

Alma Mater Studiorum Università di Bologna  
Archivio istituzionale della ricerca

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

This is the final peer-reviewed author's accepted manuscript (postprint) of the following publication:

*Published Version:*

Canosa A., Vacchiano V., D'Ovidio F., Calvo A., Moglia C., Manera U., et al. (2021). Brain metabolic correlates of apathy in amyotrophic lateral sclerosis: An 18F-FDG-positron emission tomography study. EUROPEAN JOURNAL OF NEUROLOGY, 28(3), 745-753 [10.1111/ene.14637].

*Availability:*

This version is available at: <https://hdl.handle.net/11585/802966> since: 2021-02-21

*Published:*

DOI: <http://doi.org/10.1111/ene.14637>

*Terms of use:*

Some rights reserved. The terms and conditions for the reuse of this version of the manuscript are specified in the publishing policy. For all terms of use and more information see the publisher's website.

This item was downloaded from IRIS Università di Bologna (<https://cris.unibo.it/>).  
When citing, please refer to the published version.

(Article begins on next page)

DR. ANTONIO CANOSA (Orcid ID : 0000-0001-5876-4079)

DR. VERIA VACCHIANO (Orcid ID : 0000-0002-3607-2394)

DR. FABRIZIO D'OVIDIO (Orcid ID : 0000-0001-6304-5415)

DR. ROSARIO VASTA (Orcid ID : 0000-0002-0393-4736)

PROF. ROCCO LIGUORI (Orcid ID : 0000-0002-1815-1013)

PROF. ADRIANO CHIO (Orcid ID : 0000-0001-9579-5341)

Article type : Original Article

## **Brain Metabolic Correlates of Apathy in Amyotrophic Lateral Sclerosis: a $^{18}\text{F}$ -FDG-PET study**

Antonio Canosa, MD, PhD; Veria Vacchiano, MD; Fabrizio D'Ovidio, PhD; Andrea Calvo, MD, PhD; Cristina Moglia, MD, PhD; Umberto Manera, MD; Rosario Vasta, MD; Rocco Liguori, MD; Vincenzo Arena, MD; Maurizio Grassano, MD; Francesca Palumbo, MD; Laura Peotta, PsyD; Barbara Iazzolino, PsyD; Marco Pagani, MD, PhD;\* Adriano Chiò, MD, FAAN\*

Antonio Canosa, Fabrizio D'Ovidio, Andrea Calvo, Cristina Moglia, Umberto Manera, Rosario Vasta, Maurizio Grassano, Francesca Palumbo, Laura Peotta, Barbara Iazzolino, Adriano Chiò: ALS Centre, "Rita Levi Montalcini" Department of Neuroscience, University of Turin, Turin, Italy.

Antonio Canosa, Andrea Calvo, Cristina Moglia, Adriano Chiò: Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, Turin, Italy.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/ENE.14637](https://doi.org/10.1111/ENE.14637)

This article is protected by copyright. All rights reserved

Veria Vacchiano, Rocco Liguori: IRCCS Istituto delle Scienze Neurologiche di Bologna, Bellaria Hospital, Bologna, Italy.

Veria Vacchiano, Rocco Liguori: Department of Biomedical and NeuroMotor Sciences (DIBINEM), University of Bologna, Bologna, Italy.

Andrea Calvo, Adriano Chiò: Neuroscience Institute of Turin (NIT), Turin, Italy.

Vincenzo Arena: Positron Emission Tomography Centre AFFIDEA-IRMET S.p.A., Turin, Italy.

Marco Pagani, Adriano Chiò: Institute of Cognitive Sciences and Technologies, C.N.R., Rome, Italy.

Marco Pagani: Department of Medical Radiation Physics and Nuclear Medicine, Karolinska University Hospital, Stockholm, Sweden.

\*These authors equally contributed to the manuscript

**Corresponding author:**

Antonio Canosa, MD, PhD

ALS Centre, “Rita Levi Montalcini” Department of Neuroscience, University of Turin

Via Cherasco 15, Turin, Italy, 10126

Phone +390116335439

Fax +390116336454

ORCID ID: <https://orcid.org/0000-0001-5876-4079>

antoniocanosa85@gmail.com

**Title character count: 90**

**Abstract word count: 245**

**Text word count: 3270**

**References: 26**

**Figures: 3**

**Tables: 3**

**Supplemental Tables: 2**

**Keywords:**  $^{18}\text{F}$ -FDG-PET, Amyotrophic Lateral Sclerosis, Apathy

**Running Title:** Brain  $^{18}\text{F}$ -FDG-PET and Apathy in ALS

## **Abstract**

*Objective.* To evaluate brain metabolic correlates of apathy in ALS.

*Methods.* 165 ALS patients underwent  $^{18}\text{F}$ -FDG-PET and FrSBe. FrSBe provides “before” and “after” apathy subscores, referring to premorbid and morbid conditions. “After” apathy subscore and “before-after” gap were regressed against whole brain metabolism. Among patients with pathological “after” apathy subscore (i.e.  $\geq 65$ ), we compared patients with “before” apathy subscore  $\geq 65$  and  $< 65$ , and patients with “before-after” gap  $< 22$  and  $\geq 22$ .

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

*Conclusion.* No studies on brain  $^{18}\text{F}$ -FDG-PET correlates of apathy have been performed in ALS. We found that FrSBe “after” apathy subscore correlated with metabolic changes in brain regions

known as neuroanatomical correlates of apathy. Furthermore, our findings support the relevance of the gap between premorbid and morbid conditions to detect behavioural changes due to the neurodegenerative process underlying ALS.

## **Introduction**

Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative disease affecting upper and lower motor neurons. Death usually occurs within 2-5 years, mainly due to respiratory failure.<sup>1</sup>

According to population-based studies ~50% of ALS patients show cognitive and/or behavioural impairment falling along the frontotemporal spectrum at diagnosis.<sup>2,3</sup> Apathy has been included among features characterizing behavioural dysfunction since the first diagnostic criteria for ALS-related frontotemporal syndromes.<sup>4</sup> Apathy has assumed a central role in the recently revised criteria, stating that the presence of apathy by itself allows a diagnosis of behavioural impairment associated with ALS (ALS-bi).<sup>5</sup> Apathy is shared among many neurological and psychiatric disorders. It has been defined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5),<sup>6</sup> as characterized by “diminished motivation and reduced goal-directed behaviour, accompanied by decreased emotional responsiveness.” Diagnostic criteria for apathy have been revised in 2018:<sup>7</sup> the patient must present a quantitative reduction of goal-directed activity as compared to her/his previous level of functioning; symptoms must persist for at least four 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 due 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 Behavior Scale (FrSBe).<sup>8</sup> FrSBe evaluates 3 domains (apathy, disinhibition and executive dysfunction) and provides “before” and “after” ratings, referring respectively to premorbid condition and the time the scale is performed.

Being <sup>18</sup>F-2-fluoro-2-deoxy-D-glucose-PET (<sup>18</sup>F-FDG-PET) a marker of neuronal integrity *in vivo*,<sup>9</sup> in this study we evaluated brain metabolic correlates, assessed through <sup>18</sup>F-FDG-PET, of the apathy subscore of FrSBe in an ALS series. Since we hypothesized that both the “after” apathy score and the change between “before” and “after” conditions could be relevant to characterize ALS-related behavioural dysfunction, we aimed at evaluating the relationship of both of them 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<sup>10</sup> at the ALS Centre of Turin (Italy) in the period 2009-2015 were included. 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 <sup>18</sup>F-FDG-PET and neuropsychological assessment including FrSBe. The whole test battery has been reported elsewhere.<sup>3</sup> Neuropsychological evaluation and <sup>18</sup>F-FDG-PET were performed within 1 month of each other.

#### *<sup>18</sup>F-FDG-PET acquisition*

<sup>18</sup>F-FDG-PET was performed according to published guidelines.<sup>11</sup> Patients fasted at least six hours before the exam. Blood glucose was <7.2 mmol/l in all cases before the procedure. After a 20-minute rest, about 185 MBq of <sup>18</sup>F-FDG was injected. The acquisition started 60 minutes after the injection. PET/CT scans were performed by a Discovery ST-E System (General Electric). Brain CT (thickness of 3.75 millimetres, 140 kV, 60-80 mAs) and PET scan (1 FOV of 30 transaxial centimetres) were sequentially acquired, the former being used for attenuation correction of PET data. PET images were reconstructed with 4 iterations and 28 subsets with an initial voxel size of 2.34x2.34x2.00 mm and data were collected in 128x128 matrices.

#### *Behavioural assessment*

FrSBe<sup>8</sup> 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 in a 5-point scale: 1 (almost never), 2 (seldom), 3 (sometimes), 4 (frequently), 5 (almost always). FrSBe contains “before” and “after” ratings, referring respectively to 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 of outstanding importance in light of the possible loss of insight of patients.<sup>5</sup> The higher is the score, the more severe is behavioural impairment. Scores ≥65 are interpreted as pathological according to the FrSBe manual for each section and the total score.<sup>8</sup>

We considered the “after” apathy subscore as a measure of behavioural impairment at diagnosis. The “before-after” change was estimated in two different ways. The former was the gap between “before” and “after” apathy subscores, calculated as follows: “after” apathy subscore – “before” apathy subscore. The latter assessed the apathetic/non apathetic status based on the cut off of 65 points to evaluate eventual change of status between “before” and “after” conditions. So, we could subdivide apathetic patients (i.e. “after” apathy subscore  $\geq 65$ ) into two groups: subjects with premorbid score already in the pathological range (i.e. “before” apathy subscore  $\geq 65$ ) and subjects with premorbid score within the normal range (i.e. “before” apathy subscore  $< 65$ ). Both methods were considered as possible proxies of behavioural changes due to the neurodegenerative process. In order to identify a possible cut-off to consider a “before-after” gap as significant, we examined a comparable neurological group as reference, as suggested by the manual of the scale.<sup>8</sup> We considered 517 incident ALS patients from the Piemonte and Valle d’Aosta Register for ALS,<sup>12</sup> who underwent a neuropsychological assessment, including 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 resulted 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 with the Student’s t-test or analysis of variance; comparisons between categorical variables were made with the  $\chi^2$  test and Fisher’s test when applicable.

SPM12 implemented in Matlab R2018b (MathWorks, Natick, MA, USA) was used for image normalization. A customized brain  $^{18}\text{F}$ -FDG-PET template<sup>13</sup> 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 at evaluating the correlations between brain metabolism and both “after” apathy subscore and “before-after” gap of the apathy subscore of FrSBe, performing two multiple regression analyses in the whole sample (n=165). Subsequently, we focused on patients with the “after” apathy subscore  $\geq 65$ , i.e. subjects showing 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 such group into two subgroups to compare them: subjects showing a “before” apathy subscore  $\geq 65$  (i.e. already in the pathological range) *versus* patients displaying a “before” apathy subscore  $< 65$  (i.e. within the normal range). Then, we divided the same group of patients with the “after” apathy subscore  $\geq 65$  into the following two subgroups to compare them: patients showing a “before-after” gap  $< 22$  *versus* patients with a “before-after” gap  $\geq 22$ . 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 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-FTSD)<sup>5</sup> or executive dysfunction as covariates, since they resulted highly correlated with apathy subscores ( $r=0.77$ ,  $p<0.001$ ). On the other hand, we included the FrSBe “after” subscore related to disinhibition as covariate in all the analyses, since it resulted only marginally correlated with the “after” apathy subscore ( $r=0.57$ ;  $p<0.001$ ). Details about the pitfalls of including highly correlated variables as covariates in multiple regression models are reported elsewhere.<sup>14</sup>

For all the analyses the height threshold was set at  $P<0.005_{\text{uncorrected}}$  ( $P<0.05_{\text{FWE-corrected}}$  at cluster level) and only clusters containing  $>125$  contiguous voxels were considered significant. Brodmann areas (BAs) were identified at a 0–2-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 signed a written informed consent.

#### *Data availability statement*

Data will be available upon request by interested researchers.

### **Results**

#### *Demographic and clinical data*

We compared demographic and clinical data of patients who underwent  $^{18}\text{F}$ -FDG-PET ( $n=165$ ) to the reference population-based series ( $n=330$ ). The comparison is summarized in Supplemental Table 1. No significant difference was found for sex distribution, education, and site of onset (bulbar/spinal). Otherwise, in patients who underwent  $^{18}\text{F}$ -FDG-PET age resulted slightly lower and ALSFRS-R resulted slightly higher, probably due to the higher difficulty of elderly people and patient with worse disability in reaching the PET Centre.

In the group of patients with the “after” apathy subscore  $\geq 65$ , i.e. subjects showing scores considered as pathological at diagnosis ( $n=84$ ), we compared demographic and clinical data of subjects showing a “before” apathy subscore  $\geq 65$  *versus* patients displaying a “before” apathy subscore  $< 65$ , and subjects showing a before-after gap  $< 22$  *versus* subjects 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, and ALSFRS-R at assessment. Such data are summarized in Supplemental Table 2.

#### *$^{18}\text{F}$ -FDG-PET data*

##### *Correlation between the “after” apathy subscore and brain metabolism in the whole sample ( $n=165$ )*

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

##### *Patients with the “after” apathy subscore $\geq 65$ ( $n=84$ ): “before” apathy subscore $\geq 65$ ( $n=26$ ) versus “before” apathy subscore $< 65$ ( $n=58$ )*

We found no difference between the two groups.

##### *Patients with the “after” apathy subscore $\geq 65$ ( $n=84$ ): “before-after” gap $< 22$ ( $n=44$ ) versus “before-after” gap $\geq 22$ ( $n=40$ )*

In patients with “before-after” gap  $\geq 22$  as compared to patients with “before-after” gap  $< 22$  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  $^{18}\text{F}$ -FDG-PET correlates of apathy have been performed in ALS patients. Furthermore, we aimed at evaluating the relationship between cerebral metabolism and behavioural changes, defined as the difference between “before” and “after” apathy subscores of the FrSBe scale. We found that the higher was the apathy subscore at diagnosis, the lower was the metabolism in brain regions known to be involved in apathy circuitry (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 MRI studies of apathy in FTD have been conducted. In a Voxel-Based Morphometry (VBM) study including patients with behavioural variant FTD (bvFTD,  $n=48$ ) and Primary Progressive Aphasia ( $n=14$ ), FrSBe apathy subscore resulted significantly correlated with atrophy of the right DLPFC, with trends to significance in the left DLPFC, right ACC, right lateral orbitofrontal cortex (LOFC), right temporoparietal junction, and right putamen.<sup>15</sup> A VBM and Diffusion Tensor Imaging MRI study<sup>16</sup> 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. 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<sup>17</sup> 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 resulted correlated with the thinning of bilateral orbitofrontal cortex.

Few <sup>18</sup>F-FDG-PET studies have been conducted to disclose the metabolic correlates of apathy in FTD. A study<sup>18</sup> compared 12 apathetic bvFTD patients, 6 disinhibited bvFTD patients, and 24 healthy controls (HC). Considering separately the two bvFTD subgroups in comparison with HC, the apathetic group showed a distinctive relative hypometabolism bilaterally in frontal medial cortex, frontal polar cortex, anterior orbitofrontal cortex, DLPFC, insula, and thalamus. The role of orbitofrontal cortex in apathetic manifestations has been supported also by a study<sup>19</sup> comparing two bvFTD subgroups, defined based on their apathy scores on the Neuropsychiatric Inventory: the apathetic group showed specific metabolic impairment in the orbitofrontal cortex, as compared to HC (a result not shared by the non-apathetic FTD patients).

A more recent study on the neural correlates of apathy in bvFTD and Alzheimer's Disease (AD)<sup>20</sup> evaluated the relationship between brain metabolism and apathy, employing <sup>18</sup>F-FDG-PET and the Lille Apathy Rating Scale. The authors included 42 bvFTD, 42 AD, and 30 HC. In bvFTD patients a distinct neuroanatomical correlate was found: apathy resulted 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 <sup>18</sup>F-FDG-PET.<sup>21</sup> 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 dorsomedial frontal areas (ACC, middle cingulate cortex, medial superior frontal gyrus, supplementary motor area). The involvement of ventral prefrontal areas (subgenual ACC, medial and LOFC) 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 subscores and glucose metabolism in regions including DLPFC, DMPFC, VLPFC, PMC, ACC, and insula, largely

overlapping with cortical regions previously shown to be related to different apathy components in FTD.<sup>21</sup> Clusters of positive correlation included the cerebellum and the pons. Notably, cerebellar and brainstem metabolism tends to increase as ALS-related cognitive impairment worsens.<sup>22</sup> The cerebellum is known to be involved in cognitive and behavioural processes. Cerebellar damage can lead to the cerebellar cognitive affective syndrome (Schmahmann's syndrome).<sup>23</sup> Data from neuroimaging and neuromodulation/neurostimulation studies suggest that cerebellar compensatory reorganization might be involved in neurodegenerative diseases affecting cognition, e.g. Alzheimer's Disease and Frontotemporal Dementia.<sup>24</sup> Such compensatory cerebellar changes are expected to be more prominent as clinical cognitive and behavioural impairment become more severe.<sup>25</sup> One possibility to explain 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. They 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 of the behavioural change due to the degenerative process. In agreement with the FrSBe manual,<sup>8</sup> we examined a comparable, reference, population-based series<sup>12</sup> to identify a possible cut-off of the gap to attribute a behavioural change to the neurodegenerative process. We propose to consider the threshold between the third and fourth quartile 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 of category based on the cut-off value of 65 to attribute a behavioural change to the neurodegenerative process of ALS. Therefore, we suggest to consider the entity of the "before-after" gap 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 that the different sample sizes of the two groups in the comparison between apathetic patients with a "before" apathy subscore  $\geq 65$  (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 before-after gap  $<22$  and apathetic patients with before-after gap  $\geq 22$  the two groups showed similar size ( $n=44$  and  $n=40$  respectively).

A possible limitation of our study is that MRI scans were not available for all subjects, not allowing 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.<sup>26</sup> A further 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  $^{18}\text{F}$ -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.

## **Funding**

This study was supported by a grant from the Thierry Latran Foundation (INSPIRED project), by the Italian Ministry of Health (Ricerca Sanitaria Finalizzata, grant RF-2016-02362405), the European Commission's Health Seventh Framework Programme (FP7/2007-2013, grant agreement 259867), the Italian Ministry of Education, University and Research (Progetti di Ricerca di Rilevante Interesse Nazionale, PRIN, grant 2017SNW5MB; the Joint Programme-Neurodegenerative Disease Research, Strength and Brain-Mend projects). This study was performed under the Department of Excellence grant of the Italian Ministry of Education, University and Research to the "Rita Levi Montalcini" Department of Neuroscience, University of Turin, Italy.

Funding sources had no role in study design and conduct; data collection, management, analysis, and interpretation; preparation, review, approval, and decision to submit the manuscript.

## **Disclosures**

Antonio Canosa, Veria Vacchiano, Fabrizio D'Ovidio, Cristina Moglia, Umberto Manera, Rosario Vasta, Vincenzo Arena, Maurizio Grassano, Francesca Palumbo, Laura Peotta, Barbara Iazzolino, Marco Pagani: 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 to 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.

## References

1. van Es MA, Hardiman O, Chio A, et al. Amyotrophic lateral sclerosis. *Lancet*. 2017;390(10107):2084-2098. doi: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. doi: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. doi: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. doi: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. doi:10.1080/21678421.2016.1267768
6. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*. 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. doi:10.1016/j.eurpsy.2018.07.008
8. Grace J, Malloy P. *Frontal Systems Behavior Scale (FrSBe): Professional Manual*. 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. doi: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. doi: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*. Published online July 10, 2017. doi: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. doi:10.1007/s12021-014-9235-4

14. Stevens JP. *Applied Multivariate Statistics for the Social Sciences*. 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. doi: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. doi: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. doi: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. doi: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. doi:10.1159/000091898
20. Fernández-Matarrubia M, Matías-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. doi: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. doi: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. doi:10.1212/WNL.0000000000002242
23. Schmahmann JD, Sherman JC. The cerebellar cognitive affective syndrome. *Brain*. 1998;121 ( Pt 4):561-579. doi: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. doi: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. doi: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. doi:10.1212/wnl.50.6.1585

## Figure captions

### Figure 1

- A. Clusters of negative correlation between FrsBe “after” apathy subscore and whole brain metabolism in the whole sample (n=165) are projected on brain surface.
- B. Clusters of negative correlation between FrsBe apathy “before-after” gap and whole brain metabolism in the whole sample (n=165) are projected on brain surface.

### Figure 2

- A. Clusters of positive correlation between FrsBe “after” apathy subscore and whole brain metabolism in the whole sample (n=165) are represented on a brain MRI template.
- B. Clusters of positive correlation between FrsBe apathy “before-after” gap and whole brain metabolism in the whole sample (n=165) are represented on a brain MRI template.

### Figure 3

- A. Clusters of relative hypometabolism in patients with FrsBe apathy “before-after” gap  $\geq 22$  as compared to patients with “before-after” gap  $< 22$  are projected on brain surface.
- B. Clusters of relative hypermetabolism in patients with FrsBe apathy “before-after” gap  $\geq 22$  as compared to patients with “before-after” gap  $< 22$  are represented on a brain MRI template.

**Table 1:** Clusters of negative correlation between FrsBe “after” apathy subscore and whole brain metabolism in the whole sample.

<b>P (FWE-corr)</b>	<b>Cluster Extent</b>	<b>Z-score</b>	<b>Talairach Coordinates</b>			<b>Lobe</b>	<b>Cortical Region</b>	<b>BA</b>
0.000	9655	4.42	-53	16	8	Frontal	Left Precentral Gyrus	44
		4.39	-44	19	29	Frontal	Left Middle Frontal Gyrus	9
		4.28	-38	35	31	Frontal	Left Superior Frontal Gyrus	9
		3.95	-18	28	52	Frontal	Left Superior Frontal Gyrus	6
		3.82	-40	2	35	Frontal	Left Precentral Gyrus	6
		3.81	-34	5	53	Frontal	Left Middle Frontal Gyrus	6

		3.74	-40	19	1	Sub-lobar	Left Insula	13
		3.73	10	26	21	Limbic	Right Anterior Cingulate	32
		3.67	-6	43	40	Frontal	Left Medial Frontal Gyrus	8
		3.52	8	14	53	Frontal	Right Superior Frontal Gyrus	6
		3.50	-6	34	17	Limbic	Left Anterior Cingulate	32
		3.45	6	39	33	Frontal	Right Medial Frontal Gyrus	9
0.006	2196	4.06	30	1	50	Frontal	Right Middle Frontal Gyrus	6

		3.81	55	27	28	Frontal	Right Middle Frontal Gyrus	46
		3.61	57	20	8	Frontal	Right Inferior Frontal Gyrus	45
		3.51	38	21	3	Sub-lobar	Right Insula	13
		3.32	38	29	45	Frontal	Right Middle Frontal Gyrus	8
		3.00	42	13	31	Frontal	Right Middle Frontal Gyrus	9
		2.91	42	25	36	Frontal	Right Precentral Gyrus	9
		2.78	40	20	51	Frontal	Right Superior Frontal Gyrus	8

**Table 2.** Clusters of negative correlation between FrsBe apathy “before-after” gap and brain metabolism in the whole sample.

<b>P (FWE-corr)</b>	<b>Cluster Extent</b>	<b>Z-score</b>	<b>Talairach Coordinates</b>			<b>Lobe</b>	<b>Cortical Region</b>	<b>BA</b>
0.000	11985	4.88	10	16	47	Frontal	Right Superior Frontal Gyrus	6
		4.87	-8	43	42	Frontal	Left Superior Frontal Gyrus	8
		4.39	-51	20	5	Frontal	Left Inferior Frontal Gyrus	45
		4.34	-20	6	49	Frontal	Left Medial Frontal Gyrus	6
		4.32	10	42	31	Frontal	Right Medial Frontal Gyrus	9



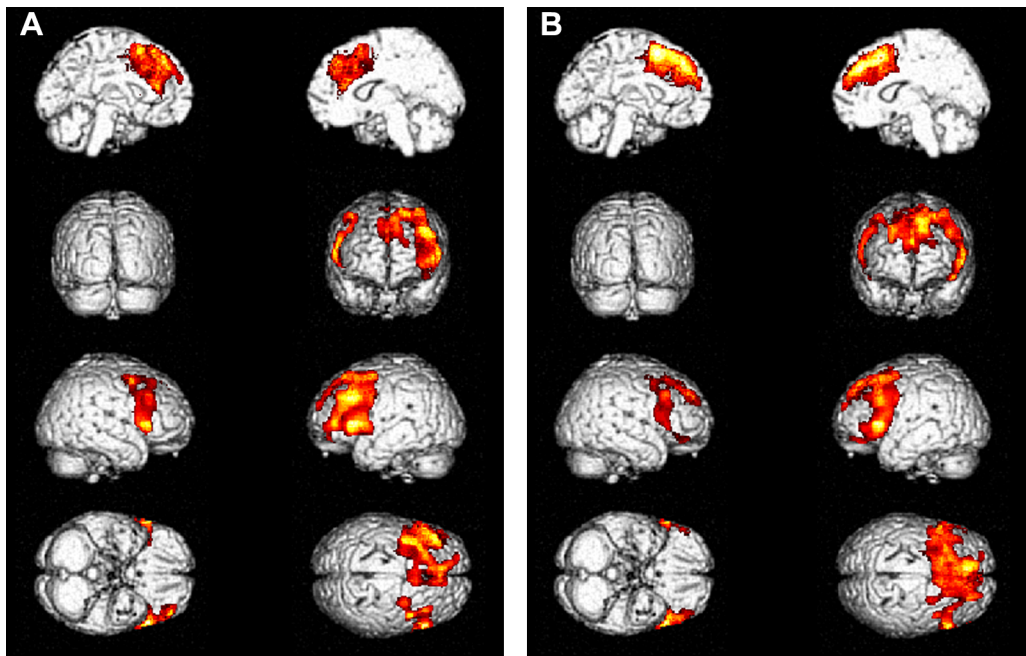
4.31	-16	14	51	Frontal	Left Superior Frontal Gyrus	6
4.06	-46	17	27	Frontal	Left Middle Frontal Gyrus	9
3.97	-50	11	18	Frontal	Left Inferior Frontal Gyrus	44
3.81	-6	12	44	Frontal	Left Medial Frontal Gyrus	32
3.76	20	29	39	Frontal	Right Middle Frontal Gyrus	8
3.72	-34	5	55	Frontal	Left Middle Frontal Gyrus	6

		3.72	-4	17	38	Limbic	Left Cingulate Gyrus	32
		3.52	55	25	26	Frontal	Right Middle Frontal Gyrus	46
		3.45	28	6	48	Frontal	Right Middle Frontal Gyrus	6
		3.38	51	21	32	Frontal	Right Middle Frontal Gyrus	9

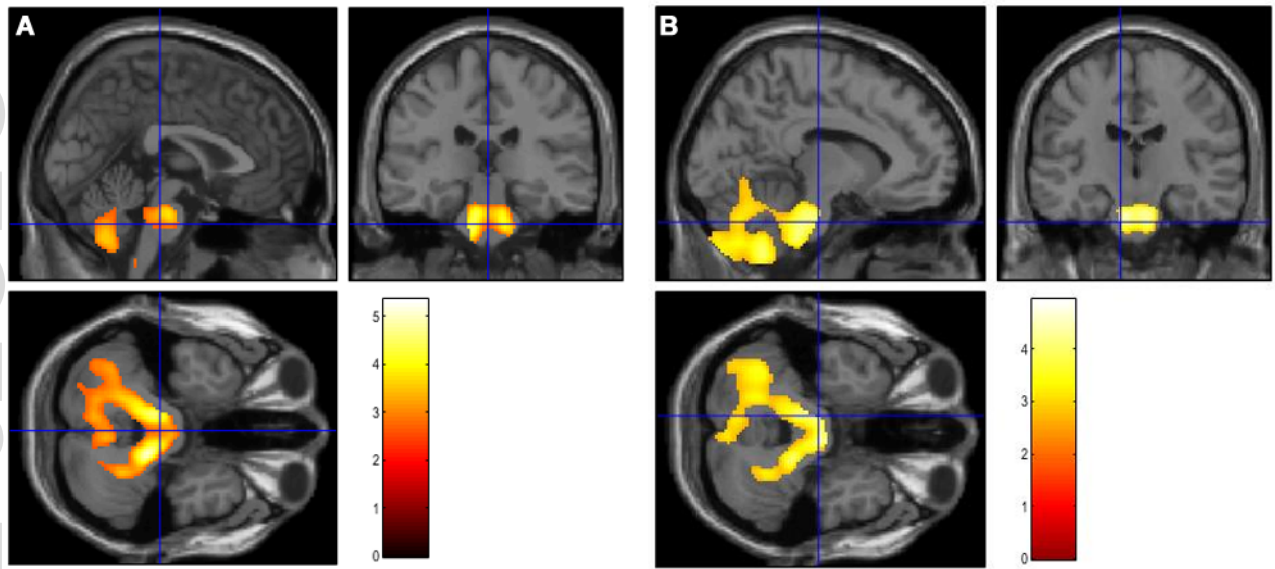
**Table 3.** Clusters of relative hypometabolism in patients with FrsBe apathy “before-after” gap  $\geq 22$  as compared to patients with “before-after” gap  $< 22$ , in the sample of patients with FrsBe “after” apathy subscore  $\geq 65$ .

P (FWE-corr)	Cluster Extent	Z-score	Talairach Coordinates			Lobe	Cortical Region	BA
0.001	3120	3.73	10	18	47	Frontal	Right Medial Frontal Gyrus	8
		3.49	-12	11	60	Frontal	Left Superior Frontal Gyrus	6
		3.33	-6	43	42	Frontal	Left Superior Frontal Gyrus	8
		3.30	-6	8	44	Frontal	Left Medial Frontal Gyrus	32
		3.18	10	46	33	Frontal	Right Superior Frontal Gyrus	9

		3.11	-32	5	53	Frontal	Left Middle Frontal Gyrus	6
		2.92	4	35	30	Frontal	Right Medial Frontal Gyrus	9
		2.91	-2	38	31	Frontal	Left Medial Frontal Gyrus	9
		2.91	32	39	42	Frontal	Right Middle Frontal Gyrus	8
		2.88	28	26	50	Frontal	Right Superior Frontal Gyrus	8
		2.62	4	55	19	Frontal	Right Medial Frontal Gyrus	10



ene\_14637\_f1.tif



ene\_14637\_f2.tif

