Brain metabolic correlates of apathy in amyotrophic lateral sclerosis: An 18F-FDG-positron emission tomography study

Antonio Canosa1,2 | Veria Vacchiano3,4 | Fabrizio D’Ovidio1 | Andrea Calvo1,2,5 | Cristina Moglia1,2 | Umberto Manera1 | Rosario Vasta1 | Rocco Liguori3,4 | Vincenzo Arena6 | Maurizio Grassano1 | Francesca Palumbo1 | Laura Peotta1 | Barbara Iazzolino1 | Marco Pagani7,8 | Adriano Chiò1,2,5,7

1ALS Centre, “Rita Levi Montalcini” Department of Neuroscience, University of Turin, Turin, Italy
2Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, Turin, Italy
3Bellaria Hospital, IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy
4Department of Biomedical and NeuroMotor Sciences (DIBINEM), University of Bologna, Bologna, Italy
5Neuroscience Institute of Turin (NIT), Turin, Italy
6Positron Emission Tomography Centre AFFIDEA-IRMET S.p.A, Turin, Italy
7Institute of Cognitive Sciences and Technologies, C.N.R, Rome, Italy
8Department of Medical Radiation Physics and Nuclear Medicine, Karolinska University Hospital, Stockholm, Sweden

Abstract

Background and purpose: The aim of this study was to evaluate brain metabolic correlates of apathy in amyotrophic lateral sclerosis (ALS).

Methods: A total of 165 ALS patients underwent 18F-2-fluoro-2-deoxy-D-glucose positron emission tomography (18F-FDG-PET) and Frontal Systems Behaviour Scale (FrSBe) evaluation. FrSBe provides “before” and “after” apathy subscores, referring to premorbid and morbid conditions. “After” apathy subscore and “before-after” gap, i.e. the difference between “before” and “after” subscores, were regressed against whole-brain metabolism. Among patients with a pathological “after” apathy subscore (i.e., ≥65), we compared patients with “before” apathy subscores ≥65 and <65, and patients with “before-after” gaps of <22 and ≥22.

Results: In the whole sample, the “after” apathy subscore negatively correlated with metabolism in the dorsolateral prefrontal cortex (DLPFC), dorsomedial prefrontal cortex (DMPFC), ventrolateral prefrontal cortex (VLPFC), premotor cortex (PMC) and anterior cingulate cortex (ACC), and insula bilaterally. A positive correlation was found in the cerebellum and pons. The “before-after” gap negatively correlated with metabolism in bilateral DLPFC, DMPFC and PMC, and left VLPFC and ACC, and positively correlated with cerebellar and pontine clusters. Among patients with an “after” apathy subscore ≥65, we found no difference between those with “before” apathy subscores ≥65 and <65. Patients with a “before-after” gap ≥22, compared to patients with a gap <22, showed relative
INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease affecting upper and lower motor neurons. Death usually occurs within 2 to 5 years, mainly due to respiratory failure [1]. According to population-based studies, approximately 50% of ALS patients show cognitive and/or behavioural impairment along the frontotemporal degeneration spectrum at diagnosis [2,3]. Apathy has been included among features characterizing behavioural dysfunction since the first diagnostic criteria were established for ALS-related frontotemporal syndromes [4]. Apathy has assumed a central role in the recently revised criteria, which state that the presence of apathy by itself allows a diagnosis of behavioural impairment associated with ALS [5]. Apathy is a feature shared among many neurological and psychiatric disorders. It has been defined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition [6] as being characterized by “diminished motivation and reduced goal-directed behaviour, accompanied by decreased emotional responsiveness.” The diagnostic criteria for apathy were revised in 2018 as follows [7]: the patient must present a quantitative reduction of goal-directed activity as compared with her/his previous level of functioning; symptoms must persist for at least 4 weeks, and affect at least two of the three apathy dimensions (behaviour/cognition; emotion; social interaction); apathy should lead to functional impairment, and should not be fully ascribable to other factors (e.g., effects of substances or major changes in the patient’s environment).

In order to determine if behavioural symptoms of ALS patients represent a change attributable to the neurodegenerative process, premorbid status must be assessed. At the ALS Centre of Turin, Italy, the neuropsychological assessment of ALS patients includes the evaluation of behavioural dysfunction based on direct observation, patient’s history, and the Frontal Systems Behaviour Scale (FrSBe) [8]. The FrSBe evaluates three domains (apathy, disinhibition and executive dysfunction) and provides “before” and “after” ratings, referring respectively to the premorbid condition and the time the scale is performed.

As 18F-2-fluoro-2-deoxy-D-glucose (18F-FDG) positron emission tomography (PET) is a marker of neuronal integrity in vivo [9], in the present study we evaluated brain metabolic correlates, assessed through 18F-FDG-PET, of the apathy subscore on the FrSBe in a series of patients with ALS. Since we hypothesized that both the “after” apathy score and the change between “before” and “after” conditions could be relevant in characterizing ALS-related behavioural dysfunction, we aimed to evaluate the associations of both of these scores with brain metabolism.

MATERIALS AND METHODS

Patients

A total of 165 patients diagnosed with definite, probable or probable laboratory-supported ALS according to El Escorial Revised Diagnostic Criteria [10] at the ALS Centre of Turin in the period 2009 to 2015 were included in this study. They were enrolled at diagnosis or, less frequently, during the first follow-up visit (usually 2 months later). Patients with a history of neurological disorders affecting cognition (major stroke, severe head injuries, mental retardation), alcohol and drug dependence, psychiatric diseases (including mood disorders), or use of high-dose psychoactive medications were not enrolled, nor were patients whose native language was not Italian. Respiratory failure was excluded through clinical assessment, peripheral blood oxygen saturation, and, when necessary, spirometry and arterial blood gases analysis, within 4 weeks before or after the enrolment. Patients underwent 18F-FDG-PET and neuropsychological assessment including the FrSBe. The complete test battery has been reported elsewhere [3]. Neuropsychological evaluation and 18F-FDG-PET were performed within 1 month of each other.

Acquisition of 18F-FDG-PET images

The 18F-FDG-PET was performed according to published guidelines [11]. Patients fasted at least 6 h before the examination. Blood glucose was <7.2 mmol/L in all cases before the procedure. After a 20-min rest, approximately 185 MBq of 18F-FDG was injected. The acquisition started 60 min after the injection. PET/computed
tomography (CT) scans were performed with a Discovery ST-E System (General Electric, Boston, MA, USA). Brain CT (thickness of 3.75 mm, 140 kVp, 60–80 mAs) and PET scan (1 field of view of 30 transaxial cm) were sequentially acquired, the former being used for attenuation correction of PET data. PET images were reconstructed with four iterations and 28 subsets with an initial voxel size of 2.34 × 2.34 × 2.00 mm, and data were collected in 128 × 128 matrices.

**Behavioural assessment**

The FrSBe [8] is a 46-item scale, including a total score and three subscores: apathy (14 items); disinhibition (15 items); and executive dysfunction (17 items). Items are rated on a five-point scale: 1, almost never; 2, seldom; 3, sometimes; 4, frequently; 5, almost always. The FrSBe contains “before” and “after” ratings, referring respectively to the premorbid condition and the time the scale is performed (in our series, at diagnosis). We used the Family version evaluated by a close relative, since reports from caregivers are extremely important given the possible loss of insight of patients [5]. The higher the FrSBe score, the more severe the behavioural impairment. Scores ≥65 are interpreted as pathological according to the FrSBe manual for each section and the total score of the scale [8]. We considered the “after” apathy subscore as a measure of behavioural impairment at diagnosis. The “before-after” change was estimated in two different ways. Firstly, it was measured as the difference, or “gap” between “before” and “after” apathy subscores, calculated as follows: "after" apathy subscore – “before” apathy subscore. Secondly, it was estimated through assessment of the apathetic/non-apathetic status based on the cut-off of 65 points to evaluate eventual change of status between “before” and “after” conditions. Thus, we could subdivide apathetic patients (i.e., “after” apathy subscore ≥65) into two groups: patients with a premorbid score already in the pathological range (i.e. “before” apathy subscore ≥65) and patients with a premorbid score within the normal range (i.e. “before” apathy subscore <65). Both methods were considered as possible proxies of behavioural changes attributable to the neurodegenerative process. In order to identify a possible threshold above which to consider a “before-after” gap as significant, we examined a comparable neurological group as the reference group, as suggested by the manual for the scale [8]. We considered 517 incident ALS patients from the Piemonte and Valle d’Aosta Register for ALS [12], who underwent a neuropsychological assessment, including the FrSBe, at diagnosis, between 2009 and 2015. We excluded 22 patients, who displayed a negative gap between “before” and “after” conditions, possibly due to misinterpretation of the scale by the rater. We also excluded those patients who underwent PET (n = 165, the present study sample). The median value of the gap was 12 (interquartile range 4–22). The threshold between the third and fourth quartile (i.e., 22) was hypothesized as a possible cut-off value to consider a “before-after” gap of the apathy subscore as significant.

**Statistical analysis**

Comparisons between means were made using the Student’s t-test or analysis of variance; comparisons between categorical variables were made using the chi-squared test and Fisher’s test when applicable.

SPM12 implemented in Matlab R2018b (MathWorks, Natick, MA, United States) was used for image normalization. A customized brain 18F-FDG-PET template [13] was utilized for spatial normalization. Intensity normalization was performed using the 0.8 default SPM value of grey matter threshold, and images were subsequently smoothed with a 10-mm filter and submitted to statistical analysis.

First, we aimed to evaluate the correlations between brain metabolism and both “after” apathy subscore and the “before-after” gap of the apathy subscore of the FrSBe, performing two multiple regression analyses in the whole sample (n = 165). Subsequently, we focused on patients with an “after” apathy subscore ≥65, that is, patients with scores considered as pathological at diagnosis (n = 84), to evaluate whether a further characterization of such patients based on the “before-after” change was worthwhile. We divided this group into two subgroups to compare them: patients with a “before” apathy subscore ≥65 (i.e., already in the pathological range) versus patients with a “before” apathy subscore <65 (i.e. within the normal range). Then, we divided the same group of patients with the “after” apathy subscore ≥65 into the following two subgroups to compare them: patients showing a “before-after” gap <22 versus patients with a “before-after” gap ≥22.

Comparisons were performed through the two-sample t-test model of SPM12.

In all analyses we did not include age, sex and education as covariates, since the FrSBe scores were already corrected for these variables. Furthermore, we did not include a measure of global cognitive status (i.e., classification according to the diagnostic criteria for ALS-frontotemporal spectrum disorder) [5] or executive dysfunction as covariates, since they were highly correlated with apathy subscores (r = 0.77, p < 0.001). We included the FrSBe “after” subscore related to disinhibition as a covariate in all the analyses, since it was only marginally correlated with the “after” apathy subscore (r = 0.57; p < 0.001). Details regarding the pitfalls of including highly correlated variables as covariates in multiple regression models are reported elsewhere [14].

For all the analyses the height threshold was set at p < 0.005/uncorrected (p < 0.05/FWE-corrected at cluster level) and only clusters containing >125 contiguous voxels were considered significant. Brodmann areas were identified at a 0- to 2-mm range from the Talairach coordinates of the SPM output isocentres corrected by Talairach Client (http://www.talairach.org/index.html).

**Protocol approvals**

The study was approved by the ethical committee, “Comitato Etico Interaziendale Azienda Ospedaliero-Universitaria Città della Salute
e della Scienza di Torino". The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Patients provided written informed consent.

RESULTS

Demographic and clinical data

We compared the demographic and clinical data of patients who underwent $^{18}$F-FDG-PET ($n = 165$) with those of the reference population-based series ($n = 330$). The comparison is summarized in Table S1. No significant difference was found for sex distribution, education, and site of onset (bulbar/spinal). Otherwise, in patients who underwent $^{18}$F-FDG-PET, age was slightly older and ALS Functional Rating Scale-Revised (ALSFRS-R) score slightly higher, probably due to the greater difficulty experienced by elderly people and patients with worse disability in reaching the PET centre.

In the group of patients with an “after” apathy subscore $\geq 65$, that is, those patients with scores considered as pathological at diagnosis ($n = 84$), we compared demographic and clinical data of those with a “before” apathy subscore $\geq 65$ versus those with a “before” apathy subscore <65, and patients with a before-after gap <22 versus patients with a before-after gap $\geq 22$. In both comparisons, we did not find any difference in terms of sex distribution, site of onset (bulbar/spinal), age at assessment, education, or ALSFRS-R at assessment. These data are summarized in Table S2.

Data obtained from $^{18}$F-FDG-PET

Correlation between the "after" apathy subscore and brain metabolism in the whole sample ($n = 165$)

The “after” apathy subscore negatively correlated with metabolism in the dorsolateral prefrontal cortex (DLPFC), dorsomedial prefrontal cortex (DMPFC), ventrolateral prefrontal cortex (VLPFC), premotor cortex (PMC) and anterior cingulate cortex (ACC), and the insula bilaterally (Table 1, Figure 1a). A positive correlation was found in the cerebellum and pons (Figure 2a).

Correlation between “before-after” gap and brain metabolism in the whole sample ($n = 165$)

The “before-after” gap negatively correlated with metabolism in bilateral DLPFC and DMPFC, left VLPFC, left ACC, bilateral PMC (Table 2, Figure 1b), and positively correlated with clusters including the cerebellum and pons (Figure 2b).

### TABLE 1

Clusters of negative correlation between Frontal Systems Behaviour Scale “after” apathy subscore and whole-brain metabolism in the whole sample

| $p$ (FWE-corrected) | Cluster extent | Z-score | Talairach coordinates | Lobe | Cortical region | BA |
|---------------------|----------------|---------|-----------------------|------|----------------|----|
| 0.000               | 9655           | 4.42    | −53 16                | 8    | Frontal        | 44 |
|                     |                | 4.39    | −44 19                | 29   | Frontal        | 9  |
|                     |                | 4.28    | −38 35                | 31   | Frontal        | 9  |
|                     |                | 3.95    | −18 28                | 52   | Frontal        | 6  |
|                     |                | 3.82    | −40 2                 | 35   | Frontal        | 6  |
|                     |                | 3.81    | −34 5                 | 53   | Frontal        | 6  |
|                     |                | 3.74    | −40 19                | 1    | Sub-lobar      | 13 |
|                     |                | 3.73    | 10 26                 | 21   | Limbic         | 32 |
|                     |                | 3.67    | −6 43                 | 40   | Frontal        | 8  |
|                     |                | 3.52    | 8 14                  | 53   | Frontal        | 6  |
|                     |                | 3.50    | −6 34                 | 17   | Limbic         | 32 |
|                     |                | 3.45    | 6 39                  | 33   | Frontal        | 9  |
|                     |                | 4.06    | 30 1                  | 50   | Frontal        | 6  |
|                     |                | 3.81    | 55 27                 | 28   | Frontal        | 46 |
|                     |                | 3.61    | 57 20                 | 8    | Frontal        | 45 |
|                     |                | 3.51    | 38 21                 | 3    | Sub-lobar      | 13 |
|                     |                | 3.32    | 38 29                 | 45   | Frontal        | 8  |
|                     |                | 3.00    | 42 13                 | 31   | Frontal        | 9  |
|                     |                | 2.91    | 42 25                 | 36   | Frontal        | 9  |
|                     |                | 2.78    | 40 20                 | 51   | Frontal        | 8  |

Abbreviation: BA, Brodmann area.
Comparison among patients with the “after” apathy subscore ≥65 (n = 84)

In patients with an “after” apathy subscore ≥65, we found no difference between those with a “before” subscore ≥65 (n = 26) and those with a “before” subscore <65 (n = 58).

In patients with “before-after” gap ≥22 (n = 40) as compared to patients with “before-after” gap <22 (n = 44), clusters of relative hypometabolism were found in bilateral DLPFC and DMPFC, left ACC, and left PMC (Table 3, Figure 3a), while clusters of relative hypermetabolism were found in cerebellum and pons (Figure 3b).

DISCUSSION

To our knowledge, no other studies on brain 18F-FDG-PET correlates of apathy have been performed in ALS patients. Furthermore,
we aimed to evaluate the relationship between cerebral metabolism and behavioural changes, defined as the difference between “before” and “after” apathy subscores on the FrSBe scale. We found that the higher the apathy subscore at diagnosis, the lower the metabolism in brain regions known to be involved in apathy circuitry (the DLPFC, DMPFC, VLPFC, PMC, ACC, and insula). Similarly, the metabolism of largely overlapping regions tended to decrease as the “before-after” gap increased, suggesting the possible metabolic correlates of behavioural changes due to the neurodegenerative process. Since motor impairment remains the core feature of ALS and bulbar onset is significantly associated with cognitive impairment, we ran further analyses to control for the possible impact of motor disability and site of onset on our results, adding the ALSFRS-R total score and spinal/bulbar onset as covariates in the multiple regression analyses. They provided substantially unchanged results (data not shown).

Many structural magnetic resonance imaging (MRI) studies of apathy in frontotemporal dementia (FTD) have been conducted.

| TABLE 2 | Clusters of negative correlation between Frontal Systems Behaviour Scale apathy “before-after” gap and brain metabolism in the whole sample |
|----------|----------------------------------------------------------------------------------------------------------------------------------|
| p (FWE-corrected) | Cluster extent | Z-score | Talairach coordinates | Lobe | Cortical region | BA |
| 0.000   | 11985          | 4.88    | 10 16 47       | Frontal | Right superior frontal gyrus | 6 |
| 0.001   | 3120           | 3.73    | 10 18 47       | Frontal | Right inferior frontal gyrus | 8 |
| 0.001   | 3120           | 3.73    | 10 18 47       | Frontal | Left superior frontal gyrus | 8 |
| 0.001   | 3120           | 3.73    | 10 18 47       | Frontal | Left inferior frontal gyrus | 45 |
| 0.001   | 3120           | 3.73    | 10 18 47       | Frontal | Left medial frontal gyrus | 6 |
| 0.001   | 3120           | 3.73    | 10 18 47       | Frontal | Right medial frontal gyrus | 9 |
| 0.001   | 3120           | 3.73    | 10 18 47       | Frontal | Left superior frontal gyrus | 6 |
| 0.001   | 3120           | 3.73    | 10 18 47       | Frontal | Left inferior frontal gyrus | 44 |
| 0.001   | 3120           | 3.73    | 10 18 47       | Frontal | Left medial frontal gyrus | 32 |
| 0.001   | 3120           | 3.73    | 10 18 47       | Frontal | Right middle frontal gyrus | 6 |
| 0.001   | 3120           | 3.73    | 10 18 47       | Frontal | Left middle frontal gyrus | 46 |
| 0.001   | 3120           | 3.73    | 10 18 47       | Frontal | Right middle frontal gyrus | 9 |

Abbreviation: BA, Brodmann area.

| TABLE 3 | Clusters of relative hypometabolism in patients with Frontal Systems Behaviour Scale (FrSBe) apathy “before-after” gap ≥22 as compared to patients with “before-after” gap <22, in the sample of patients with FrSBe “after” apathy subscore ≥65 |
|----------|----------------------------------------------------------------------------------------------------------------------------------|
| p (FWE-corrected) | Cluster extent | Z-score | Talairach coordinates | Lobe | Cortical region | BA |
| 0.001   | 3120           | 3.73    | 10 18 47       | Frontal | Right medial frontal gyrus | 8 |
| 0.001   | 3120           | 3.73    | 10 18 47       | Frontal | Left superior frontal gyrus | 6 |
| 0.001   | 3120           | 3.73    | 10 18 47       | Frontal | Left superior frontal gyrus | 8 |
| 0.001   | 3120           | 3.73    | 10 18 47       | Frontal | Left inferior frontal gyrus | 32 |
| 0.001   | 3120           | 3.73    | 10 18 47       | Frontal | Right superior frontal gyrus | 9 |
| 0.001   | 3120           | 3.73    | 10 18 47       | Frontal | Left middle frontal gyrus | 6 |
| 0.001   | 3120           | 3.73    | 10 18 47       | Frontal | Right middle frontal gyrus | 9 |
| 0.001   | 3120           | 3.73    | 10 18 47       | Frontal | Left middle frontal gyrus | 8 |
| 0.001   | 3120           | 3.73    | 10 18 47       | Frontal | Right superior frontal gyrus | 10 |

Abbreviation: BA, Brodmann area.
In a voxel-based morphometry study including patients with behavioural variant FTD (bvFTD, n = 48) and primary progressive aphasia (n = 14), FrSBe apathy subscore was significantly correlated with atrophy of the right DLPFC, with trends towards significance in the left DLPFC, right ACC, right lateral orbitofrontal cortex, right temporoparietal junction, and right putamen [15]. A voxel-based morphometry and diffusion tensor imaging MRI study [16] evaluated the grey and white matter correlates of apathy across the three components of initiation, planning and motivation as measured by the Philadelphia Apathy Computerized Test, in a sample of 18 bvFTD patients. DLPFC atrophy was predominantly related to the cognitive component (planning) and to deficits in set-shifting, task setting and abstraction. ACC atrophy was linked to the initiation component deficit. The PMC was found to play an important role in energization and intentional movement planning. These data suggest that the components of apathy underlie partially distinct circuits.

A more recent study [17] applied principal component analysis to identify clusters of behavioural changes based on the Frontal Behaviour Inventory subscores in 102 non-demented ALS patients. The apathetic profile was correlated with thinning of the bilateral orbitofrontal cortex.

Few 18F-FDG-PET studies have been conducted to disclose the metabolic correlates of apathy in FTD. One study [18] compared 12 apathetic bvFTD patients, six disinhibited bvFTD patients, and 24 healthy controls. Considering separately the two bvFTD subgroups in comparison with healthy controls, the apathetic group showed a distinctive relative hypometabolism bilaterally in the frontal medial cortex, frontal polar cortex, anterior orbitofrontal cortex, DLPFC, insula and thalamus. The role of the orbitofrontal cortex in apathetic manifestations has also been supported by a study [19] comparing two bvFTD subgroups, defined based on their apathy scores on the Neuropsychiatric Inventory scale: the apathetic group showed specific metabolic impairment in the orbitofrontal cortex, as compared to healthy controls (a result not shared by the non-apathetic FTD patients).

A recent study focused on the neural correlates of apathy in bvFTD and Alzheimer’s disease [20] evaluated the relationship between brain metabolism and apathy, employing 18F-FDG-PET and the Lille Apathy Rating Scale. The authors included 42 patients with bvFTD, 42 patients with Alzheimer’s disease, and 30 healthy controls. In bvFTD patients, a distinct neuroanatomical correlate was found: apathy was found to be associated with lower metabolism in the left lateral prefrontal, medial frontal/anterior cingulate, and orbitofrontal and anterior insular cortices.

A recent review focused on the neuroanatomical correlates of the components of apathy in FTD, assessed through MRI and 18F-FDG-PET [21]. The authors suggested that DLPFC atrophy was mainly related to the cognitive component (planning) and associated with deficits in set-shifting, task setting and abstraction. The impairment of the initiation component and the energization deficits were reported to be mainly related to neuronal loss in the dorso-medial frontal areas (ACC, middle cingulate cortex, medial superior frontal gyrus and supplementary motor area). The involvement of ventral prefrontal areas (subgenual ACC, medial and lateral orbitofrontal cortex) was reported to be predominantly associated with the emotional/affective components (subjective motivation) and social cognition. The anterior insula could also have a role in the subjective motivation state across all components, given its role in the
perception of emotionally significant stimuli, integration of interoceptive inputs and close connections with prefrontal structures.

In our study we identified clusters of negative correlation between apathy sub-scores and glucose metabolism in regions including the DLPFC, DMPFC, VLPFC, PMC, ACC, and insula, largely overlapping with cortical regions previously shown to be related to different apathy components in FTD [21]. Clusters of positive correlation included the cerebellum and the pons. Notably, cerebellar and brainstem metabolism tends to increase as ALS-related cognitive impairment worsens [22]. The cerebellum is known to be involved in cognitive and behavioural processes. Cerebellar damage can lead to cerebellar cognitive affective syndrome (Schmahmann's syndrome) [23]. Data from neuroimaging and neuromodulation/neurostimulation studies suggest that cerebellar compensatory reorganization might be involved in neurodegenerative diseases affecting cognition, for example, Alzheimer's disease and FTD [24]. Such compensatory cerebellar changes are expected to be more prominent as clinical cognitive and behavioural impairment become more severe [25]. A possible explanation for the finding of a positive correlation between cerebellar metabolism and both the "after" apathy score and the "before-after" gap is the involvement of the cerebellum in compensatory mechanisms. These might be prevalent in earlier stages and represent an adaptive mechanism to overcome frontal cognitive impairment, with effect dissipation over time. This point strengthens the view of ALS as a disease involving multiple neural systems and networks.

Clusters of negative and positive correlation between apathy subscores and brain metabolism were substantially overlapping for the "after" apathy subscore and the "before-after" gap. This finding underlines the importance of the "before-after" gap in the clinical use of the scale, since it could represent a proxy for the behavioural change attributable to the degenerative process. In agreement with the FrSBe manual [8], we examined a comparable, reference, population-based series [12] to identify a possible cut-off value for the gap to attribute a behavioural change to the neurodegenerative process. We propose that the threshold between the third and fourth quartile be considered as a possible cut-off value. The results of group comparisons support the hypothesis that the entity of the "before-after gap" might be more relevant than the change in category based on the cut-off value of 65 to attribute a behavioural change to the neurodegenerative process of ALS. Therefore, we suggest the "before-after gap" be considered along with the classification based on the cut-off value of 65 points in the clinical assessment of apathy through the FrSBe. However, we cannot exclude the possibility that the different sample sizes of the two groups in the comparison between apathetic patients with a "before" apathy subscore ≥65 (n = 26) versus apathetic patients with "before" apathy subscore <65 (n = 58), might have had a minimal effect on the results. Otherwise, in the comparison between apathetic patients with a before-after gap of <22 and apathetic patients with a before-after gap ≥22, the two groups were similar in size (n = 44 and n = 40, respectively).

A possible limitation of the present study is the fact that MRI scans were not available for all patients, which precluded partial volume effect correction for cortical atrophy. Nevertheless, studies employing voxel-based atrophy correction of resting glucose metabolism showed that metabolic measurements were relatively independent of brain atrophy [26]. Another possible limitation is that we did not characterize brain metabolic changes associated with different components of apathy.

In conclusion, to our knowledge, no other studies on brain 18F-FDG-PET correlates of apathy have been performed in ALS patients. We found that FrSBe "after" apathy subscore correlated with metabolic changes in brain regions known as neuroanatomical correlates of apathy. Furthermore, our data suggest the relevance of the gap between the premorbid and morbid conditions to detect behavioural changes attributable to the neurodegenerative process underlying ALS.

CONFLICT OF INTEREST
Antonio Canosa, Veria Vacchiano, Fabrizio D’Ovidio, Cristina Moglia, Umberto Manera, Rosario Vasta, Vincenzo Arena, Maurizio Grassano, Francesca Palumbo, Laura Peotta, Barbara Iazzolino and Marco Pagani have no disclosures. Andrea Calvo has received a research grant from Cytokinetics. Rocco Liguori reports personal fees from Biogen, Sanofi-Genzyme, Argon Healthcare s.r.l., Amicus Therapeutics s.r.l. and Alfasigma for Advisory Board consultancy and Lecture fees from Dynamicom Education, SIMG Service, Adnkronos salute unipersonale s.r.l. and DOC Congress s.r.l., outside the submitted work. Adriano Chiò serves on scientific advisory boards for Mitsubishi Tanabe, Roche, Biogen, Cytokinetics and AveXis, and has received a research grant from Italfarmaco. The sponsor organizations had no role in data collection and analysis and did not participate in writing and approving the manuscript. The information reported in the manuscript has never been reported elsewhere.

AUTHOR CONTRIBUTIONS
Study concept and design: Antonio Canosa, Veria Vacchiano, Fabrizio D’Ovidio, Marco Pagani, Adriano Chiò. Data acquisition: Antonio Canosa, Andrea Calvo, Cristina Moglia, Umberto Manera, Rosario Vasta, Vincenzo Arena, Maurizio Grassano, Francesca Palumbo, Laura Peotta, Barbara Iazzolino. Data analysis and interpretation: Antonio Canosa, Veria Vacchiano, Fabrizio D’Ovidio, Laura Peotta, Barbara Iazzolino, Marco Pagani, Adriano Chiò. Drafting of the manuscript: Antonio Canosa, Veria Vacchiano, Fabrizio D’Ovidio, Laura Peotta, Barbara Iazzolino, Marco Pagani, Adriano Chiò. Critical revision of the manuscript for important intellectual content: Antonio Canosa, Veria Vacchiano, Fabrizio D’Ovidio, Andrea Calvo, Cristina Moglia, Umberto Manera, Rosario Vasta, Rocco Liguori, Vincenzo Arena, Maurizio Grassano, Francesca Palumbo, Laura Peotta, Barbara Iazzolino, Marco Pagani, Adriano Chiò. Administrative, technical, material support: Andrea Calvo, Cristina Moglia, Umberto Manera, Rosario Vasta, Vincenzo Arena, Maurizio Grassano, Francesca Palumbo. Obtained Funding: Marco Pagani, Adriano Chiò. Study supervision: Antonio Canosa, Marco Pagani, Adriano Chiò.
DATA AVAILABILITY STATEMENT

Data are available upon request by interested researchers.

ORCID

Antonio Canosa https://orcid.org/0000-0001-5876-4079
Veria Vacchiano https://orcid.org/0000-0002-3607-2394
Fabrizio D’Ovidio https://orcid.org/0000-0001-6304-5415
Rosario Vasta https://orcid.org/0000-0002-0393-4736
Rocco Liguori https://orcid.org/0000-0002-1815-1013
Adriano Chiò https://orcid.org/0000-0001-9579-5341

REFERENCES

1. van Es MA, Hardiman O, Chio A, et al. Amyotrophic lateral sclerosis. Lancet. 2017;390(10107):2084-2098. https://doi.org/10.1016/S0140-6736(17)31287-4
2. Phukan J, Elamin M, Bede P, et al. The syndrome of cognitive impairment in amyotrophic lateral sclerosis: a population-based study. J Neurol Neurosurg Psychiatry. 2012;83(1):102-108. https://doi.org/10.1136/jnnp-2011-300188
3. Montuschi A, Iazzolino B, Calvo A, et al. Cognitive correlates in amyotrophic lateral sclerosis: a population-based study in Italy. J Neurol Neurosurg Psychiatry. 2015;86(2):168-173. https://doi.org/10.1136/jnnp-2013-307223
4. Strong MJ, Grace GM, Freedman M, et al. Consensus criteria for the diagnosis of frontotemporal cognitive and behavioural syndromes in amyotrophic lateral sclerosis. Amyotroph Lateral Scler. 2009;10(3):131-146. https://doi.org/10.1080/17482960802654364
5. Strong MJ, Abrahams S, Goldstein LH, et al. Amyotrophic lateral sclerosis - frontotemporal spectrum disorder (ALS-FTSD): Revised diagnostic criteria. Amyotroph Lateral Scler Frontotemporal Degener. 2017;18(3-4):153-174. https://doi.org/10.1080/21678421.2016.1267768
6. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-5). United States: American Psychiatric Publishing; 2013.
7. Robert P, Lanctôt KL, Agüera-Ortiz L, et al. Is it time to revise the diagnostic criteria for apathy in brain disorders? The 2018 international consensus group. Eur Psychiatry. 2018;54:71-76. https://doi.org/10.1016/j.eurpsy.2018.07.008
8. Grace J, Malloy P. Frontal Systems Behavior Scale (FrSBe): Professional Manual. United States: Psychological Assessment Resources; 2001.
9. Jack CR, Vemuri P, Wiste HJ, et al. Shapes of the trajectories of 5 major biomarkers of Alzheimer disease. Arch Neurol. 2012;69(7):856-867. https://doi.org/10.1001/archneurol.2011.3405
10. Brooks BR, Miller RG, Swash M, Munsat TL. World federation of neurology research group on motor neuron diseases. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotroph Lateral Scler Other Motor Neuron Disord. 2000;1(5):293-299.
11. Pagani M, Chiò A, Valentini MC, et al. Functional pattern of brain FDG-PET in amyotrophic lateral sclerosis. Neurology. 2014;83(12):1067-1074. https://doi.org/10.1212/WNL.0000000000000792
12. Chiò A, Mora G, Moglia C, et al. Secular trends of amyotrophic lateral sclerosis: the piemonte and valle d'aosta register. JAMA Neurol. 2017;74(9):1097. https://doi.org/10.1001/jamaneurol.2017.1387
13. Della Rosa PA, Cerami C, Gallivanone F, et al. A standardized [18F]-FDG-PET template for spatial normalization in statistical parametric mapping of dementia. NeuroInformatics. 2014;12(4):575-593. https://doi.org/10.1007/s12263-014-9235-4
14. Stevens JP. Applied Multivariate Statistics for the Social Sciences. United States: Lawrence Erlbaum Associates; 1996.
15. Zamboni G, Huey ED, Krueger F, Nichelli PF, Grafman J. Apathy and disinhibition in frontotemporal dementia: insights into their neural correlates. Neurology. 2008;71(10):736-742. https://doi.org/10.1212/01.wnl.0000324920.96835.95
16. Massimo L, Powers JP, Evans LK, et al. Apathy in frontotemporal degeneration: neuroanatomical evidence of impaired goal-directed behavior. Front Hum Neurosci. 2015;9:611. https://doi.org/10.3389/fnhum.2015.00611
17. Consonni M, Cappa SF, Dalla Bella E, Contarino VE, Lauria G. Cortical correlates of behavioural change in amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry. 2019;90(4):380-386. https://doi.org/10.1136/jnnp-2018-318619
18. Franceschi M, Anchisi D, Pelati O, et al. Glucose metabolism and serotonin receptors in the frontotemporal lobe degeneration. Ann Neurol. 2005;57(2):216-225. https://doi.org/10.1002/ana.20365
19. Peters F, Perani D, Herholz K, et al. Orbitofrontal dysfunction related to both apathy and disinhibition in frontotemporal dementia. Dement Geriatr Cogn Disord. 2006;21(5-6):373-379. https://doi.org/10.1159/000091898
20. Fernández-Maturraba M, Matias-Guiu JA, Cabrera-Martín MN, et al. Different apathy clinical profile and neural correlates in behavioral variant frontotemporal dementia and Alzheimer’s disease. Int J Geriatr Psychiatry. 2018;33(1):141-150. https://doi.org/10.1002/gps.4695
21. Ducharme S, Price BH, Dickerson BC. Apathy: a neurocircuitry model based on frontotemporal dementia. J Neurol Neurosurg Psychiatry. 2018;89(4):389-396. https://doi.org/10.1136/jnnp-2017-316277
22. Canosa A, Pagani M, Cistaro A, et al. 18F-FDG-PET correlates of cognitive impairment in ALS. Neurology. 2016;86(1):44-49. https://doi.org/10.1212/01.wnl.0000000000002242
23. Schmahmann JD, Sherman JC. The cerebellar cognitive affective syndrome. Brain. 1998;121(PT 4):561-579. https://doi.org/10.1093/brain/121.4.561
24. Guo CC, Tan R, Hodges JR, Hu X, Sami S, Hornberger M. Network-selective vulnerability of the human cerebellum to Alzheimer’s disease and frontotemporal dementia. Brain. 2016;139(PT 5):1527-1538. https://doi.org/10.1093/brain/aww003
25. Mitoma H, Buffo A, Gelfo F, et al. Consensus paper. cerebellar reserve: from cerebellar physiology to cerebellar disorders. Cerebellum (London, England). 2020;19(1):131-153. https://doi.org/10.1007/s12311-019-01091-9
26. Ibáñez V, Pietrini P, Alexander GE, et al. Regional glucose metabolic abnormalities are not the result of atrophy in Alzheimer’s disease. Neurology. 1998;50(6):1585-1593. https://doi.org/10.1212/wnl.50.6.1585

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Canosa A, Vacchiano V, D’Ovidio F, et al. Brain metabolic correlates of apathy in amyotrophic lateral sclerosis: An 18F-FDG-positrone emission tomography study. Eur J Neurol. 2021;28:745-753. https://doi.org/10.1111/ejn.14637