Cortical thinning and phenotypic heterogeneity of cognitive and behavioural syndromes in ALS

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Introduction

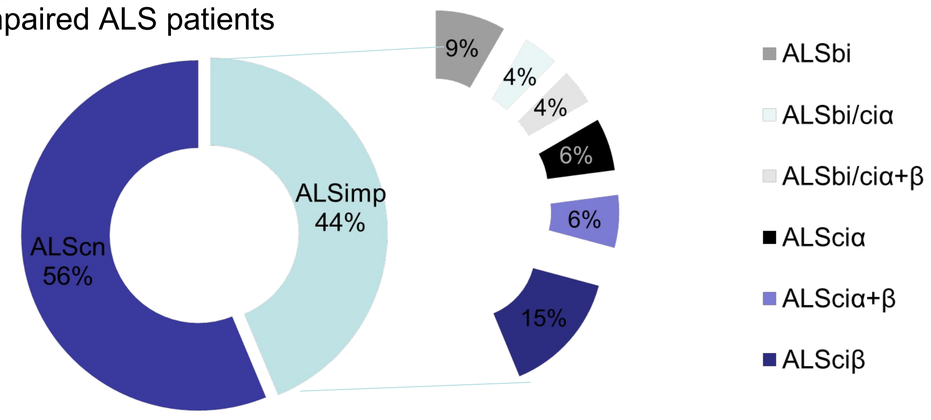
Recent understanding of the neuropsychological profile of ALS patients not fulfilling criteria for frontotemporal dementia (FTD) shows that cognitive impairment may include executive dysfunctions, social cognition, and language impairment.

Knowledge of the anatomical counterpart of this phenotypical heterogeneity is however limited because of past studies focused mainly on the involvement of the fronto-striatal system, possibly overlooking temporal, parietal and insular contribution.

Methods

Forty-eight non-demented patients with probable or definite ALS and 26 healthy controls (HC) were submitted to cognitive assessment and structural 3T MRI (**Table 1**). Behavioural and cognitive impairment was defined on the basis of a data-driven multi-domain approach (Consonni et al., 2016) in 21 ALS patients (ALSimp) (**Figure 1**)
Averaged cortical thickness of 74 bilateral brain regions (Destrieux et al., 2010) was used as a measure of cortical atrophy
Statistics:
- ANCOVA (covariate = age) with FDR correction + simple contrasts → testing between-group differences (**Figure 2**)
- Partial correlations → relationship between brain regions showing CT reductions and behavioural/cognitive measures **(Table 2)**

FIGURE 1
Patient Classification
27 ALScn → cognitively-normal ALS patients
21 ALSimp →impaired ALS patients



ALSbi = behavioural impairment; ALSciα = dysexecutive impairment; ALSciβ = non-executive (memory, language and social cognition) impairment (≥ 2 performances below cut-off)

TABLE 1 Demographical & clinical data	HC	ALScn	ALSimp
Age (years)	56.8 ± 9.96	58.3 ± 10.44	58.8 ± 10.76
Education (years)	11.8 ± 3.58	11.0 ± 3.84	9.6 ± 3.87
Sex (Male/Female)	10 / 16	11 / 16	10 / 11
Disease duration (months)	-	21.92 ± 15.8	19.95 ± 15.3
Bulbar onset (Yes/No)	-	5 / 22	7 / 14
ALSFRS-R (range 0-48)	-	38.6 ± 6.87	37.7 ± 5.68
C9ORF72 mutations (Yes/No)	n.a.	4 / 19 (4 n.a.)	2 / 13 (6 n.a.)

Results and Discussion

Our results demonstrated distinctive patterns of focal cortical atrophy for different non-motor clinical profiles of ALS.
Specifically, language impairment was mainly related to temporal pole and insular involvement, whereas social cognition impairment was related to anterior cingulate thinning.
These specific correlates support the concept of a spectrum of deficits, with an overlap between the ALS cognitive phenotypes and the FTD syndromes.

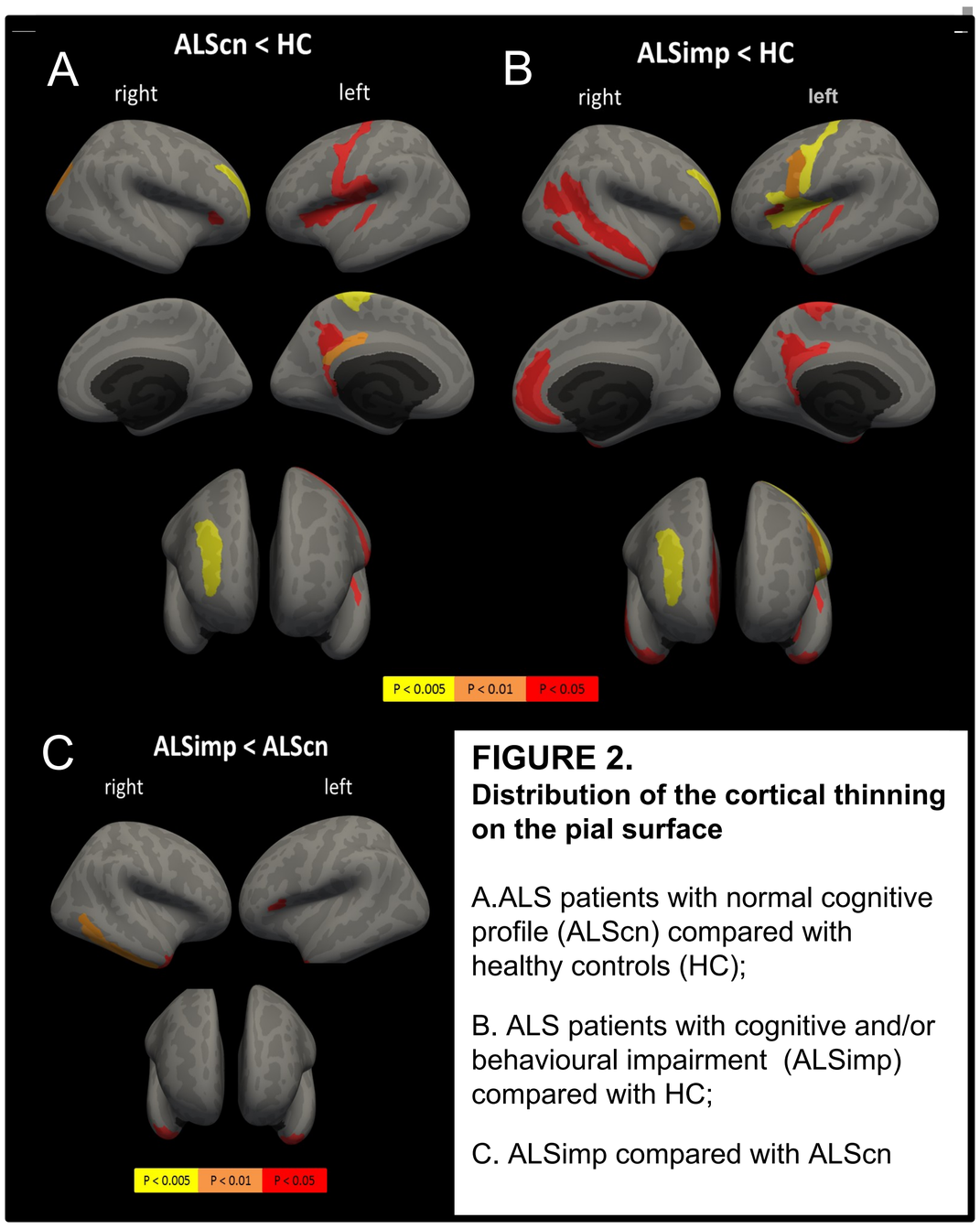


FIGURE 2.
Distribution of the cortical thinning on the pial surface

A.ALS patients with normal cognitive profile (ALScn) compared with healthy controls (HC);

B. ALS patients with cognitive and/or behavioural impairment (ALSimp) compared with HC;

C. ALSimp compared with ALScn

TABLE 2 CT & neuropsychological data of 48 ALS patients	Executive functions	Social cognition	Language	Memory	Behaviour
FRONTAL LOBE					
L precentral gyrus	ns	ns	ns	DR .313*	ns
L paracentral lobule	ns	ns	ns	RM .390**	ns
L IFG pars opercularis	ns	ns	N .362*	DR .419***	ns
L precentral sulcus (inferior)	S -.376*	ns	N .360*	DR .345*	ns
L lateral sulcus (vertical)	F -.310*	ns	N .291*	DR .316*	ns
R lateral sulcus (horizont.)	F -.419**	EK .406**	ns	ns	ns
TEMPORAL LOBE					
L temporal pole	BD .311*	ns	N .479***	DR .413**	ns
R temporal pole	ns	ns	N .400**	DR .310*	ns
R inferior temporal sulcus	ns	ns	ns	DR .358*	DEX -.335*
R inferior temporal gyrus	F -.356*	ns	ns	ns	ns
LIMBIC LOBE					
L post. cingulate gyrus	ns	ns	ns	RM .333*	ns
R anterior cingulate gyrus	ns	EA .298*	AC .326*	ns	ns
INSULA					
L superior circular sulcus	ns	ns	N .397**	ns	ns
L Central sulcus/long gyri	ns	ns	N .310*	ns	ns
PARIETAL LOBE					
L subparietal sulcus	ST .419**	ns	ns	ns	ns

AC = Auditory Comprehension; BD = Backward Digit Span; DEX = Dysexecutive Questionnaire; DR = Delayed Recall of the RAVLT; EA = Emotion Attribution subtest of the Story-based Empathy Task; EK = Ekman Test; F = Phonemic Fluency index; N = Naming; RM = Recognition Memory; S = Stroop test; ST = STEP (cognitive estimation task).

References

Consonni M, Catricalà E, Dalla Bella E, Gessa VC, Lauria G, Cappa SF. Beyond the consensus criteria: multiple cognitive profiles in amyotrophic lateral sclerosis? Cortex 2016;81:162-167.
Destrieux, C, Fischl B, Dale A, Halgren, E. Automatic parcellation of human cortical gyri and sulci using standard anatomical nomenclature. Neuroimage 2010;53:1-15.