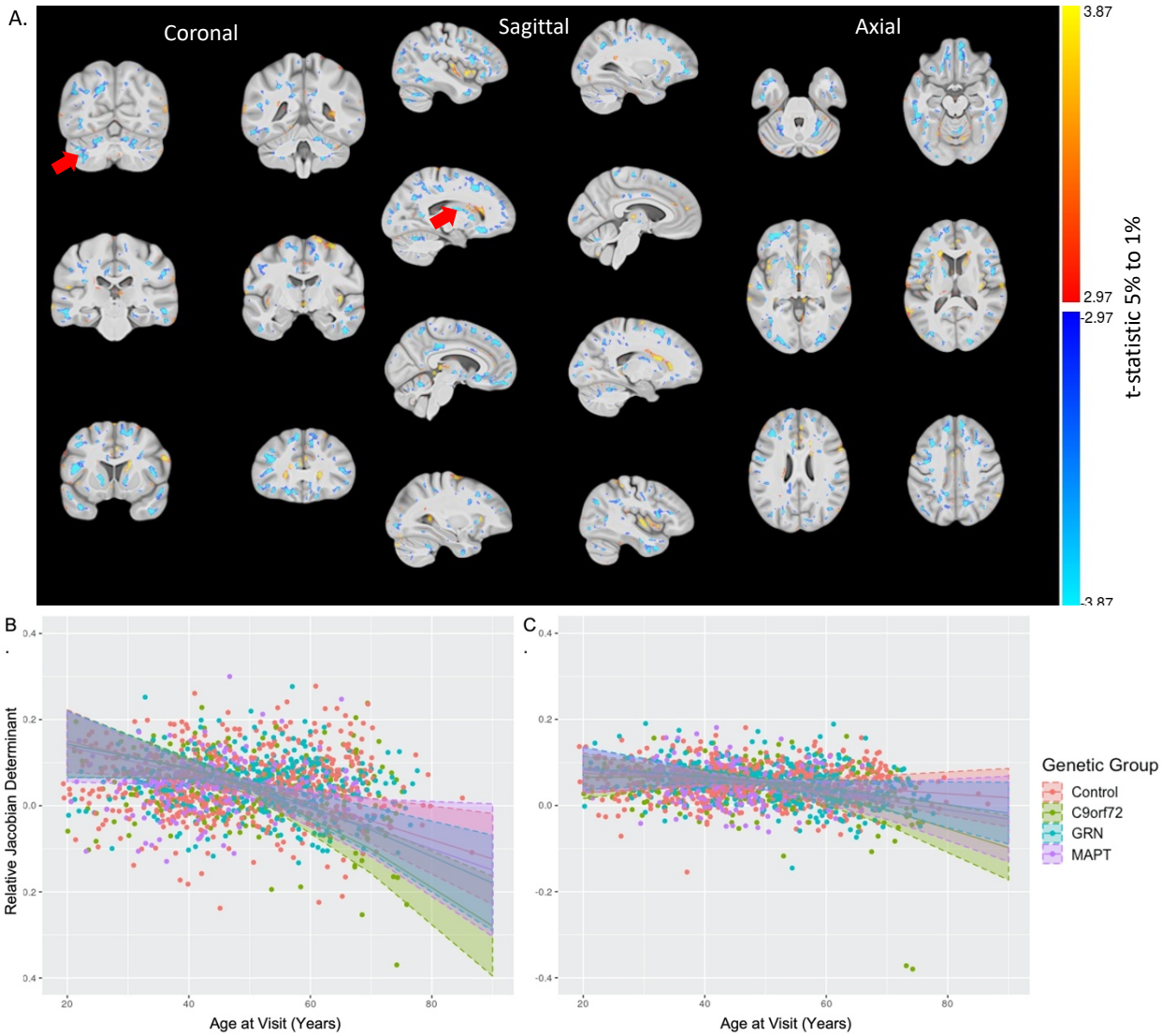


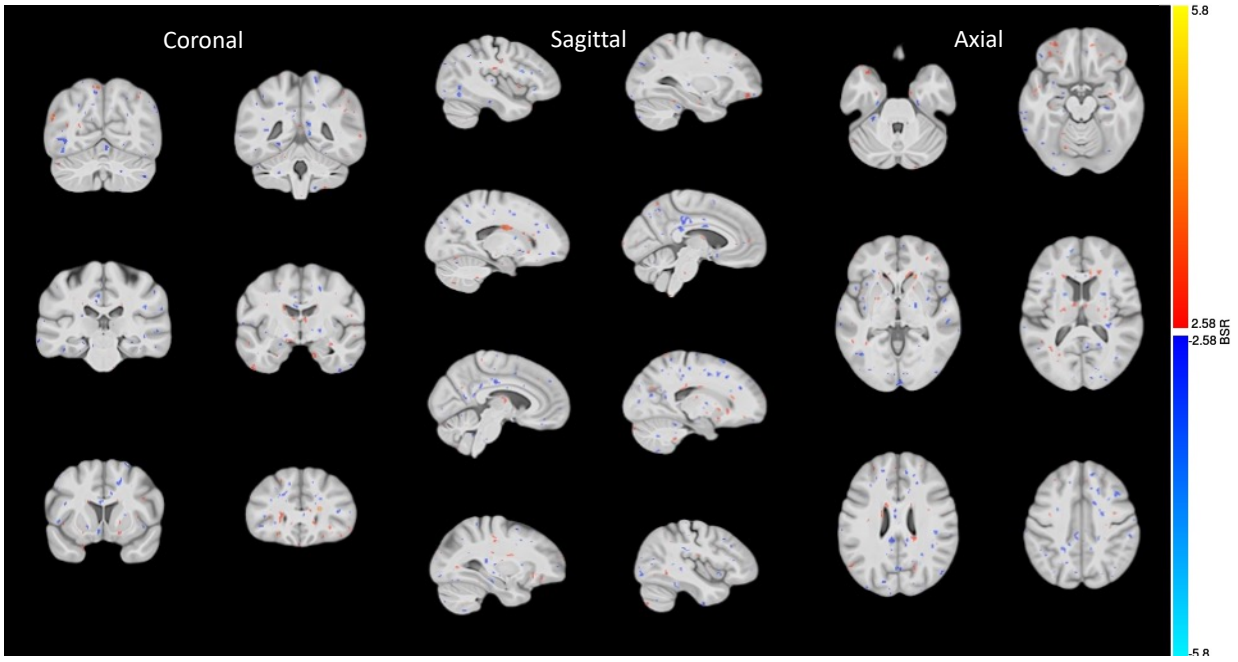
Figure 3.4 Brain slices highlighting significant voxels in *C9orf72* carriers from the longitudinal DBM analyses. t-value maps represent significant p-values between 1% and 5% post-FDR correction. B. Peak Voxels highlighting second order relationship between relative Jacobians and age in years in left cerebellum C. Peak Voxels highlighting second order relationship between relative Jacobians and age in years in left thalamus.

3.4.1 Two-year within-subjects results

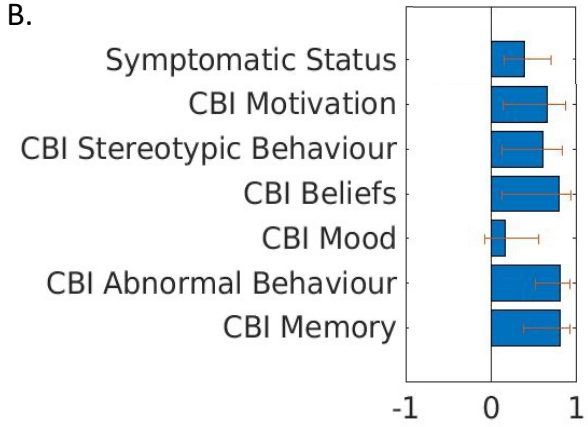
PLS results demonstrated one significant latent variable for *GRN*, *MAPT*, and *C9orf72* mutation carriers and none for controls (Fig 3.5). The *C9orf72* latent variable explained 65.18% of the covariance. The brain map showed increased ventricular size, alongside some decreased volumes of small areas scattered across the cortex, including posterior cingulate cortex and

striatum, with some atrophy in the posterior cerebellum were associated to worsening behavioural and neuropsychiatric symptoms, save for changes in mood in symptomatic subjects. The *GRN* latent variable explained 55.8% of the covariance. The *GRN* brain map demonstrated decreases volumes across the brain, including frontal, temporal, and parietal lobes, alongside subcortical involvement, primarily in the thalamus and anterior striatum, and some cerebellar involvement, mainly in posterior regions, were associated with worsened motivation, stereotypic behaviours, mood, and abnormal behaviour in symptomatic subjects. The *MAPT* latent variable explained 71.92% of the covariance. The *MAPT* brain map displayed decreased volumes in medial prefrontal, temporal, anterior cingulate cortex alongside atrophy in the thalamus and increased ventricular volumes were associated with worsening motivational, stereotypic, and abnormal behaviours and poorer memory performance, in symptomatic subjects.

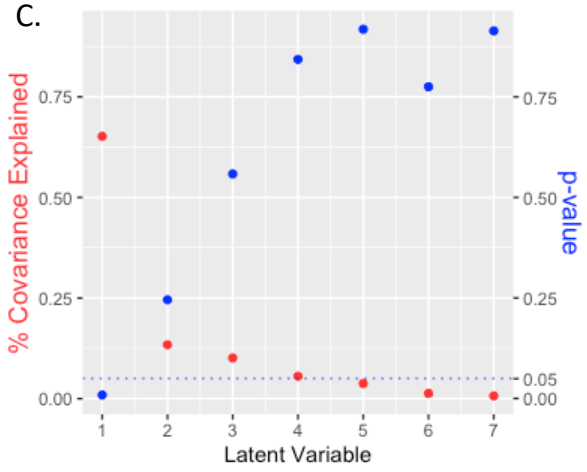
1.A.



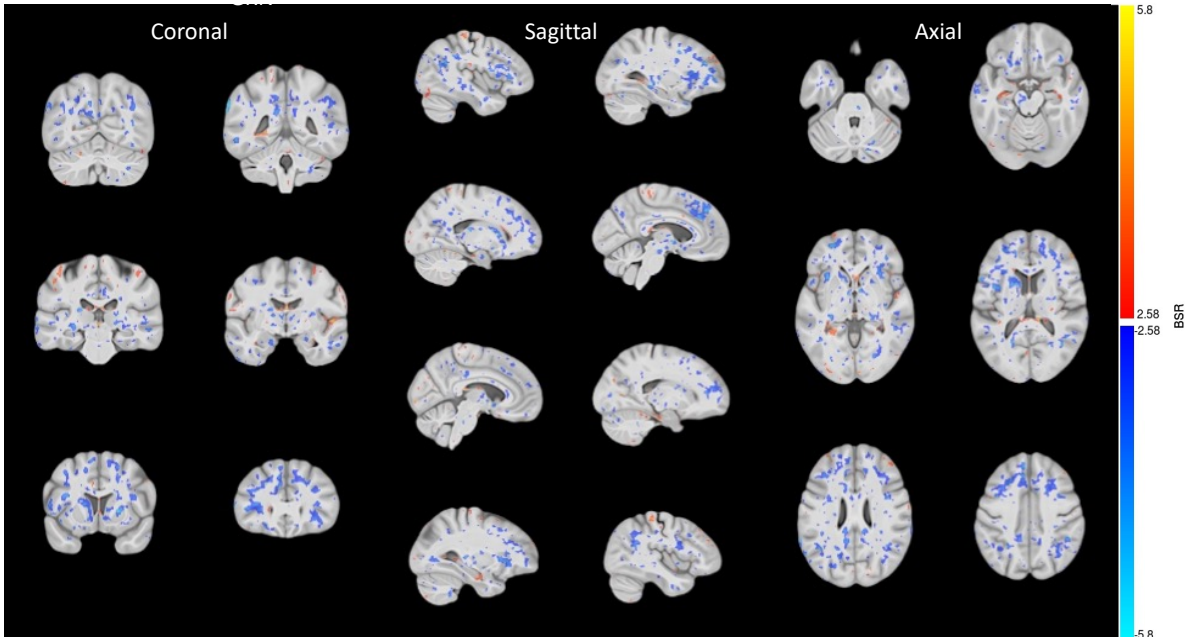
B.


Symptomatic Status
CBI Motivation
CBI Stereotypic Behaviour
CBI Beliefs
CBI Mood
CBI Abnormal Behaviour
CBI Memory
-1
0
1

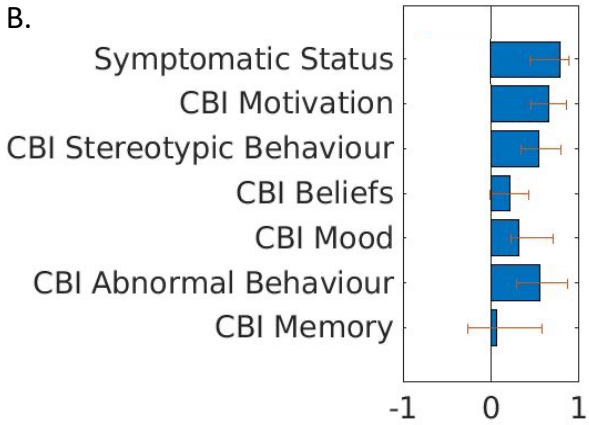
C.


% Covariance Explained
p-value
0.00
0.25
0.50
0.75
0.05
1
2
3
4
5
6
7
Latent Variable

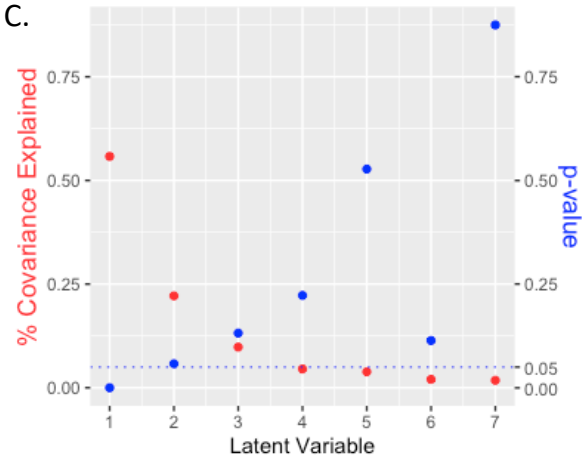
2.A.


Coronal
Sagittal
Axial
5.8
2.58
-2.58
BSR

B.


Symptomatic Status
CBI Motivation
CBI Stereotypic Behaviour
CBI Beliefs
CBI Mood
CBI Abnormal Behaviour
CBI Memory
-1
0
1

C.


% Covariance Explained
p-value
0.00
0.25
0.50
0.75
0.05
1
2
3
4
5
6
7
Latent Variable

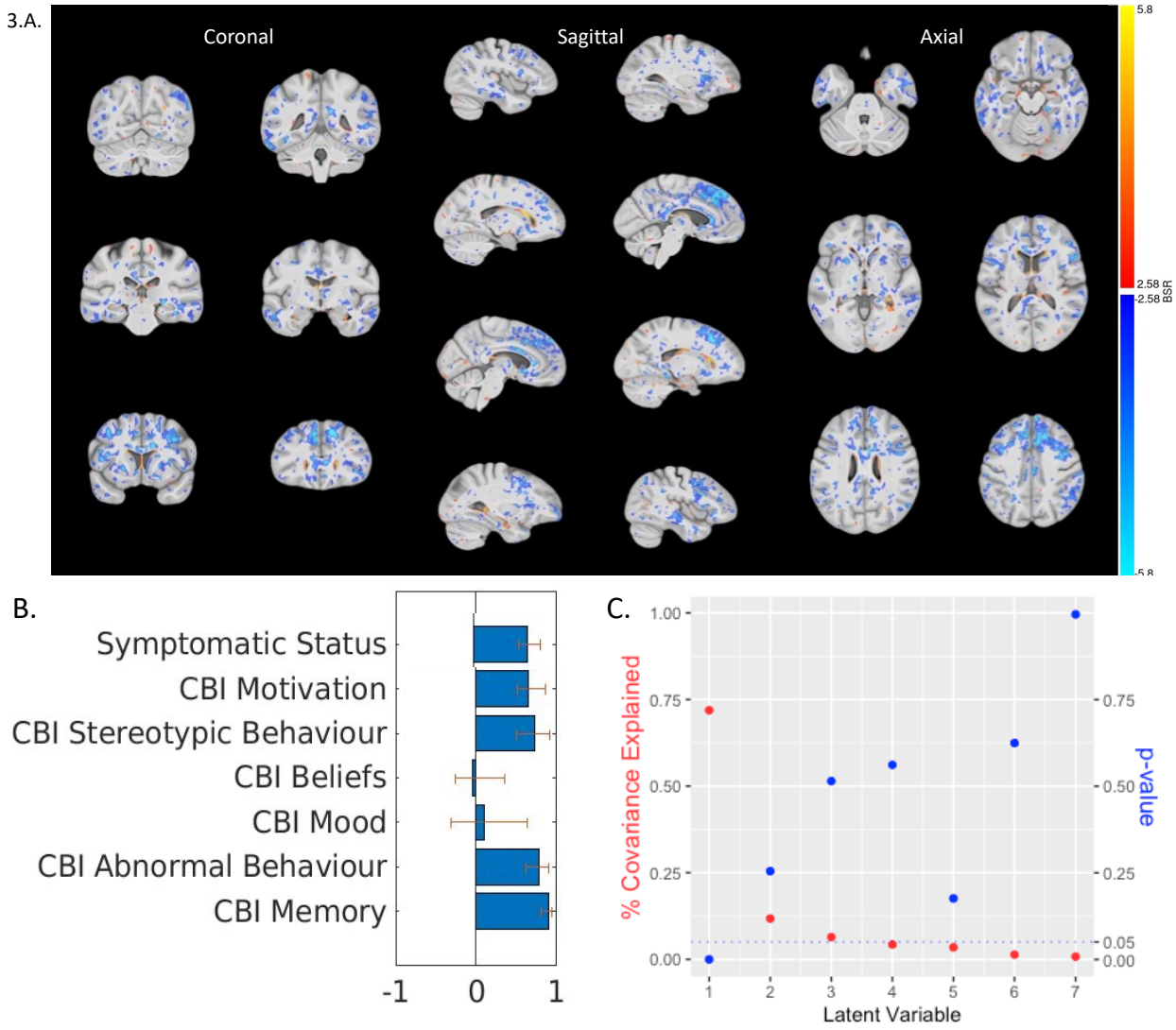


Figure 3.5. PLS analyses between voxel-wise 2 year within-subject changes in relative Jacobians and the CBI-R variables for each mutation group. 1. Describes *C9orf72* carriers. 2. Describes *GRN* carriers. 3. Describes *MAPT* carriers. A1-3. Brain scores of each latent variable using the BSR threshold of 2.58 ($p < 0.01$). B1-3. Bar plots describe the correlation of each CBI-R variable with each latent variable. Error bars denote 95% confidence intervals. C1-3. Graph highlighting the p-value and % covariance explained of each latent variable.

3.4.1 Two-year within-subjects post hoc results

Brain and behaviour scores, which described the extent to which individual subjects loaded onto the atrophy and behavioural pattern respectively, were examined to determine they could be explained by the demographic information of the participants (figure 3.6). Overall, brain and behaviour scores in *GRN* ($q = 0.019$ and $q = 0.015$ respectively) and *MAPT* ($q = 0.042$, $q = 0.035$

respectively) mutation carriers were related to EYO, with increasing EYO being related to greater brain scores. While brain and behaviour scores were related to age solely in *GRN* mutation carriers *(*$q = 0.004$ and $q = 0.013$ respectively), with increasing age being associated with greater brain and behaviour scores. Lastly, in C9orf72 expansion carriers, one site scanning site (blinded site CV) was associated with increased brain scores ($q = 0.001$). There were no significant associations between sex and brain or behaviour variables that survived correction for multiple correction.

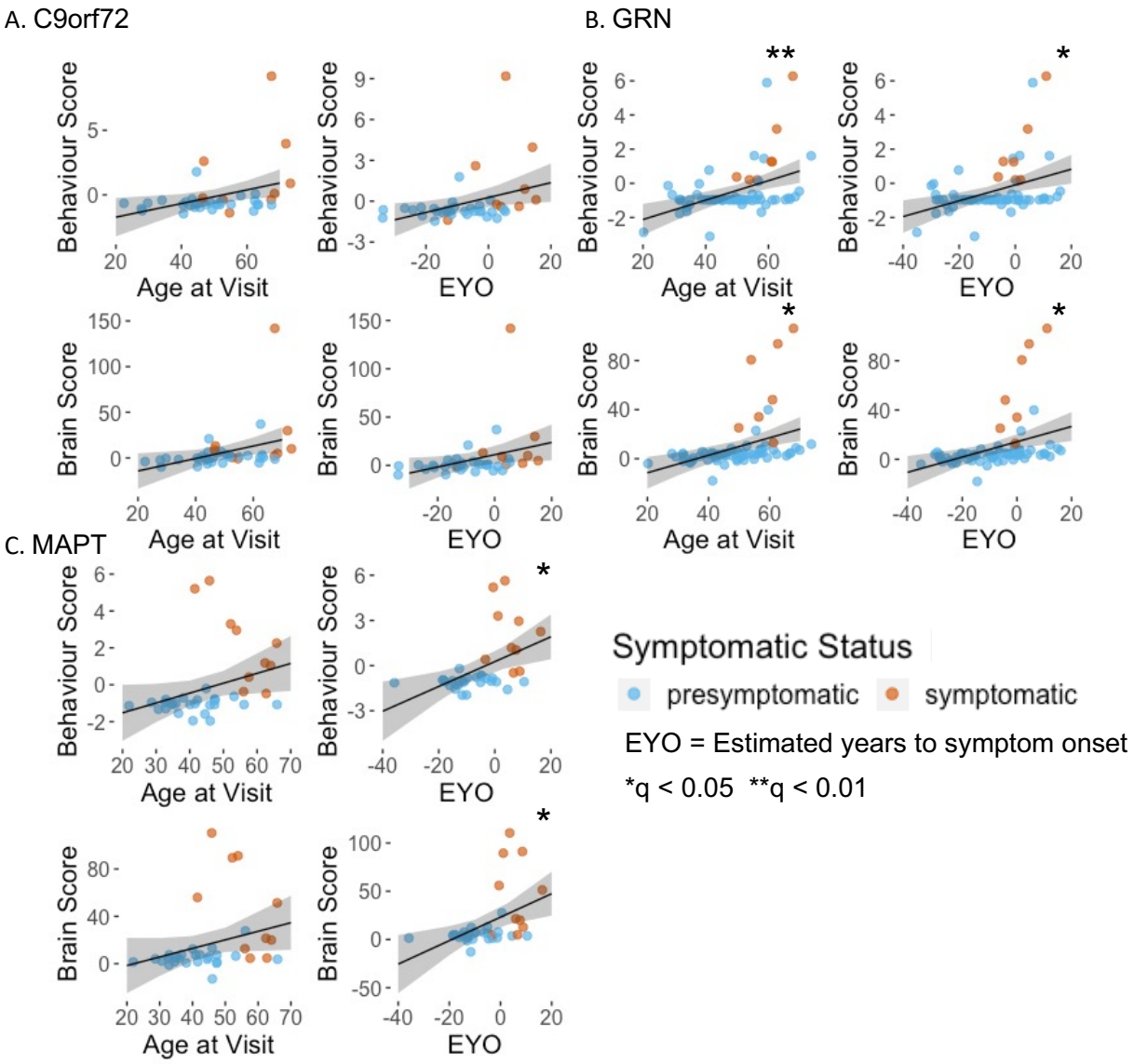


Figure 3.6. Plots describing the relationship of the brain and behaviour scores for **A.** *C9orf72* ***B.*** *GRN* and **C.** *MAPT* mutation carriers with age at the time of visit and estimated years to symptom onset. Blue points are used to denoted presymptomatic individuals and orange points are used to denote symptomatic individuals. * is used to highlight variables with q-values < 0.05 and ** for variables with q-values < 0.01. Shaded areas represent 95% Confidence intervals.

3.5 Discussion

The objectives of this paper were to better understand the longitudinal mutation specific neuroanatomical changes associated with genetic FTD. Further, we sought to understand the roles of these longitudinal changes and changes in behavioural and neuropsychiatric symptoms. The main findings of this project were three-fold. First, we observed differential patterns and rates of atrophy unique to each mutation carrier group when we examined morphometric changes over the time. Ubiquitous across all mutation carrier groups, however, were increasing ventricular volumes. Second, when modeling longitudinal changes in neuroanatomical changes across the lifespan, we observed only significant changes in *C9orf72* expansion carriers, where changes began around mid-life. Third, the PLS analyses revealed distinct longitudinal brain and behaviour relationships that were unique to each mutation carrier group and were largely driven by symptomatic carriers of FTD-related mutation. Where, despite largely overlapping behavioural patterns across mutations, we observed specificity in regard to neuropsychiatric symptom associations for each mutation carrier group.

Our longitudinal analyses indicated a mutation specific spatial and temporal pattern of atrophy over time. Previous cross-sectional work has shown that *C9orf72* expansions carriers have widespread patterns of cortical atrophy, alongside significant subcortical and cerebellar atrophy (Bocchetta et al., 2016; Bocchetta et al., 2020; Cash et al., 2018). Our findings are largely in line with these patterns of atrophy. Interestingly, we observed progressive atrophy in regions suggested to be associated with psychotic symptoms in FTD, namely associative regions in the cerebellum as well as the thalamus (Bussy et al., 2021; Devenney et al., 2017; Ducharme et al., 2017).

Conversely, in *GRN* mutation carriers we observed a relatively sparse pattern of atrophy over time when compared to controls. This finding was surprising, as we were expecting a more prominent and asymmetric pattern of atrophy among these subjects. This finding, however, may be due to the large number of presymptomatic mutation carriers (102 out of 116 participants). This does allow us, however, to speculate that atrophy in this group is somewhat minimal prior to symptom onset and examinations of neural phenotypes post-symptom onset is still necessary. Previous MRI-based cross-sectional studies have suggested that GRN mutation carriers exhibit few presymptomatic neuroanatomical insults, however, have a rapid decline in brain structure at symptom onset (Bocchetta Todd, et al., 2021; Cash et al., 2018; Staffaroni et al., 2020; Whitwell et al., 2015). These findings are bolstered by fluid-based biomarker studies using neurofilament light chain (NFL), a major constituent of the neuroaxonal cytoskeleton and a marker of axonal injury (Petzold, 2005; Yuan et al., 2015). Low levels of serum NFL were observed in presymptomatic *GRN* mutation carriers, followed by a several-fold increase in NFL as subjects approached symptom onset (Meeter et al., 2016; Wilke et al., 2022). As such, these observations may be driven by the large proportion of presymptomatic carriers with limited, however imminent, neurodegeneration. Interestingly, the atrophy we did observe was largely localized to white matter structures including the corpus collosum and along the grey matter boundary in frontal, temporal and parietal cortices. This finding, though not what was expected, is consistent with some previous cross-sectional studies that report white matter atrophy (Caroppo et al., 2014) as well as the presence of white matter hyperintensities (Paternicò et al., 2016; Sudre et al., 2017; Woollacott et al., 2018) in symptomatic *GRN* carriers. White matter hyperintensities are the consequence of cerebral small vessel disease and are associated with several neuropathologies including demyelination, axonal loss, ischaemic damage, and cerebral atrophy,

and are easily detectable in T2-weighted or fluid attenuated inversion recovery (FLAIR) MRI imaging (Debette & Markus, 2010; Prins & Scheltens, 2015; Wardlaw et al., 2015). Further, other studies have also found reduced white matter integrity, relative to controls, in presymptomatic *GRN* carriers (Jiskoot et al., 2018). Additionally, animal models of *GRN* mutations have found white matter pathology in *GRN* knockout mice (Wu et al., 2021). In summary, our findings, taken together with previous work, supports the hypothesis that GRN mutations are associated with significant changes in white matter structures, and as such, may be a useful biomarker, in a clinical context, in differentiating GRN carriers from other forms of FTLD (Caroppo et al., 2014).

Cerebral findings in *MAPT* carriers are largely commensurate with previous work that has suggested that anteromedial temporal atrophy is a hallmark feature of *MAPT* mutations. These changes have been observed in both cross-sectional (Cash et al., 2018; Chen et al., 2019; Chu et al., 2021; Jonathan D. Rohrer et al., 2015; Rohrer & Rosen, 2013) and longitudinal studies in *MAPT* carriers (Panman et al., 2019). Findings regarding atrophy in the cerebellum, however, have been mixed. Some work has suggested little to no volumetric differences between *MAPT* carriers and controls (Bocchetta Todd, et al., 2021) and others suggesting subtle, yet significant differences, located primarily in the vermis (Bocchetta et al., 2016; Bussy et al., 2021). Our findings are in more line with the latter, where we observed neurodegeneration in both the vermis and posterior cerebellum, suggesting that *MAPT* carriers may have more cerebellar involvement than previously expected.

Ventricular enlargement has been well documented in sporadic and genetic FTD (Knopman et al., 2009; Manera et al., 2019; Whitwell et al., 2015) and has been suggested as a valuable imaging biomarker for discriminating between symptomatic bvFTD patients and

healthy controls (Knopman et al., 2009; Manera et al., 2019). Moreover, ventricular enlargement has been shown to be detectable early in the disease course in FTD-related mutation carriers, with an average of four years prior to the estimated onset of clinical symptoms (Tavares et al., 2019). Notably, across all mutation carrier groups, we observed a significant volume increase in the ventricles, over time, relative to controls. Our findings, taken together with previous work on the topic, further support ventricular enlargement as a potential sensitive imaging biomarker that, despite not being able to discriminate between mutation types, may be useful early in the disease course as a marker of disease progression.

In contrast with our analyses on longitudinal changes over the course of the study, we observed differences solely between *C9orf72* expansion carriers and controls that survived correction for multiple comparisons. The lack of findings in *GRN* and *MAPT* mutation carriers may be due to the large proportion of presymptomatic mutation carriers based on previous work (Staffaroni et al., 2020) showing fewer presymptomatic neuroanatomical changes, and a more rapidly progressing neurodegeneration in these groups when compared to *C9orf72* expansion carriers (Bocchetta Todd, et al., 2021; Cash et al., 2018; Staffaroni et al., 2020). Interestingly, in *C9orf72* expansion carriers however, our findings show that brain structure was largely homologous with controls until mid-life, around age 50, where we see a steep and significant decline across various brain volumes. This pattern of change is consistent with what would be expected given both the anticipated age of onset of clinical symptoms and when we would expect to be able to observe atrophy. Previous cross-sectional work has suggested that neuroanatomical changes may begin up to decades before the onset of clinical symptoms (Cash et al., 2018; Jonathan D. Rohrer et al., 2015), with *C9orf72* carriers having a median age of symptom onset in the late 50's (Moore et al., 2020; Murphy et al., 2017).

Our PLS analyses revealed characteristic associations between brain and behaviour for each genetic group that were largely driven by symptomatic subjects. Notably, in our PLS behavioural results we observed few differences between mutation carriers in behavioural symptoms, apart from memory, however marked differences in neuropsychiatric symptom profiles. Brain maps for *C9orf72* expansions carriers exhibited very limited and scattered atrophy. Though unexpected, these findings may be related to the relatively short two-year timeframe. Previous work has found at symptom onset, similar levels of neurodegeneration yet much slower rates of change in *C9orf72* expansion carriers as compared to *MAPT* and *GRN* (Staffaroni et al., 2020). This may suggest that, although the fate of the brain is similar across mutations, the path may be different, with *C9orf72* carriers progressing at an early and relatively slow pace (Khan et al., 2012; Panman et al., 2019; Staffaroni et al., 2020). Notably, an association between brain structure and change in psychotic symptoms was found solely in *C9orf72* carriers. This finding is interesting, as previous work has suggested that psychotic symptoms may be particularly salient in *C9orf72* as compared to sporadic FTD and other mutation carriers (Benussi et al., 2021; Devenney et al., 2017; Ducharme et al., 2017). Although our findings cannot speak to changes in neuroanatomical structures driving these changes, the results from our DBM analyses and previous work may hold clues. We observed progressive changes in the cerebellum and thalamus, two structures previously implicated in psychotic symptomatology in *C9orf72*-related FTD (Bussy et al., 2021; Devenney et al., 2017; Ducharme et al., 2017). Given the shorter timeframe of our PLS analyses and the slowly progressing nature of *C9orf72*-related neurodegeneration (Khan et al., 2012; Panman et al., 2019; Staffaroni et al., 2020), perhaps there was insufficient neurodegeneration at this shorter two-year timescale to be

detectable. As such, future longitudinal work, over a wider spectrum of time, will help elucidate the role of these structures in psychotic symptoms.

In contrast with *C9orf72* expansion carriers, brain maps in *GRN* carriers, exhibited a more prominent pattern of atrophy spread throughout the brain, though like our DBM findings, are largely localized in white matter structures. The behavioural symptom profile for *GRN* carriers illustrated worsening mood symptoms. This finding is in line with previous work, which found that symptomatic *GRN* carriers, exhibited the most severe and frequent mood symptoms relative to other genetic groups (Benussi et al., 2021). Further, reduced white matter integrity and white matter hyperintensities has previously been associated with depressive and anxiety symptoms in individuals with other related neurodegenerative disorders (Berlow et al., 2009; Tully et al., 2017). As such, future work should focus on the associations between structural connectivity and mood symptoms in *GRN*, particularly the corpus collosum, cingulum, and the anterior limb of the internal capsule, structures which have previously been associated to mood symptoms in psychiatric disorders (Dillon et al., 2018).

The *MAPT* LV brain map showed a more severe atrophy pattern relative to the other genetic groups, though these changes are in line with our expectations based on previous work that found symmetrical losses in temporal and frontal cortices (Cash et al., 2018; Rohrer & Rosen, 2013) and medial temporal subcortical structures (e.g., the amygdala) (Bocchetta et al., 2015; Bocchetta et al., 2019; Bocchetta Todd, et al., 2021) in symptomatic *MAPT*-related FTD. In the behavioural PLS results we observed a strong association to worsening memory. This finding is consistent with previous cross-sectional work which has found episodic memory deficits in both presymptomatic and symptomatic *MAPT* mutation carriers that have been

associated with atrophy in bilateral medial temporal lobes (Poos et al., 2021). These findings, taken together, may suggest a more amnestic phenotype as a key feature of *MAPT*-related FTD.

Notably, while we observed an increase in brain and behaviour scores across all mutation carrier groups as they aged and approached the estimated symptom onset, these findings were only significant in *GRN* and *MAPT* carriers. Notably, *GRN* brain and behaviour scores showed a stronger association with age than EYO. These finding are largely in line with previous work which has found strong associations between individual and familial age of onset in *MAPT* mutation carriers, with this association being weaker in *C9orf72* and *GRN (Moore et al., 2020)*.

We acknowledge that there are limitations in the present study that must be highlighted and should be addressed. First, the CBI-R scales used in this study provide a limited and aggregate assessment of various behavioural and psychiatric symptoms derived from knowledgeable informant report. For example, the CBI-R beliefs subscale (Wear et al., 2008), provides a combined and subjective assessment of auditory and visual hallucinations as well as delusions. Despite several neuroanatomical structures, such as the thalamus and cerebellum (Hwang et al., 2021; Lawn & ffytche, 2021; Steullet, 2020), being related to psychotic features in primary psychiatric and neurodegenerative disorders, there are noted differences in the neural correlates of these symptoms (Zmigrod et al., 2016). Due to the large number of presymptomatic carriers in our cohort (82.4% and 81.4% of FTD-related mutation carriers for DBM and PLS analyses respectively) and the relatively low symptom endorsement for individual symptoms, we used these combined metrics. Future work, however, should aim to disentangle these metrics in order to provide a clearer snapshot of the neural underpinnings of these psychiatric symptoms.

Second, due to the selection criteria for the PLS analyses, i.e., multiple scans with an interval of approximately 2 years, and the large proportion of presymptomatic mutation carriers,

we had limited observational timeframe and a relatively small sample of symptomatic carriers in these analyses. As such, we may not have had sufficient time to capture slower and potentially larger changes in *C9orf72* mutation carriers. Moreover, results in these symptomatic mutation groups may be driven by a small number of individuals. Future work, therefore, would benefit from a longer period of time and a larger number of symptomatic carriers in order to confirm the findings made in this study. Lastly, as our PLS analyses were run separately for each mutation carrier group, we have qualitatively compared results between mutation carrier groups, however, no tests were conducted to quantitatively compare brain maps in PLS.

This project was the first to examine how true longitudinal brain changes influenced change in behavioural and neuropsychiatric symptomatology using a novel longitudinal multivariate statistical technique in genetic FTD. As such, these findings may contribute to our understanding of the neural mechanisms underlying neuropsychiatric symptoms in genetic FTD which in turn may inform the neurobiology underlying these symptoms in other neurodegenerative or primary psychiatric disorders.

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Chapter 4 - Hypothalamic change associated to sleep disturbances in genetic FTD

4.1 Preface

The work presented in Chapter 4 represents the first examination of the relationship between hypothalamic atrophy and its effect on sleep dysfunction in genetic frontotemporal dementia. While Chapter 3 was focused primarily on psychiatric symptoms and their neural correlates, these are not the sole atypical adverse symptoms profiles that are poorly understood in genetic FTD. Sleep dysfunction, such as insomnia, hypersomnia, and frequent night-time awakenings, has previously been found to be very common in sporadic FTD (McCarter et al., 2016), however, has remained a relatively underexplored topic in genetic variants of the disease.

Previous work has suggested that *MAPT* and *C9orf72* mutation carriers may be at increased risk of sleep dysfunction (Daoud et al., 2014; Gemignani et al., 2005; Sani et al., 2019), with evidence of sleep dysfunction in *MAPT* carriers occurring prior to the onset of more typical FTD symptoms(Tavares et al., 2020). Like psychiatric symptoms, the neural correlates of this dysfunction remain poorly understood, however, evidence points to atrophy in the hypothalamus as an important contributor (Saper & Lowell, 2014; Warren & Clark, 2017). As such, the following chapter, Chapter 4, we continued the work we had conducted in Chapter 3, however, we examined another atypical symptom profile, in this case sleep dysfunction, as well as their underlying neural correlates in those with genetic mutations causative of FTD

Hypothalamic change associated to sleep disturbances in genetic FTD

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List of Figures & Tables: Figure 4.1. Flowchart describing participant selection process; Table 3.4: Baseline demographic and clinical characteristics in mutation carriers and healthy controls used for behavioural and hypothalamus analyses; 3.2; Baseline demographic and clinical characteristics in mutation carriers and healthy controls used for cortical thickness analyses; Figure 4.2. A. Scores on the CBI-R sleep subscale; Figure 4.3. Cortical thinning patterns; Figure 4.4. Volumes across the lifespan; Figure 4.5. Cortical thinning patterns associated with increased CBI R sleep subscale; Figure 4.6. Association between hypothalamic region and scores on the CBI-R sleep subscale.

List of Abbreviations: FTD: Frontotemporal Dementia; *C9orf72*: chromosome 9 open reading frame 72; *GRN*: progranulin; *MAPT*: microtubule associated protein tau; AD: Alzheimer's Disease; REM: Rapid-eye movement; SCN: Suprachiasmatic nucleus; LHA: Lateral hypothalamic area; MCH: melanin-concentrating hormone; OX: orexin; GENFI: Genetic Frontotemporal Dementia Initiative; CBI-R: Cambridge Behavioural Inventory - Revised ; T1-w: T1-weighted; FDR: False Discovery Rate; CTh: Cortical Thickness; MMSE: Mini Mental State Exam; TIV: Total Intracranial Volume; *VCP*: Valosin-Containing Protein ; TBK-1: *TANK-binding kinase 1*; EYO: estimated years to onset.

4.2 Rationale, Hypotheses, and Aim

Frontotemporal Dementia (FTD) is a heterogeneous neurodegenerative brain disorder, presenting with various clinical, neuropathological, and genetic features (Boxer et al., 2011; Boxer & Miller, 2005; Olszewska et al., 2016). FTD is also highly heritable, with up to 30% of cases presenting with a strong family history (Greaves & Rohrer, 2019). Of those with a familial history of the disorder, the majority of the heritability is derived from one of three fully penetrant autosomal dominant mutations: chromosome 9 open reading frame 72 (*C9orf72*), progranulin (*GRN*), or microtubule associated protein tau (*MAPT*) (Greaves & Rohrer, 2019).

Sleep disturbances are common and have been widely reported in related neurodegenerative disorders, such as Alzheimer's Disease (AD) and Lewy Body dementia-Parkinson's disease (Cipriani et al., 2015; Comella, 2006; Vaou et al., 2018). Between 33-76% of FTD patients experience some sort of sleep disturbance (e.g., insomnia, hypersomnia, narcolepsy-like attacks, and frequent nighttime awakening; more common than in AD (Anderson et al., 2009; Bonakis et al., 2014; Guarnieri et al., 2012; McCarter et al., 2016)). Sleep dysfunction is associated with reduced cognitive performance across the lifespan (Dzierzewski et al., 2018; Scullin & Bliwise, 2015) and may further contribute to caregiver distress (Merrilees et al., 2014). There are grounds to suspect that *MAPT* mutation and *C9orf72* expansion carriers may be at particular risk of experiencing sleep dysfunction. In *MAPT* carriers, severe sleep symptomatology has previously been observed in FTD patients and animal models of the pathogenic mutations (Gemignani et al., 2005; Koss et al., 2016; Liu et al., 2018; Spector et al., 2011). Further, sleep symptoms may precede the onset of more core clinical symptoms. A recent study observed that preclinical *MAPT* carriers endorsed significantly greater sleep dysfunction compared to non-carriers (Tavares et al., 2020). Further, rapid-eye movement (REM) behaviour

disorder, which is typically associated to synucleinopathies, has previously been associated with *C9orf72* mutations (Daoud et al., 2014) . Furthermore, in a small sample of FTD mutation carriers, uniquely *C9orf72* carriers experienced additional disruptive sleep events, such as shouting or acting out dream content in addition the sleep dysfunction experienced by all participants (Sani et al., 2019).

There is significant evidence supporting hypothalamic atrophy in relation to the observed sleep dysfunction. The hypothalamus contains two nuclei critical to the regulation of sleep and wakefulness (Saper & Lowell, 2014) and projects widely to the cortex (Warren & Clark, 2016). The suprachiasmatic nucleus (SCN), located at the base of the anterior hypothalamus, serves as the circadian pacemaker, controlling the timing of sleep and wakefulness (Hastings et al., 2018; Moore, 2007). The lateral hypothalamic area (LHA), in contrast, serves as the central region for feeding and sleep (Yamashita & Yamanaka, 2017). The LHA contains the cell bodies of neurons containing melanin-concentrating hormone (MCH), which are primarily found in the LHA and adjacent zona incerta (Yamashita & Yamanaka, 2017). MCH neurons are known to be activated during rapid-eye movement sleep (Jego et al., 2013; Konadhode et al., 2013; Tsunematsu et al., 2014). The LHA also contains orexin (OX; also known as hypocretin) neurons, which are only found in the LHA and prefornical area (Yamashita & Yamanaka, 2017). OX in contrast to MCH, is wake promoting (Yamashita & Yamanaka, 2017). Given the importance of the hypothalamus in the timing, regulation, and maintenance of sleep and wakefulness, damage to this structure should have an outsized impact on sleep performance. This structure has been heavily implicated in disordered sleep in AD (Stopa et al., 1999; Van Erum et al., 2018), PD (Fronczek et al., 2007; Kalaitzakis et al., 2013), and sporadic FTD (Anderson et al., 2009; Çoban et al., 2013). Reduced

OX-A levels in CSF in FTD patients has been directly correlated to increased daytime somnolence (Liguori et al., 2014).

Previous work on this topic has primarily been focused on sporadic FTD patients. Comparatively, little work has been done to examine the neural correlates of sleep disturbances in those with genetic mutations causative of FTD. The present study aims to improve our understanding of disordered sleep and its potential neural correlates in individuals with mutations causative of FTD. To achieve this goal, we analyzed a large cohort of 983 participants, including presymptomatic and symptomatic subjects with mutations causative of FTD or related non-carriers. The objectives of this project are two-fold. 1) To ascertain the levels of sleep dysfunction in mutation carriers relative to non-carriers across the lifespan and as participants approached the estimated onset of clinical symptoms. We expect greater sleep dysfunction in mutation carriers as compared to controls, and that this would be most pronounced in *MAPT* and *C9orf72* carriers. Further, we expect increased sleep dysfunction as participants approached the predicted onset of clinical symptoms. 2) To evaluate if there is an association between sleep dysfunction and hypothalamic or cortical atrophy, and whether this differed between mutation carrier groups. We expect that reduced volumes in hypothalamic regions associated with the regulation of sleep and wakefulness to correlate with increase sleep disturbances.

4.3 Methods

4.3.1 Participants

All data were taken from data freeze 5 of the Genetic Frontotemporal dementia Initiative (GENFI) study (https://www.genfi.org), which includes participants tested between January 30, 2012, and May 31st, 2019. 1108 subjects have been recruited across 25 sites across the UK, the Netherlands, Belgium, France, Spain, Portugal, Italy, Germany, Sweden, Finland, and Canada.

All aspects of this study were approved by institutional review boards at each of the GENFI sites and all participants provided written informed consent.

4.3.2 Symptom assessment and Cambridge Behavioural Inventory

All participants underwent a standardized clinical and neuropsychological assessment as previously described (Jonathan D. Rohrer et al., 2015). A binary variable of symptomatic vs. non-symptomatic was defined by clinicians, based on clinician judgement, at the time of visit. Individuals were deemed "non-symptomatic" should they not exhibit typical FTD symptoms or "symptomatic" should they exhibit these symptoms. Of particular interest to this project is the Cambridge Behavioural Inventory Revised (CBI-R) (Wear et al., 2008). The CBI-R is a validated, informant-based questionnaire designed to assess and quantify behavioural and psychiatric symptoms common in neurodegenerative disorders within the previous 4 weeks (Wear et al., 2008). Cognitively normal informants who know the participant well completed the CBI-R. Items were evaluated on a 5-point scale, from 0 to 4. A score of 0 suggests that there was no impairment, a score of 1 suggests that there was an occasional occurrence, i.e., a few times a month, 2 a repeated occurrence, where the symptom was present several times per week, 3 a daily occurrence, and 4 represents a constant occurrence. A score of 3 or 4 would denote a severe behavioral deficit (Wear et al., 2008). Of import to the current study is the sleep subscale of the CBI-R. The CBI-R sleep subscale contains two items that assess (1) sleep disruption during the night and (2) excessive daytime somnolence is the sleep subscale of the CBI-R which contains two items that assess (1) sleep disruption during the night and (2) excessive daytime somnolence. A composite score, ranging from 0 to 8 of these two items were used as the measure of sleep dysfunction in the present study (Wear et al., 2008).

4.3.3 Image Acquisition

Participants were recruited and scanned at a GENFI site. All participants underwent whole-brain 1.1-mm isotropic resolution volumetric T1-weighted (T1-w) magnetic resonance imaging. MRI scans were acquired using 3T scanner, or 1.5T should 3T not be available. Protocols were designed to harmonize across scanners and imaging sites as much as possible (Jonathan D. Rohrer et al., 2015). Volumetric T1-w MRI were acquired for 983 subjects. Acquisition parameters were as follows: slice thickness 1.1mm (1 to 1.2 mm), repetition time of 2000 ms (6.6 to 2400), echo time 2.9ms (2.2 to 9 ms), flip angle 8 deg. (8 to 11), number of slices 208 (140 to 208).

4.3.4 Raw Image Quality Control

Involuntary subject motion during MRI acquisition such as swallowing, blinking, cardiac, or respiratory movement can cause imaging artifacts, such as ringing or blurring, that can negatively impact the quality of the data (Bellon et al., 1986; Reuter et al., 2015; Zaitsev et al., 2015). Reduced image quality can bias derived cortical volumes and thickness estimates and reduce the reliability of these measures (Ducharme et al., 2016; Reuter et al., 2015). To control for these imaging artifacts, quality control of the raw images were assessed using the guidelines developed in the Computational Brain Anatomy (CoBrA) Laboratory (Bedford et al., 2020) (https://github.com/CoBrALab/documentation/wiki/Motion-Quality-Control-(QC)-Manual).

4.3.5 Preprocessing

Preprocessing of the raw T1-w images was completed using the minc-bpipe-library pipeline (https://github.com/CoBrALab/minc-bpipe-library) to improve image quality and standardize the images that were used as inputs to the volumetric and cortical thickness analyses. The minc-bpipe-pipeline allows supervision of each step through providing quality control

images at several preprocessing stages. The minc-bpipe-pipeline performed the following steps: (1) N4 bias field correction (Tustison et al., 2010), (2) registration of the image into Montreal Neurological Institute (MNI) space using beastlinereg (Collins et al., 1994; Dadar et al., 2018), (3) field-of-view standardization and brain orientation into MNI space using an inverse-affine transformation of an MNI space head mask, and (4) extraction of the brain using the BEaST technique (Eskildsen et al., 2012).

4.3.6 Cortical Thickness

Skull-striped preprocessed brains derived from the minc-bpipe-library pipeline were used as inputs into the CIVET 2.1.1 pipeline (https://www.bic.mni.mcgill.ca/ServicesSoftware/CIVET-2-1-0-Introduction). In brief, MR images were registered from native space to stereotaxic space through linear and affine registration using the average ICBM152 model as the target of registration. As images were already preprocessed and corrected for image inhomogeneities using minc-bpipe-library, N3 intensity normalization was not performed. Brain masks were then computed, and tissues were classified into three classes: cerebrospinal fluid, grey-matter, and white-matter. Brains were then split into the left and right hemispheres for surface extraction. Inner and outer cortical surfaces were extracted (Kim et al., 2005). The inner boundary is the grey/white matter interface, and the outer boundary is the pial surface. The tlaplace method was used to measure cortical thickness and resampled surfaces were spatially smoothed using a 30 mm blurring kernel. Outputs were quality controlled to ensure that the grey and white matter surfaces tissue classification and surface extraction were successful.

4.3.7 Volumetric measurement of the hypothalamus

The N4 bias field corrected preprocessed brains derived from the minc-bpipe-library were used as inputs for the hypothalamus segmentation. We used a convolutional neural network based automated hypothalamus segmentation algorithm (Billot et al., 2020) to obtain volumes in five hypothalamic subunits: anterior-inferior (suprachiasmatic nucleus and supraoptic nucleus), anterior-superior (preoptic area and paraventricular nucleus), posterior (mamillary body, posterior lateral hypothalamus, tuberomammillary nucleus), tubular inferior (infundibular nucleus, ventromedial nucleus, supraoptic nucleus, lateral tubular nucleus, tuberomammillary nucleus), and the tubular superior subunit (dorsomedial nucleus, paraventricular nucleus, anterior lateral hypothalamus). While manual segmentation is the gold standard for segmentation of the hypothalamus regarding segmentation accuracy, it is time consuming and exacting, rendering manual segmentation not scalable to larger datasets (Billot et al., 2020). As such, automated tools, such as the one used in the present project are useful for addressing these shortcomings. Compared to a sample of images manually segmented by an expert rater, the algorithm showed comparatively high Dice coefficient for the whole hypothalamus, as well as the posterior and tubular subunits (< 0.80) and moderate Dice coefficients for the anterior subunits (< 0.54) (Billot et al., 2020). These findings suggest, that while not as accurate as manual segmentation, this algorithm can provide reliable and accurate segmentation of the hypothalamus and its subregions. Left and right volumes, in mm^3, of the hypothalamus and the five subunits were extracted. Left and right volumes of each subunit were summed for subsequent analyses. Quality control, through visual inspection of the segmentations, was then performed to ensure that the hypothalamic subunits were adequately segmented.

4.3.8 CBI-R statistical analyses

Linear mixed-effects models (*lmer* from the *lme4* 1.1-14 package R 4.1.0) were used to test if there were differences in the trajectories of sleep disturbances across the lifespan, as measured by scores on the CBI sleep subscale, in carriers of genetic mutations causative of FTD compared to controls. This model (eq. 1) included genetic mutation status, the participant's age at visit (to account for mutation specific changes across the lifespan), as well as the interaction between these terms, and sex as fixed effects. Participant ID as well as family ID, to account for potential clustering effects based on family membership, were included in the model as random effects. To evaluate differences in the CBI-R sleep subscale between mutation carriers and controls, as a function of the estimated years to age of onset of symptoms, linear mixed-effects models were used. The model (eq. 2) included as fixed effects genetic mutation status, as well as the interaction between these terms, participant age at baseline, and sex as fixed effects. Participant ID and family ID were included in the model as random effects. These models, alongside the statistical models used for the hypothalamic analyses were corrected for multiple comparisons, using False Discovery Rate (FDR) with a threshold of $q \leq 0.05$ to control for the expected proportion of discoveries that are falsely rejected (Benjamini et al., 2001; Benjamini & Hochberg, 1995) and as such, we will be reporting q-values. Further, to confirm that these findings were not solely driven by symptomatic mutation carriers, additional analyses, conducted separately for presymptomatic and symptomatic mutation carriers relative to controls were performed.

*CBI-R Sleep ~ Sex + Genetic mutation status * Age at visit + (1|Id) + (1|Family ID) (eq. 1)*

*CBI-R Sleep ~ Sex + Age at baseline + Genetic mutation status * EYO + (1|ID) + (1|Family ID) (eq. 2)*

4.3.9 Cortical thickness statistical analyses

Vertex-wise linear mixed-effects models (*vertexLmer* from *RMINC_1.5.2.2* package from R 3.6.3) were used to model changes in cortical thickness (CTh) between mutation carriers and controls across the lifespan. This model (eq. 3) included genetic mutation status, age at visit, the interaction between these terns, and sex as fixed effects. Participant ID and scanning site, to control for scanning site specific effects, were included in the model as random effects. Due to non-convergence, family ID was omitted from the model cortical thickness models. The resulting maps were corrected for multiple comparisons using FDR with a threshold of ≤ 0.05.

*CTh ~ Sex + Age at visit * Genetic mutation status + (1|ID) + (1|Scanning site) (eq. 3)*

To examine how changes in cortical thickness related to measures of sleep disturbances, vertex-wise linear mixed-effects models were used. This model (eq. 4) included genetic mutation status, z-scored CBI-R sleep subscale scores, the interaction between the preceding terms, the participants baseline age, sex, and z-scored Mini Mental State Exam scores (MMSE), as a global measure of disease severity, as fixed effects. Random effects included the participant ID and scanning site.

*CTh ~ Sex + Age at baseline + MMSE + Genetic mutation status * CBI-R sleep + (1|ID) + (1|Scanning site) (eq. 4)*

4.3.10 Volumetric hypothalamus statistical analyses

To examine changes in hypothalamic volume over time in mutation carriers as compared to controls, linear mixed-effects models were used. Models (eq. 5) included genetic mutation

status, participants age at visit, the interaction between the preceding terms, sex, and total intracranial volume (TIV), to control for differences in brain size, as fixed effects. Random effects included participant ID and scanning site. Again, due to non-convergence, family ID as a factor was omitted from the volumetric models.

*Volume ~ Sex + TIV + Age at Visit * Genetic mutation status + (1|ID) + (1|Scanning site) (eq. 5)*

To examine if sleep dysfunction can be related to atrophy in the hypothalamus and its subunits in mutation carriers, linear mixed-effects models were used. Models (eq. 6) included genetic mutation status, z-scored CBI-R sleep subscale scores, the interaction between the preceding terms, baseline age, sex, z-scored MMSE, and TIV as fixed-effects. Random effects included participant ID and scanning site.

*Volume ~ Sex + Baseline age + MMSE + TIV + Genetic mutation Status * CBI-R sleep + (1|ID) + (1|Scanning site) (eq. 6)*

4.4 Results

4.4.1 Participants

From the 983 subjects with at least 1 T1-weighted MR image, scans from 130 participants were discarded due to poor image quality. A further 11 subjects were excluded as they had a rarer mutation causative of FTD (i.e., VCP or TBK-1). A further 14 participants were excluded due to MR image preprocessing failure, leaving 828 participants (scans = 1818). These scans were processed to obtain volumes in the hypothalamus and its subunits and for cortical thickness. 50 scans from 16 participants were excluded due to poor segmentation of the hypothalamus, leaving 812 participants (scans = 1768). These data were used for all behavioural and hypothalamic analyses. 795 participants (scans = 1735) were included for cortical thickness statistical analyses, due to 83 scans from 33 participants being excluded due to insufficient

quality surface extraction or tissue classification. A summary of this process can be found in figure 4.1. Details regarding demographic and clinical information of the samples can be found in tables 4.1 & 4.2.

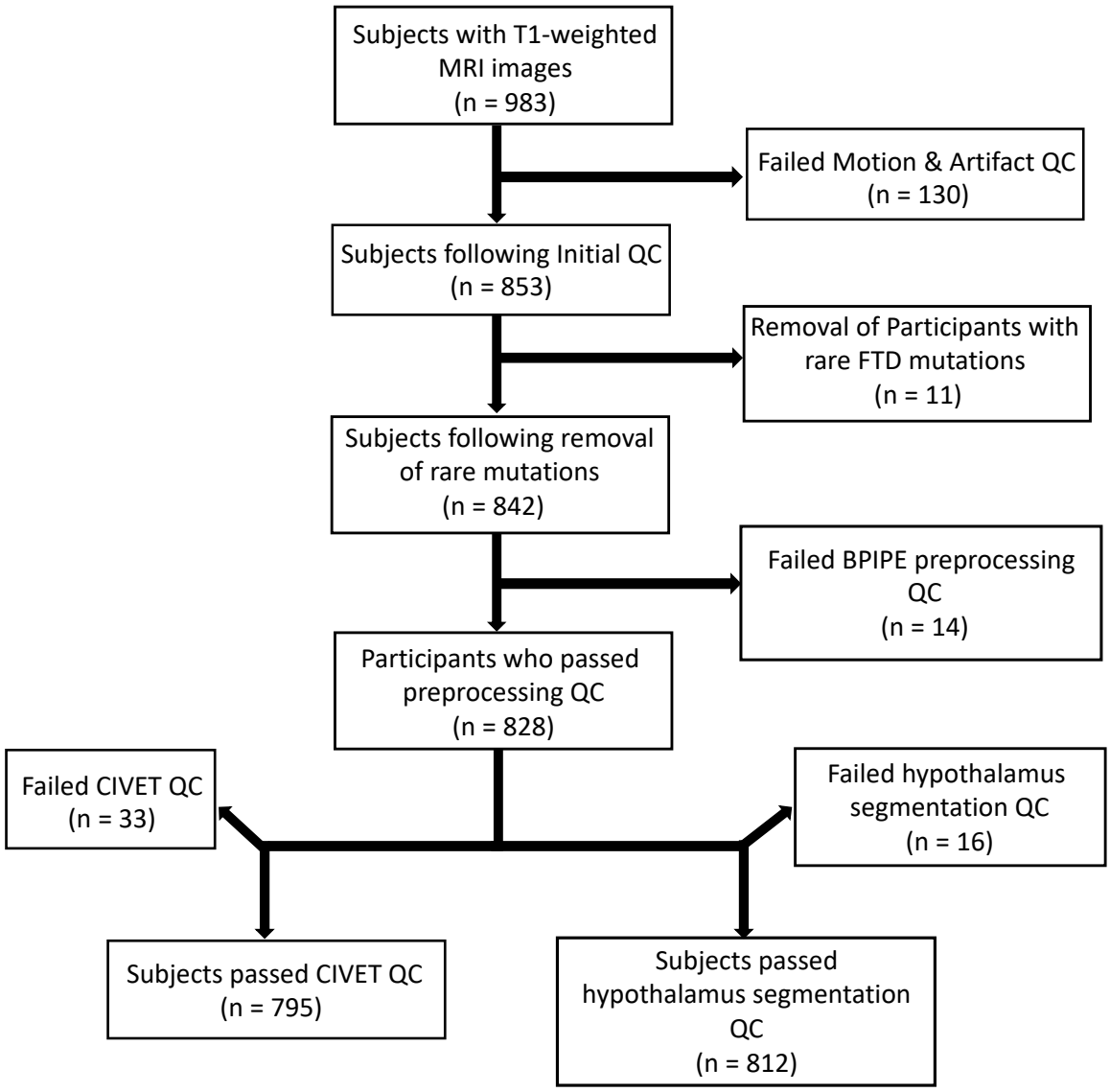

Figure 4.1. Flowchart describing participant selection process.

Table 4.1. Baseline demographic and clinical characteristics in mutation carriers and healthy controls used for behavioural and hypothalamus analyses.

Characteristic	Controls *N* = 321	*C9orf72* *N* = 209	*GRN* *N* = 196	*MAPT* *N* = 86
Symptomatic, No (%)	-	68 (32.5%)	46 (23.5%)	23 (26.7%)
Female Sex, No (%)	184 (57.3)	109 (52.2)	124 (63.3)	44 (51.2)
Age, y	45.9 (13.2)	50.3 (14.0)	50.0 (13.1)	45.0 (13.3)
Education, y	14.3 (3.53)	13.8 (3.38)	14.0 (3.71)	14.1 (3.24)
MMSE, M	29.4 (1.09)	27.4 (4.23)	27.6 (4.64)	27.9 (3.88)
Interscan interval, y	1.39 (0.64)	1.33 (0.55)	1.36 (0.61)	1.36 (0.63)
CBI Sleep	0.44 (0.98)	1.20 (1.90)	0.95 (1.64)	1.38 (1.90)

Values listed as means (standard deviations) unless otherwise specified.

Table 4.2. Baseline demographic and clinical characteristics in mutation carriers and healthy controls used for cortical thickness analyses.

Characteristic	Controls *N* = 323	*C9orf72* *N* = 191	*GRN* *N* = 193	*MAPT* *N* = 88
Symptomatic, No (%)	-	56 (29.3%)	41 (21.2%)	24 (27.3%)
Female Sex, No (%)	184 (57.0)	102 (53.4)	124 (64.2)	45 (51.1)
Age, y	45.5 (13.1)	49.0 (13.7)	49.3 (13.0)	44.7 (13.3)
Education, y	14.3 (3.52)	13.9 (3.18)	14.0 (3.69)	14.0 (3.34)
MMSE, M	29.3 (1.13)	27.7 (3.99)	28.0 (3.84)	28.1 (3.49)
Interscan interval, y	1.32 (0.53)	1.40 (0.69)	1.38 (0.62)	1.33 (0.58)
CBI Sleep	0.43 (0.97)	1.14 (1.84)	0.86 (1.50)	1.33 (1.79)

Values listed as means (standard deviations) unless otherwise specified.

4.4.2 CBI-R Sleep Analyses

Group comparisons on the CBI-R sleep subscale across the lifespan revealed significant differences between controls and all mutation carrier groups (*C9orf72,* $p = 1.86x10^{-4}$; *GRN,* q = 0.002; *MAPT*, q = 0.003) (figure 4.2). Increased age was significantly associated with increased sleep scores, suggesting greater sleep dysfunction, across all mutation carrier groups, with MAPT carriers exhibiting greater mean sleep scores across the lifespan. Furthermore, when examining the association between the CBI-R sleep subscale scores and expected age of onset interaction, all mutation carrier groups, relative to controls, showed an increase in sleep scores closer to the onset of symptoms ($q < 0.001$).

4.4.3 Cortical Thickness Analyses

Comparisons of all mutation carrier groups with controls reveals overlapping but differential patterns of cortical thinning over time (figure 4.3). *C9orf72* carriers showed significant and widespread thinning, relative to controls, across the cortex in the frontal, parietal, cingulate cortex, and temporal lobes. Further, we observe some bilateral occipital thinning, except in primary visual cortex. *GRN* carriers by contrast, showed thinning in frontal, parietal and superior temporal lobes, in particular the supramarginal and angular gyrus, as well as posterior cingulate cortex. *MAPT* carriers showed significant thinning in the temporal lobes, with some supramarginal gyrus involvement, alongside thinning in the dorsal prefrontal cortex, and anterior cingulate cortex.

1. A.

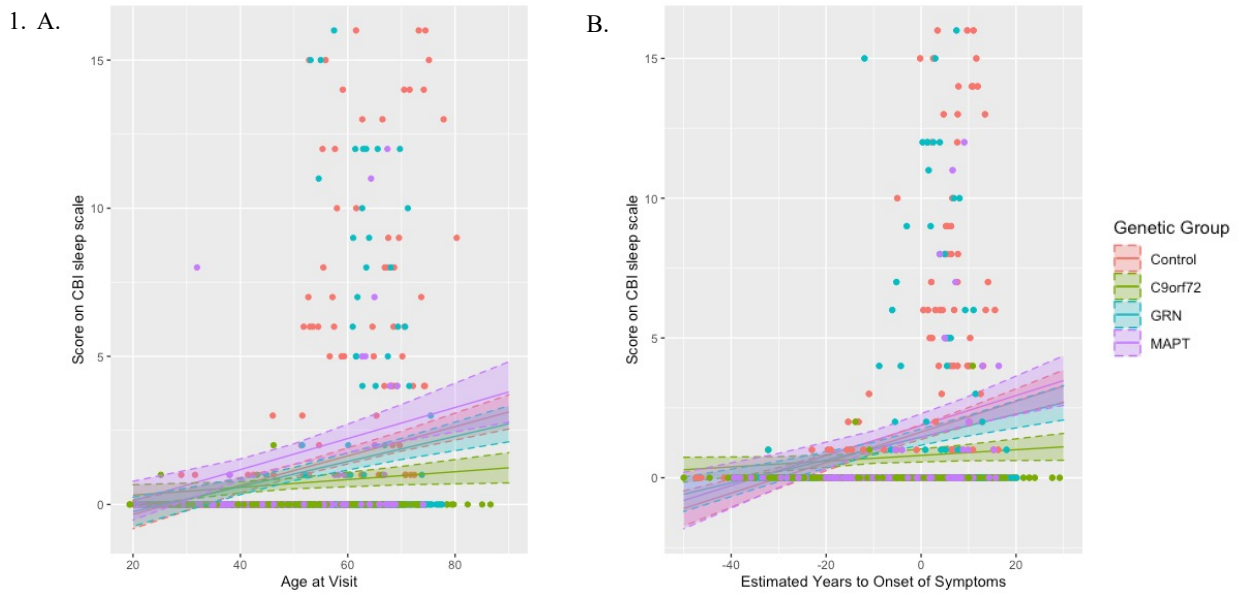

Figure 4.2. A. Scores on the CBI-R sleep subscale across the lifespan Model = CBI Sleep ~ Sex + Age at visit * Genetic Group + (1|Id) + (1|blinded family). B. Scores on the CBI-R sleep subscale as a function of estimated years to onset of symptoms. Model = CBI Sleep ~ Sex + Estimated Years to Onset * Genetic Group + (1|Id) + (1|blinded family). Dotted line-represents 95% confidence intervals.

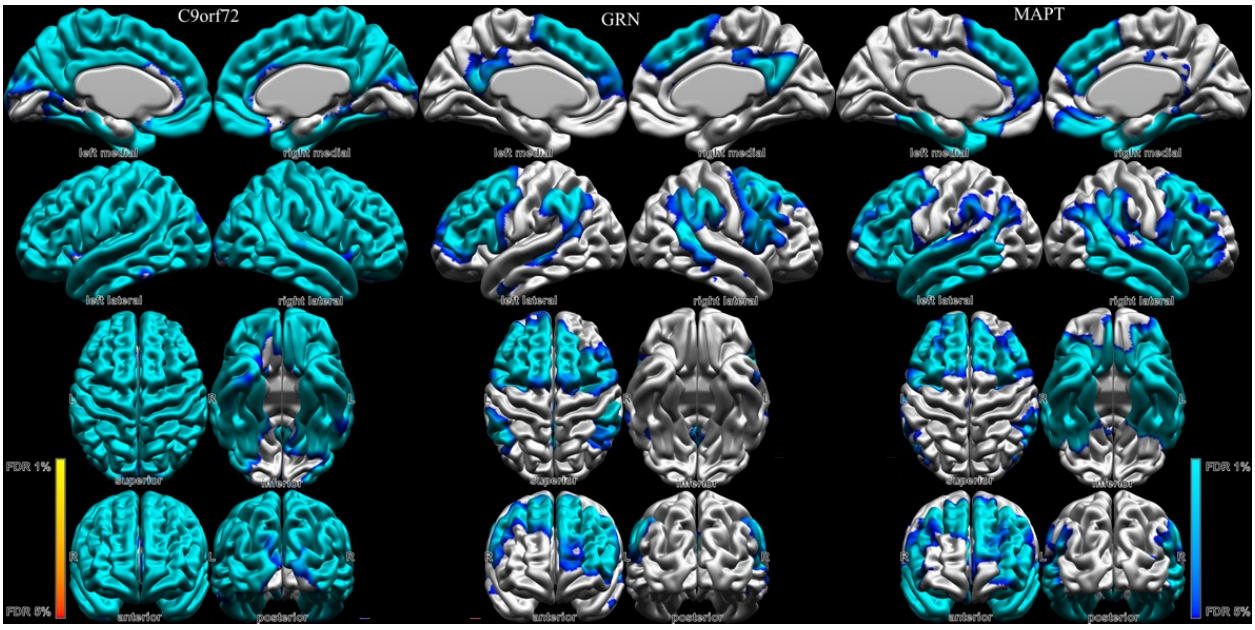

Figure 4.3. Cortical thinning patterns in C9orf72, GRN, and MAPT carriers over the lifespan compared to controls (FDR = False Discovery Rate, Model = CTh ~ Sex + Age at Visit * Genetic Group + (1|Id) + (1| Scanning Site)).

4.4.4 Hypothalamus Analyses

Group comparisons of hypothalamic volumes across the lifespan in mutation carriers compared to controls revealed significant differences between mutation carriers and controls. These results are presented in figure 4.4. There were significant differences in the trajectories of bilateral hypothalamic volumes in all mutation carrier groups when compared to controls that survived corrections for multiple comparisons. Trajectories of volume loss in the anterior superior subunit were significantly reduced in both *C9orf72* and *MAPT* mutation carrier groups ($qs < 0.001$), however the differences in *GRN* mutation carriers were not significant ($q = 0.085$). Similar to the anterior superior subunit, trajectories of the volumes in the anterior inferior subunit were significantly reduced in *C9orf72* ($q = 0.028$) and *MAPT* mutation carriers ($q < 0.001$) as compared to controls. Again, there were no significant differences between the trajectories of *GRN* mutation carriers and controls ($q = 0.319$). The trajectories of posterior subunit volumes ($qs < 0.001$) and superior tubular subunits ($qs < 0.005$) were significantly reduced in all mutation carrier groups as compared to controls. In contrast with other subunits, trajectories of volumes in the inferior tubular subunit, in *C9orf72* and *MAPT* mutation carriers were not statistically different from controls ($q > 0.05$), while the trajectories of volumes in *GRN* carriers increased in volume when compared to controls ($q = 0.013$).

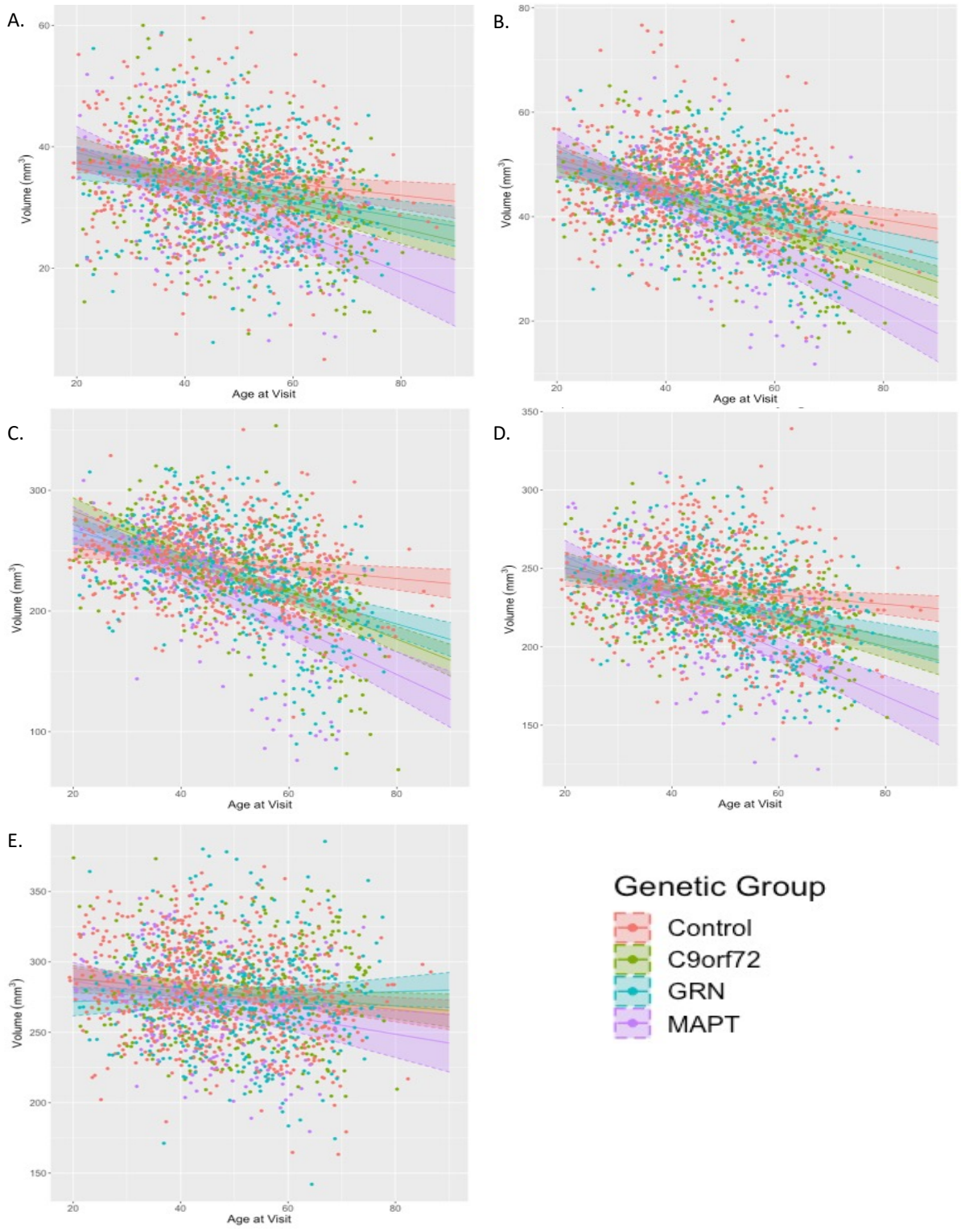

Figure 4.4. Volumes across the lifespan superior tubular region volume across the lifespan. A. Anterior Inferior B. Anterior Superior C. Posterior D. Superior Tubular E. Inferior Tubular. Dotted line-represents 95% confidence intervals. Models = Vol ~ Sex + Total Intracranial Volume + CBI-R Sleep * Genetic Group + (1|Id) + (1|Scanning site).

4.4.5 Neural Correlates of CBI-R Sleep Scores

Associations between cortical thinning and scores on the CBI-R sleep scale are described in figure 4.5. In brief, greater scores on the CBI-R sleep scale, indicative of greater sleep dysfunction, are associated to increased atrophy in *C9orf72* carriers in the left prefrontal, parietal, posterior cingulate cortex, and lateral temporal lobe, alongside some right prefrontal involvement. In *GRN* mutation carriers, greater scores on the CBI-R sleep scale are associated with cortical thinning in right posterior frontal lobe, parietal lobe and with some posterior temporal lobe involvement. There were no significant associations between sleep measures and cortical thinning in *MAPT* mutation carriers.

Figure 4.6 describes associations between hypothalamic volumes and scores on the CBI-R sleep scale. In brief, *MAPT* mutation carriers showed trends of associations that approached significance between anterior-inferior volumes and scores on the CBI-R sleep scale, with greater scores being associated with reduced hypothalamic volumes ($q = 0.06$). This association was not significant in *C9orf72* or *GRN* mutation carriers. Further, both *C9orf72* and *MAPT* carriers, had significant associations between volumes in the superior tubular region and scores on the CBI-R sleep scale, where, again, lower volumes were associated with greater CBI-R sleep scores ($q = 0.002$ and $q = 0.021$ respectively). Greater CBI-R sleep scores were associated with reduced volumes in the posterior hypothalamic subunit across all mutation carrier groups ($q < 0.003$). Lastly, there were no significant associations between anterior-superior subunit or tubular-inferior subunit volumes and score the CBI-R sleep scale that survived correction for multiple comparisons.

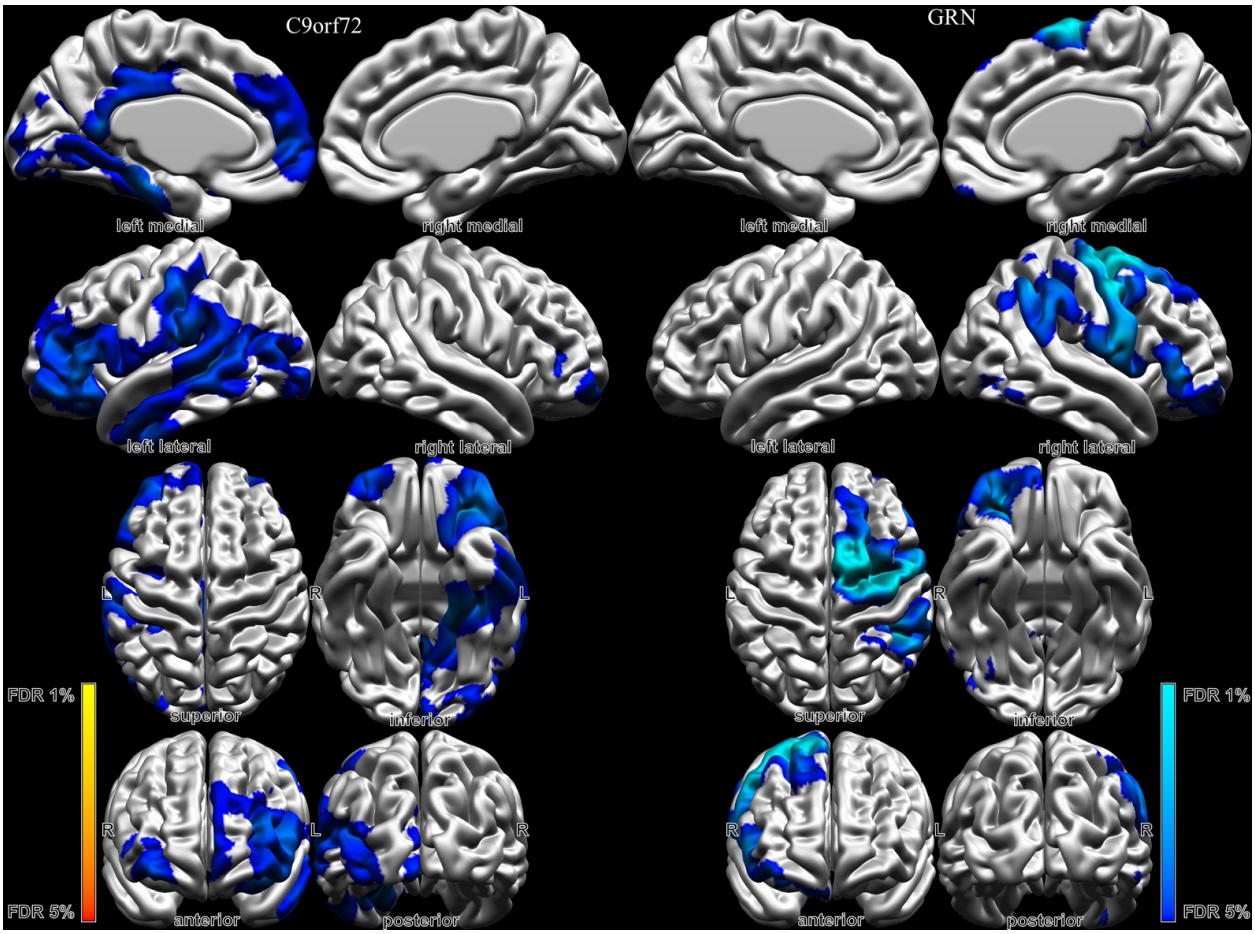

Figure 4.5. Cortical thinning patterns associated with increased CBI R sleep subscale scores in C9orf72 and GRN carriers compared to controls (FDR = False Discovery Rate, Model = CTh ~ Sex + Age at Visit + MMSE + CBI-R Sleep * Genetic Group + (1|Id) + (1| Scanning Site)).

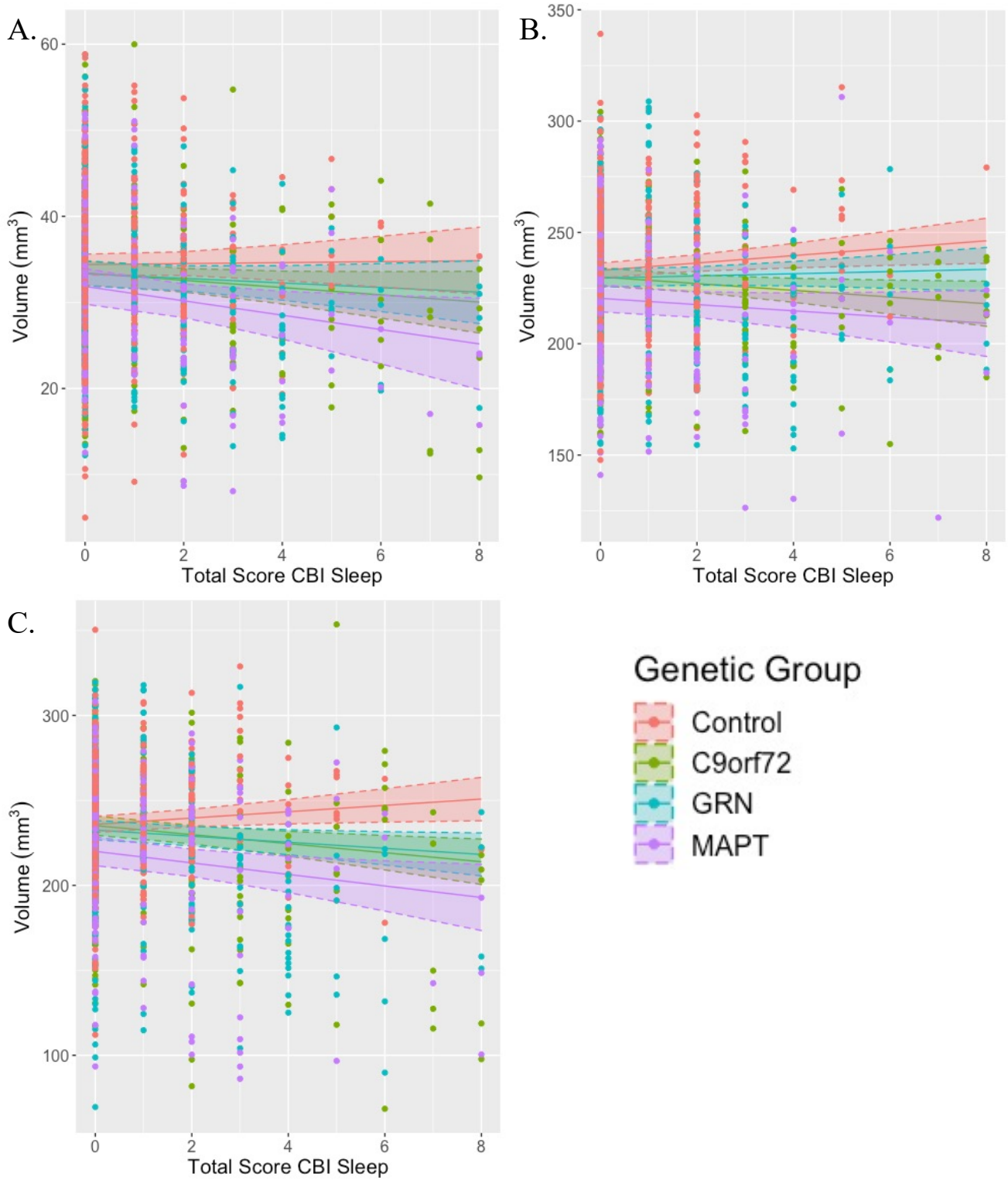

Figure 4.6. Association between hypothalamic region and scores on the CBI-R sleep subscale. A. Anterior inferior region B. Superior tubular region C. Posterior region. Dotted line represents 95% confidence intervals. Models = Volume ~ Sex + Age at visit + Total Intracranial Volume + MMSE + CBI R sleep subscale * Genetic Group + (1|Id) + (1| Scanning Site).

4.5 Discussion

The main findings of this project were threefold. First, we observed an increase in the prevalence and severity of sleep disturbances across the lifespan across all mutation carrier groups, with *MAPT* carriers having the most severe symptomatology. Further, these differences between carriers and non-carriers may begin years before the estimated onset of clinical symptoms. Second, we found significant differences in patterns of cortical thinning between mutation carriers and controls (figure. 4.2) alongside differences in the trajectories of hypothalamic volumes. *MAPT* carriers in particular, showed pronounced volume differences across all hypothalamic subunits, save for the tubular inferior region. Lastly, measures of sleep dysfunction were correlated to cortical thinning in frontal, parietal, and temporal lobes, however, this was limited to *C9orf72* and *GRN* mutation carriers. Further, reduced hypothalamic volumes were related to sleep dysfunction in both *C9orf72* and *MAPT* carriers, with *MAPT* carriers showing the strongest associations.

Our results indicate a differing evolution of sleep dysfunction across the lifespan in all mutation carrier groups compared to controls. As expected, we observed increased sleep disturbances as participants aged across all mutation carrier groups, with increases in sleep symptomatology closer to the predicted onset of clinical symptoms, regardless of mutation type. Further, following symptom onset, all mutation carrier groups showed increased sleep dysfunction relative to controls. Importantly, sleep dysfunction was more frequent and more severe in *MAPT* carriers as compared to other mutation carriers and controls. Moreover, we found that *MAPT* carriers alone exhibited greater sleep dysfunction than controls prior to the onset of clinical symptoms. This finding was in line with our expectations based on past work that found that *MAPT* mutations were associated with adverse sleep symptomatology both in

symptomatic and pre-symptomatic carriers (Gemignani et al., 2005; Spector et al., 2011; Tavares et al., 2020), corroborating previous suggestions that sleep dysfunction may be more salient in MAPT carriers. Findings in prior studies have indicated that symptomatic *C9orf72* carriers may have increased sleep symptomatology (Sani et al., 2019), namely frequent disruptive sleep events, such as shouting or otherwise acting out dream content, not observed in other mutation carrier groups. Our findings cannot speak to this result, as our measure of sleep disturbance was comprised solely of an assessment of daytime somnolence and sleep disruption during the night. As such, *C9orf72* carriers may have other disruptive sleep symptomatology not captured in the present study, such as REM sleep disorder (Daoud et al., 2014). Thus, continued work on sleep dysfunction in genetic mutations causative of FTD should seek to address a wider spectrum of negative sleep disturbances.

Significant changes in cortical thickness were observed across the spectrum of mutation carrier groups, however the spatial distribution of these changes differed greatly between mutation carrier groups (Fig. 4.3). Namely, *C9orf72* carriers exhibited widespread changes across the cortex. *GRN* carriers, in contrast, showed bilateral parietal lobe thinning including thinning of the caudal cingulate, alongside asymmetric dorsal frontal lobe thinning, and some lateral temporal involvement. *MAPT* carriers displayed cortical thinning in the frontal lobes, including the anterior cingulate cortex alongside widespread temporal lobe atrophy with limited parietal involvement. These patterns of cortical thinning were overall unsurprising and reflected patterns of cortical atrophy commensurate with previous work (Cash et al., 2018; Convery et al., 2019; Rohrer & Rosen, 2013).

We found significant differences in the trajectories of the volumes of the hypothalamus and its subunits, with significantly reduced volumes being observed in the majority of measured

subunits across the lifespan in mutation carriers as compared to controls (Fig 4.4). Including subunits which contain nuclei (i.e., the SCN and LHA) relevant to the regulation of sleep and wakefulness. *MAPT* mutation carriers, in particular, showed the greatest volumetric changes across these subunits. This finding is line with previous work, which has found reduced hypothalamic volumes in symptomatic *MAPT* carriers in anterior and posterior regions, when compared to other mutation carrier groups (Bocchetta et al., 2015; Bocchetta Todd, et al., 2021). Interestingly, histopathological work in bvFTD found that subjects with tau pathologies had greater abnormal protein deposition in the hypothalamus as compared to those with TDP-43 pathologies, though mutation status was not specified. Further, they found increased atrophy and neuronal loss in these regions, (Piguet et al., 2011) suggesting tau pathology, as seen in *MAPT* carriers, may differentially impact hypothalamic integrity. Additionally, another study had found no TDP-43 deposition in the SCN in *C9orf72* expansion carriers, however, dipeptide repeat protein inclusions were observed, suggesting a differential mechanism of hypothalamic atrophy unique to *C9orf72* carriers. The inferior tubular subunit, the sole preserved region in this study, has previously been shown to be preserved in bvFTD, in both sporadic bvFTD and when associated to *MAPT* mutations and *C9orf72* expansions(Bocchetta et al., 2015). Though it has been shown to be implicated later in the disease course in *MAPT* mutation carriers (Bocchetta Todd, et al., 2021). Further in vivo imaging combined with ex vivo histopathological work would be useful to elucidate the differential mechanistic underpinnings of the observed hypothalamic atrophy.

We observed a significant association between cortical thinning and sleep symptomatology in *C9orf72* expansion carriers and *GRN* mutation carriers, however, not in *MAPT (Fig. 4.5)*. Adverse sleep symptomatology, e.g., poor sleep quality and reduced sleep

duration, has previously been associated with atrophy patterns largely overlapping with the observed patterns in *GRN* mutation and *C9orf72* expansion carriers (Sexton et al., 2014; Spira et al., 2016), namely, in medial and lateral prefrontal cortex. The frontal cortex is suspected to be one of the key regulatory structures in the of non-REM sleep (Muzur et al., 2002). Reduced slow wave activity during non-REM sleep has also been associated to structural changes frontal medial frontal cortex and this may be driven by reduced frontal lobe-hippocampal connectivity (Mander et al., 2013). The current study cannot speak to this hypothesis and thus future work should seek to encompass a wider spectrum of subcortical structures in their analyses to address this lingering question. The absence of association between CTh and CBI-sleep in *MAPT* carriers was unexpected as *MAPT* carriers endorsed the most severe sleep symptomatology and showed cortical thinning in regions previously shown to be related to sleep disturbances, namely the medial prefrontal cortex, anterior cingulate cortex, and anterior medial lobes (Ahmed et al., 2021; Mander et al., 2013; Sexton et al., 2014). This discrepancy may suggest that the sleep symptomatology observed in *MAPT* carriers may be driven by hypothalamic alterations.

Of interest, we observed significant associations between hypothalamic structure and our measure of sleep dysfunction, however, this was only consistent in *C9orf72* and *MAPT* carriers (Fig. 4.6). Importantly, the three hypothalamic subunits, posterior, anterior inferior, and superior tubular, containing nuclei important to the regulation of sleep and wakefulness, i.e., the SCN and LHA(Hastings et al., 2018; Moore, 2007; Yamashita & Yamanaka, 2017), were significantly correlated with sleep disturbances. Further, subunits in which we expected no association with sleep dysfunction (i.e., anterior-superior), were not significantly related to sleep disturbances. These findings, taken together, suggests that structural changes in the SCN and LHA may be driving the adverse sleep symptoms observed in these mutation carriers. This is further

corroborated through *MAPT* mutation carriers exhibiting the greatest hypothalamic atrophy as well as the most severe sleep symptomatology. Interestingly, atrophy in the posterior subunit of the hypothalamus, which contains the posterior regions of the LHA, was significantly associated with sleep dysfunction across all mutation carrier groups. This may suggest a role of the orexigenic neurons in sleep symptomatology in mutation carriers. Reduced orexin A levels in plasma and CSF have previously been associated to sleep disturbances in sporadic FTD (Çoban et al., 2013; Liguori et al., 2014). Lastly, orexin has been a neuropeptide of interest in regards to sleep in FTD (Hwang et al., 2020; Warren & Clark, 2016). It is hypothesized that orexin dysregulation may impact not only sleep function but may also instigate downstream alterations in other neurotransmitter pathways known to be effected in FTD and may contribute to other symptomatology in this disorder (Hwang et al., 2020). As such, these findings highlight the need for more in-depth research on orexigenic systems in FTD related mutation carriers.

We acknowledge that there are limitations to the present study. First, the CBI-R sleep subscale provides a limited and aggregate assessment of sleep dysfunction derived from informant report rather than objective measures such as polysomnography or actigraphy. The CBI-R sleep subscale, as previously described (Wear et al., 2008), provides a combined and subjective assessment of sleep disruption during the night and excessive daytime somnolence. Given the limited nature of the behavioural assessment for the present study, future projects should aim to assess objective measures of sleep dysfunction in this population. Additionally, further work should seek to disentangle the relationships between other sleep disturbances that have previously been observed in FTD, such as sleep disordered breathing, REM sleep behaviour disorder (RBD), or alterations in circadian rhythms (McCarter et al., 2016), and their potentially distinct neural correlates in FTD-related mutation carriers.

Additionally, it is important to note that the present study contained a limited number of *MAPT* mutation carriers, representing 11% of the sample. It is expected that, given that *MAPT* mutations appear to be the least frequently observed worldwide (23.2%) compared to *GRN* mutations (34.6.1%) and *C9orf72* expansions (42.1%) (Moore et al., 2020), fewer individuals with *MAPT* mutations would be included in the sample. As such, future work, with a larger sample of *MAPT* mutation carriers would be needed to confirm the observations made in the present study.

Lastly, although we have examined volumetric change in individual subunits of the hypothalamus, but not their multiple nuclei due to the limitations of structural MR imaging, structural change of individual nuclei was outside of the scope of this study. The hypothalamus is comprised of a number of cytoarchitectonically distinguishable nuclei, within a very small structure, roughly 4 cm^3 and accounting for 0.3% of the human brain (Hofman & Swaab, 1992). As such, imaging and subsequent segmentation of these nuclei is outside of the purview of the present study. This methodological limitation could be addressed in future studies, through imaging these structures at a higher field strength (e.g., 7T), allowing for better spatial resolution as well as integrating the high-definition MR imaging with post-mortem histological analysis of these subunits.

In summary, this study shows that hypothalamic structure is involved in sleep dysfunction in FTD related mutation carriers. We have shown that sleep dysfunction is common across mutation carrier groups, however, may be more severe *MAPT* mutation carriers, and increases closer to the onset of clinical symptoms. While cortical thinning in *C9orf72* and *GRN* mutation carriers non-specifically correlate with increased sleep dysfunction, the increased severity of sleep dysfunction observed in *MAPT* carriers may be attributable to increased

hypothalamic atrophy. This study would be the first to specifically examine sleep dysfunction in FTD-related mutation carriers. Moreover, we would be the first to provide evidence that underlying neurodegenerative changes in the hypothalamus relate to this sleep dysfunction in those with these mutations. This, in turn, may inform the neurobiology of sleep disturbances in other related neurodegenerative disorders such as AD and Parkinson's Disease where sleep disturbances are common (Cipriani et al., 2015).

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Chapter 5 - Discussion

5.1 Summary of main findings and Implications

This thesis sought to better understand the progression and underlying neural correlates of symptoms that, although are not the core features of genetic FTD, contribute significantly to patient distress. More precisely, we used longitudinal structural MRI images, from presymptomatic and symptomatic subjects with FTD-related mutations derived from a large-scale study (GENFI) to explore progressive changes in brain structure and their relation to symptoms typically not thought to be core to FTD pathophysiology.

In chapter 3, we examined the relationship between longitudinal whole brain structural changes and changes in psychiatric symptoms such as depression, anxiety, as well as auditory and visual hallucinations. We found longitudinal, mutation specific, patterns of structural change. Moreover, using a novel longitudinal multivariate statistical method, we related these changes to progressive changes in behavioural and psychiatric symptoms. In summary, despite relatively few neuroanatomical changes, *C9orf72* expansion carriers showing greater behavioural and psychotic symptoms features. *GRN* carriers in contrast, showed atrophy, largely in white matter, being related to worsening behavioural and mood symptoms. Lastly, in *MAPT* carriers, we observed changes in medial prefrontal and temporal cortices alongside medial temporal subcortical structures, that resulted in worsening behavioural symptoms, with a particularly amnestic phenotype.

In chapter 4, we focused on sleep disturbances, such as insomnia and increased daytime somnolence, another atypical symptom commonly observed in genetic FTD. We explored the role of neurodegeneration in sleep critical nuclei of the hypothalamus and their relation to sleep

dysfunction. We found a more severe sleep phenotype and increased hypothalamic atrophy in *MAPT* mutations relative to other mutation carriers. Moreover, we observed a significant relationship between sleep dysfunction and volumes in hypothalamic subunits critical to the regulation of sleep and wakefulness, that were strongest in *MAPT* carriers.

Inclusively, the analyses presented in this thesis emphasize the need to better understand the trajectory of mutation specific changes in neuroanatomical structure, including structures often ignored in neuroimaging research, such as the cerebellum, subcortical structures, and white matter. Further, we highlight the critical role of these structures in how they may relate to behavioural and psychiatric symptom profiles in genetic FTD. Our findings provide critical evidence for the importance of these structures and underscore the need for continued investigation into the dynamics of FTD-related mutation derived neurodegeneration and their symptomatic outcomes.

The investigations presented in this thesis also highlight the difficulties in analysing multifaceted, heterogeneous diseases, as well as the limitations of the current dataset. Given that a large proportion of the subjects in our analyses were presymptomatic, who may be decades away from the onset of symptoms, we would expect subtle neuroanatomical alterations which would remain difficult to detect. Despite these limitations, however, we were able to observe mutation specific brain changes which related to specific symptom profiles. Future work, however, would benefit from the inclusion of a wider spectrum mutation carriers, including additional symptomatic individuals.

5.2 Future Directions

5.2.1 Identifying early life changes in genetic FTD

In this thesis, we have largely focused on mutation carriers in adulthood, however there is reason to believe that these genetic mutations, present prior to birth, and which lead to alterations in neuroanatomy at mid- to late-life, may have an impact on neurodevelopment in early life. Recent evidence from another monogenic neurodegenerative disorder, namely Huntington's Disease (HD), has found significant abnormalities in developing human fetus brain carrying the mutant gene (Barnat et al., 2020). HD is caused by a mutation in the Huntingtin gene (HTT) located on the 4th chromosome (McColgan & Tabrizi, 2018). These neurodevelopmental abnormalities included defects in neuroprogenitor cells, abnormal ciliogenesis, and changes in mitosis and cell cycle progression (Barnat et al., 2020). Similar findings were observed in embryonic mouse models of HD (Barnat et al., 2017). Others have found subtle, albeit significant alterations in normal development and intracranial volumes in HD-related mutation carriers as young as age 7 (Lee et al., 2012; Nopoulos et al., 2010). Taken together, these findings suggest a neurodevelopmental profile in HD, however, little is known whether neurodevelopmental alterations occur in another monogenic neurodegenerative disease, such as genetic FTD.

Interestingly, recent work in zebrafish, has suggested that *C9orf72* regulates neurogenesis and apoptosis. Further *C9orf72* protein deficiencies may lead to impacted axon formation and spinal motor activity (Yeh et al., 2018). These findings may suggest a neurodevelopmental profile in genetic FTD. To date, however, no work has been done in humans regarding the neurodevelopmental changes in utero or in early life when the brain is developing. Recently, there have been calls for the consideration of *C9orf72* expansions to be considered a

neurodevelopmental disorder (Bede et al., 2020), however, there have been no explicit studies that have investigated neurodevelopmental changes in youth with FTD-related mutations.

An exciting new research paradigm, using brain charts across the early lifespan (Bethlehem et al., 2022), may be an optimal way of approaching this subject. In brief, brain charts can be thought of like normative growth charts for anthropometric features such as height and weight, where individual comparisons can be made against standardized norms of development. Instead of tracking the development of anthropometric features, however, one would track, using MRI based metrics, the trajectory of neuroanatomical structures, such as cortical thickness, surface area, or volumes (Bethlehem et al., 2022). Using this paradigm, one could track the trajectory of FTD-related mutation carriers from a young age relative to normative brain growth models to detect any subtle deviations in neuroanatomical structure. Given this prospect, future work should seek to elucidate any potential early life changes caused by FTD-related mutations and how they may contribute to the mid- to late-life neurodegenerative processes. This research would provide valuable clues into, not only, the progression of neurodevelopmental changes caused by FTD-related mutations but may also provide valuable insight into the structural changes that directly precede the onset of symptoms.

5.2.2 Identifying interventions for atypical symptoms in genetic FTD

It remains important to consider the clinical implications of the analyses presented in this thesis. Knowledge of the patterns of behavioural and neuropsychiatric symptoms as well as their neural correlates is pertinent information, which may help inform translational research and guide the expectations of physicians, patients, and caregivers alike in how these symptoms may evolve over time. Although psychotic symptoms have severe implications for patients and caregivers alike, they have consistently been found to be treatment resistant in *C9orf72*-related

FTD (Ducharme et al., 2017). Treatments for sleep dysfunction, however, remain an exciting prospect that may be of particular benefit to individuals with *MAPT* mutations. Recent work has examined targeted intervention in the orexin system in narcolepsy/cataplexy syndromes, with replacement and supplementation being a promising model (Nepovimova et al., 2019).

Given our findings, discussed in Chapter 4, orexin replacement therapies may be a promising treatment for those with sleep dysfunction in genetic FTD. These treatments may be particularly useful in *MAPT* mutation carriers, where hypothalamic changes were more pronounced. Although this remains to be tested clinically, our work also suggests that orexin receptors agonist medications such as lemborexant or suvorexant could have a role to treat neuropsychiatric symptoms in FTD (Kuriyama & Tabata, 2017; Scott, 2020). Interestingly, some have proposed that sleep dysfunction may be integral to the pathogenesis of FTD and a key driver of neurodegeneration (Warren & Clark, 2017). In brief, they posited that the disruption of restorative and reparative sleep processes due to sleep dysfunction, could lead to a vicious cycle where sleep dysfunction would lead to increasing neuronal cell death, which in turn would lead to increased sleep dysfunction. Therefore, treatment of sleep dysfunction early in the disease course may be beneficial, not only to treat the symptoms, but may also serve to slow the progression of neurodegeneration. As such, future work to elucidate the interplay between treatments for sleep dysfunction and slowing neurodegeneration would, should one exist, be beneficial.

5.3 Limitations

5.3.1 Clinical phenotypic variation within genetic FTD

In this thesis, we have largely considered, symptomatic individuals with FTD-related mutations to be largely homologous. There is however, as previously stated, considerable

heterogeneity regarding the presenting clinical manifestations of genetically derived FTLD. While behavioural variant FTD (bvFTD) is the most common clinical presentation across mutation types, all phenotypes within the FTD spectrum can be observed (Greaves & Rohrer, 2019). The presenting phenotype typically observed, however, varies by mutation. *C9orf72* expansions, can rarely cause primary progressive aphasias (PPA), and are the sole cause of ALS (Amyotrophic lateral sclerosis) or the combined phenotype FTD-ALS. *GRN* mutations conversely, tend to cause PPA, often the non-fluent variant (Rohrer et al., 2010). PPAs are rare, however, in *MAPT* mutations, who tend to exhibit more motor presentations such as corticobasal syndrome (CBS) or progressive supranuclear palsy (PSP) (Greaves & Rohrer, 2019). The presenting phenotypes of the symptomatic subjects in the studies presented in this thesis, are consistent with these findings.

Using the sample from Chapter 4 as an example, 67.9% of symptomatic *C9orf72* carriers had a presenting diagnosis of bvFTD, 7.3% had a diagnosis for ALS, and 12.8% had a diagnosis for the combined phenotype FTD-ALS, with the remainder having a differing diagnosis (typically dementia-not otherwise specified or PPA). Conversely, *MAPT* carriers were overwhelmingly presenting with bvFTD, accounting for 93.6% of carriers, with the remainder being CBS or PPA. Lastly, *GRN* carriers, exhibited significant phenotypic variability, with bvFTD and PPA accounting for 41.1% and 43.8% respectively, and the remainder being scattered between CBS, Dementia NOS, among others. Given the phenotypic variability observed in both the literature and in our samples, it remains important to consider our findings in light of these features and their implications for where early neurodegeneration may be occurring. As such, future work would benefit from accounting for this variability in order to

disentangle the relationships between underlying genotype, presenting clinical phenotype, and how these may interact to influence atypical symptom profiles in genetic FTD.

5.3.2 Intra-mutational differences in genetic FTD

Potentially underlying the variation in the presenting clinical phenotypes are considerable intra-mutational difference in each FTD-related genetic mutation. In this thesis, although we have focused on inter-mutational differences in pathophysiology and clinical profiles in genetic FTD, we have not considered the variation within each mutation that may have an impact on phenotypic outcomes. There are, to date, at least 114 and 63 identified pathogenic mutations that cause FTLD in *GRN* and *MAPT* mutations respectively (Greaves & Rohrer, 2019). Moreover, these mutations have exhibited differential pathological and phenotypic outcomes (Redaelli et al., 2018; Strang et al., 2019; van Swieten & Heutink, 2008). Likewise, in *C9orf72* mutations, the expansion length of the pathogenic G_4C_2 repeat expansion has been suggested to be a potential moderating factor in neuropsychiatric features (Ng & Tan, 2017) and clinical phenotype (Van Mossevelde et al., 2017), although findings have been conflicting and are largely based on small sample sizes.

In all mutations, despite variability in mutation type or length of the pathogenetic repeat expansion, neural loss and atrophy occurs (Murphy et al., 2017; Strang et al., 2019; Wauters et al., 2017). The path to this outcome, however, may differ. Strikingly similar clinical and neuroimaging features have been observed in monozygotic twins carrying a *GRN* mutation (McDade et al., 2012), however, a cohort of 30 families carrying the Arg493X nonsense GRN mutation found considerable variation in clinical presentations and a 25-year range of age of onset (Rademakers et al., 2007). These findings, taken together, may suggest that these genetic mutations alone may not be sufficient to account for phenotypic variability, but their interactions

with the wild-type and other genes may also play a significant role. Given the complexity of the problem, research on the topic of genetic variability within FTD-related mutations is in its infancy. However, this intra-mutational genetic variability may play a key role in elucidating the phenotypic variation observed in genetic FTD. Future work should seek to address variability within mutations to further our understanding of intra-mutational differences in genetic FTD, and their potential moderating effects on phenotypic presentation.

5.4 Conclusions

In summary, this thesis sought to characterize the mutation specific progression of neuropsychiatric and behavioural symptom profiles in FTD-related mutation carriers. Moreover, we sought to better understand the neuroanatomical underpinnings of these adverse symptoms through the application of univariate and multivariate analyses using MRI imaging data derived from a large-scale, multi-site, longitudinal study. The analyses presented here have provided strong evidence for mutation specific trajectories of atrophy across the brain, while highlighting the associations between these patterns of change and atypical symptom profiles in genetic FTD.

The work presented in Chapter 3 represented the first longitudinal examination of the relationship between neuroanatomical changes and changes in behavioural and neuropsychiatric symptoms in genetic FTD. Moreover, the work presented in Chapter 4 represented the first thorough characterization of the trajectory of sleep dysfunction across the lifespan as well as their neural underpinnings of this dysfunction in genetic FTD.

Overall, the results described in this thesis contribute to our understanding of the neural correlates of symptom profiles, that though are not at the core of FTD, may have a distinctive, and outsized impact on the wellbeing of patients and caregivers alike.

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