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Neuroimaging in genetic frontotemporal dementia and amyotrophic lateral sclerosis

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Abstract

Frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) have a strong clinical, genetic and pathological overlap. This review focuses on the current understanding of structural, functional and molecular neuroimaging signatures of genetic FTD and ALS. We overview quantitative neuroimaging studies on the most common genes associated with FTD (*MAPT*, *GRN*), ALS (*SOD1*), and both (*C9orf72*), and summarize visual observations of images reported in the rarer genes (*CHMP2B*, *TARDBP*, *FUS*, *OPTN*, *VCP*, *UBQLN2*, *SQSTM1*, *TREM2*, *CHCHD10*, *TBK1*).

Keywords

frontotemporal dementia; amyotrophic lateral sclerosis; motor neuron disease; presymptomatic; genetics; neuroimaging

1 INTRODUCTION

Frontotemporal dementia (FTD) is a clinically heterogeneous group of neurodegenerative diseases characterized by early prominent changes in behavior and/or language accompanied by focal atrophy in frontal and temporal cortices. In contrast, amyotrophic lateral sclerosis (ALS) involves progressive degeneration of both upper and lower motor neurons, leading to progressive muscle weakness, and paralysis. Despite these distinctions in clinical presentation, the clinical, genetic, and pathological overlap between FTD and ALS has been well established, framing these diseases as part of a continuum. Clinically, 15% of patients with FTD develop motor neuron disease, and conversely, most patients with ALS develop increasing cognitive and behavioral deficits as their disease progresses (Burrell et al., 2011; Crockford et al., 2018; Lomen-Hoerth et al., 2002). Certain genetic variants such as the *C9orf72* expansion and mutations in *TBK1*, *VCP*, and *TARDBP* are known to cause FTD,

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ALS, or both, whereas other genetic mutations are predominantly associated either with FTD or ALS (Fig. 1; Nguyen et al., 2018).

Because mutation-specific therapies are currently undergoing human clinical trials for genetic FTD and ALS, determining the neuroanatomical regions and selective cell populations that are targeted in each genetic mutation is critical for understanding disease trajectories. While the earliest imaging studies characterized patients by clinical syndrome, genotypic stratification has revealed mutation-specific vulnerabilities in neuroanatomical regions targeted in genetic FTD (Chen and Kantarci, 2020; Greaves and Rohrer, 2019) and ALS (Dharmadasa et al., 2018) that appear distinct from the sporadic forms of these diseases. For example, in FTD due to the *C9orf72* expansion, the characteristic frontotemporal atrophy may be milder or even absent and the atrophy pattern includes parietal (Cash et al., 2018; Irwin et al., 2013; Sha et al., 2012; Whitwell et al., 2012) and occipital (Sha et al., 2012; Whitwell et al., 2012) cortices. Patient-level findings in *C9orf72* expansion carriers suggest even greater heterogeneity with little or no atrophy in some patients with mild, slowly progressive, or even advanced dementia (Boeve et al., 2012; Khan et al., 2012).

Studying the genetic forms of FTD and ALS has also enabled the characterization of the earliest symptomatic and even presymptomatic phases in mutation carriers, with neuroimaging changes preceding symptom onset by years. Most studies have focused on identifying regional atrophy patterns as measured by brain volumetrics in structural T1-weighted magnetic resonance imaging (MRI) (Dopper et al., 2014; Olm et al., 2018; Panman et al., 2019; Rohrer et al., 2015). Microstructural changes (e.g. myelin thickness, axon density, cell swelling) in the white matter of presymptomatic carriers have been measured with diffusion MRI (Bertrand et al., 2018; Floeter et al., 2018; Olm et al., 2018; Panman et al., 2019). Functional MRI, which indirectly measures neural activity by assessing hemodynamics, has revealed presymptomatic abnormalities in resting-state or task-free network connectivity (Dopper et al., 2014; Lee et al., 2017; Menke et al., 2016). Metabolic and molecular imaging provide information about physiological changes such as abnormalities in cellular glucose metabolism measured by [^{18F}]-fluorodeoxyglucose (FDG) positron emission tomography (PET) or perfusion weighted MRI (Dopper et al., 2016; Jacova et al., 2013; Mutsaerts et al., 2019), and in the concentrations of specific metabolites measured by proton magnetic resonance spectroscopy (^{1}H MRS) (Carew et al., 2011a; Chen et al., 2019d). While none of these imaging modalities enable identification of the specific neuropathological diagnoses in FTD or ALS, they provide useful data on alterations in brain function and structure. Here, we review neuroimaging studies of genetic mutations that cause 1) FTD, 2) ALS, and 3) FTD and/or ALS. First, we briefly examine neuroimaging studies in sporadic FTD and ALS as a backdrop to a more in-depth review of neuroimaging literature in patients with genetic forms of these diseases.

2 SPORADIC FTD AND ALS

2.1 FTD

FTD serves as an umbrella term for three clinical subtypes, which include behavioral variant FTD (bvFTD), and the semantic (svPPA) and nonfluent variants (nfvPPA) of primary

progressive aphasia (Gorno-Tempini et al., 2011; Neary et al., 1998; Rascovsky et al., 2011). While these three syndromes converge on frontotemporal atrophy (Gorno-Tempini et al., 2004; Rosen et al., 2002), each clinical syndrome targets a distinct network of regions whose dysfunction is associated with changes in social and emotional cognition and cognitive and motor function (Fig. 2; Seeley et al., 2009). Focal neurodegeneration can be asymmetric: in bvFTD, the right hemisphere often shows greater atrophy than the left, while the PPAs typically feature left hemispheric atrophy, corresponding to the higher frequency of left-sided language dominance in the population (Schroeter et al., 2007). With disease progression, atrophy spreads next to homologous regions in the contralateral hemisphere (Kumfor et al., 2016; Rohrer et al., 2009c, 2012).

2.1.1. bvFTD—BvFTD presents with early changes in personality or behavior, with absent or mild cognitive symptoms in early stages of the disease. Clinical criteria include a wide variety of neuropsychiatric behaviors, including disinhibited behavior, profound apathy, loss of empathy, repetitive or compulsive behavior, and hyperorality or rigid food preferences (Neary et al., 1998; Rascovsky et al., 2011). In bvFTD, neurodegeneration starts in the pregenual anterior cingulate and the frontoinsular cortex (Kim et al., 2012; Seeley et al., 2007a, 2008), with orbitofrontal cortex, striatum, amygdala, thalamus, and brainstem also targeted later in the disease (Broe et al., 2003). Unlike Alzheimer's disease, the parietal lobes are typically spared. Axonal degeneration, likely associated with gray matter neuron loss, often arises in the anterior corpus callosum, cingulum bundle and uncinate fasciculus (Agosta et al., 2012; Elahi et al., 2017; Lam et al., 2014; Mahoney et al., 2015, 2014; Whitwell et al., 2010; Zhang et al., 2013).

Studies show that specific types of behavioral symptoms in bvFTD are related to atrophy in distinct neuroanatomical regions. Disinhibited behavior has been associated with atrophy in right orbitofrontal cortex, while apathy is related to atrophy in anterior cinguate and medial prefrontal cortex (Rosen et al., 2005, 2002). Loss of empathy is associated with atrophy in several key hubs, including the right anterior temporal lobe, right anterior cingulate, anterior insula, and ventral striatum (Rankin et al., 2006). Simple stereotyped motor behavior relates to striatal atrophy, while more complex compulsions correlate with orbitofrontal, temporal lobe, and caudate atrophy (Josephs et al., 2008; Perry et al., 2012; Rosen et al., 2005; Rosso et al., 2001). Eating behaviors, which include increased carbohydrate consumption, eating of inedible objects, or rigid or ritualistic food preferences or schedules, are linked to degeneration of orbitofrontal cortex, right temporal lobe, right insula, striatum, and hypothalamus (Henry et al., 2014; Piguet et al., 2011; Whitwell et al., 2007b; Woolley et al., 2007).

Neurodegenerative syndromes target specific networks of distributed regions that are identifiable in healthy individuals, as measured by task-free fMRI intrinsic connectivity network (ICN) analysis (Greicius et al., 2004; Seeley et al., 2009). The key hubs of neurodegeneration in bvFTD form the salience network, proposed to evaluate the importance of emotionally significant stimuli (Seeley et al., 2007b). BvFTD typically is associated with disrupted connectivity within the salience network (Day et al., 2013; Filippi et al., 2013; Zhou et al., 2010), though some studies report hyperconnectivity or connectivity similar to controls (Farb et al., 2013; Hafkemeijer et al., 2015; Rytty et al., 2013). Intriguingly, the

default mode network, targeted in Alzheimer's disease, shows decreased but also increased connectivity in bvFTD, proposed to underlie enhanced visuospatial abilities and emerging visual artistic creativity in some patients (Zhou et al., 2010).

[^{18}F]FDG-PET shows glucose hypometabolism within orbitofrontal, dorsomedial and dorsolateral prefrontal regions, anterior temporal pole and basal ganglia, which may be detectable in early stages before patients meet clinical criteria for probable bvFTD (Ber et al., 2006; Morbelli et al., 2016; Varma et al., 2002). Studies have reported that [^{18}F]FDG-PET may distinguish patients with bvFTD from other patients with dementia (Buhour et al., 2017a; Diehl-Schmid et al., 2007; Morbelli et al., 2016; Tosun et al., 2016; Verfaillie et al., 2015; Vijverberg et al., 2016), yet frontal hypometabolism has also been reported in psychiatric disorders and Alzheimer's disease, which confounds diagnostic accuracy (Vijverberg et al., 2016). Tau PET tracers, such as [^{18}F]flortaucipir, show limited sensitivity and specificity in FTD (Tsai et al., 2019).

2.1.2. svPPA—SvPPA is a progressive language disorder characterized by loss of word and object meaning and surface dyslexia, yet fluent, grammatically correct speech (Gorno-Tempini et al., 2011; Hodges and Patterson, 1996; Snowden et al., 1989). The anterior temporal lobe, typically more atrophied on the left compared with the right, shows prominent focal degeneration, sometimes with "knife-edge" gyri in patients with severe atrophy (Gorno-Tempini et al., 2004; Rogalski et al., 2011). DTI studies consistently show disruption in anterior and inferior temporal white matter tracts, including the inferior longitudinal fasciculi and uncinate fasciculi (Agosta et al., 2015, 2012; Lam et al., 2014; Mahoney et al., 2013; Schwindt et al., 2013; Tu et al., 2015; Zhang et al., 2013).

Task-free fMRI studies in healthy individuals show that the anterior temporal lobe has strong intrinsic connectivity to the anterior cingulate, orbitofrontal cortex, frontoinsula, striatum and thalamus (Guo et al., 2013; Seeley et al., 2009). Patients with svPPA also show disrupted connectivity within this anterior temporal network, also known as the semantic appraisal network, which processes semantic stimuli across various modalities (Agosta et al., 2014b; Guo et al., 2013).

Mirroring gray matter atrophy patterns, [^{18}F]FDG-PET in svPPA typically features asymmetrical bilateral temporal hypometabolism (Cerami et al., 2017).

2.1.3. nfvPPA—In contrast to svPPA, the hallmarks of nfvPPA include effortful speech production and agrammatism with preservation of object knowledge and single-word comprehension (GornoTempini et al., 2011; Grossman et al., 1996; Hodges and Patterson, 1996; Snowden et al., 1989). The left posterior frontoinsula and the left inferior frontal gyrus usually show the most profound atrophy (Gorno-Tempini et al., 2011, 2004). Left orbitofrontal and intrafrontal tracts, the superior longitudinal fasciculus and frontostriatal pathways are involved (Agosta et al., 2015, 2012; Lam et al., 2014; Mahoney et al., 2013; Mandelli et al., 2014; Schwindt et al., 2013; Zhang et al., 2013).

In healthy individuals, the inferior frontal gyrus is intrinsically connected to frontal operculum, middle frontal gyrus, primary and supplementary motor cortices, and inferior

parietal lobule, a network of regions critical for language and motor speech fluency (Battistella et al., 2020; Seeley et al., 2009), and patients with nfvPPA show atrophy and reduced connectivity with these regions. [^{18}F]FDG-PET shows hypometabolism reported in left inferior frontal gyrus, dorsolateral frontal cortex, anterior cingulate and insula (Cerami et al., 2017; Mesulam, 2003).

2.2 ALS

ALS is a progressive motor neuron disease that causes degeneration in upper and lower motor neurons. Clinical heterogeneity exists with respect to the site of onset, the degree of upper and lower motor neuron involvement, the rate of progression, and cognitive and behavioral symptoms (Strong et al., 2017). Patients with ALS have clinical overlap with FTD. Most patients develop some degree of behavioral and cognitive impairment with disease progression (Crockford et al., 2018; Lomen-Hoerth et al., 2002), with 15% of patients meeting clinical criteria for FTD (Ringholz et al., 2005).

Clinically, MRI has been used in ALS to exclude mimics of motor neuron disease, such as nerve root compression and neoplastic, vascular, and demyelinating diseases of the brain and spinal cord. Typically, conventional MRI shows mild or absent gray matter atrophy (Bede and Hardiman, 2018; Grieve et al., 2016; Walhout et al., 2015b). Upon visual assessment of the corticospinal tract or precentral gyrus, hypointensities on T2-weighted, fluid-attenuated inversion recovery or proton density sequences are variably noted, yet not adequately sensitive or specific to confirm a diagnosis of ALS (Filippi et al., 2010).

Quantitative MRI approaches such as voxel-based morphometry show that patients with ALS have atrophy in the precentral gyrus and inferior frontal cortex (Grosskreutz et al., 2006; Mezzapesa et al., 2013; Shen et al., 2016) with subcortical regions such as the striatum, thalamus and the cerebellum also targeted (Bede et al., 2013c; Bede and Hardiman, 2018; Menke et al., 2014; Westeneng et al., 2015). Cervical and upper thoracic spinal cord atrophy is associated with clinical severity and disease duration (El Mendili et al., 2014; Valsasina et al., 2006) and progressive longitudinal changes are detectable (Agosta et al., 2009; El Mendili et al., 2014). Those patients with bulbar versus limb onset show the expected corresponding atrophy within primary motor cortex (Bede et al., 2013a). Patients with ALS and FTD harbor more widespread frontotemporal atrophy (Lillo et al., 2012; Masuda et al., 2016; Omer et al., 2017).

Reflecting the disruption to upper motor neuron axons in ALS, diffusion MRI studies consistently revealed microstructural changes along the corticospinal tracts and in mid and posterior corpus callosum (Fig. 3; Bede and Hardiman, 2018; Broad et al., 2019; Müller et al., 2016; van der Graaff et al., 2011). Patients with primary lateral sclerosis, which involves upper motor neurons but not lower motor neurons, have more pronounced white matter disruption compared to patients with ALS (Agosta et al., 2014a). Studies of patients with lower motor neuron predominant presentations may also show extensive white matter disruption, suggesting that DTI may be capturing subclinical upper motor neuron disease in these patients (Müller et al., 2018). Patients with ALS who also feature behavioral or cognitive symptoms, including patients with frank bvFTD, additionally show white matter

involvement in frontotemporal tracts (Agosta et al., 2016; Lillo et al., 2012; Omer et al., 2017; Spinelli et al., 2016; Trojsi et al., 2013).

In task-free fMRI, the most consistent intrinsic connectivity network alteration is decreased sensorimotor network connectivity (Agosta et al., 2013; Douaud et al., 2011; Tedeschi et al., 2012; Trojsi et al., 2015). Most whole-brain investigations have additionally discovered connectivity decreases or increases between motor and non-motor regions and within extra-motor networks such as salience, default mode, and frontoparietal networks (Agosta et al., 2013; Menke et al., 2018; Mohammadi et al., 2009; Qiu et al., 2019; Tedeschi et al., 2012; Trojsi et al., 2015). Similary, task-based fMRI studies have highlighted additional recruitment of non-motor brain regions during motor tasks in patients with ALS compared to controls (Abidi et al., 2019; Konrad et al., 2006; Poujois et al., 2013; Schoenfeld et al., 2005; Stanton et al., 2007). This functional reorganization is commonly interpreted to result from both degenerative and compensatory mechanisms.

Extra-motor involvement in ALS has been long suggested by PET studies, which show hypometabolism in non-motor cortex (Dalakas et al., 1987; Hatazawa et al., 1988; Kew et al., 1993). More recently, larger [^{18}F]FDG PET studies have converged on hypometabolism within the premotor and frontal cortices (Buhour et al., 2017b; Cistaro et al., 2012; Pagani et al., 2014; Van Laere et al., 2014). Several studies have also observed increased [^{18}F]FDG uptake, particularly in the brainstem (Cistaro et al., 2012; Pagani et al., 2014; Van Laere et al., 2014) and cervical spinal cord (Marini et al., 2016; Yamashita et al., 2017) of ALS patients, hypothesized to be due to glial cells surrounding degenerating neurons. Increased uptake of PET tracers that are associated with microglial activation and oxidative stress and decreased binding of GABAergic, serotonergic, and dopaminergic ligands has also been reported (Fu et al., 2017; Ikawa et al., 2015; Lloyd et al., 2000; Turner, 2005; Turner et al., 2005).

^{1}H MRS studies have revealed decreased NAA (an estimate of neuronal density) and, less consistently, low concentrations of myoinositol, glutamate, glutamine, and GABA along the corticospinal tract, posterior limb of the internal capsule, periventricular white matter (Atassi et al., 2017; Cheong et al., 2017; Pyra et al., 2010; Westeneng et al., 2017). NAA and myoinositol levels also correlate with measures of clinical severity in cervical spinal cord (Carew et al., 2011b; Ikeda et al., 2013) and prefrontal cortex (Hanstock et al., 2020).

Despite these advances, neuroimaging features alone are not able to diagnose bvFTD, PPA or ALS and instead are supportive in rendering clinical diagnoses. For bvFTD, frontal and/or anterior temporal atrophy on MRI or CT and/or hypoperfusion on PET and SPECT in these regions are supportive criteria in concert with symptoms, neuropsychological testing and functional assessment (Rascovsky et al., 2011). Similarly, diagnostic criteria for PPA also incorporate imaging features. Predominant left posterior fronto-insular atrophy on MRI or predominant left posterior fronto-insular hypoperfusion or hypometabolism on SPECT or PET supports the diagnosis of nfvPPA (Gorno-Tempini et al., 2011). Predominant anterior temporal lobe atrophy (MRI) and/or hypoperfusion (SPECT/PET) support a diagnosis of svPPA. For ALS, neuroimaging studies are currently used only to exclude other conditions that may cause upper or lower neuron signs that mimic ALS (Brooks et al., 2000).

3 NEUROIMAGING STUDIES OF GENETIC MUTATIONS FOR FTD AND ALS

3.1 Genetic mutations for FTD and ALS: a brief overview

In 1994, autosomal dominant inheritance was first identified in a family with FTD and parkinsonism which was linked to chromosome 17q21.2 (Lynch et al., 1994) and the causative genetic mutation was identified as the microtubule protein-associated tau (*MAPT*) (Clark et al., 1998; Hutton et al., 1998; Poorkaj et al., 1998; Spillantini et al., 1998), which plays a role in microtubule stabilization and assembly. In 2006, the second autosomal dominant mutation for FTD was identified as *GRN*, a mere 6.2 MB away from *MAPT* (Baker et al., 2006). *GRN* encodes for progranulin, a protein that is ubiquitously expressed and involved in wound repair, inflammation and lysosomal function (Kao et al., 2017; Petkau and Leavitt, 2014).

For ALS, the first autosomal dominant mutation was discovered in a cytosolic, Cu/Zn-binding superoxide dismutase (*SOD1*). Although the clinical overlap between FTD and ALS syndromes had been noted as early as the 1980s, the discovery of rare genetic mutations such as *CHMP2B* (Gydesen et al., 2002), *TARDBP* (Sreedharan et al., 2008), *FUS* (Kwiatkowski et al., 2009; Sreedharan et al., 2008), and *VCP* (Johnson et al., 2010) that cause either FTD, ALS or both syndromes united these two syndromes based on their underlying pathobiology. In 2011, a hexanucleotide expansion in the *C9orf72* gene was discovered as the most common cause of familial and FTD and ALS (DeJesus-Hernandez et al., 2011; Renton et al., 2011). For ALS, the *C9orf72* expansion and *SOD1* mutations account for the majority of familial ALS in Caucasian populations, causing 30 to 40 percent and 15 to 20 percent of cases, respectively (Renton et al., 2014). Since the discovery of the *C9orf72* expansion, other rare mutations that cause either FTD and/or ALS have been identified, including *SQSTM1* (Fecto, 2011), *CHCHD10* (Bannwarth et al., 2014), and *TBK1* (Cirulli et al., 2015; Freischmidt et al., 2015).

3.2 Genetic FTD

3.2.1 MAPT—*MAPT* mutations typically cause bvFTD with or without parkinsonism. Some patients with parkinsonism meet criteria for progressive supranuclear palsy (PSP) or corticobasal syndrome (CBS) (Ghetti et al., 2011). Less commonly, *MAPT* mutations have been identified in patients with primary progressive aphasia (PPA) (Munoz et al., 2007; Rohrer et al., 2009b) and, rarely, ALS (Karch et al., 2018; Origone et al., 2018). Over 50 pathogenetic mutations in *MAPT* have been described (Greaves and Rohrer, 2019), yet the rarity of *MAPT* mutations in the population and clinical heterogeneity found even within families carrying the same *MAPT* mutation (Janssen et al., 2002; van Herpen et al., 2003; Van Swieten et al., 1999) has made it challenging to ascertain genotype-phenotype correlations. Nevertheless, mutations that do not affect the splicing of exon 10 are typically associated with the bvFTD phenotype, while mutations that affect exon 10 splicing and increase the ratio of four repeat (4R) tau to three repeat (3R) tau most frequently cause bvFTD with PSP or parkinsonism (Delisle et al., 1999; Iijima et al., 1999; Skoglund et al., 2008).

Structural neuroimaging: Due to the rarity of *MAPT* mutations, most neuroimaging-studies have examined *MAPT*-FTD cohorts with a mixture of mutation subtypes. *MAPT*-related neuroimaging studies are summarized in Supplementary Table S1. In general, *MAPT*-FTD features frontotemporal atrophy similar to sporadic disease, yet atrophy is typically relatively symmetric and most prominent within anterior and mesial temporal lobes, while involvement of orbitofrontal, lateral prefrontal, and parietal regions is less consistent (Fig. 4; Beck et al., 2008; Boeve, 2005; Cash et al., 2018; Deters et al., 2014; Fumagalli et al., 2018; Olney et al., 2020; Rohrer et al., 2010, 2011a; Whitwell et al., 2009a, 2009b, 2012). A distinctive feature of *MAPT*-FTD is pronounced mesial temporal lobe atrophy (Deters et al., 2014; Olney et al., 2020; Rohrer et al., 2010; Whitwell et al., 2009a), associated with correspondingly greater memory impairment than seen in sporadic bvFTD (Rascovsky et al., 2011; Rohrer and Warren, 2011; Ygland et al., 2018). Longitudinal studies suggest that atrophy progresses symmetrically within the regions atrophied at baseline, namely the anteromedial temporal lobes and orbitofrontal cortex (Rohrer et al., 2010; Whitwell et al., 2015). Different *MAPT* mutation subtypes may be associated with distinct atrophy patterns (Ghetti et al., 2015; Whitwell et al., 2009a), yet it remains unknown whether *MAPT* mutations that share pathophysiological mechanisms selectively target specific neuroanatomical regions.

Early studies with smaller cohorts suggested that presymptomatic *MAPT* mutation carriers may lack gray matter volume differences (Dopper et al., 2014; Whitwell et al., 2011). In contrast, studies with larger cohorts have shown that presymptomatic carriers have subtle gray matter deficits (Cash et al., 2018; Domínguez-Vivero et al., 2020; Fumagalli et al., 2018; Panman et al., 2019; Rohrer et al., 2015) in temporal lobe, cingulate and lingual cortices (Domínguez-Vivero et al., 2020) as well as hippocampi and amygdala (Rohrer et al., 2015). These mixed results across studies could be attributable to differences in cohort size or subject heterogeneity with respect to actual time from symptom onset. Yet, even in presymptomatic carriers with no gray matter deficits at baseline, greater longitudinal temporal lobe (Chen et al., 2019b) and hippocampal (Panman et al., 2019) grey matter volume decline compared to noncarriers has been reported. In 5 presymptomatic carriers converting to bvFTD, declines in frontal and temporal volume appeared around 2 years before symptom onset (Jiskoot et al., 2019). These studies suggest that the characteristic mesial temporal atrophy of *MAPT* mutations may also be detectable in presymptomatic carriers, but further studies are needed to determine this relationship.

Cross-sectional and longitudinal DTI studies have revealed that in *MAPT*-FTD the most prominent white matter deficits appear within entorhinal white matter, limbic tracts, and frontotemporal tracts such as the left uncinate fasciculus (Chen et al., 2019a; Jiskoot et al., 2018; Mahoney et al., 2015, 2014). Similarly, reduced white matter integrity arises in presymptomatic carriers principally within frontotemporal tracts such as the uncinate fasciculus and parahippocampal cingulum bundle (Chen et al., 2019a; Dopper et al., 2014; Jiskoot et al., 2018; Panman et al., 2019; Rohrer et al., 2015). White matter deficits are estimated to appear as early as 20–30 years before estimated onset and may predate low gray matter volume change during the presymptomatic phase (Dopper et al., 2014; Greaves and Rohrer, 2019; Jiskoot et al., 2018).

Functional and molecular neuroimaging: Studies have probed the question of whether brain function as measured by task-free fMRI, [^{18}F]FDG-PET, and ^{1}H MRS may be more sensitive to early-stage or preclinical deficits. One task-free fMRI connectivity study of 9 presymptomatic *MAPT* mutation carriers showed no network connectivity alterations (Dopper et al., 2014), while another study of 8 carriers showed regions with increased and decreased default mode network connectivity compared to noncarriers (Whitwell et al., 2011). Both of these studies had small cohorts of *MAPT* carriers which may account for disparate results. Compared to healthy controls, patients with *MAPT*-FTD have reduced [^{18}F]FDG uptake (Deters et al., 2014) or hypoperfusion (Seelaar et al., 2011) in frontal, temporal, and parietal lobes. Presymptomatic metabolic changes have been elusive with studies reporting either negative findings (Dopper et al., 2016; Mutsaerts et al., 2019) or hypometabolism in a medial temporal ROI (Deters et al., 2014). The disparate results may suggest that hypometabolism is not a prominent early imaging finding across all carriers or *MAPT* mutational variants, but hypometabolism has been found in two presymptomatic carriers known to have converted soon after imaging (Arvanitakis et al., 2007; Dopper et al., 2016).

Tau PET tracers such as [^{18}F]AV 1451 and [^{11}C]PBB3 have been less promising in FTD, since off-target binding has led to false-positive tau positivity in subjects who are unlikely to harbor tau neuropathology (Tsai et al., 2019; Wang and Edison, 2019). [^{18}F]AV-1451, however, has shown strong binding to neurofibrillary tangles matching the pattern of paired helical filament (PHF) immunochemistry in a subset of *MAPT* mutations such as V337M and R406W (Jones et al., 2018; Smith et al., 2016; Tsai et al., 2019). Other PET studies have reported high levels of microglial activation in *MAPT*-FTD postmortem (Lant et al., 2014) and dopaminergic dysfunction and glial activation in presymptomatic carriers (Bevan-Jones et al., 2019; Miyoshi et al., 2010; Wu et al., 2018). In ^{1}H MRS, patients with *MAPT*-FTD show abnormalities in the posterior cingulate and medial frontal cortex, such as decreased NAA/Cr and increased mI/Cr ratios in line with neuronal dysfunction and inflammation, respectively (Chen et al., 2019c; Kantarci et al., 2010), with abnormalities in medial frontal regions observed even presymptomatically (Chen et al., 2019d). In contrast, the posterior cingulate has increases in mI/Cr but normal NAA/Cr, which may reflect a period of reactive astrocytosis in *MAPT*-related degeneration (Chen et al., 2019d; Kantarci et al., 2010).

3.2.2 GRN—Mutations in the *GRN* gene cause missense and premature termination codons in GRN mRNA that are degraded by nonsense-mediated decay, which results in a haploinsufficiency of progranulin protein (Baker et al., 2006; Cruts et al., 2006), most commonly leading to bvFTD and less frequently PPA, CBS or an Alzheimer's-like amnestic syndrome (Le Ber et al., 2008). FTD-ALS has been reported infrequently in association with *GRN* mutations, and pure ALS is rare (Chen-Plotkin et al., 2011; Yu et al., 2010). Interestingly, *GRN* mutation carriers show the most clinical heterogeneity among the common FTD mutations, despite the fact that the 79 *GRN* mutations identified to date all cause a haploinsuffiency of progranulin which has been hypothesized to be the underlying cause of neurodegeneration. *GRN* mutation carriers also show incomplete disease penetrance, with 90% of carriers becoming symptomatic by age 70 (Cruts et al., 2006). TDP-43 type A neuropathology is most commonly found at autopsy (Beck et al., 2008;

Mackenzie et al., 2006), yet the mechanisms by which progranulin deficiency lead to TDP pathology remain unknown.

Structural neuroimaging: *GRN*-related neuroimaging findings are summarized in Supplementary Table S2. Patients with FTD due to *GRN* mutations may have markedly asymmetric cortical atrophy that involves frontotemporal but also parietal cortices (Fig. 4; Beck et al., 2008; Borroni et al., 2012; Bozzali et al., 2013; Cash et al., 2018; Fumagalli et al., 2018; Le Ber et al., 2008; Olm et al., 2018; Premi et al., 2016; Rohrer et al., 2010; Whitwell et al., 2015, 2012, 2009b, 2007a). Longitudinal studies suggest that atrophy in most brain regions is faster in FTD due to *GRN* mutations than atrophy in *MAPT* mutations and the *C9orf72* expansion (Whitwell et al., 2015). After symptom onset, atrophy accelerates particularly in the temporal cortex (Chen et al., 2020) and grows more asymmetrical in the later stages of disease (Rohrer et al., 2010)

Many studies using voxel-based morphometry or cortical thickness measurements in presymptomatic *GRN* mutation carriers have found no detectable abnormalities in gray matter (Borroni et al., 2012, 2008; Fumagalli et al., 2018; Jacova et al., 2013; Lee et al., 2019; Moreno et al., 2013; Panman et al., 2019; Popuri et al., 2018). Other studies of presymptomatic carriers have identified low cortical grey matter volume (Cash et al., 2018; Cruchaga et al., 2009; Dopper et al., 2014; Olm et al., 2018; Olney et al., 2020; Rohrer et al., 2015), thickness (Pievani et al., 2014), and morphological abnormalities (Gazzina et al., 2018). Three longitudinal studies in presymptomatic carriers show converging evidence of volumetric loss in frontal cortex, though in contrast to studies of symptomatic carriers, insular, temporal and parietal involvement is less consistent (Caroppo et al., 2015b; Chen et al., 2020; Olm et al., 2018). In general, the studies that report low gray matter volume analyzed larger subject cohorts, suggesting that gray matter deficits may be detectable, yet subtle during the presymptomatic stage. Overall, the literature suggests that presymptomatic carriers may have targeted regions of gray matter deficits, but when present, these are mild. The mixed results across these studies may be attributable to heterogeneity across study cohorts with respect to subjects' age of future symptom onset and clinical syndrome or targeted neuroanatomy.

White matter hyperintensities are uncommon in FTD, yet several studies have reported white matter hyperintensities in some patients with *GRN*-FTD (Ameur et al., 2016; Caroppo et al., 2014; Le Ber et al., 2008; Paternicò et al., 2016; Sudre et al., 2017). Recent studies have revealed an association between longitudinal accumulation of white matter hyperintensities and atrophy and executive deficits in patients with *GRN*-FTD (Sudre et al., 2019) and also found white matter hyperintensities in presymptomatic carriers (Benussi et al., 2019; Sudre et al., 2019). A report of a patient with *GRN*-FTD with severe white matter hyperintensities showed that white matter disease on MRI scans (*in vivo* and cadaveric) corresponded to promient microglial activation and microglial dystrophy at autopsy, but only mild axonal loss and minimal vascular pathology, supporting the notion that white matter hyperintensities in *GRN*-FTD are not due to small vessel cerebrovascular disease (Woollacott et al., 2018).

DTI studies show that white matter tracts such as the inferior longitudinal and uncinate fasciculi, anterior corpus callosum, and the long intrahemispheric association tracts have reduced integrity in *GRN*-FTD (Bozzali et al., 2013; Premi et al., 2016; Rohrer et al., 2010). Across various cross-sectional DTI studies, presymptomatic *GRN* mutation carriers also show diminished white matter integrity within tracts affected during the symptomatic phase. These tracts include the superior longitudinal and uncinate fasciculi, the corticospinal tract, and anterior corpus callosum (Borroni et al., 2008; Dopper et al., 2014; Jiskoot et al., 2018; Olm et al., 2018; Pievani et al., 2014). Differences in white matter integrity have been proposed to develop 10 years before symptom onset (Jiskoot et al., 2018). Longitudinal DTI studies in presymptomatic carriers have been mixed, either showing no change (Panman et al., 2019) or a greater annualized FA reduction in the right superior longitudinal fasciculus and frontal corpus callosum (Olm et al., 2018). One possible explanation is that differences across studies could be attributable to subject heterogeneity, and subjects either farther from or closer to symptom onset could be driving the overall group result in each study.

Functional and molecular neuroimaging: The first studies that identified task-free fMRI connectivity alterations in presymptomatic FTD mutation carriers explored salience and default mode networks, which show prominent alterations in patients with sporadic FTD. For the salience network, a region of reduced connectivity was found in the midcingulate cortex in 9 presymptomatic *GRN* mutation carriers (Borroni et al., 2012), while another study of 28 presymptomatic *GRN* mutation carriers revealed connectivity disruption of an anterior midcingulate seed region and parietal regions including precuneus, posterior cingulate, and lateral parietal cortex (Dopper et al., 2014). Neither of these studies showed default mode network differences in presymptomatic carriers compared to controls. A study of 5 carriers showed no differences within functional networks (Pievani et al., 2014), suggesting that the differences across studies are due to different sample sizes, methodological differences, and/or subject heterogeneity. Recently, Lee et al. (2019) showed that presymptomatic carriers have hyperconnectivity within the four networks that correspond to the most common clinical syndromes reported during the symptomatic stage of *GRN*, which included salience network for bvFTD, nfvPPA and CBS networks, and the default mode network for AD. For each four networks, hyperconnectivity converged in the thalamus, paralleling the finding in *GRN* −/− mice that the thalamus is a key region implicated in *GRN* pathobiology (Lui et al., 2016).

In addition to these studies examining seed-based and ICA-derived connectivity network alterations, presymptomatic carriers and patients with FTD due to *GRN* mutations have shown alterations in measures of local connectivity (Premi et al., 2014). Another study compared the ability of various imaging modalities such as gray and white matter volume loss, ICA-derived connectivity networks (salience, frontoparietal, dorsal attentional, executive, and default mode), and local connectivity measures to classify *GRN*-FTD and presymptomatic *GRN* versus controls (Premi et al., 2016). Overall, reduced gray matter volume was able to best distinguish patients with *GRN*-FTD from controls, while decreases in local fMRI connectivity (fractional amplitude of low frequency fluctuations) in frontoparietal cortex and increases in local connectivity in prefrontal areas most accurately distinguished presymptomatic carriers from controls. Early involvement of the prefrontal

cortex in *GRN* related disease is also supported by task-based fMRI studies (Alexander et al., 2018; Cruchaga et al., 2009).

Metabolic imaging by [^{18}F]FDG-PET and arterial spin labeling (ASL) MRI have revealed frontotemporal hypometabolism and hypoperfusion in *GRN* mutation carriers, even in presymptomatic carriers that show no significant differences in brain volume. Patients with *GRN*-FTD have [^{18}F]FDG-PET hypometabolism in frontotemporal and parietal cortices, corresponding to regional atrophy patterns seen in structural imaging (Cruchaga et al., 2009; Huey et al., 2006). Similar to symptomatic carriers, group studies of presymptomatic carriers show discrete regions of hypometabolism appear in right anterior cingulate, insula and orbitofrontal cortex (Jacova et al., 2013), left lateral temporal lobe (Caroppo et al., 2015b), and frontal, parietal, and hippocampal regions (Le Ber et al., 2008). Longitudinally, more pronounced hypometabolism has been found within regions of lateral temporal and frontal cortex (Caroppo et al., 2015b). For ASL, presymptomatic *GRN* mutation carriers have shown hypoperfusion cross-sectionally in frontoparietal cortex, and longitudinally in frontal, temporal, parietal, and subcortical regions (Dopper et al., 2016). Across studies, metabolic changes are estimated to emerge 7–25 years before symptom onset (Alexander et al., 2019; Caroppo et al., 2015b; Jacova et al., 2013).

GRN-FTD is typically associated with TDP-43 type A pathology. While there is no molecular imaging available for TDP to date, Alzheimer's co-pathology has been described in *GRN* mutation cariers (Perry et al., 2013). Consistent with this report, *GRN*-FTD shows amyloid beta accumulation as measured by [^{11}C]PiB-PET more frequently than seen in sporadic disease and *MAPT* and *C9orf72* expansion carriers (Tan et al., 2017).

The hexanucleotide expansion in *C9orf72* is the most common cause of genetic FTD and ALS and neuroimaging studies are discussed in section 3.4.1 below.

3.3 Genetic ALS

3.3.1 SOD1—To date, more than 180 mutations in superoxide dismutase (*SOD1*) have been identified. Superoxide dismutase is an abundant enzyme ubiquitously expressed in the body and its main function is to bind copper and zinc to eliminate toxic superoxide radicals that cause oxidative stress. While it remains unknown how *SOD1* mutations lead to ALS, the mutations cause a toxic gain of function (Rothstein, 2009). The neuropathological hallmark of *SOD1*-ALS is the deposition of misfolded SOD1 protein inclusions in motor neurons (Saberi et al., 2015), and curiously, the TDP-43 pathology that is characteristic of sporadic ALS is absent (Mackenzie et al., 2007). Co-occurrence of FTD in *SOD1*-ALS is rare (Millecamps et al., 2012) but cognitive impairment, principally executive dysfunction, is seen in *SOD1*-ALS as in sporadic ALS (Agosta et al., 2018). *SOD1* variants show phenotypic heterogeneity. For example, D90A carriers have a markedly long disease duration ranging between 14–20 years in contrast to the 2–5 years typical of sporadic ALS (Andersen et al., 1996; Weber et al., 2000), while the A4V mutation is typically associated with death within a year of symptom onset (Aggarwal and Nicholson, 2005; Cudkowicz et al., 1997).

SOD1-related neuroimaging studies are summarized in Supplementary Table S3. As in genetic FTD, most neuroimaging studies have investigated different *SOD1* mutations in a combined cohort, although some have focused exclusively on D90A homozygous recessive carriers. The earliest structural imaging studies focused on D90A *SOD1* mutation carriers with ALS and compared them to sporadic ALS. While both D90A *SOD1* and sporadic ALS have atrophy in motor and premotor cortex, D90A *SOD1*-ALS showed more prominent atrophy in anteromedial frontal cortex (Turner et al., 2007a). Patients with D90A *SOD1*-ALS show a lesser degree of corticospinal tract deficits than sporadic patients with similar disease severity (Blain et al., 2011; Stanton et al., 2009) as measured by DTI fractional anisotropy. PET imaging of GABAergic [^{11}C]flumazenil (Turner et al., 2005) and serotonergic [^{11}C]WAY100635 (Turner et al., 2007b) ligands have shown that both sporadic and D90A *SOD1*-ALS patients have reduced binding compared to controls. Interestingly, sporadic ALS had reduced binding of GABA in premotor and motor cortex and posterior motor association areas, while D90A *SOD1*-ALS was associated with lower binding in the left frontotemporal junction and anterior cingulate.

A multimodal imaging study with a larger cohort of 20 patients with *SOD1*-ALS, most of whom carried the L144F mutation, also found that *SOD1*-ALS showed distinct patterns of corticospinal tract and sensorimotor network functional connectivity compared with sporadic ALS despite no group differences on manual muscle testing (Agosta et al., 2018). Both sporadic ALS and *SOD1*-ALS showed decreased corticospinal tract white matter integrity compared to controls, but corticospinal tract integrity was more preserved in *SOD1*-ALS compared to sporadic ALS. Another DTI study, which included a wider range of *SOD1* mutations, did not find significant FA differences in the corticospinal tract and frontal and prefrontal tracts in *SOD1*-ALS patients compared to controls (Müller et al., 2020). Additionally, while sporadic ALS has been shown to be associated with alterations in sensorimotor network connectivity, Agosta et al. (2018) found that patients with *SOD1*-ALS had sensorimotor network connectivity similar to controls, but cervical cord atrophy greater than seen in sporadic disease. Overall, these DTI and task-free fMRI studies suggest that *SOD1*-ALS shows relatively spared motor networks and corticospinal tract integrity compared to sporadic disease, but with greater cervical cord atrophy which may be a distinguishing characteristic of *SOD1*-ALS. The relative sparing of motor networks may reflect the milder motor cortex and corticospinal tract involvement reported in certain patients with *SOD1*-ALS at autopsy when compared to sporadic ALS (Cudkowicz et al., 1998; Ince et al., 1998).

During the presymptomatic phase, *SOD1* carriers do not typically show structural brain deficits (Menke et al., 2016; Vucic et al., 2010), but one DTI study showed reduced integrity in the posterior limb of the internal capsule (Ng et al., 2008). Consistent with the notion that *SOD1*-ALS targets the cervical cord, presymptomatic *SOD1* carriers show in ^{1}H MRS reduced NAA/Cho and NAA/mIns ratios in the cervical spinal cord relative to healthy controls (Carew et al., 2011a). Echoing the finding that *SOD1*-ALS spares cortical motor networks, an fMRI functional connectivity study found no sensorimotor network alterations in presymptomatic *SOD1* carriers, although they showed increased precuneus-cingulate-middle frontal network connectivity as did the sporadic ALS patients in their study (Menke et al., 2016).

3.4 Mutations that cause either FTD or ALS, or both

The *C9orf72* expansion is the most common known genetic cause of FTD and ALS in people with Northern European ancestry. *CHMP2B, TARDBP*, *FUS, VCP*, *SQSTM1*, *TBK1*, *CHCHD10*, are all rare genes that may cause FTD or ALS.

3.4.1 C9orf72—Abnormal G_4C_2 hexanucleotide repeats in either the promoter region or the first intron of chromosome 9 open reading frame 72 (*C9orf72*) usually manifest as bvFTD, ALS, or both (DeJesus-Hernandez et al., 2011; Renton et al., 2011). Less commonly, *C9orf72* expansion carriers may have clinical phenotypes such as an Alzheimer's disease-like syndrome, a Huntington's disease-like syndrome, progressive muscular atrophy, or corticobasal or ataxic syndromes (Anor et al., 2015; Lesage et al., 2013; Lindquist et al., 2013; Liu et al., 2014). Although the function of the C9orf72 protein remains unclear, three proposed pathophysiological mechanisms include haploinsufficiency of C9orf72 protein, toxic gain-of-function due to the accumulation of aberrant RNA foci (DeJesus-Hernandez et al., 2011) and dipeptide repeat proteins both derived from the repeat expansion (Mori et al., 2013). Diverse neuropathological features have been described, but in addition to RNA foci and the dipeptide repeat proteins, TDP-43 type B pathology is most common at autopsy (Mackenzie et al., 2013; Murray et al., 2011; Snowden et al., 2012).

The age of onset in *C9orf72*-related FTD and ALS ranges widely between 30 to 90 years (Murphy et al., 2017). Similar to sporadic FTD, *C9orf72*-FTD has an average disease duration of 14 years (Kaivorinne et al., 2013), but with a subset of cases progressing considerably slower (Devenney et al., 2014; Gómez-Tortosa et al., 2014; Khan et al., 2012; Llamas-Velasco et al., 2018). *C9orf72*-ALS tends to progress more rapidly than sporadic and most other genetic ALS subtypes (Cooper-Knock et al., 2012; DeJesus-Hernandez et al., 2011; Millecamps et al., 2012). In FTD, the expansion is associated with an increased risk of psychosis, hallucinations, and parkinsonism (Cooper-Knock et al., 2012; Snowden et al., 2012). ALS patients with the *C9orf72* expansion have a three times higher frequency of cognitive impairment compared to those with sporadic ALS (Byrne et al., 2012; Smith et al., 2013). Factors such as the size of the repeat expansion, environmental influences, and disease-modifying genes have been speculative and are not clearly established (Chi et al., 2016).

Structural neuroimaging: Neuroimaging studies related to the *C9orf72* expansion are summarized in Supplementary Table S4. Similar to sporadic bvFTD, patients with bvFTD due to the *C9orf72* expansion have frontotemporal and insular atrophy that is often accompanied by parietal, occipital, thalamic, and cerebellar atrophy (Fig. 4; Boeve et al., 2012; Boxer et al., 2011; Cash et al., 2018; Irwin et al., 2013; Lee et al., 2014; Mahoney et al., 2012a; McMillan et al., 2015; Sha et al., 2012; Whitwell et al., 2012). Cortical atrophy is generally symmetric, and longitudinal changes are most apparent in core regions affected at baseline, such as frontotemporal cortex, thalamus and cerebellum (Boeve et al., 2012; Floeter et al., 2016; Le Blanc et al., 2020; Mahoney et al., 2012b; Whitwell et al., 2015). Individual patients have notable heterogeneity, at times exhibiting minimal atrophy (Boeve et al., 2012; Devenney et al., 2015, 2014; Solje et al., 2015) or a more posterior pattern with relatively spared frontal or temporal lobes (Boeve et al., 2012; Boxer et al., 2011; Sha et al.,

2012). *C9orf72* expansion carriers also show heterogeneity at the individual subject level with respect to which brain regions are most prominently targeted. For example, a recent data-driven modelling study suggested that *C9orf72*-FTD features two distinct subtypes of atrophy patterns, either predominantly frontotemporal atrophy or predominantly subcortical atrophy (Young et al., 2018).

C9orf72 expansion carriers with ALS or MND typically exhibit relatively symmetric volume loss and cortical thinning. *C9orf72*-ALS appears clinically similar to sporadic ALS, yet gray matter volume loss is pronounced in expansion carriers, particularly in frontotemporal and parieto-occipital cortex (Agosta et al., 2017; Bede et al., 2013b; Byrne et al., 2012; Floeter et al., 2016; van der Burgh et al., 2020; Westeneng et al., 2016) and in subcortical structures such as the thalamus, cerebellum, and hippocampi (Agosta et al., 2017; Bede et al., 2013c; Schönecker et al., 2018; van der Burgh et al., 2020; Westeneng et al., 2016). These cortical deficits correlate with the cognitive impairment in *C9orf72*-ALS (Bede et al., 2013b; Floeter et al., 2016). In parallel, frontotemporal and insular changes have been found to be associated with cognitive and behavioral impairments in sporadic ALS (Agosta et al., 2017, 2016; Christidi et al., 2018; Consonni et al., 2019; Tsujimoto et al., 2011; Westeneng et al., 2016). In addition to these cortical and subcortical volume differences, *C9orf72*-ALS do not have extensive cervical cord thinning compared to sporadic ALS (van der Burgh et al., 2019).

Patients with *C9orf72* with both FTD and ALS show a lesser degree of cortical atrophy compared with sporadic FTD-ALS (Omer et al., 2017) and a distinct pattern of subcortical atrophy mainly in thalamic nuclei connected to motor and sensory cortical areas (Bede et al., 2018). One hypothesis is that abnormalities in subcortical brain structures such as the thalamus and cerebellum may be a more robust imaging signature of the *C9orf72* expansion than cortical atrophy patterns (Mahoney et al., 2012b, 2012a). Low gray matter volume is detectable in presymptomatic *C9orf72* expansion carriers, generally within regions atrophied in *C9orf72*-bvFTD and *C9orf72*-ALS (Bertrand et al., 2018; Cash et al., 2018; De Vocht et al., 2020; Lee et al., 2017; Panman et al., 2019; Papma et al., 2017; Popuri et al., 2018; Rohrer et al., 2015; Walhout et al., 2015a). In particular, atrophy of the posterior thalamus correlates with disease severity in *C9orf72*-FTD and -ALS (Agosta et al., 2017; McMillan et al., 2015; Schönecker et al., 2018) and low gray matter in this region is apparent even in young presymptomatic carriers (Bertrand et al., 2018; Cash et al., 2018; Lee et al., 2017; Olney et al., 2020; Papma et al., 2017; Rohrer et al., 2015). Recent investigations focused on the involvement of individual thalamic nuclei in FTD–ALS have characterized pulvinar nucleus atrophy as unique to *C9orf72* expansion carriers with FTD (Bocchetta et al., 2020) but other thalamic nuclei have been associated with the *C9orf72* expansion with motor neuron disease (Chipika et al., 2020).

DTI studies reveal that white matter tracts are also disrupted in *C9orf72* expansion carriers. Studies of patients with *C9orf72*-bvFTD have revealed disruption of frontotemporal association tracts and corpus callosum similar to the white matter tracts affected in sporadic bvFTD (Mahoney et al., 2015, 2014). Both *C9orf72*-bvFTD and sporadic bvFTD show the greatest longitudinal decline in the paracallosal cingulum bundle (Mahoney et al., 2015). Patients with *C9orf72*-ALS/MND and varying degrees of cognitive impairment show motor

tract involvement similar to sporadic ALS, but also systematic involvement of frontotemporal tracts such as the uncinate fasciculus, superior longitudinal fasciculus, and inferior longitudinal fasciculus (Agosta et al., 2017; Bede et al., 2013b; Floeter et al., 2018; Müller et al., 2020; Omer et al., 2017; van der Burgh et al., 2019; Westeneng et al., 2016). Though gray matter atrophy patterns overlap in *C9orf72*-FTD and -ALS, white matter tract involvement may better reflect each phenotype than do volumetric deficits (Bertrand et al., 2018; Floeter et al., 2018; Querin et al., 2019). For example, a longitudinal DTI study on a cohort of *C9orf72* expansion carriers with different clinical diagnoses found that changes in cognitive-behavioral and motor symptom severity correlated with progressive deficits along the frontotemporal and corticospinal tracts, respectively, over a 6 month interval (Floeter et al., 2018).

In presymptomatic *C9orf72* expansion carriers, white matter deficits commonly appear in tracts connecting the frontal lobe, the thalamic radiation, and tracts associated with motor functioning (Bertrand et al., 2018; Jiskoot et al., 2018; Lee et al., 2017; Panman et al., 2019; Papma et al., 2017; Wen et al., 2018). Cross-sectionally, both gray and white matter deficits in presymptomatic carriers emerge early, up to 30 years before symptom onset (Jiskoot et al., 2018; Lee et al., 2017), and are present even in presymptomatic carriers younger than 40 years old (Bertrand et al., 2018; Le Blanc et al., 2020; Lee et al., 2017). These regions of low gray matter volume and reduced white matter integrity are generally congruent with regions of gray matter atrophy found during the symptomatic phase. In the cervical spinal cord, only presymptomatic carriers older than 40 years showed atrophy at each vertebral level, and corticospinal tract FA reductions were detectable at an 18 month follow up (Querin et al., 2019). Consistent with cross-sectional studies, a recent study of 137 carriers that included longitudinal data for a subset of subjects estimated that the thickness of the medial frontal and parietal cortex and scattered lateral frontal, parietal, and temporal regions begins to decline during the early thirties with no acceleration around the estimated age of symptom onset (Le Blanc et al., 2020). Longitudinal changes in grey matter volume (Floeter et al., 2016; Panman et al., 2019) and white matter integrity (Panman et al., 2019) have been elusive in presymptomatic cohorts thus far. Taken together, these studies point to gray and white matter deficits at an early age during the presymptomatic phase, suggesting that these abnormalities may represent neurodevelopmental differences in *C9orf72* expansion carriers (Bertrand et al., 2018; Lee et al., 2017).

Functional and molecular imaging: Although patients with *C9orf72*-bvFTD have a distinct, yet overlapping atrophy pattern compared to those with sporadic bvFTD, both converge on salience and sensorimotor network connectivity disruption, suggesting that ICN maps rather than atrophy patterns may better represent the clinical syndrome (Lee et al., 2014). Salience network connectivity disruption correlated with left medial pulvinar thalamic atrophy, suggesting that the medial pulvinar degeneration may contribute to the bvFTD syndrome in *C9orf72* by disrupting salience network connectivity. In contrast to sporadic bvFTD, which shows both default mode network connectivity increases and decreases, *C9orf72*-bvFTD shows default mode network connectivity similar to controls (Lee et al., 2014). A study comparing 7 *C9orf72*-bvFTD to those with sporadic disease described pronounced anti-correlation between thalamic nodes of the salience network and

the default mode network and also found connectivity increases within the right dorsal attention network (Rytty et al., 2014). A comparison between 19 *C9orf72*-MND and 24 sporadic MND with comparable cognitive deficits revealed that *C9orf72*-MND have sensorimotor network decreases but enhanced visual network connectivity (Agosta et al., 2017). During the presymptomatic stage, robust intrinsic connectivity network disruption is detectable in the salience, sensorimotor and default mode networks and to the medial pulvinar, and these anomalies are apparent as early as the third decade of life (Lee et al., 2017).

Metabolic imaging in patients with *C9orf72*-FTD typically reveals hypoperfusion and hypometabolism in the frontal and/or temporal lobes and limbic structures, in keeping with the clinical phenotype (Boeve et al., 2012; Castelnovo et al., 2019; Diehl-Schmid et al., 2019). Likely due to individual subject heterogeneity, a notable subset of patients with *C9orf72*-bvFTD lack hypometabolism in frontotemporal cortex or show at least a comparable degree of hypometabolism in the parietal lobe, thalamus, or cerebellum (Boeve et al., 2012; Devenney et al., 2014; Diehl-Schmid et al., 2019; Khan et al., 2012; Solje et al., 2015). Compared to sporadic bvFTD, *C9orf72*-bvFTD show pronounced focal hypometabolism in bilateral thalami (Diehl-Schmid et al., 2019). In *C9orf72*-ALS, metabolic signatures are more variable (Castelnovo et al., 2019). Group studies in patients with ALS suggest, however, that the expansion is associated with pronounced [^{18}F]FDG-PET hypometabolism in thalamus and posterior cingulate (Cistaro et al., 2014; Van Laere et al., 2014; Verschueren et al., 2013) and hypermetabolism in midbrain and occipital and inferior temporal cortices (Cistaro et al., 2014). Metabolic abnormalities also occur in presymptomatic *C9orf72* expansion carriers (De Vocht et al., 2020; Mutsaerts et al., 2019; Westeneng et al., 2017). Mutsaerts et al. (2019) estimated that insular, temporal, and parietal hypoperfusion emerges early, at least 12 years from estimated symptom onset. De Vocht et al. (2020) identified [^{18}F]FDG-PET hypometabolism in the insular cortices, central opercular cortex, and thalami in 82% of presymptomatic participants studied, whereas abnormally low gray matter volume and elevated neurofilament light levels (a marker of axonal injury) were less frequently observed (62% and 19%, respectively).

3.5 Rare genetic mutations that cause either FTD or ALS

In recent years, genome-wide association studies have revealed a range of causal and risk variants for FTD and ALS. While rare genes such as *CHMP2B* and *TREM2* have been associated with FTD and *OPTN* has been associated with ALS, other genes including *TARDBP*, *DCTN1, FUS*, *VCP*, *UBQLN2*, *SQSTM1, CHCHD10*, *TBK1*, *CCNF*, are associated with a heterogeneous array of disorders in the FTD-ALS spectrum. Below we review imaging findings for these rarer genetic FTD or ALS variants, including studies reporting visual assessment of structural MRI brain or [^{18}F]FDG-PET scans in addition to quantitative neuroimaging studies.

3.5.1 CHMP2B—Charged multivesicular body protein 2B (CHMP2B) is expressed in multiple human tissues, including frontal and temporal lobes. CHMP2B protein is a component of the endosomal secretory complex required for transport III, and in cell culture, mutations in *CHMP2B* disrupt the protein's localization and results in the formation of

dysmorphic organelles of the late endosomal pathway (Skibinski et al., 2005). The pathology associated with *CHMP2B* mutations is poorly understood, with the FTLD UPS aggregates either representing an unknown disease-specific protein or a more general defect in endosomal trafficking and lysosomal protein degradation (Neumann and Mackenzie, 2019). *CHMP2B* mutations comprise less than 1% of FTD mutations, and have been described in large Danish and Belgian families (Gydesen et al., 2002; van der Zee et al., 2008), but are rare in other cohorts. Most *CHMP2B* mutation carriers develop bvFTD, although FTD-ALS and CBS and PSP syndromes have been reported (Isaacs et al., 2011). Dyscalculia, limb apraxia and dynamic aphasia have also been described (Gydesen et al., 2002).

Patients with bvFTD due to truncating *CHMP2B* mutations generally show atrophy and reduced cerebral blood flow in frontotemporal and sometimes parietal regions (Gydesen et al., 2002; Isaacs et al., 2011; Lindquist et al., 2008). In contrast to sporadic FTD, FTD due to *CHMP2B* mutations additionally involves parietal and posterior central regions, hypothesized to correspond to dyscalculia and limb apraxia, also unusual features of sporadic FTD (Gydesen et al., 2002; Isaacs et al., 2011). Both FTD and ALS have also been associated with missense *CHMP2B* mutations (Isaacs et al., 2011). Autopsy studies reveal that truncating and missense *CHMP2B* mutations have pathologically distinct features (Neumann and Mackenzie, 2019), but the associated imaging signatures of each type of mutation have not been systematically compared.

Group comparisons between presymptomatic carriers of truncating *CHMP2B* mutations and non-carrier family members have revealed focal atrophy in inferotemporal, superior frontal, and insular cortex (Eskildsen et al., 2009; Rohrer et al., 2009a). Presymptomatic *CHMP2B* carriers also show significantly decreased cerebral blood flow in occipital and parietal regions (Lunau et al., 2012).

3.5.2 TARDBP—TAR DNA-binding protein (TARDBP) is a nuclear protein involved with RNA processing and metabolism (Xia et al., 2016). During stress conditions, hyperphosphorylated, ubiquitinated and cleaved TDP-43 deposits aggregate in the cytoplasm. In addition to TDP pathology, other neuropathologies such as tau, amyloid and alpha-synuclein have been found in *TARDBP* mutation carriers (Gelpi et al., 2014; Kovacs et al., 2009; Moreno et al., 2015). *TARDBP* mutations account for 3% of familial ALS, but rarely cause dementia or parkinsonism (Lattante et al., 2013b), and account for less than 1% of patients with FTD (Caroppo et al., 2016). When *TARDBP* mutation carriers develop dementia, bvFTD is the most frequent syndrome, though both nonfluent and semantic PPA have been reported (Caroppo et al., 2016; Floris et al., 2015), and less than half develop motor neuron disease (Caroppo et al., 2016). Among the FTD syndromes, svPPA is usually sporadic and not genetic, yet patients with *TARDP* mutations develop svPPA at a higher rate compared to patients with the *C9orf72* expansion and *MAPT* and *GRN* mutations (Caroppo et al., 2016).

Case series describe that patients with *TARDBP*-FTD have atrophy in frontotemporal and less commonly in parietal cortex, hippocampus, and amygdala (Caroppo et al., 2016; Cheng et al., 2016; Floris et al., 2015; Synofzik et al., 2014). Correspondingly, hypoperfusion and

hypometabolism has been observed in frontotemporal cortex and more rarely in parietal cortex and the caudate (Benajiba et al., 2009; Borroni et al., 2009; Caroppo et al., 2016; Cheng et al., 2016; Floris et al., 2015; Synofzik et al., 2014). As expected, those with the svPPA syndrome typically develop left-lateralized anterior temporal and sometimes frontal gray matter loss, hypoperfusion and hypometabolism (Benajiba et al., 2009; Caroppo et al., 2016; Cheng et al., 2016; Floris et al., 2015; Gelpi et al., 2014; González-Sánchez et al., 2018).

Most case reports on pure *TARDBP*-MND or -ALS have found no apparent imaging abnormalities upon visual inspection of brain or cervical cord MRI (Agosta et al., 2020; Cheng et al., 2016; Chiò et al., 2010; Del Bo et al., 2009), but individual imaging reports have described abnormalities such as frontotemporal hypometabolism in SPECT and [^{18}F]FDG-PET (Borghero et al., 2011) and temporal atrophy (Del Bo et al., 2009). In *TARDBP*-ALS with concomitant FTD or behavioral deficits, cortical atrophy and metabolic changes appear common within frontal and/or temporal lobes and less often involve parietal and anterior cingulate cortex and the head of the caudate (Cheng et al., 2016; Chiò et al., 2010).

3.5.3 FUS—*FUS* encodes the fused in sarcoma protein, an RNA-binding protein involved in cell proliferation, DNA repair, transcription regulation, and RNA splicing and transport (Deleon and Miller, 2018). ALS patients with *FUS* mutations show aggregated FUS protein in the cytoplasm. Interestingly, no patient with FTLD with FUS neuropathology has yet been identified to carry a *FUS* mutation (Neumann and Mackenzie, 2019).

Studies in patients with FTD or FTD-ALS with *FUS* mutations have reported frontal, temporal and parietal atrophy and hypometabolism (Akiyama et al., 2016; Blair et al., 2010; Broustal et al., 2010; Huey et al., 2012). Individual case reports on *FUS*-ALS generally describe normal brain imaging (Blair et al., 2010; Chiò et al., 2009; Rademakers et al., 2010; Zhou et al., 2020), although other reports have described instances of individual patients with cortical and cerebellar atrophy (Yan et al., 2010), nonspecific scattered white matter changes (Wongworawat et al., 2020), and decreases in cerebral blood flow in the right striatum, thalamus, and frontotemporal lobe (Tateishi et al., 2010).

3.5.4 OPTN—The *OPTN* gene encodes optineurin, a multifunctional protein involved in protein degradation via autophagy. *OPTN* mutations are associated with ALS, primary open-angle glaucoma (Rezaie, 2002), and Paget's disease of bone (Albagha et al., 2010). *OPTN* mutations have been reported in 1–2 % of familial ALS and up to 3.5 % of sporadic cases (Belzil et al., 2011; Del Bo et al., 2011). While *OPTN* mutations are rarely found in patients with FTD, they are not considered causative of FTD (Pottier et al., 2015). Imaging reports on patients with *OPTN*-ALS have reported atrophy in frontal, temporal and motor cortices (Feng et al., 2019; Ito et al., 2011; Kamada et al., 2014; Ueno et al., 2011) as well as brainstem and cerebellum (Ueno et al., 2011).

3.5.5 VCP—The valosin-containing protein (*VCP*) gene is involved with various cellular activities, and pathological mutations are hypothesized to disrupt its role in protein degradation (Watts et al., 2004; Weihl et al., 2009). *VCP* mutations are associated with a

disease characterized by inclusion body myopathy, Paget's disease of bone, early onset FTD (IBMPFD) (Taylor, 2015; Watts et al., 2004) and other clinical syndromes including ALS (Johnson et al., 2010). The FTD phenotype develops in about one third of *VCP* mutation carriers, whereas ALS is rarer (Abramzon et al., 2012; Al-Obeidi et al., 2018; Johnson et al., 2010; Kimonis and Watts, 2005; Koppers et al., 2012).

Imaging reports on *VCP*-FTD range from having no apparent atrophy to focal frontotemporal or diffuse cortical and subcortical atrophy (Djamshidian et al., 2009; Kimonis et al., 2008; Kovach et al., 2001; Saracino et al., 2018; van der Zee et al., 2009). Rare reports also describe hippocampal or parietal atrophy (Fanganiello et al., 2011; Kim et al., 2011; Rohrer et al., 2011b). [^{18}F]FDG-PET typically shows predominantly frontotemporal hypometabolism with parietal and cerebellar involvement in patients with *VCP*-FTD (Kim et al., 2011; Rohrer et al., 2011b; van der Zee et al., 2009; Viassolo et al., 2008). Compared to sporadic svPPA, patients with *VCP*-svPPA have more extensive frontal (Krause et al., 2007) or posterolateral temporal and parietal cortical atrophy (Kim et al., 2011), and curiously, the anterior temporal lobe is relatively spared. *VCP*-FTD and *VCP*-ALS have been suggested to share a focal atrophy in the temporal lobes and hippocampi (Hirano et al., 2017, 2015).

3.5.6 UBQLN2—The ubiquilin-2 (*UBQLN2)* gene encodes for a protein involved in proteasomal degradation (Deng et al., 2011; Hjerpe et al., 2016). *UBQLN2* mutations have been associated with juvenile and adult onset ALS (Daoud et al., 2012; Deng et al., 2011; Gellera et al., 2013) and more rarely with FTD, FTD-ALS, and PSP (Synofzik et al., 2012; Vengoechea et al., 2013). Imaging reports in two *UBQLN2*-related FTD cases described bilateral frontotemporal atrophy and hypometabolism (Leger et al., 2017; Synofzik et al., 2012), whereas findings in *UBQLN2*-ALS with cognitive impairment have ranged from a lack of apparent atrophy (Kotan et al., 2016) to diffuse atrophy patterns in a family with heterogeneous clinical presentations (Fahed et al., 2014).

3.5.7 SQSTM1—The sequestome 1 (*SQSTM1*) gene encodes for p62, a multi-functional protein that targets specific cargoes for autophagy (Rea et al., 2014). *SQSTM1* mutations are associated with Paget's disease of bone (Goode and Layfield, 2010), FTD (Rubino et al., 2012) and ALS (Fecto, 2011; Yilmaz et al., 2020). In FTD and ALS cohorts, the mutation frequency of *SQSTM1* is estimated to be 1–3% and *SQSTM1* mutations are associated with TDP-43 neuropathology (Fecto, 2011; Le Ber, 2013; Rubino et al., 2012; van der Zee et al., 2014).

Imaging findings of individual patients with *SQSTM1*-bvFTD suggest atrophy and hypometabolism predominantly in frontotemporal and cingulate cortices, putamen, and basal ganglia, often more pronounced in one hemisphere (Kovacs et al., 2016; Le Ber, 2013; Rubino et al., 2012; Sun et al., 2018). Compared to sporadic FTD, ten patients with *SQSTM1*-FTD showed pronounced atrophy in inferior and medial orbitofrontal cortex, anterior insula, and precentral gyri (Luis et al., 2016). Brain imaging signatures in *SQSTM1*-ALS have not yet been systematically investigated.

3.5.8 TREM2—*TREM2* (triggering receptor expressed on myeloid cells 2) encodes a receptor exclusively expressed in immune cells, and is thought to interfere with anti-inflammatory function and the removal of apoptotic tissue (Giraldo et al., 2013). *TREM2* mutations were first detected in Nasu-Hakola disease, which manifests as recurrent bone fractures and early-onset dementia (Paloneva et al., 2002). Since then, *TREM2* variants have been identified to cause familial FTD and to increase risk of AD and FTD without bone involvement (Borroni et al., 2014; Giraldo et al., 2013; Guerreiro et al., 2013; Lattante et al., 2013a; Le Ber et al., 2014). Parkinsonism is common in *TREM2* mutation carriers, but genetic association studies do not support an association with ALS (Rayaprolu et al., 2013). Characteristic neuroimaging features in Nasu-Hakola disease include atrophy and white matter abnormalities most prominent in frontal cortices along with calcifications of the basal ganglia (Klünemann et al., 2005). Mild hypoperfusion in basal ganglia has also been reported in two preclinical *TREM2* carriers (Montalbetti et al., 2005). *TREM2* carriers with a pure FTD diagnosis exhibit frontal and/or temporal atrophy with parietal and hippocampal involvement along with extensive white matter lesions and reduced thickness of the corpus callosum (Giraldo et al., 2013; Guerreiro et al., 2013; Le Ber et al., 2014).

3.5.9 CHCHD10—*CHCHD10* encodes for coiled-coil-helix-coiled-coil-helix domain containing protein 10, a mitochondrial protein located in the intermembrane space and enriched at cristae junctions (Bannwarth et al., 2014). Mutations in *CHCHD10* cause structural abnormalities of mitochondria leading to fragmentation and suggest a role for mitochondrial dysfunction in FTD-ALS. The first report of a family with a *CHCHD10* mutation revealed clinical heterogeneity within the family and included features such as motor neuron disease, cerebellar ataxia, frontal cognitive and behavioral changes, parkinsonism, and mitochondrial myopathy (Bannwarth et al., 2014). Subsequent reports have described other clinical phenotypes including pure ALS and pure FTD, mitochondrial myopathy, and spinal motor neuronopathy (Ajroud-Driss et al., 2015; Dols-Icardo et al., 2015; Jiao et al., 2016; Penttilä et al., 2015; Zhang et al., 2015). Based on mutation frequencies in ethnically matched FTD and ALS cohorts, *CHCHD10* mutations appear to be more frequently associated with FTD phenotypes than with pure ALS (Chaussenot et al., 2014; Jiao et al., 2016; Marroquin et al., 2016; Teyssou et al., 2016; Wong et al., 2015). Disease progression in *CHCHD10*-related FTD and MND/ALS can be markedly slow, lasting up to 40 years (Bannwarth et al., 2014; Müller et al., 2014; Zhang et al., 2015).

Neuroimaging in patients with *CHCHD10* related FTD and ALS with cognitive impairment generally shows atrophy or [^{18}F]FDG-PET hypometabolism in frontal regions, and insular, temporal, parietal and cerebellar involvement have also been described (Bannwarth et al., 2014; Chaussenot et al., 2014; Dols-Icardo et al., 2015; Zhang et al., 2015). Structural MRI scans of *CHCHD10* mutation carriers with a pure MND/ALS phenotype, however, have not shown apparent abnormalities upon visual inspection (Bannwarth et al., 2014; Müller et al., 2014; Ronchi et al., 2015).

3.5.10 TBK1—The tumor necrosis factor receptor-associated factor NF-κB activator (TANK)-binding kinase 1 (*TBK1*) gene encodes for a protein that is active in autophagy and inflammatory signaling (Weidberg and Elazar, 2011). Clinically, *TBK1* loss-of-function

mutations manifest as bvFTD, PPA, and ALS and are associated with TDP-43 type B pathology (Freischmidt et al., 2015; Gijselinck et al., 2015). Movement disorders such as PSP and cerebellar syndromes have also been reported (Wilke et al., 2018). It is estimated that over half of carriers develop a pure ALS phenotype and less than fifth develop FTD or a mixed phenotype, yet cognitive impairment is among the most common initial symptoms and found in up to half of *TBK1* carriers (Freischmidt et al., 2015; Yu et al., 2019). In addition to bvFTD-ALS, patients with *TBK1* may develop svPPA-ALS and nfvPPA-ALS (Caroppo et al., 2015a).

Imaging reports of *TBK1*-FTD show asymmetrical atrophy and hypometabolism in frontal and/or temporal lobes, reflecting the clinical phenotype (Caroppo et al., 2015a; Hirsch-Reinshagen et al., 2019; Koriath et al., 2017; Lamb et al., 2019; Pottier et al., 2015; Van Mossevelde et al., 2016; Yu et al., 2019). In the majority of *TBK1*-FTD patients, hypometabolism extends to parietal regions (Hirsch-Reinshagen et al., 2019; Koriath et al., 2017; Schönecker et al., 2016; Van Mossevelde et al., 2016), though parietal symptoms are not common. The few reports with imaging on pure ALS and FTD-ALS due to *TBK1* mutations have described variable vulnerable brain regions, but involvement of temporal cortex, hippocampi, and cerebellum appear common across various reports (Jiao et al., 2018; McCombe et al., 2018; Tohnai et al., 2018; Van Mossevelde et al., 2016).

4 DISCUSSION

Literature overview

Taken together, neuroimaging studies of genetic FTD and ALS suggest that each genetic mutation shows a distinct pattern of targeted neuroanatomy that overlaps with the focal degeneration seen in the sporadic forms of these diseases. Because clinical trials for disease-modifying treatments have failed in symptomatic patients thus far, an ongoing hypothesis in the field of neurodegenerative diseases is that treatments may only be effective prior to profound neurodegeneration and may need to be administered during the presymptomatic phase. Numerous studies spanning various imaging modalities have revealed abnormalities in presymptomatic genetic mutation carriers for FTD and ALS, which generally converge within anatomical regions affected during the symptomatic stage. These studies suggest that abnormalities in functional connectivity networks, brain metabolism, gray matter volume and white matter integrity are detectable prior to the onset of profound neurodegeneration.

Clinical application of neuroimaging findings

As mentioned in the sections describing sporadic FTD and ALS, the clinical diagnostic criteria for bvFTD and PPA incorporate neuroimaging findings such as atrophy patterns on structural MRI or regions of hypometabolism on PET as supportive criteria. For ALS, neuroimaging is currently used only to exclude other conditions that may mimic ALS. In our opinion, the literature supports the idea that certain imaging features that may increase the clinician’s suspicion of genetic FTD or ALS. Although the ultimate confirmation of genetic FTD or ALS is made by genetic testing and not with neuroimaging, the following neuroimaging features may raise the index of suspicion for a genetic etiology, perhaps even in people without a known family history. For FTD or ALS due to the *C9orf72* expansion,

structural and functional MRI studies suggest that subcortical structures, the thalamus in particular, are more likely to be involved compared to sporadic disease. Patients with bvFTD due to *MAPT* mutations often have early memory impairment with corresponding focal mesial temporal involvement (atrophy or hypometabolism), both of which are not typical in sporadic bvFTD, *GRN* or *C9orf72*. Parietal lobe involvement has been reported in *C9orf72*, *GRN* and *TBK1* carriers, while sporadic bvFTD typically spares the parietal lobes. Patients with FTD due to *GRN* or *TBK1* mutations have been reported to have prominently asymmetric atrophy, most evident in the late stages of disease. Compared to sporadic ALS, more widespread frontotemporal involvement emerges in *C9orf72*-ALS, even in the absence of cognitive or behavioral symptoms, and many *SOD1* variants are associated with more prominent cervical spinal cord atrophy with relative sparing of cortical motor networks.

Limitations in the current literature and future directions

Thus far, many neuroimaging studies of genetic FTD and ALS have however been performed in relatively small cohorts in group analyses using cross-sectional data. In the past decade, international consortia for genetic FTD and ALS that collect harmonized multisite data have addressed this need for larger longitudinal cohorts. These longitudinal studies have begun building neuroimaging biomarker trajectories for different genetic mutations. For example, research on both genetic FTD and ALS suggests that patients with different mutations show differences in the order of involvement and rate of decline of specific brain structures (Jiskoot et al., 2019; Müller et al., 2020; Rohrer et al., 2015; van der Burgh et al., 2020; Whitwell et al., 2012; Young et al., 2018). Cross-sectional fMRI connectivity studies suggest that network connectivity may change dynamically throughout the lifespan in carriers of *GRN* (Borroni et al., 2012; Lee et al., 2019) or *SOD1* (Menke et al., 2016) mutations, or the *C9orf72* expansion (Agosta et al., 2017; Lee et al., 2017).

While these studies have been groundbreaking, group analyses are more vulnerable to individual subject heterogeneity and have limited ability to determine trajectories in individual patients. Assessing longitudinal trajectories at the individual-subject level will be necessary for developing neuroimaging as a biomarker for disease detection and monitoring.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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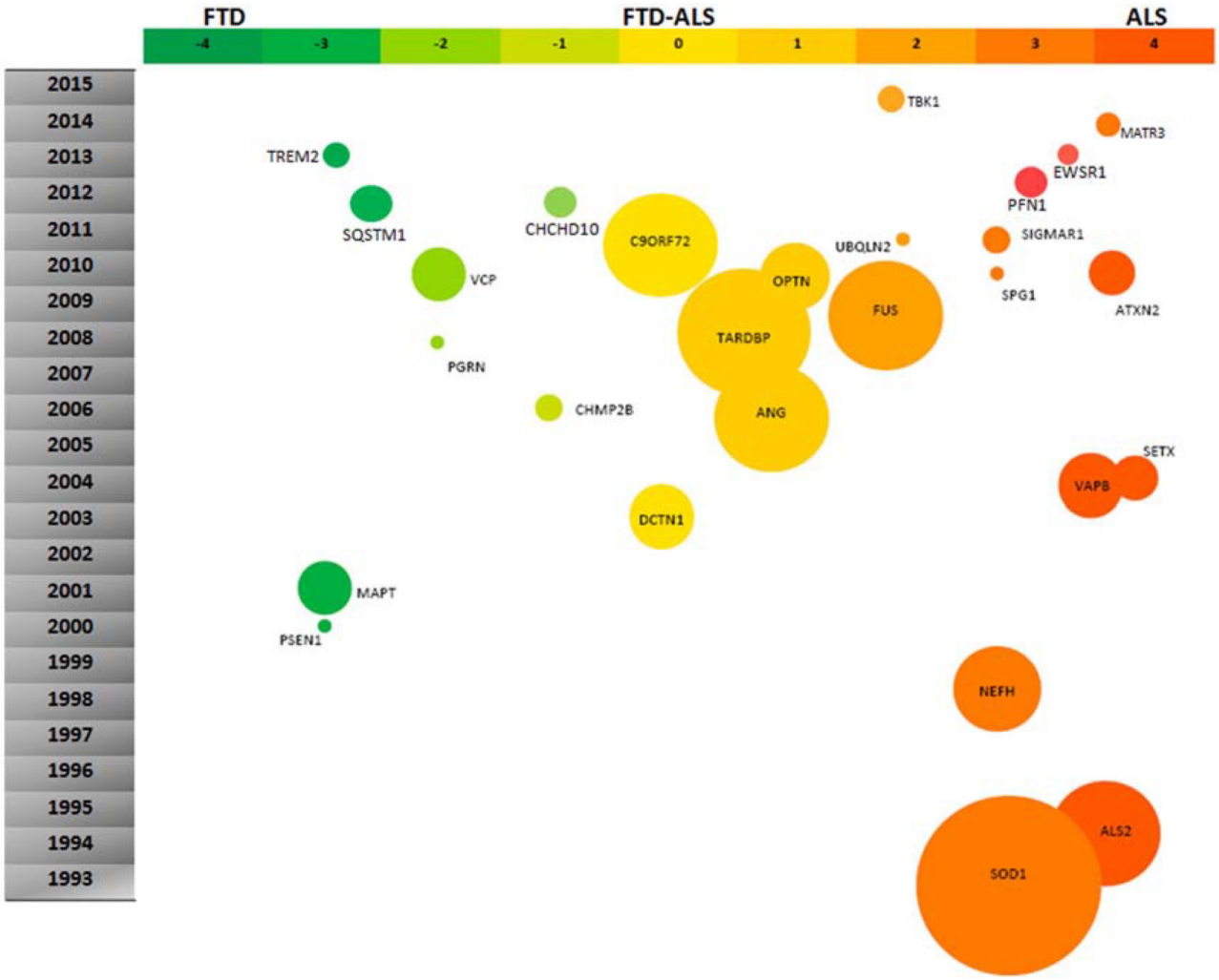

Fig. 1.

Genes whose mutations are associated with FTD-ALS spectrum disorders. Reprinted from Kumar et al. (2016) with permission from Elsevier.

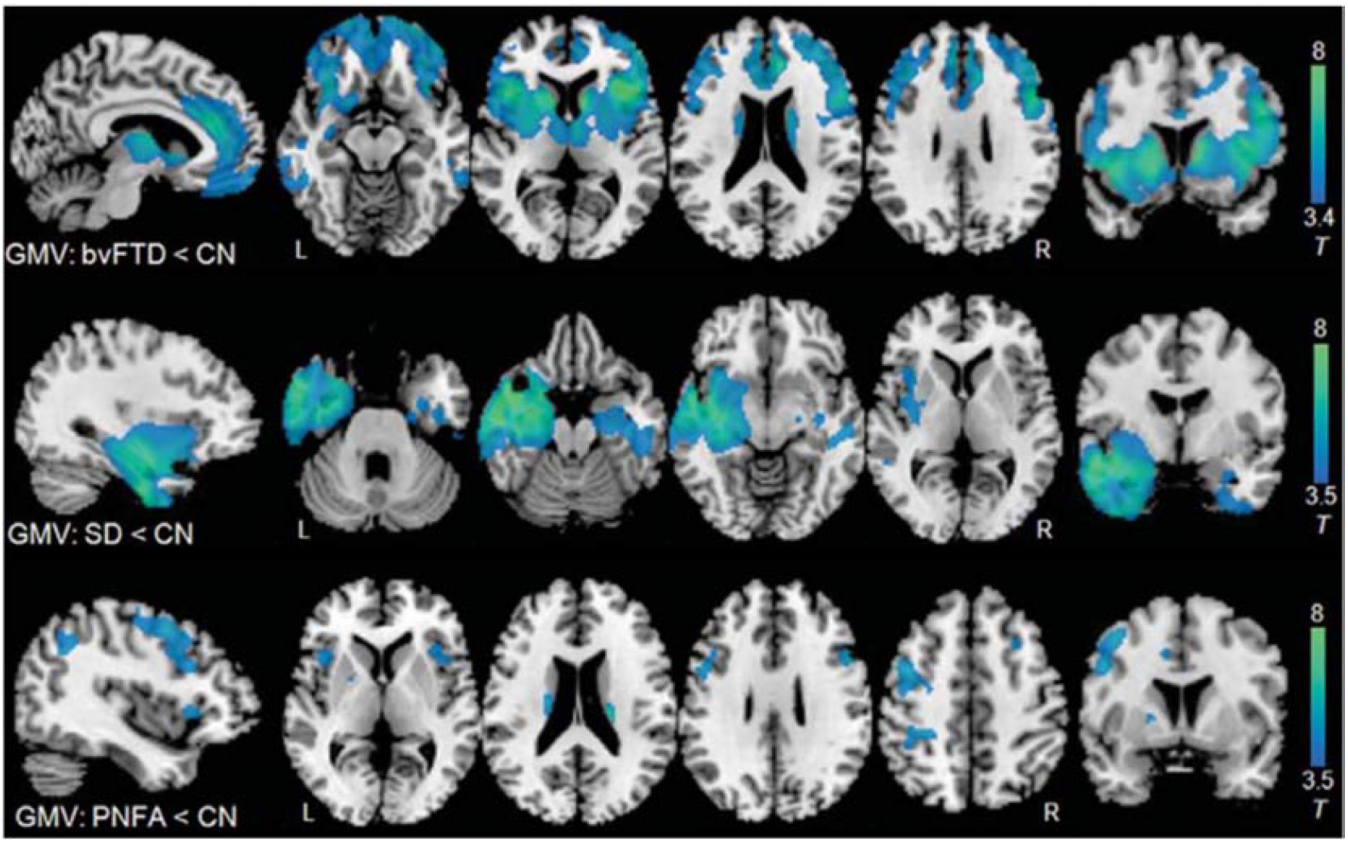

Fig. 2.

Comparison of grey matter atrophy patterns in three FTD syndromes. Patients with bvFTD, svPPA, nfvPPA were compared to healthy age-matched control subjects using voxel-based morphometry. Maps are thresholded at $p < 0.001$ uncorrected and superimposed on a study-specific template. BvFTD, behavioral variant frontotemporal dementia; SD, semantic dementia, also known as semantic variant PPA; PNFA, progressive nonfluent aphasia, also known as nonfluent variant PPA; GMV, grey-matter volume. Adapted from Zhang et al. (2013).

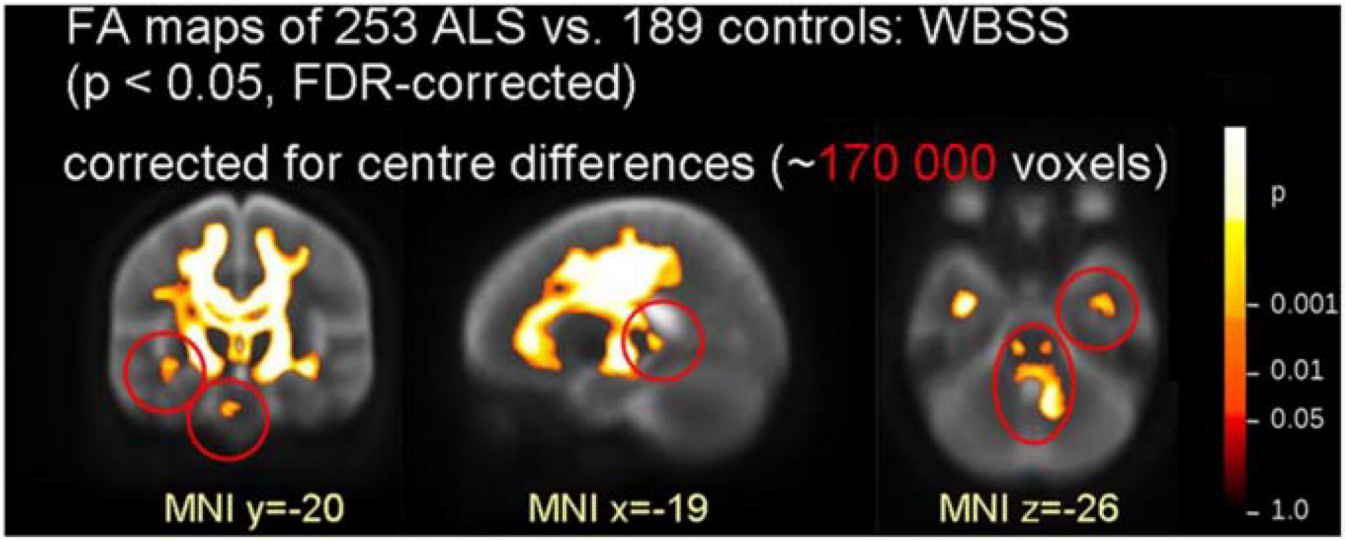

Fig. 3.

White-matter involvement in sporadic ALS revealed by a multi-site DTI study. FA decreases were found along the corticospinal tracts, frontal lobe, brainstem and hippocampi. Red circles indicate deficits only significant with correction for site differences. ALS, amyotrophic lateral sclerosis; WBSS, whole-brain-based spatial statistics; FA, fractional anisotropy; FDR, false discovery rate. Adapted from Müller et al. (2016) with permission from BMJ Publishing Group Ltd.

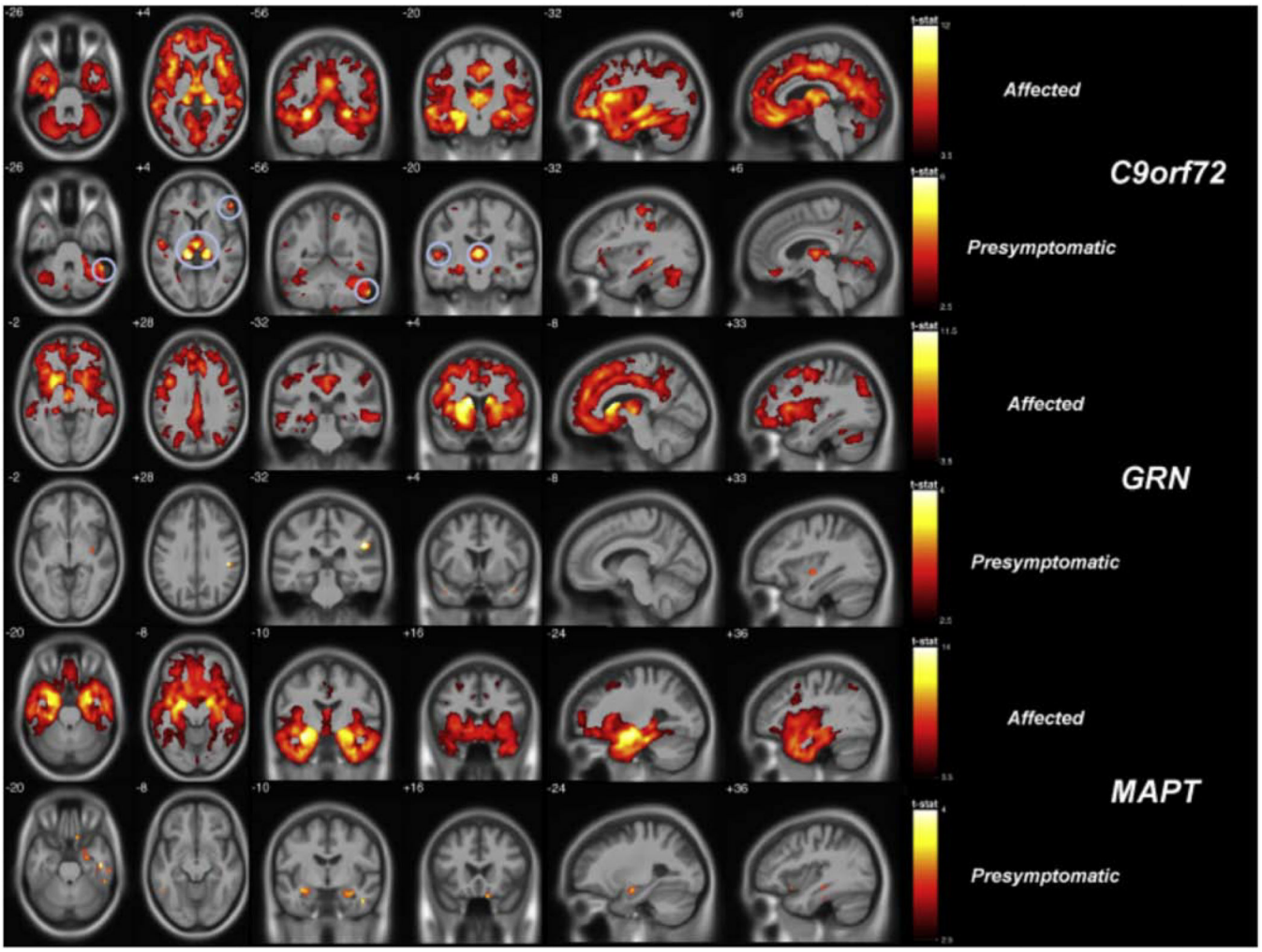

Fig. 4.

Gray matter deficits in FTD mutation carriers measured by voxel-based morphometry. In both affected (symptomatic) and presymptomatic stages of disease, carriers of the *C9orf72* expansion, *MAPT* and *GRN* mutations each exhibited distinct atrophy patterns with overlap in frontotemporal cortex and insula. Both *C9orf72* and *GRN* feature parieto-occipital atrophy in addition to frontotemporal atrophy, while *MAPT* targets the mesial temporal lobe. In the presymptomatic *C9orf72* group, circles indicate significantly low gray matter volume in the thalamus. Maps illustrate brain regions with reduced grey matter probability in affected ($p < 0.05$ FWE-corrected) and presymptomatic ($p < 0.001$ uncorrected) carriers compared to noncarriers. FTD, frontotemporal dementia; FWE, familywise error rate. Reprinted from Cash et al. (2018).