“Brain Volume and Cortical Thickness characterization of the FTD-ALS continuum”

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INTRODUCTION

Fronto-temporal dementia (FTD) is a neurodegenerative condition characterized by cognitive and behavioral alterations (bvFTD) or linguistic deficits (Primary Progressive Aphasia, PPA). Amyotrophic Lateral Sclerosis (ALS) is a neurological disease following the degeneration of the first and second motoneurons. These conditions have been thought to be distinct but recent clinical and epidemiological evidences have suggested the existence of a FTD-ALS continuum. It is unknown which features characterize the continuum and which patients are prone to develop it. Several MRI studies have tried to solve this issue using different techniques, e.g. Voxel-Based Morphometry (VBM) that is useful to detect atrophic areas, but the findings are incomplete and partially inconsistent. In this study, VBM was used to identify specific patterns of gray matter (GM) volume alterations for each group of patients. Furthermore, cortical thickness (CT) was used as complementary parameter to the volumetric analysis aiming at assessing the relation between the regions affected by the pathology and the clinical aspects evaluated with neuropsychological testing.

MATERIALS AND METHODS

Subjects

Forty-five patients were recruited as follow: 20 patients were diagnosed as FTD, according to the Rascovsky criteria (Rascovsky and Grossman 2014) for bvFTD and to Gorno-Tempini criteria (Gorno-Tempini et al. 2011) for PPA, 18 patients were diagnosed as ALS, according to El Escorial criteria (de Carvalho et al. 2008) and 7 patients were considered belonging to the continuum FTD-ALS, because they matched both FTD/PPA and ALS criteria. A group of 39 age- and gender-matched control subjects were selected as reference group.

MRI acquisition and neuropsychological testing

All subjects underwent MRI acquisition on a Siemens Skyra 3T scanner with 32 channel head-coil. Furthermore, patients underwent neuropsychological (NPS) evaluation comprising tests to identify frequent cognitive alteration in FTD: Frontal Assessment Battery (FAB), Verbal Fluency (FAS) and Semantic Fluency (SF).

VBM analysis

3DT1 images of all subjects were segmented into gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF) using CAT12 toolbox (C. Gaser R. D., 2016). The segmented images were normalized to the MNI space (ICBM-152) with 1,5 mm isotropic voxels, and CT estimation was assessed with CAT12 to obtain the mean CT value over the whole cortex. The resulting images, i.e.

GM normalized images, underwent to smoothing process using a kernel of 6-6-6 mm in SPM toolbox (Ashburner et al. 2013). The smoothed images were used as inputs for the statistical analysis that was conducted on different levels: One Way ANOVA analysis was performed on all subjects, to identify the atrophic regions of GM specific for each pathology, while multiple regression analysis was performed on (i)all subjects, (ii)patients, (iii)each group of patients, to correlate GM atrophy with CT values, and then with NPS. Gender, age and Total Intracranial Volume (TIV) were used as covariates, then One-Way ANOVA and regression were repeated including mean CT as covariate. The significance was set at $p<0.05$ with FWE correction, otherwise uncorrected $p<0.001$ was chosen with extension of 160 voxels for the One-Way ANOVA, 420 voxels for the CT regression and 170 voxels for the NPS regression.

RESULTS

The atrophic regions in FTD compared to controls (Table 1) were mainly located in the frontal lobe (bilaterally), right insula and right Crus I. With the addition of CT as covariate (Table 1) the number and extension of the atrophic frontal regions decreases but *parahippocampal gyrus* and *amigdala* were identified. FTD patients resulted more atrophic in the right *insula* in comparison to FTD-ALS patients, while they were more atrophic in spread frontal and temporal regions compared to ALS (Figure 1 and 2). If CT was included only *bilateral insula, parahippocampal gyrus and left fusiform gyrus* were atrophic. No atrophic areas were found in controls, FTS-ALS and ALS compared to FTD patients.

The atrophic regions in FTD-ALS (Table 1) were similar to those of FTD but smaller at bilateral *parahippocampal gyri, right uncus and amygdala, left middle and inferior frontal gyrus, precentral gyrus, superior and middle frontal gyrus, insula and fusiform gyrus*. Considering CT as covariate, FTD-ALS patients were more atrophic than ALS patients at *left superior and middle temporal gyrus, insula, fusiform gyrus, parahippocampal gyrus and hippocampus* (plus *left inferior temporal gyrus and uncus* if CT was considered).

ALS resulted to be more atrophic than controls at *bilateral inferior frontal gyri, middle and inferior temporal gyri, amigdala, hippocampus, parahippocampal gyrus, insula; left superior frontal gyrus, precentral gyrus, postcentral gyrus, uncus and fusiform gyrus.* If CT was considered, just *left precentral and postcentral gyri* were more atrophic.

The correlation between CT and GM volume was found in all subjects in all lobes with (Table 2). The correlation in the FTD group was present at *right middle and inferior frontal gyrus, superior orbital frontal gyrus, inferior parietal lobule, supramarginal gyrus; left anterior cingulus.* No correlation between CT and Volume was found in the FTD-ALS group and the relation was present in the ALS group at cerebellar level (*bilateral IX and right VIII areas*).

The NPS results are shown on Table 2 and in Figures 3, and 4.

DISCUSSION AND CONCLUSIONS

Our study revealed the presence of common atrophic areas among different groups of patients confirming previous findings (Kanda et al. 2008) and supporting the FTD-ALS continuum. In FTD patients cerebellar atrophy has already been found in C9orf72 mutated ones (Tan et al. 2014), but atrophy in ventromedial and posterior orbital frontal cortex has not previously been reported. The cognitive impairment in ALS patients is known (Cosottini et al. 2012; Menke et al. 2014) and reinforces the multi-systemic involvement in pathology, but the preservation of motor areas in our cohort is outstanding. Furthermore, previous work (Lillo et al. 2012) have revealed that FTD patients are more atrophic in insulae(Davies et al. 2009) and limbic regions compared to ALS.

The inclusion of CT values as covariate affected the number and the extension of atrophic regions highlighting the highest atrophy of the insula in FTD and suggesting that this region is precociously damaged in FTD-ALS patients, before the motor deficits appear. Thus, CT inclusion could increase the ability of identifying group-specific areas and the specificity of atrophic areas in distinguishing among pathologies. Moreover, it could increase the sensibility as the emergence of new areas with this parameter can explain as it has been observed in previous studies where CT than volumetric analysis was able to identify atrophic areas (Hartikainen et al. 2012).

In addition, our study detected a correlation between GM volume and CT in several regions (Das et al. 2009), but which is more representative of cerebral degeneration between volume and CT should be established. As a previous study suggested, the two techniques may be complementary since VBM is able to detect white matter changes not visualized by CT measurement, whereas CT is easier to interpret than VBM probabilistic maps since it can consider surface anatomy and sulci position (Pioro, 2015). Consequently, it is more sensible to detect focal alterations (Simon F. Eskildsen, 2009). Interestingly the cerebellum was identified as the most important region because correlations were found both for all subjects and for each group of patients separately. This confirmed that the cerebellum is a key affected area in the FTD-ALS spectrum, and its involvement in cognitive deficits was found to be of primary importance. Not all atrophic areas have a correlation between volume and CT, this elicits a further reflection about the role of each parameter to establish the damage grade. The CT regression conducted in each group of patients highlights the common areas involved in the FTD-ALS continuum pathology. The cerebellum proved again to be a critical zone affected in this spectrum of disease and a further study to establish how this involvement on the clinical aspects and prognosis should be led. Indeed, our findings demonstrated that the Crus I volume correlated with all the NPS scores, namely FAB, FAS, SF. These results agree with literature (Agosta et al. 2016; Gellersen et al. 2017) and support the cerebellar role in executive, memory and language processes. Another interesting result that is reported here for the first time was the correlation between parietal lobe volume and linguistic functions in FTD patients.

In conclusion, using for the first time CAT12 tool in this spectrum of diseases, our VBM results gave important evidence in supporting the disease continuum FTD-ALS and highlighted the different role of volume and CT in the characterization of these pathologies. The key role of the cerebellum was detected both in morphologic and NPS context. Furthermore, our results suggested that NPS and clinical deficits could partially be explained via morphological alterations. Further studies are warranted to investigate in a larger cohort of subjects WM involvement in order to better understand how these morphometric alterations impact on clinical aspects and prognosis.

Table 1: atrophic regions pathology specific in comparison to controls

Brain regions	FTD		FTD-ALS		ALS	
Frontal lobe	No CT	CT	No CT	CT	No CT	CT
	IFG (l)	OI (r)			IFG (bil)	
	MFG (bil)	MFG (r)	MFG (l)	MFG (l)		
	SFG (bil)		IFG (l)	IFG (l)	SFG (l)	
	PcG (l)		PcG (l)	PcG (l)	PcG (l)	PcG (l)
Temporal lobe	Insula (r)	Insula (bil)	Insula (l)	Insula (l)	Insula (bil)	
	MTG (r)		MTG (l)	MTG (l)	MTG (bil)	
	STG (l)		STG (l)	ITG (l)	ITG (bil)	
	FusG (r)					
Limbic Lobe	AntCing (r)	ParahG (bil)	Uncus (r)		Uncus (l)	
	CinG (bil)	Uncus (bil)	Am (r)		Hipp (bil)	
		Am (r)	ParahG (bil)		ParahG (bil)	
			FusG (l)		FusG (l)	
Parietal lobe					PostcG (l)	PostcG (l)
Occipital Lobe						
Cerebellum	Crus I					

Table 2: NPS results

Brain regions	FAB		FAS		SF	
Frontal Lobe	noCT	CT	noCT	CT	noCT	CT
			MFG (r)	MFG (r)		
			IFG (r)	IFG (r)		
Parietal lobe					SupramG (l)	SupramG (l)
						AngG (l)
						InfLob (l)
Cerebellum	Crus I (l)	Crus I (l)				
	Crus II (l)	Crus II (bil)				
	VII (l)	VII (bil)				
	VIII (l)	VIII (bil)				
		IX (bil)				

Figure 1: Right insula more atrophic in FTD patients than FTD-ALS.

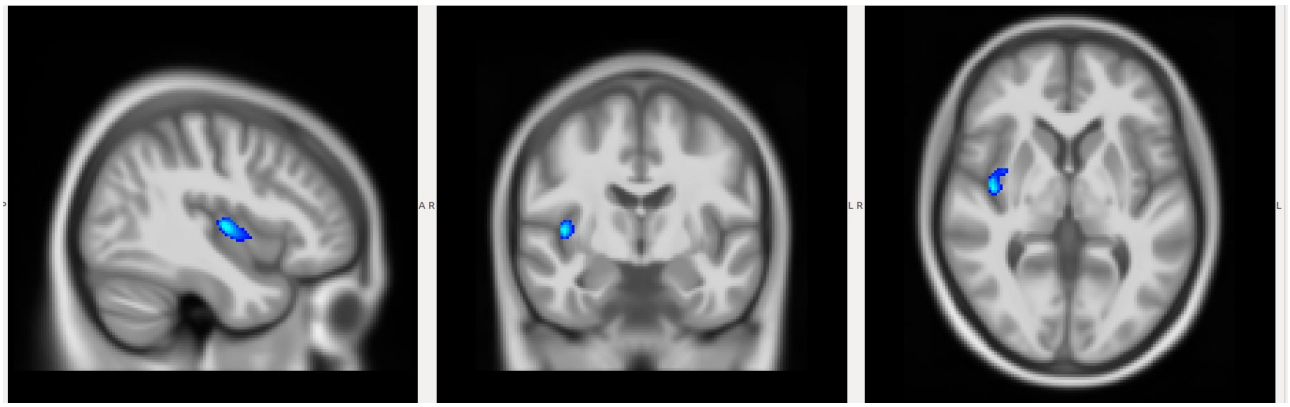


Figure 2: More atrophic regions in FTD than in ALS.

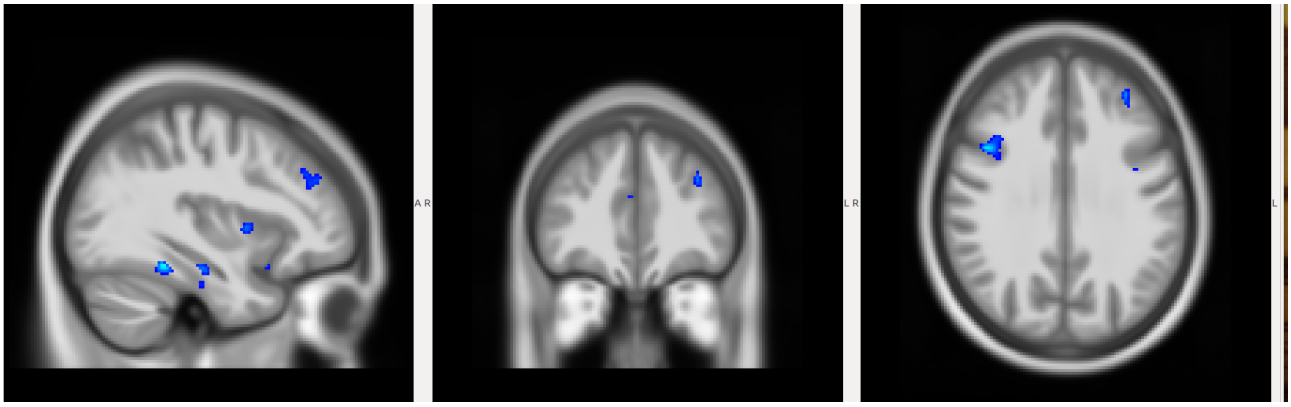


Figure 3: Correlation between FAB score and cerebellum volume in all patients.

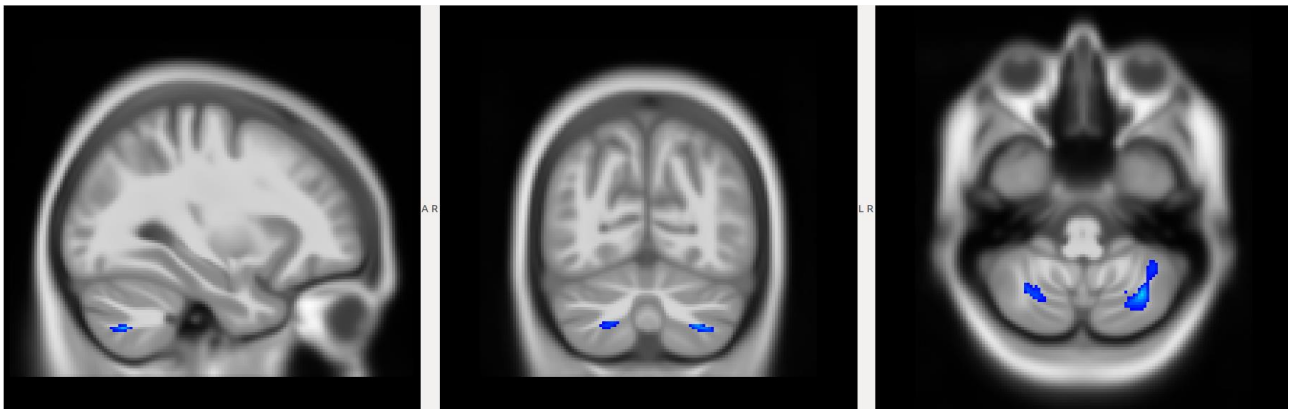
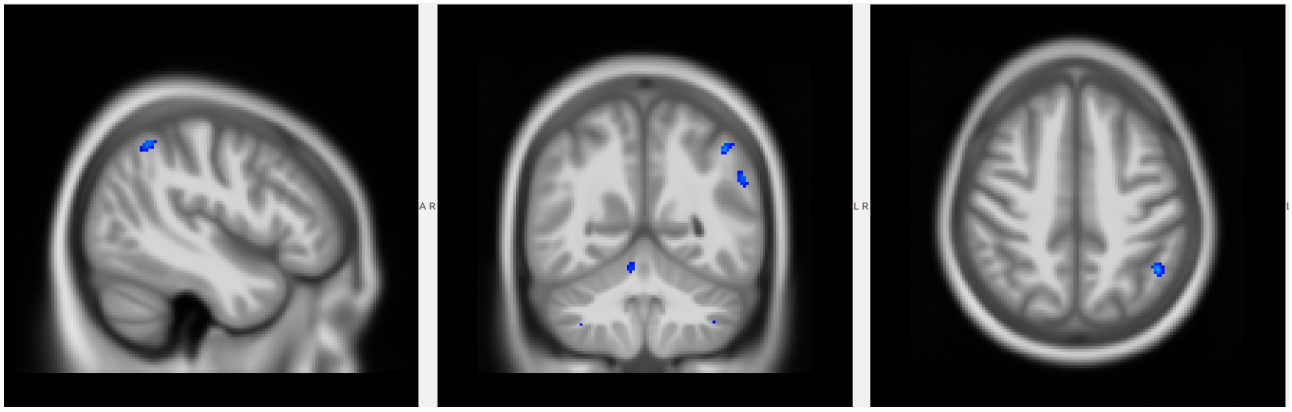


Figure 4: Correlation between SF and parietal lobe volume in all patients.



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