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Recent Advances in the Imaging of Frontotemporal Dementia

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Abstract

Neuroimaging has played an important role in the characterization of the frontotemporal dementia (FTD) syndromes, demonstrating neurodegenerative signatures that can aid in the differentiation of FTD from other neurodegenerative disorders. Recent advances have been driven largely by the refinement of the clinical syndromes that underlie FTD, and by the discovery of new genetic and pathological features associated with FTD. Many new imaging techniques and modalities are also now available that allow the assessment of other aspects of brain structure and function, such as diffusion tensor imaging and resting state functional MRI. Studies have utilized these recent techniques, as well as traditional volumetric MRI, to provide further insight into disease progression across the many clinical, genetic and pathological variants of FTD. Importantly, neuroimaging signatures have been identified that will improve the clinician's ability to predict underlying genetic and pathological features, and hence ultimately improve patient diagnosis.

Keywords

Magnetic Resonance Imaging; Diffusion Tensor Imaging; Resting-state functional MRI; behavioral variant frontotemporal dementia; semantic dementia; agrammatic; apraxia of speech; C9ORF72 hexanucleotide repeat; progranulin; tau; TDP-43; fused in Sarcoma; atrophy; white matter tracts; functional connectivity

INTRODUCTION

Frontotemporal dementia (FTD) is an umbrella term describing a group of clinical syndromes that are characterized by behavioral and language deficits and atrophy of the frontal and temporal lobes. Clinical syndromes can be separated into those in which behavioral and personality abnormalities are the most salient feature, and those in which speech and language deficits are the most salient feature, particularly early in the disease course. Early neuroimaging studies helped to define these disorders and identified characteristic patterns of frontotemporal atrophy on magnetic resonance imaging (MRI) and hypometabolism on 18-F fluorodeoxyglucose (FDG) PET that could be useful to separate FTD from other neurodegenerative disorders, such as Alzheimer's disease. Recent advances in neuroimaging have been driven largely by the refinement of the clinical syndromes that underlie FTD, and by the discovery of new genetic and pathological features of FTD. In addition, many new imaging techniques and modalities are now available that allow the assessment of other aspects of brain structure and function. Two such MRI-based techniques that have been utilized in FTD are diffusion tensor imaging (DTI) and resting state functional MRI (fMRI). Diffusion tensor imaging measures the diffusion of water through

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the brain tissue and can be used to visualize and measure the integrity of white matter tracts. Resting state fMRI was developed relatively recently and has already become a highly valuable technique since it allows the assessment of a novel aspect of brain function, namely neuronal connectivity between different regions of the brain. Spontaneous neural activity occurs in the brain during rest and is organized into specific functional networks that appear to relate to structurally connected neuroanatomical systems, such as the visual, executive and memory networks, and can each be measured using resting state fMRI. Utilizing these recent techniques, as well as traditional volumetric MRI, can provide insight into disease progression across the many clinical, genetic and pathological variants of FTD. In addition, these studies can help develop imaging biomarkers to improve the prediction of underlying pathology and patient prognosis.

In this review, we will discuss recent studies, particularly MRI-based studies, which have utilized neuroimaging in the different clinical, genetic and pathological variants of FTD (summarized in Table 1). We will focus on group-level imaging studies, rather than case reports, since they help identify consistent patterns of abnormalities that could be clinically useful.

NEUROIMAGING ASSOCIATIONS WITH CLINICAL SYNDROME

Behavioral variant frontotemporal dementia

The behavioral variant of FTD (bvFTD) is characterized by changes in behavior and personality, with language dysfunction also often noted later in the disease course[1]. Early imaging studies assessing bvFTD consistently observed patterns of atrophy on MRI in the frontal lobes, involving medial, dorsolateral and orbitofrontal regions, as well as the anterior temporal lobes[2] (Figure 1). Atrophy in bvFTD has been shown to be progressive, with greatest rates of atrophy observed in the frontal lobes[3, 4], particularly the medial frontal cortex[5].

Recent studies using DTI have demonstrated relatively bilateral and widespread degeneration of a number of white matter tracts in bvFTD[6-8]. Degeneration is particularly observed in white matter tracts with reciprocal projections into the frontal lobes, such as the superior longitudinal fasciculus, anterior cingulum, and genu of the corpus callosum, as well as tracts that project to the temporal lobes, such as the uncinate fasciculus and the inferior longitudinal fasciculus. Changes are typically most severe in anterior portions of the superior longitudinal fasciculus and inferior longitudinal fasciculus corresponding to the fact that atrophy is most severe in anterior regions of the frontal and temporal lobes. However, changes are also observed in posterior white matter tracts, including the posterior cingulate and posterior aspects of the superior longitudinal fasciculus, reflecting the fact that the lateral and medial parietal lobe can become involved as the disease progresses. Abnormal diffusivity in the anterior corpus callosum may be particularly useful to differentiate patients with bvFTD from those with other clinical variants of FTD[6].

A couple of studies have assessed resting state fMRI in bvFTD, and identified abnormal functional connectivity[9, 10]. Decreased functional connectivity has been observed in the salience network which is essentially a monitoring system that determines the salience of internal and external stimuli, and hence is important in processing socially relevant information, and involves the anterior cingulate and fronto-insular regions. Conversely, increased connectivity has been observed in the medial parietal lobe of the default mode network. The default mode network includes a network of brain regions that are active when the individual is at rest, and is hence associated with task-independent thought processes, and may subserve aspects of episodic memory function. The salience and default node networks are anti-correlated and therefore the increase in parietal connectivity is thought to

be caused by decreasing salience connectivity. While reduced connectivity in the frontally located salience network could be caused by atrophy in this region, there is evidence that abnormalities in functional connectivity may precede the development of atrophy[9]. This pattern of connectivity changes may be useful to differentiate bvFTD subjects from subjects with Alzheimer's disease[10], which typically show reduced connectivity in the default mode network, although much more work is needed before metrics can be developed that would be clinically useful.

Although the majority of studies assess bvFTD as a single syndromic entity it is being increasingly recognized that it is in fact a heterogeneous syndrome, both clinically and on neuroimaging. One study used a cluster analysis approach to assess in blinded fashion the anatomical heterogeneity in a cohort of bvFTD subjects[11], and identified four different anatomical subtypes which differ in the degree of frontal and temporal atrophy. Two subtypes show a large amount of frontal atrophy, with one showing both frontal and temporal atrophy and the other showing atrophy relatively restricted to the frontal lobes. Conversely, the other two subtypes showed predominant temporal atrophy, with one subtype showing atrophy restricted to the temporal lobe and the other showing atrophy in the temporal, frontal and parietal lobes. Importantly, clinical and neuropsychological findings differed across subtypes, and rates of future functional decline were found to be greater in the subtypes associated with predominant frontal atrophy[12], suggesting firstly that this is a clinically meaningful sub classification and secondly that frontal lobe volumes could be a useful prognostic tool to predict faster clinical decline. These subtypes may also have different pathological and genetic underpinnings, with, for example, the majority of subjects in the temporal-dominant subtype having familial disease with mutations in the microtubule associated protein tau (MAPT) gene (as will be discussed in more depth below)[11, 13]. The degree of hemispheric asymmetry can also vary across bvFTD subjects, with the majority showing symmetric patterns of atrophy, but some showing either left or right-sided dominant atrophy[14, 15]. Symmetric subjects are more likely to have a temporofrontoparietal subtype, while asymmetric subjects more likely to be frontotemporal or frontal dominant subtypes[14]. The anatomical patterns therefore vary across bvFTD subjects, and it is likely that that DTI and resting state data will also be heterogeneous. However, in addition to these anatomical variants, it has also been recognized that there is another subtype of bvFTD subjects which do not show any observable atrophy on MRI despite presenting with the clinical features of bvFTD[16, 17]. These subjects have been referred to as having a bvFTD "phenocopy syndrome" and tend to progress very slowly clinically. The majority of these subjects also have normal FDG-PET scans[18]. Some of these subjects may not have an underlying FTD pathology and instead may be a psychiatric phenocopy, although others may have FTD pathology[19]. Therefore, if a patient presents with bvFTD with normal imaging they likely have a low risk of progression.

Recent studies have also further refined the association between behavioral features and neuroimaging abnormalities in bvFTD. A greater burden of behavioral deficits has been associated with atrophy of the right frontotemporal lobes[14, 20], and there is increasing evidence that different specific frontal and temporal regions are associated with different behavioral features. Disinhibition is a common feature of bvFTD and early studies suggesting neuroanatomical correlates in the medial orbitofrontal cortex/subgenual cingulate gyrus region[20, 21] have been replicated in more recent studies[22-24], although correlations have also been observed in the temporal lobe[22, 25, 26]. White matter tract degeneration of the uncinate, forceps minor, and genu of corpus callosum have also been associated with disinhibition[22]. The neuroanatomical correlates of one of the other common behavioral deficits in bvFTD, apathy, have been more variable and are hence less clear, with studies implicating the medial prefrontal cortex[20, 25], dorsolateral prefrontal cortex[24, 26], anterior cingulate[24], temporal lobe[27], and caudate[27]. Variability is

likely due to studies including different patient populations and using different analysis methods. Other behavioral deficits that have been assessed include abnormalities in eating (such as binge eating and sweet tooth) which tend to correlate to atrophy and hypometabolism in the right anterior insula and orbitofrontal cortex[25, 28, 29], although a recent study has also implicated the hypothamalus[30], and obsessive-compulsive features which correlate to atrophy in the globus pallidus, left putamen and lateral temporal lobe[31]. Atrophy of the frontal lobe has also been associated with impaired decision making[32], empathic deficits[33], and even deficits in episodic memory[34]. Subjects with bvFTD can also often suffer from stereotypies which are repetitive, predictable, coordinated movements that are performed without any purpose, e.g tapping one's own leg or protruding ones tongue. These abnormalities have been shown to be associated with atrophy of the striatum in bvFTD[35].

Speech-language variants of frontotemporal dementia

The clinical classification of the speech and language disorders has evolved substantially over recent years. The language disorders semantic dementia (SD) and progressive non-fluent aphasia (PNFA) have long been considered variants of frontotemporal dementia since both can develop behavioral features and overlap clinically with bvFTD[1]. Patients with SD however present initially with word finding and single word comprehension difficulties, while patients with PNFA present with halting speech and agrammatism[1]. Both variants have also been classified under the umbrella term primary progressive aphasia (PPA) as the language deficits tend to occur in isolation for the first couple of years of the disease. Given this association with PPA, recent clinical criteria have described SD as the semantic variant of PPA (svPPA), and PNFA as the agrammatic variant of PPA (agPPA)[36]. A third variant of PPA has also been described in which patients present with impaired sentence repetition, anomia and phonological difficulties, and has been termed the logopenic variant of PPA (lvPPA)[36, 37]. Recent pathological studies, and studies that utilize amyloid-binding imaging ligands and PET[38], have however demonstrated that the majority of patients with lvPPA have underlying Alzheimer's disease, rather than a frontotemporal dementia pathology. Although Alzheimer's disease has been observed in a few patients with svPPA and agPPA, the majority of these patients have a frontotemporal dementia pathology and will hence be the focus of our discussion.

Early studies showed that svPPA is associated with very consistent patterns of atrophy and hypometabolism that target the left anterior temporal lobe, with particularly severe involvement of inferior temporal regions[39-42] (Figure 1). The orbitofrontal lobe, insula, caudate and right anterior temporal lobe can also be affected. Longitudinal MRI studies have demonstrated that the fastest rates of atrophy occur in the temporal lobes, with increased rates of atrophy also observed in the frontal lobes [3, 4, 43, 44], insula, caudate nucleus and thalamus[45]. Some studies have found that the left temporal lobe has the fastest rates [3, 43], but others have found greatest rates in the right temporal lobe suggesting that the right hemisphere will catch up with the left, as the disease progresses[45, 46]. However, it has also been recognized that patients can have greater involvement of the right anterior temporal lobe at baseline, suggesting that the disease in these subjects starts in the right temporal lobe and may later progress to the left temporal lobe[13, 45]. These patients typically present with prosopagnosia (an inability to recognize familiar faces) and behavioral abnormalities[47-49], although they can also have word finding problems depending on the degree of involvement of the left temporal lobe; language deficits are however not the dominant symptom in these cases. An assocation between verbal semantic memory (e.g. object naming) and abnormalities in the left anterior temporal lobe in svPPA has been well established, with studies particularly implicating the left fusiform gyrus[50, 51]. Studies have also found associations between abnormalities in the right anterior temporal lobe and

prosopagnosia[52], deficits in the recognition of facial emotions[53], and deficits recognising famous musical tunes[54, 55]. Prosopagnosia has been particularly linked to the right fusiform gyrus[52]. The fusiform gyrus therefore appears to be particularly important for both verbal and visual semantic memory.

Recent studies have utilized DTI to assess patterns of white matter tract degeneration in typical left-sided svPPA, and have shown degeneration primarily in the uncinate fasciculus and inferior longitudinal fasciculus, with more severe abnormalities observed in the left hemipshere[7, 56-59]. Degeneration has also been observed in the genu of the corpus callosum and the arcuate fasciculus, with a relative sparing of tracts in posterior regions of the brain, such as the parietal aspects of the superior longitudinal fasciculus[7, 57, 58]. Decreased integrity of the inferior longitudinal fasciculus, with sparing of the superior longitudinal fasciculus, can help differentiate svPPA from bvFTD and agPPA[6]. White matter tract degeneration of these regions matches well with the regions of grey matter atrophy in svPPA, as one would expect.

In contrast to the temporal lobe patterns observed in svPPA, agPPA largely targets the frontal lobes with atrophy and hypometabolism observed primarily in the posterior frontal premotor cortex, involving both Broca's area and superior premotor regions, as well as the insula[7, 37, 60-64] (Figure 1). The superior temporal gyrus has also been implicated in number of studies[58, 64], as well as the striatum[65]. White matter tract degeneration has been observed primarily throughout the left superior longitudinal fasciculus[7, 58, 59], particularly the arcuate fasciculus that projects into the inferior frontal lobe. It has recently been acknowledged that as well as having agrammatic aphasia, patients with agPPA usually always also have a motor speech abnormality known as apraxia of speech (AOS)[61, 66] in which speech production is affected as a result of impaired planning or programming of syllables across words, or within multisyllabic words. Subjects that show dominant AOS tend to have greater atrophy and hypometabolism of the superior premotor cortex, while those with more dominant aphasia show greater involvement of inferior posterior frontal regions[60, 61]. In fact, it has also recently been recognized that patients can have an isolated AOS, without any evidence of agrammatic aphasia (referred to as primary progressive apraxia of speech)[67]. These PPAOS subjects show focal patterns of atrophy and hypometabolism in both medial and lateral superior premotor cortex, and show white matter tract degeneration of the superior longitudinal fasciculus[67]. All these findings suggest that AOS results from abnormalities in the superior premotor cortex, while agrammatic aphasia results from abnormalities in the inferior premotor cortex and Broca's area. Indeed, language fluency has been shown to correlate to atrophy in the inferior and middle frontal gyri[68].

NEUROIMAGING ASSOCIATIONS WITH GENETIC ABNORMALITIES

A high proportion of FTD subjects have familial disease with an autosomal dominant pattern of inheritance. A number of genetic mutations responsible for FTD have been identified, including mutations in the progranulin (*PGRN*) and *MAPT* genes, and the recently identified hexanucleotide repeat expansion in *C9ORF72*[69, 70]. Mutations in the *MAPT* gene and the *C9ORF72* repeat expansion tend to be associated with bvFTD, with amyotrophic lateral sclerosis also associated with the *C9ORF72* repeat expansion and additional semantic deficits often associated with *MAPT* mutations. The clinical phenotypes associated with *PGRN* mutations are more varied and include bvFTD and agPPA, as well as corticobasal syndrome. Despite variability across individual subjects with these mutations[71, 72], neuroimaging studies have shown distinct and consistent patterns of atrophy associated with these different genetic mutations. Mutations in the *MAPT* gene have consistently been associated with frontotemporal atrophy, with the most severe abnormalities observed in the

temporal lobes[73-75]. Predominant temporal atrophy is a consistent finding across different *MAPT* mutations, although the medial temporal lobes tend to be the most severely affected regions in some mutations, with the lateral temporal lobes worse in others[76]. In contrast, patterns of atrophy in subjects with mutations in *PGRN*, while widespread, tend to heavily involve the lateral temporal and parietal lobe and are highly asymmetric[73, 74, 77]; some with greater involvement of the left hemisphere and others with greater involvement of the right hemisphere. Patterns of atrophy have been shown to be more asymmetric in patients with *PGRN* mutations than those with *MAPT* mutations[74].The neuroanatomical pattern of atrophy associated with the *C9ORF72* hexanucleotide repeat has only recently been studied, with some variability observed across studies. The majority of studies have found that this genetic abnormality is associated with relatively symmetric patterns of atrophy[14] that particularly target the frontal lobes[78-80], with unusual and characteristic atrophy also observed in the cerebellum[79, 80]. The cerebellar findings concur with pathological data that demonstrates TDP-43 inclusions in cerebellar tissue[81]. Cortical patterns of atrophy are however generally widespread with heavy involvement of posterior cortices, in addition to the frontal lobe[78, 80]. One study has demonstrated that atrophy in the occipital lobes and cerebellum can help differentiate subjects with the *C9ORF72* hexanucleotide repeat from those with *MAPT* or *PGRN* mutations, and from sporadic disease, within subjects that have the same clinical presentation of bvFTD[80]. Both subjects with *MAPT* and *PGRN* mutations tend to show greater atrophy in the temporal lobes than subjects with *C9ORF72*[79, 80]. One center has reported involvement of the thalamus in the *C9ORF72* subjects[79], although this has not been replicated across all studies and does not appear to have a pathological correlate.

Rates of atrophy have also been assessed across these genetic variants, and studies have consistently found that *PGRN* mutations are associated with faster rates of whole brain atrophy than *MAPT* mutations[74, 82], and the *C9ORF72* hexanucleotide repeat[79]. The *PGRN* mutations are therefore associated with a more rapidly progressive disease phenotype. However, rates of atrophy of the hippocampus are similar across *PGRN* and *MAPT* mutations, reflecting the heavy medial temporal burden in the *MAPT* cohort[82].

A significant advantage of studying patients with familial disease with known genetic mutations is that it provides a construct to assess neuroimaging in the very earliest stages of the disease. Many asymptomatic subjects from genetic families are followed by centers around the world allowing the assessment of imaging changes before the onset of symptoms. There is a suggestion from a number of studies that atrophy measured on MRI is not abnormal at the group-level in asymptomatic carriers of the *PGRN* and *MAPT* mutations, but that other modalities may prove to be more useful early biomarkers. A study assessing asymptomatic *PGRN* mutation carriers failed to find any evidence of grey matter atrophy, but did find DTI abnormalities in the left uncinate fasciculus and fronto-occipital fasciculus[83]. Studies in asymptomatic *MAPT* mutation carriers have also failed to identify grey matter atrophy, but have demonstrated functional connectivity abnormalities in the salience and default-mode network on resting state fMRI[9], and abnormalities in metabolite levels using magnetic resonance spectroscopy[84], that match the findings observed in bvFTD. There is also a suggestion that abnormalities on PET using microglial activation and striatal dopaminergic ligands could be identified in asymptomatic *MAPT* carriers[85]. These modalities could therefore have potential as biomarkers to be able to identify very early disease associated with these mutations.

NEUROIMAGING ASSOCIATIONS WITH PATHOLOGY

Frontotemporal dementia is associated with a heterogeneous range of different pathologies that have only recently been elucidated[86]. Pathologies underlying the FTD syndromes can

be classified according to the abnormal protein identified at autopsy. Three major proteins have now been identified: tau, TAR DNA binding protein of 43 kDa (TDP-43) and fused in sarcoma (FUS). A range of specific pathologies are then associated with each of these different proteinopathies. Magnetic resonance imaging studies that have utilized autopsy confirmed cases have demonstrated specific neuroanatomical signatures associated with the different FTD pathologies, which can be identified even within groups of subjects with the same clinical syndrome[87]. These signatures therefore have the potential to be useful biomarkers of pathology in FTD.

Two common tau pathologies underlying FTD include Pick's disease with Pick bodies and FTD with microtubule-associated tau (with *MAPT* gene mutations). However, the tau pathologies of progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) can also underlie the clinical syndromes of FTD. As discussed above, mutations in the *MAPT* gene have been associated with anterior temporal atrophy. In contrast, Pick's disease is associated with striking involvement of the prefrontal cortex, including orbitofrontal, medial and dorsolateral aspects, and less severe involvement of the anterior temporal lobe[88-90], and shows greater frontal atrophy than subjects with *MAPT* mutations[88]. More focal patterns of atrophy are associated with PSP and CBD. Both target the posterior frontal cortex, particularly premotor regions, although CBD often shows more widespread and asymmetric frontal involvement and can also show involvement of the parietal lobes[89-93]. The striatum has been implicated in both PSP and CBD, although appears to show greater involvement in CBD[91]. Brainstem atrophy and degeneration of the superior cerebellar peduncle are typical features of PSP, although it is unclear whether these features are observed when PSP pathology is associated with an FTD clinical syndrome[91].

Pathology characterized by deposition of TDP-43 has been subdivided into four different types (A-D) according to the morphology of the inclusions[94]. Each type has different clinical associations, with bvFTD, agPPA and corticobasal syndrome associated with type A, bvFTD with motor neuron disease associated with type B, and svPPA associated with type C[86]. Patterns of atrophy also differ across the types. Type A is associated with widespread and asymmetric patterns of loss involving frontal, temporal and parietal lobes[95, 96]. Type B shows predominant frontal atrophy[95, 96], consistent with the clinical diagnoses of bvFTD and bvFTD with motor neuron disease[97]. Type C however is associated with asymmetric anterior temporal lobe patterns of atrophy, again consistent with the clinical diagnosis of svPPA[95, 96]. Patterns in type C can be either left or right-sided[13]. Progranulin mutations have been associated with TDP type A, and one study has shown that TDP type A subjects with these mutations have greater atrophy in the lateral temporal lobe than those without *PGRN* mutations[96]. The findings also help explain why *PGRN* mutations are associated with such widespread asymmetric patterns of atrophy; it reflects the underlying pathology. Similarly, the *C9ORF72* hexanucleotide repeat expansion is associated with TDP types A and B[81] which likely contributes to the patterns of atrophy observed in these cases.

The pathologies characterized by the presence of FUS pathology are much rarer than the tau or TDP pathologies. A few group neuroimaging studies have assessed these subjects, although in total they only assess a handful of subjects. Nevertheless, very consistent patterns of atrophy have been observed across the studies, with involvement of the frontotemporal lobes and particularly striking atrophy of the caudate nucleus[93, 98, 99]. The caudate is actually involved to a greater degree in FUS pathologies, than in both tau or TDP-43 pathologies[98], and therefore could be a useful biomarker of FUS pathology.

Importantly, the signature patterns of atrophy observed across the different FTD pathologies have been shown to be independent of clinical syndrome. For example, even within subjects

with the same bvFTD diagnosis, patterns of atrophy have been shown to differ between those with underlying Pick's disease, TDP type A and CBD[89, 90]; perhaps explaining some of the heterogeneity observed in neuroimaging studies of bvFTD. Pathology therefore appears to be an important determinant of neurodegeneration in FTD, and neuroimaging therefore has potential to help predict underlying pathology during life in FTD. It appears however to be the specific pathologies that determine patterns of neurodegeneration, with patterns differing across pathologies defined by the same abnormal protein. This explains why studies have not been able to identify one specific neuroanatomical signature of the abnormal proteins, especially tau or TDP-43[100, 101].

CONCLUSION

The last few years have been an exciting time for neuroimaging research in FTD. The clinical, genetic and pathological classifications of FTD have constantly evolved which has allowed further refinement of the imaging features associated with FTD. Neuroimaging has proven to be an invaluable tool which not only helps characterize the many different aspects of FTD, but has demonstrated clear differences across genetic and pathological groupings which have the potential to be important biomarkers to aid diagnosis. Future studies will likely focus further on investigating recently developed technologies and will no doubt provide more insight into the structural and functional dysfunction in FTD.

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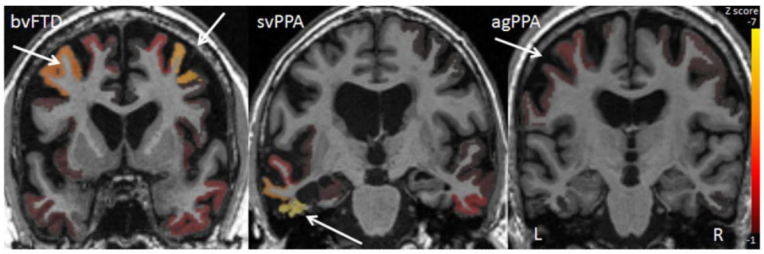

FIGURE 1.

Representative 3 Tesla T1-weighted MRI from subjects diagnosed with bvFTD, svPPA and agPPA. Regional volumes were z transformed compared to a control cohort accounting for age and regions showing atrophy (greater than 1 z score from controls) are color coded (most severe atrophy shown in yellow). The bvFTD subject shows relatively bilateral prefrontal and anterior temporal atrophy. In contrast, the svPPA subject shows severe atrophy of the left temporal lobe, particularly the inferior temporal and fusiform gyri, with some loss also observed in the inferior right temporal lobe. The agPPA subject shows a milder pattern of atrophy particularly affecting the left inferior and middle frontal gyri. Z transformation and resultant maps (STANDmaps) courtesy of Dr. Prashanthi Vemuri, Mayo Clinic, Rochester, MN.

TABLE 1

Summary of imaging findings across clinical, genetic and pathological variants of FTD

	Prefrontal	Premotor	Med TL	Lat TL	PL	OL	Striatum	Cerebellum
Clinical syndromes								
bvFTD	+++	+	++	++	+	−	+	−
svPPA	+	−	+++	+++	−	−	+	−
agPPA	−	++	−	−	−	−	+	−
Genetic mutations								
MAPT	++	−	+++	+++	+	−	+	−
PGRN	++	−	+	++	++	−	−	+
C9ORF72	+++	++	+	++	++	+	+	++
Tau pathologies								
Pick's disease	+++	+	++	++	+	−	+	−
PSP	−	+	−	−	−	−	+	+
CBD	+	++	−	−	+	−	++	−
TDP pathologies								
TDP type A	+++	−	+	++	++	−	−	+
TDP type B	++	+	+	+	−	−	+	−
TDP type C	+	−	+++	+++	−	−	+	−
FUS pathology	++	−	+	+	−	−	+++	−

Atrophy has been graded as follows: relatively spared (−), mildly involved (+), moderately impaired (++), severely impaired (+++)

TL = temporal lobe; PL = parietal lobe; OL = occipital lobe