PN 54

Progression of brain functional connectivity changes associated with altered cognition in amyotrophic lateral sclerosis.

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INTRODUCTION AND OBJECTIVES

This study aimed to investigate the progression of brain functional connectivity alterations in patients with amyotrophic lateral sclerosis (ALS) and to define the relationship between ALS cognitive alterations and resting state-functional connectivity (RS-FC) changes over time.

METHODS

At baseline and after six months, 25 newly diagnosed ALS patients underwent 3D T1-weighted MRI and RS functional MRI (Philips, Intera, 3.0 T scanner), and a neuropsychological computer-based battery (Test of Attentional Performance-TAP) investigating the whole spectrum of frontal involvement in ALS accounting for patients' motor impairment. Thirty-nine age-, sex- and education-matched healthy controls (HC) underwent the same MRI sequences and a standard neuropsychological assessment at the baseline.

Table 1. Sociodemographic and clinical features of the sample at baseline.

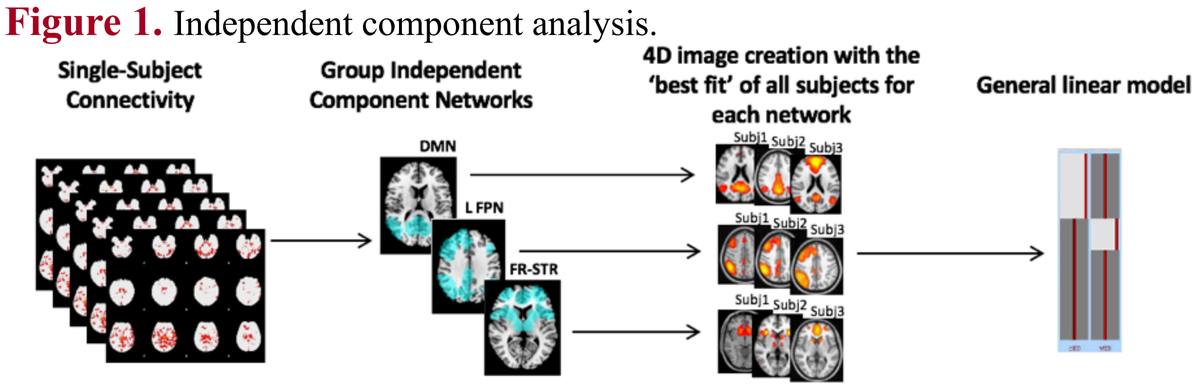
	ALS	HC	P-value
N	25	39	
Sex, women	6 (24%)	18 (46%)	0.07
Age at MRI [years]	61.5 ± 10.8	64.2 ± 7.4	0.24
Education [years]	11.0 ± 3.9	12.3 ± 4.2	0.20
Disease duration [months]	17.6 ± 14.1	-	-
ALSFRS-R	41.7 ± 5.1	-	-
Disease Progression Rate	0.5 ± 0.4	-	-
Site of onset [limb/bulbar/limb+bulbar]	21/3/1	-	-
Cognitive/behavioral classification	3 (ALSci)	-	-

Values denote means ± standard deviations or frequencies (percentages). ALS=Amyotrophic Lateral Sclerosis; ALSFRS-R=ALS Functional Rating Scale Revised; ALSci=ALS with cognitive impairment.

MRI preprocessing and analysis

- To assess RS-FC over time, an independent component analysis (ICA) was performed using MELODIC in FSL (**Figure 1**).

Figure 1. Independent component analysis.



- For each network of interest, we obtained delta images between baseline and follow-up.
- General linear models accounting for voxel-based grey matter assessed: RS-FC changes over time; the relationship between RS-FC changes, baseline cognitive scores and cognitive changes over time.
- A seed-based FC analysis was run in FSL to assess FC changes over time between the left and right middle frontal gyrus (MFG, a key region observed in the ICA analysis) and the rest of the brain.

RESULTS

Longitudinally, ALS patients showed an increased FC in the left anterior cingulate cortex, left middle frontal and bilateral superior frontal gyri within the frontostriatal network, and in the left middle frontal, right inferior frontal and bilateral inferior parietal gyri within the left frontoparietal network (**Figure 2**).

RESULTS

Independent Component Analysis (Figures 2; 3)

Figure 2. Increased resting state functional connectivity in the investigated networks in ALS after 6 months accounting for changes at ALS-FRS-R, time between scans and gray matter atrophy. Results are overlaid on the MNI standard brain and displayed at p<0.05 FWE corrected for multiple comparisons. Coloured bar represents p values.

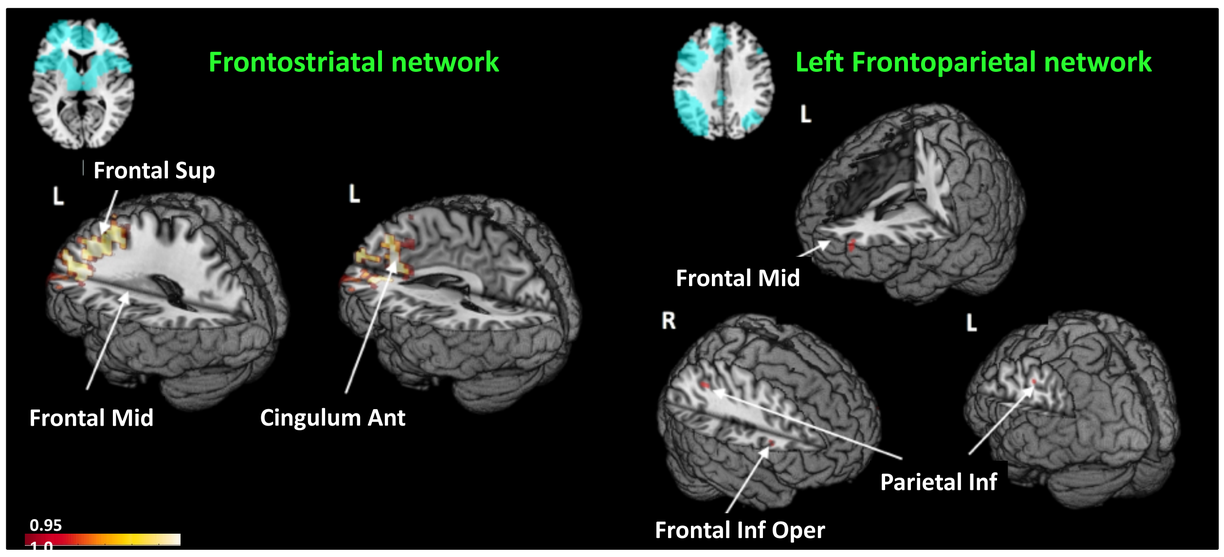
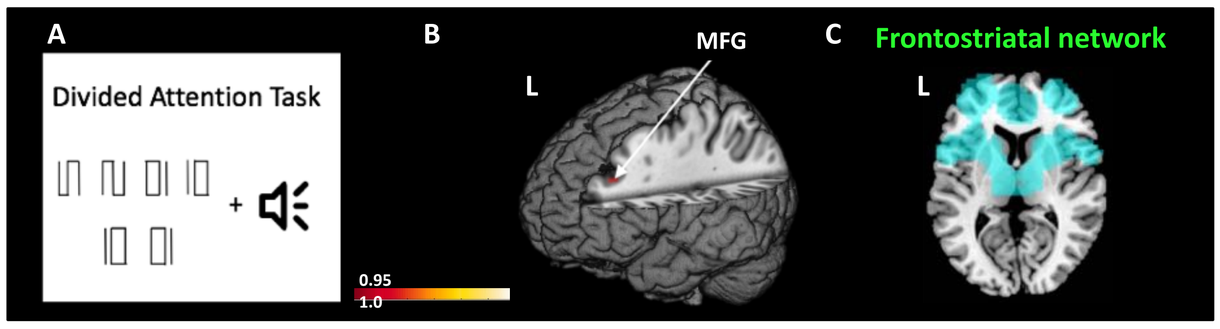
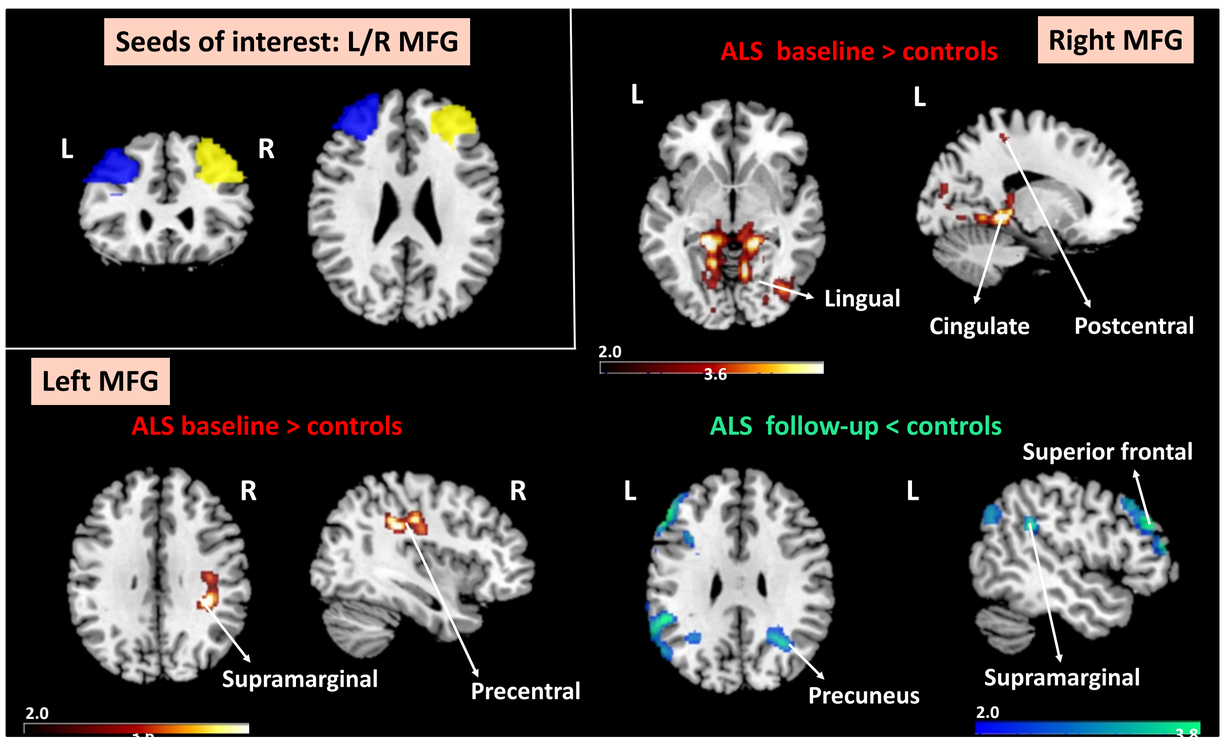


Figure 3. In ALS patients, we observed that a worse performance at baseline TAP divided attention subtest (A) was related with increased FC over time in the left middle frontal gyrus (MFG; B) within the frontostriatal network (C; R: -0.721, p=0.001). Results are overlaid on the MNI standard brain and displayed at p<0.05 FWE corrected for multiple comparisons. Coloured bar represents p values.



Seed-based analysis (Figure 4)

Figure 4. Enhanced (red colours) and reduced (green colours) functional connectivity between the left (blue colour) and right (yellow colour) middle frontal gyrus (MFG) seeds of interest and the rest of the brain in ALS compared to controls at baseline and after 6 months. Results are overlaid on the MNI standard brain and displayed at p<0.05 FWE corrected for multiple comparisons. Coloured bar represents Z values.



CONCLUSIONS

- Over six months, FC progressed beyond the brain motor network.
- Increased connectivity in frontal regions in relation with greater frontal-executive deficits at baseline suggests that it is likely not a mechanism of compensation but rather a sign of disease progression. This is also revealed by the reduced FC between MFG and posterior regions at follow-up, that could reflect an anterior-posterior functional disconnection as observed in the frontotemporal-lobar degeneration.
- These findings offer new potential markers for monitoring the ALS progression.

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