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REVIEW

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How predictive are temporal lobe changes of underlying TDP-43 pathology in the ALS-FTD continuum?

Ana Paula Arantes Bueno[1], Maxime Bertoux[2,3], Leonardo Cruz de Souza[4], and Michael Hornberger[2,3]

[1]Center of Mathematics, Computation and Cognition, Universidade Federal do ABC, Santo André, Brazil
[2]Department of Medicine, Norwich Medical School, University of East Anglia, Norwich, United Kingdom
[3]Dementia and Complexity in Later Life, NHS Norfolk and Suffolk Foundation Trust, Norwich, United Kingdom
[4]Departament of Internal Medicine, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil

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Correspondence to
Michael Hornberger
Department of Medicine, Norwich Medical School, University of East Anglia, Norwich Research Park, James Watson Road, Norwich, Norfolk, NR4 7TJ, United Kingdom
Tel: +441603597139
Fax: +441603593752
E-mail: m.hornberger@uea.ac.uk

Detection of underling proteinopathies is becoming increasingly important across neurodegenerative conditions due to upcoming disease intervention trials. In this review, we explored how temporal lobe changes in amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) can potentially predict underlying TDP-43 pathology subtypes in FTD. To date, emphasis has been given to frontal lobe changes in the study of the cognitive and behavioural impairments in both syndromes but an increasing number of pathological, imaging and neuropsychological studies suggest how temporal lobe changes could critically affect the cognition and behaviour of these conditions. In this current article, we reviewed pathological, imaging as well as clinical/neuropsychological findings of temporal involvement in the ALS-FTD continuum, how they relate to temporal lobe changes and the underlying TDP-43 pathology in FTD. Findings across studies show that TDP-43 pathology occurs and coincides in many structures in ALS and FTD, but especially in the temporal lobes. In particular, anterior and medial temporal lobes atrophy is consistently found in ALS and FTD. In addition, memory and language impairment as well as emotional and Theory of Mind processing deficits that are characteristics of the two diseases are highly correlated to temporal lobe dysfunction. We conclude by showing that temporal lobe changes due to TDP-43 type B might be particular predictive of TDP-43 type B pathology in behavioural variant FTD, which clearly needs to be investigated further in the future.

Key words: Amyotrophic lateral sclerosis; Frontotemporal dementia; Memory; Temporal lobes

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INTRODUCTION

TDP-43 is one of the most common proteinopathies in neurodegeneration and overlaps between many different clinical phenotypes. Still, it is not clear whether specific clinical or biomarker features overlap between these clinical syndromes, and in turn would allow detecting TDP-43 pathology in vivo. This is becoming particularly relevant with upcoming disease modifying therapies that will target the underling proteinopathy. In the current review, we will explore how such a view would apply to amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD), two different syndromes sharing many clinical features. More specifically, the majority of ALS patients have underlying TDP-43 pathology whereas in FTD there is a mix of underlying TDP-43 and tau pathology. The question arises whether based on the ALS findings one can determine which clinical features or biomarkers in FTD will be predictive of underling TDP-43 pathology.

ALS is a progressive neurodegenerative disease affecting the motor neuron function. The clinical manifestation of ALS is characterized by progressive weakness concomitant with signs of spasticity, hyperreflexia, fasciculations and muscle wasting. Severe dysarthria and dysphagia is also commonly present and respiratory failure often leads to death in 3 to 5 years.[1] By contrast, FTD is a neurodegenerative disease characterized by focal atrophy of frontal and temporal lobes.[2] It is commonly regarded more as a cognitive or behavioural disease encompassing a behavioural variant (behavioural variant of frontotemporal dementia - bvFTD) and two language variants (semantic dementia – SD and progressive non-fluent aphasia - PNFA).[3] Significant progressive changes in personality, behaviour and social cognition mainly characterizes bvFTD, while language impairments are the hallmark of SD and PNFA.[4]

Both ALS and FTD are multisystem neurodegenerative disorders with overlapping clinical and pathological characteristics.[5,6] Clinically, ALS and FTD patients can even present a combination of both syndromes (ALS-FTD) or develop symptoms of each other with disease progression.[7] More specifically, ALS patients can present with behavioural/cognitive symptoms, whereas FTD patients can develop motor symptoms. Similarly, neuroimaging studies have reported anatomical changes in frontal, temporal and limbic areas for ALS, FTD and ALS-FTD patients as well as decreased integrity of gray matter (GM) and white matter (WM) in the frontal, temporal and parietal lobes, including long association fibers.[8,9]

On a pathological level, it is well established that TDP-43 is the main pathology found in most of ALS cases.[10-13] Interestingly, TDP-43 is also one of the main pathologies (~50%) of FTD, in particular in SD as it accounts for 75% of the cases.[14] Although there are different subtypes of TDP-43 depositions, the presence of a shared proteinopathy reinforces the idea of a continuum across ALS and FTD. Convergences in the clinical manifestations between them can be possibly attributed to the topographical distribution of the pathology in critical brain regions, especially in the frontotemporal network as TDP-43 in these regions have been particularly reported.[15-17]

There has been particular interest in the frontal changes in ALS and FTD to show how both diseases overlap for atrophy and clinical symptomology.[10,18,19] Despite this shared overlap of frontal changes, these do not seem predictive of underlying pathology in FTD.[20] However, less emphasis has been given to the temporal lobe changes and how they might relate to TDP-43 proteinopathy. Since it is currently not possible to clinically distinguish the underlying pathology in FTD, as cases are an admixture of tau and TDP-43, being able to identify the pathology would have major implications for future disease intervention therapies targeting specific proteins.

Whether temporal lobe changes can be predictive of TDP pathology, in particular Type B, in ALS and FTD is thus a critical question with a high clinical relevance. In order to explore this field, a Pubmed database search was performed using terms as ALS, FTD, TDP-43, temporal lobes (and related structures) and MRI. Only articles in English and presenting changes in temporal lobes were considered. In the following sections, we will explore temporal lobe changes in ALS and FTD from a multi-disciplinary angle, via neuropathological, neuroimaging and clinical/neuropsychological findings before attempting to synthesis the information towards the temporal lobe contribution related to TDP-43 pathology.

TDP-43 PATHOLOGY IN THE ALS-FTD CONTINUUM

Neurodegenerative diseases are characterized by the presence of abnormal intracellular protein aggregates in the brain.[10] TDP-43 depositions are specially found in ALS, FTD and ALS-FTD patients. Based on the morphologic appearanc-

es and anatomical distribution of the immunoreactive inclusions, TDP pathology is classified as being of type A, B, C or D.[21]

The vast majority of ALS cases is associated with TDP-43 type B pathology.[13,16] TDP-43 deposition is reported to be first accumulated across the motor system before spreading to the temporal lobes.[22,23] Brettschneider and colleagues[23] proposed a TDP-43 staging scheme from 1 to 4 to account for spatial and temporal development of the pathology, considering TDP stage 4 when the pathology is also present in the hippocampal formation.

TDP pathology in bvFTD is initiated in the orbitofrontal cortex and amygdala, progressing then to frontal and temporal cortices before affecting the motor system, visual cortex and cerebellum.[22,24,25] bvFTD patients are associated with TDP type A and B, with type A involving the frontal, temporal and parietal lobes and type B, the hippocampus.[20,21,26] However, it is still not possible to clinically distinguish between types A and B.[27] In a recent study on bvFTD with TDP-43 pathology, 100% of the cases investigated showed TDP-43 in the amygdala and the majority had the pathology in the medial temporal lobe (MTL; dentate gyrus and entorhinal cortex). TDP pathology is particularly reported in SD, with TDP-43 type C associated to anterior temporal lobe (ATL) atrophy and with type A and, more important, type B in ALS-FTD.[16,20,21,28]

In addition, it is suggested that the C9orf72 gene mutation is the most frequent cause of familial ALS and FTD and accounts for up to 10% of sporadic ALS cases.[29,30] The temporal lobes are shown to be critically affected in C9orf72 patients [31] linked to TDP-43 pathology types A and B.[32]

In sum, ALS and FTD could be considered as different manifestations of a shared proteinopathy.[16] Although the presence of TDP pathology in some structures can help to distinguish between the disorders, the pathology coincide in many regions and reinforce the idea of a continuum across the diseases. In particular, immunoreactive inclusions of TDP-43 in the amygdala, parahippocampal gyrus, hippocampus, as well as in other temporal lobe structures have been reported in both conditions.[23,25,33]

Neuroimaging findings

Voxel based morphometry (VBM)

Atrophy of the temporal lobes in ALS, FTD and ALS-FTD have been well documented.[5,34-37] ALS patients show temporal lobe atrophy, including ATL, hippocampal formation and left temporal gyrus.[7,38-40] In bvFTD patients, temporal lobe atrophy, particularly in temporal poles, temporal gyrus, hippocampus, parahippocampal cortices and amygdala have been reported.[41-46] Temporal atrophy is also characteristic of SD with marked atrophy of ATL, temporal poles, fusiform gyrus, amygdaloid complex and temporal gyrus.[3,47-49] Lillo and colleagues[6] have reported atrophy of temporal regions in both bvFTD and ALS-FTD with no significant differences between these two diseases. ALS-FTD patients have shown temporal atrophy, including the ATL, temporal gyrus, hippocampus and amygdala.[5,18,47,50] Interestingly, temporal atrophy dominance is found in ALS-FTD compared with pure ALS patients.[51] Supplementary Table 1 (Supplementary material) summarizes the most common areas with GM changes reported in the literature for ALS and FTD (results include VBM and other analyses).

Diffusion tensor imaging (DTI)

DTI analyses consistently report WM changes in tracts connecting temporal lobes to frontal and occipital regions in ALS patients, specifically, the uncinate fasciculus and superior longitudinal fasciculus.[52-54]Atrophy in temporal regions for both bvFTD and SD has been reported with WM changes found to be particularly important in the uncinate and longitudinal fasciculus.[2,55-57] Atrophy in the inferior longitudinal fasciculus has been observed in ALS-FTD.[6] ALS and ALS-FTD patients showed more WM degeneration than bvFTD, including in the temporal poles.[6] ALS, bvFTD and ALS-FTD showed overlapping WM degeneration in the inferior longitudinal fasciculus.[6] Supplementary Table 2 (Supplementary material) shows common areas with WM changes found in the literature for the ALS-FTD spectrum (results include DTI and other analyses).

Functional imaging

Positron emission tomography (PET) with Fluoro-Desoxy-Glucose (FDG) studies found hypermetabolism in the temporal poles, superior temporal gyri and hippocampus in ALS patients.[58] FTD patients showed metabolic impairment in temporal lobes.[59] In more details, hypometabolism was found in temporal regions in bvFTD.[41,60] In SD, hypometabolism was found in anterior poles, hippocampal region and fusiform gyrus.[61-63] Metabolic changes in ALS-FTD patients

corresponded well with structural changes observed in extra motor areas with hypometabolism reported in the temporal lobes.[30,50]

Despite specific patterns of atrophy in each of the syndromes, ALS and FTD show many common areas of atrophy. Taken together, these imaging findings support the notion that ALS and FTD overlap in their neural correlates although some regions may be more affected than others in each of the diseases. Table 1 presents a summary of common findings related to the temporal lobes regarding pathology, anatomical changes and neuropsychological deficits.

Clinical/Neuropsychological findings

Behaviour/social cognition

Temporal lobe changes are most commonly associated with episodic and semantic memory, as well as social cognition symptoms, and social inappropriateness among other features consistent with the Klüver-Bucy syndrome are documented in animals and humans with temporal lobe damage.[64,65] Interestingly, FTD patients are often reported with features closely similar to this syndrome,[28,66-69] and although less common in ALS patients, the syndrome or some of its features have also been reported.[70] Still, the contributions of temporal changes on behavioural symptoms have been little explored so far in ALS or FTD.

ToM deficits in ALS and FTD patients are reported in the literature and correlated to frontal lobe change.[71-74] However, an increasing number of studies also support the critical involvement of temporal lobe structures in successful social functioning.[75-77] Recently, ToM deficits have been correlated to changes in temporal regions, including temporal gyrus, temporal poles and MTL in SD patients in both cognitive and affective tasks[78-80] and in bvFTD, including right temporal fusiform cortex, temporal pole, hippocampus and amygdala.[80]

Investigations of cognitive deficits in ALS, FTD and ALS-FTD patients have been found to covary with reduction of GM in several regions of the temporal lobes, including the hippocampal formation and amygdala as well as a loss of integrity of the WM networks connecting frontotemporal areas to parietal and occipital areas, including uncinate and longitudinal fasciculus.[9,54,81-93]

Episodic memory

Amnesia, in particular, is problematic as a symptom in ALS and FTD, as it is currently considered as the diagnosis gold standard for underlying Alzheimer's disease pathophysiology. By contrast, episodic memory is considered to be preserved in the ALS-FTD spectrum and therefore, severe amnesia is even stated as a diagnostic exclusion criterion for the behavioural variant of FTD.[68] Contradicting this classical view that memory is relatively spared in ALS and FTD patients, a growing number of studies have recently reported severe and genuine memory impairments in these disorders.[72,94-96] Indeed, a good proportion of pathologically confirmed FTD patients show significant episodic memory problems, indicating that MTL areas, particularly hippocampal and parahippocampal regions, are clearly affected in the syndrome [43,45,46,97] and that

Table 1. Summary of overlapping findings in ALS and FTD

	Cognitive deficits				WM atrophy			GM atrophy	TDP pathology
	Memory	Linguistic abilities	Emotion recognition	ToM deficits	ILF, CC	AC, UnF, SLF	FOR, IC, CR	TP, PrG, FG, HF, A	Subtype
ALS	+	+	+	–	+	+	+	+	B
bvFTD	+	+	+	+	+	+	+	+	A, B
SD	+	+	+	+	+	+	–	+	C
ALS-FTD	+	+	–	–	+	–	–	+	A, B

ALS, amyotrophic lateral sclerosis; FTD; frontotemporal dementia; WM, white matter; GM, gray matter; TDP, TDP-43; ToM, theory of mind; ILF, inferior longitudinal fasciculus; CC, corpus callosum; AC, anterior commissure; UnF, uncinate fasciculus; SLF, superior longitudinal fasciculus; FOR, fornix; IC, internal capsula; CR, corona radiata; TP, temporal pole; PrG, parahippocampal gyrus; FG, fusiform gyrus; HF, hippocampal formation; A, amygdala; bvFTD, behavioural variant FTD; SD, semantic dementia; +, affected; –, not reported.

executive dysfunctions caused by frontal atrophy are not the main contributor of memory impairment in FTD.[43] As for ALS, memory deficits have been controversial and most studies link memory impairment to executive dysfunction.[81,98,99] However, recent studies report authentic episodic memory deficits and implicate MTL structures, showing that memory impairment in non-demented ALS patients is not exclusively a disturbance of the executive functioning.[52,82,83,88,100-103]

Semantic memory

Semantic memory is the knowledge of everyday objects and events and its loss is attributed to the deterioration of the ATL.[61,104] In particular, the temporal poles, the most anterior part of the ATL, are proposed to have a general function to form the basis of semantic memory and is also linked to face recognition, processing of auditory, olfactory and visual stimuli and ToM processing.[77] ALS and FTD patients have been found to present with semantic memory deficits.[47,49,62,105,106]

Still in the semantic domain, deficits in linguistic abilities and social communication have been recently reported in ALS patients found with structural and functional temporal lobe changes.[47,90,107,108] Phukan and colleagues[102] found that 14% of non-demented ALS patients presented with cognitive impairment, including language deficits, but without executive dysfunction. Language impairments have also been found in bvFTD and SD patients, and executive deficits did not fully account for the impairments but also temporal lobe atrophy.[49,109-111] ALS-FTD patients have also shown impairment in linguistic processing.[47]

Emotion recognition

Finally, both ALS and FTD patients present with emotion recognition deficits.[37,93,110-118] The main area involved in emotion face processing is the amygdala, also shown to be strongly involved in emotional memories, learning and recall.[113-115,119-123] The amygdala has been proposed as a critical nexus modulating memory processing.[124] Interestingly, the structure is often seen as central to TDP-43 pathology and thus might provide a critical insight into the underlying pathology.[25] In addition to face processing deficits, sarcasm recognition, a social ability associated to the temporal lobes is reported to be impaired in both non-demented ALS and FTD patients.[125,126]

Conclusions and future directions

Structures of the temporal lobes have shown overlapping anatomical changes in ALS, FTD and ALS-FTD.[32,47,51,116] Specifically, the temporal poles and the MTL are found with anatomical changes consistently reported in this continuum.[43,127-129] Beyond the MTL involvement, particularly hippocampal and parahippocampal regions, the amygdala appeared to be a critical structure identified with anatomical changes affecting both ALS and FTD patients.[130,131]

The knowledge of the cognitive and behavioural impairments in ALS and FTD has developed substantially over the past decades. The description of the phenotypic variation found across ALS and FTD patients, in combination with imaging and post mortem pathological findings strengthen the contemporary approach of a clinical spectrum between these diseases. It is increasingly clear that these two conditions form a continuum of clinical manifestations of the same proteinopathy linked to TDP-43 abnormalities, and the symptomology can be highly related to temporal lobe function. The evidences presented in this article demonstrate the critical contribution of the temporal lobe pathology to the features presented by the patients. The relationship between abnormal TDP-43 deposition and anatomical/functional changes in the temporal lobes should be further investigated to better define the correlation with cognitive and neuropsychiatric symptoms, especially in the ALS cases where impaired memory and social behaviour is controversial and therefore have been underestimated or not thoroughly investigated. Further studies investigating social cognition, memory and behaviour are needed to better characterize ALS and to fully understand its clinical overlap with FTD. The contribution that ATL and MTL atrophy could, respectively, have on social cognition and memory deficits in ALS and FTD should also be investigated further by imaging studies that should take into account and control the already well-described executive and frontal deficits that characterize these diseases and could influence both cognitive domains. Finally, post-mortem studies on FTD and ALS should contrast cases with TDP-43 and other pathology in order to find the better clinical, cognitive and anatomical markers of TDP-43 pathology. Clinicians should increase the information delivered to patients about the usefulness of brain donations and their practical aspects. In addition, public services should communicate more widely about these do-

nations and then increase knowledge critical for the development of future treatments.

It is worth noting that TDP-43 type B is critically involved in most ALS, bvFTD and ALS-FTD cases, suggesting that the temporal lobe changes reported in these conditions, especially in the hippocampal regions and amygdala could be predictive of this pathology type in bvFTD. Further investigation on the origin and nature of the cognitive impairments and the pathological TDP-43 expression behind them, in conjunction with neuroimaging techniques will shed light to the mechanisms of the diseases, potentially improve diagnosis of bvFTD and contribute to the development of new drugs targeting specifically TDP-43 type B. Fostering on these results, novel neuropsychological tests tapping specifically into these temporal lobes functions would likely help the diagnosis and the assessment of these new drugs.

Conflicts of Interest

The authors report no conflict of interest.

Supplementary Materials[132-167]

Supplementary materials are available at Annals of Clinical Neurophysiology website (https://www.e-acn.org/).

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