BRAIN METABOLIC CONNECTIVITY IN ALS PATIENTS CARRYING THE HEXANUCLEOTIDE EXPANSION OF *C9ORF72*: A 2-[^{18}F]FDG-PET STUDY

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INTRODUCTION

- *C9ORF72* expansion is the most common cause of genetic Amyotrophic Lateral Sclerosis (ALS)
- *C9ORF72* expansion is a strong risk factor for cognitive impairment up to full-blown frontotemporal dementia (FTD)
- The Investigation of **brain connectivity** in an MRI-based study showed greater involvement of frontal white matter tracts and enhanced functional connectivity of the visual network in *C9ORF72* ALS patients compared ALS patients not carrying the expansion [1]
- **Aim**: to investigate brain metabolic connectivity in patients with ALS carrying the pathogenic expansion of *C9ORF72* gene using brain 2-[^{18}F]FDG-PET

METHODS

- 70 ALS patients carrying *C9ORF72* expansion (***C9*-ALS**) from the ALS Centre of Turin
- 70 ALS patients without any mutations in the major ALS-related genes (**ctrl-ALS**)
- Comparison between *C9*-ALS and ctrl-ALS through the **two-sample t-test model of SPM12** (height threshold at P<0.001, P<0.05 FWE-corrected at cluster level)
- Metabolic clusters showing a significant difference between *C9*-ALS and ctrl-ALS used as seed regions in a **multiple regression analysis** in each patient group to evaluate brain metabolic connectivity (interregional correlation analysis, **IRCA**; height threshold at P<0.001, P<0.05 FWE-corrected at cluster level)

RESULTS

1 Demographic and clinical features of participants

- Comparison between *C9*-ALS sample and *C9ORF72* positive subjects of the Piemonte and Valle d'Aosta Register for ALS (PARALS): statistically significant lower proportion of patients with comorbid frontotemporal dementia (ALS/FTD) in *C9*-ALS sample (p=0.017)
- Comparison between *C9*-ALS sample and ctrl-ALS sample: *C9*-ALS patients showed a significantly lower age at onset (p=0.0005)

2 2-[18F]FDG-PET data: direct comparison between *C9*-ALS and ctrl-ALS

- Clusters of relative **hypometabolism** in bilateral **thalamus** (bilateral pulvinar and left medial dorsal nucleus) and left precentral and postcentral gyri in *C9*-ALS compared to ctrl-ALS *(marked in **green** in figure 1);*
- Cluster of relative **hypermetabolism** in bilateral **cerebellum** and **brainstem** in *C9*-ALS compared to ctrl-ALS *(marked in **red** in figure 1)*

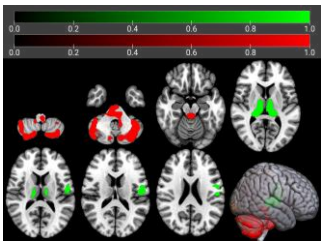

***Figure 1**. Comparison between C9-ALS and ctrl-ALS*

3 2-[18 F]FDG-PET data: IRCA in *C9*-ALS and in ctrl-ALS

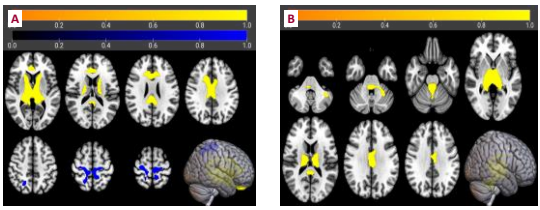

Figure 2. *IRCA in C9-ALS (A) and ctrl-ALS (B) using the thalamic cluster as seed region → C9-ALS* showed:

- Broader **positive correlation** of metabolism between the **thalamic** seed region and the cingulate cortex, compared to ctrl-ALS *(marked in yellow in figure 2)*;
- **negative correlation** of the **thalamic** seed region metabolism with sensorimotor cortex, not found in ctrl-ALS *(marked in blue in figure 2).*

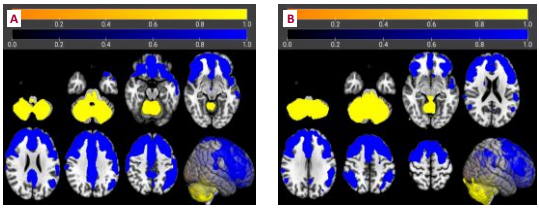

Figure 3. *IRCA in C9-ALS (A) and ctrl-ALS (B) using the cerebellar/brainstem cluster as seed region:*
***C9*-ALS** showed more evident **inverse correlation** between the **cerebellar/brainstem** seed region and frontal metabolism, than ctrl-ALS *(clusters marked in blue).*

DISCUSSION

- ✓ The **Salience Network (SN)** is involved in cognitive and behavioural control and could act as a pathway for brain degeneration. The pulvinar, the medial dorsal thalamic nucleus and the anterior cingulate cortex are hubs of the SN.
- ✓ ***C9*-ALS**, compared to ctrl-ALS, seem to show a predominant involvement of the **Salience Network (SN)**
- ✓ The negative correlation of the thalamic seed region with **sensorimotor cortex** in *C9*-ALS seems to parallel the thalamic hyperconnectivity with sensorimotor cortex found in schizophrenia [2].
- ✓ **Thalamic damage** seems to be part of network degeneration associated with psychotic manifestations typically detected in *C9ORF72* subjects [3].
- ✓ The inverse correlation between the **cerebellar/brainstem** seed region and frontal metabolism may suggest a compensatory role of the cerebellum to cope with cognitive impairment to greater extent in *C9*-ALS than ctrl-ALS.

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