Cortical correlates of behavioural change in amyotrophic lateral sclerosis

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ABSTRACT

Background Behavioural changes in amyotrophic lateral sclerosis (ALS) are heterogeneous. The study aim was to identify the behavioural profiles of non-demented patients with ALS and their neuroimaging correlates and to elucidate if they are comparable to those reported in studies of the behavioural-variant of frontotemporal dementia (bvFTD).

Methods Behavioural changes of 102 non-demented patients with ALS were assessed through the Frontal Behavioural Inventory (FBI), a 24-item scale assessing different behavioural modifications, mainly chosen from the core clinical features of FTD. Principal component analysis (PCA) was used to detect distinct clusters of behavioural changes based on FBI subscores. The cortical thinning related to each behavioural profile was analysed in 29 patients with ALS. Cronbach's α was used to test the reliability of bvFTD-related FBI clustering in our cohort.

Results Sixty patients with ALS had FBI score ≥1. PCA identified three phenotypic clusters loading on disinhibited/hostile, dysexecutive and apathetic FBI subscores. Imaging analyses revealed that the thinning of bilateral orbitofrontal cortex was related to apathy, the right frontotemporal and circular cortex to the disinhibited/hostile profile and the left precuneus cortex to the dysexecutive behaviours. The bvFTD-associated aggressive profile reliably applied to our cohort.

Conclusions In non-demented patients with ALS, different behavioural profiles could be identified. The right frontotemporal and circular cortex thinning was the hallmark of the behavioural profile mostly overlapping that described in bvFTD. Our findings provide the unbiased identification of determinants relevant for a novel stratification of patients with ALS based on their behavioural impairment, which might be useful as proxy of cognitive decline.

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a clinical and genetic heterogeneous neurodegenerative disorder often associated with frontotemporal syndromes, ranging from mild cognitive and behavioural dysfunction to frontotemporal dementia (FTD).1 In past years, a considerable amount of research has been devoted to the identification of the cognitive profiles in non-demented patients with ALS (ALSc).1,2 The specific patterns of ALS-associated behavioural impairment have been investigated less often. The most commonly described behavioural changes in non-demented patients with ALS are apathy, disinhibition and irritability, affecting up to 60% of patients.1,4 Current consensus criteria established that the diagnosis of behavioural impairment (ALSbi) in non-demented ALS individuals requires the identification of apathy or the presence of at least two non-overlapping, supportive diagnostic features for behavioural variant FTD (bvFTD).3 In a large ALS population including patients with ALS-FTD, five specific subdomains of behavioural impairment have been identified, comprising disinhibited behaviours, irregularity of reward/impulse control, dysexecutive behaviours, cognitive rigidity and neuropsychiatric features.5 A comprehensive investigation of the anatomical correlates of specific ALS behavioural phenotypes is still lacking. Only the apathetic profile has been related to bilateral atrophy of the orbitofrontal cortex and nucleus accumbens.5,6

The study aims to identify behavioural profiles within a large sample of non-demented patients with ALS and their association with clinical, cognitive and neuroimaging features. Our hypothesis is that patients with ALS have distinct behavioural profiles associated with different patterns of cortical changes, only partially overlapping to those observed in bvFTD.7,8 For this purpose, we verified if the described behavioural features of bvFTD were reliable in non-demented ALS.

METHODS

Participants

One-hundred and two patients, meeting the revised El Escorial criteria for definite, probable and laboratory-supported probable ALS,9 were recruited over a 4 year period (May 2012 to May 2016) at the Motor Neuron Diseases Centre of the ‘Carlo Besta’ Neurological Institute of Milan, Italy. Exclusion criteria were: clinical and imaging evidence of cerebrovascular disease, comorbid FTD,10 Alzheimer’s disease (NIA-AA), neurological or psychiatric (eg, depression, post-traumatic stress disorder) disease affecting cognition, diabetes and respiratory insufficiency (forced vital capacity in the upright position <70%). All patients and their relatives gave consent on the use of individual data in retrospective clinical research studies and the internal ethical review board approved the study.

Neuropsychological assessment

All participants underwent a clinical neurological evaluation and a broad battery of standardised neuropsychological tests, with published norms for
the Italian population, assessing executive functions, language, memory, social cognition, visuospatial abilities and mood. The assessment of the behavioural features was performed through an interview with an adult family member or caregiver of each patient and was based on the Italian version of the Frontal Behavioural Inventory (FBI). The FBI is a 24-item scale assessing the presence of negative or positive behavioural modifications, mainly chosen from the core clinical features of FTD (figure 1 and online supplementary appendix E-1 for details). Each item is scored on a 4-point scale, from 0 (no behavioural change) to 3 (severe behavioural change). Items of the original interview schedule addressing language impairment (aphasia, logopenia and semantic dementia), alien-hand and incontinence were not analysed because they were beyond the scope of the current study. For all patients, changes in habits due to physical disability were not rated as behavioural changes (eg, stopped playing football or no longer plays a musical instrument were not rated as behavioural changes in patients with muscle weakness, while stopped watching football matches on TV or stopped listening to music were rated as mild-to-severe behavioural change according to the frequency of occurrence).

The presence of cognitive (ALSci), behavioural (ALSbi) and combined cognitive and behavioural (ALScbi) impairment was defined on the basis of recent classification criteria. Specifically, the diagnosis of ALSbi required the identification of apathy with or without other behavioural changes or the presence of at least two non-overlapping supportive diagnostic features from the Raschovsky criteria, including loss of insight and psychotic symptoms. The FBI questionnaire allowed us to measure the severity of apathy (first item) and to recognise supportive features such as disinhibition (items 16, 18, 20 and 22); loss of sympathy/empathy (third item); perseverative/stereotyped/compulsive/ritualistic behaviours (13th item); hyperorality/dietary changes (21st item) and loss of insight (8th item). ALSci was diagnosed in patients with moderate-to-severe behavioural changes.

Data analyses

Demographic, clinical and neuropsychological variables

Patients were grouped according to the presence of behavioural changes and differences in demographic, clinical, neuropsychological profiles were evaluated (table 1 and online supplementary table E-1). The Kolmogorov-Smirnov test was used to test the normality of data distribution separately for each ALS subgroup. Accordingly, Fisher’s exact test, Independent-sample T tests and Mann-Whitney U tests were then applied. The Benjamin-Hochberg procedure for false discovery rate was used to control for multiple comparisons and effects of sample sizes (Hedges’ g and OR) were reported.

Behavioural profiling

The principal component analysis (PCA) with varimax rotation was used to identify the clustering pattern of FBI items highly correlated with each other (exclusion criteria for PCA are reported in online supplementary file 1, Appendix E-2). All patients with changes in at least one of the domains investigated by the FBI (FBI total score≥1) were included in PCA. Each FBI item was considered and standardised (z-score). Clusters with eigenvalues over the Kaiser criterion of 1 were retained. The consistency of PCA solutions was evaluated calculating the Cronbach’s α for each PCA clustering pattern. Only clusters with Cronbach’s α above 0.7 were used to identify ALS behavioural phenotypes. In addition, in order to measure the severity of apathetic behaviour, a well-defined ALS-associated behavioural phenotype, we used the apathy score of the FBI.

Correlation analyses

Z-scores of the FBI apathy item (the first item) and averaged z-scores of FBI items of each PCA cluster were calculated and correlated (partial correlations controlling for age and education) with disease length, time between diagnosis and neuropsychological assessment, motor disability, progression rate index, geriatric depression scale and cognitive performances of patients with ALS with FBI total score≥1. Significant correlations were bias corrected, and accelerated bootstrap 95% CIs were computed with 1000 bootstrap equally-sized samples obtained.

Figure 1 Percentage of patients with ALS (n=102) showing behavioural changes measured with the FBI questionnaire. ALS, Amyotrophic Lateral Sclerosis; FBI, Frontal Behavioural Inventory.
by randomly resampling with replacement from the original data. Only partial correlations with p<0.05 and CIs not crossing ‘0’ surviving the Benjamin-Hochberg procedure for false discovery rate controlling for multiple comparisons were reported.

Reliability analysis of bvFTD behavioural phenotypes

We verified if the classification of behavioural profiles of bvFTD is consistent with the behavioural features of ALS. Specifically, if bvFTD and ALS are equivalent in terms of behavioural impairment, the same clustering pattern should be observed. We tested if the FBI clustering pattern of patients with bvFTD were reliable in our sample of non-demented patients with ALS by measuring Cronbach’s α. Only one previous study characterised the behavioural profiles of bvFTD using the FBI.7 The authors identified, with factor analysis, distinct profiles within the FBI, namely apathetic (apathy, aspontaneity), disinhibited (loss of insight, perseveration, hoarding, excessive jocularity, impulsivity, roaming, hyperorality, utilisation behaviour), aggressive (mental rigidity, irritability, aggression) and linguistic (logopenia, aphasia, semantic deficit) behaviours. We measured the consistency of the apathetic (two FBI subscores), disinhibited (eight FBI subscores) and aggressive (three FBI subscores) profiles in our sample of non-demented patients with ALS with FBI score >1, calculating Cronbach’s α. The language phenotype was not used in the analysis, since patients with evidence of language dysfunction had been excluded from the study sample. A Cronbach’s α above 0.7 was considered to reveal consistency between ALS and FTD behavioural profiles.13 We also verified the reliability of bvFTD profiles in a small group of seven patients with ALS-bFTD with the behavioural/cognitive symptoms of bvFTD (online supplementary table E-2).14

Imaging data analyses

Whole-brain structural MRIs were acquired and processed in a subsample of 29 patients with ALS as described in Consonni et al (online supplementary appendix E-3).14 The clinical and neuro-psychological features of these patients did not differ from those of 31 patients with ALS who did not perform the neuroimaging study (online supplementary table E-3). Cortical thickness (CT) values were calculated in each subject15 and averaged on each gyral and sulcal structure of 74 bilateral regions as defined in Destrieux et al.16 This approach has been shown to be a sensitive tool to detect the extramotor cortical involvement in patients with ALS.17 The relationship between cortical involvement (CT values) and behavioural profiles (cluster scores) of patients with ALS was examined with partial correlations (corrected for age, education and total intracranial volume). For this purpose, we used standardised z scores for each CT value, the averaged z-scores of FBI items loading on PCA clusters with α>0.07 and the FBI apathy z-scores. Significant correlations were then bias corrected, and accelerated bootstrap 95% CIs were computed with 1000 bootstrap equally sized samples obtained by randomly resampling with replacement from the original data. Only partial correlations with p<0.05 and CIs not crossing ‘0’ surviving the Benjamini-Hochberg procedure for false discovery rate controlling for multiple comparisons (behavioural profiles) were reported. Then, to control if cortical thinning associated with behavioural phenotypes were also related to concomitant cognitive involvement, CT measures of regions resulting significantly associated to behavioural profiles were used for partial correlations (corrected for age, education and total intracranial volume) with cognitive performances of patients with ALS.

RESULTS

Behavioural profiling

The occurrence of behavioural changes revealed by FBI is shown in figure 1. Sixty patients with ALS had FBI total score ≥1, and 26 of them satisfied criteria for behavioural impairment (ALScbi). PCA analysis was run in the group of 60 patients with ALS with FBI total score ≥1, which had longer disease duration and lower performance at verbal episodic memory testing than 42 patients with ALS without behavioural changes (table 1 and online supplementary file 1). The Kaiser-Meyer-Olkin (KMO) measure tested the sample adequacy of 11 FBI items for PCA (KMO

Table 1  
Clinical data of patients with ALS subdivided on the basis of the FBI total score

<table>
<thead>
<tr>
<th></th>
<th>42 ALS FBI=0</th>
<th>60 ALS FBI≥1</th>
<th>Group comparison</th>
<th>Effect sizes</th>
</tr>
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<tr>
<td>Age</td>
<td>59.2±8.7</td>
<td>60.4±10.7</td>
<td>ns</td>
<td>0.121*</td>
</tr>
<tr>
<td>Education</td>
<td>10.9±4.6</td>
<td>10.2±3.9</td>
<td>ns</td>
<td>0.166*</td>
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<tr>
<td>ALSFRS-R</td>
<td>39.7±5.7</td>
<td>38.4±6.2</td>
<td>ns</td>
<td>0.216*</td>
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<tr>
<td>ALS-MITOS</td>
<td>0.21±0.5</td>
<td>0.25±0.5</td>
<td>ns</td>
<td>0.080*</td>
</tr>
<tr>
<td>ALS-MITOS stage</td>
<td>34/71/10</td>
<td>47/11/20</td>
<td>ns</td>
<td>–</td>
</tr>
<tr>
<td>Male/Female</td>
<td>18/24</td>
<td>35/25</td>
<td>ns</td>
<td>0.535†</td>
</tr>
<tr>
<td>Disease duration (months)</td>
<td>14.9±9.0</td>
<td>20.8±14.4</td>
<td>p=0.014</td>
<td>0.473*</td>
</tr>
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<td>Progression rate index</td>
<td>0.76±0.9</td>
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<td>0.297*</td>
</tr>
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<td>Months between diagnosis and behavioural assessment</td>
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<td>4.0±8.2</td>
<td>ns</td>
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<td>Bulbar onset</td>
<td>12/30</td>
<td>17/43</td>
<td>ns</td>
<td>1.012†</td>
</tr>
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<td>Predominance (UMN/LMN)</td>
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<td>20/32 (8 na)</td>
<td>ns</td>
<td>0.995†</td>
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<td>C9orf72 (yes/no)</td>
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<td>8/52</td>
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<td>ALScn</td>
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<td>N=20</td>
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<td>N=14</td>
<td>–</td>
<td>–</td>
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<td>–</td>
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<tr>
<td>ALScbi</td>
<td>N=0</td>
<td>N=14</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*Hedges.
†OR.
ALS, Amyotrophic Lateral Sclerosis; ALSFRS-R, the Revised ALS Functional Rating Scale; ALS-MITOS, ALS Milano-Torino Staging system38; ALScbi, patients with ALS fulfilling criteria for cognitive impairment; ALScn, cognitively normal patients with ALS (ie, patients not fulfilling Strong criteria for ALS); ALScbi, patients with ALS fulfilling Strong criteria for cognitive impairment; ALScn, cognitively normal patients with ALS (ie, patients not fulfilling Strong criteria for ALS); ALScni, cognitively normal patients with ALS (ie, patients not fulfilling Strong criteria for ALS and ALScbi); FBI, Frontal Behavioural Inventory; LMN, Lower Motor Neuron; ns, Not Significant difference; UMN, Upper Motor Neuron.
The rotation converged on six iterations. Three clusters had eigenvalues over Kaiser criterion of 1 and in combination explained 63.64% of the variance (table 2). Cluster 1 included FBI items assessing disinhibition/aggression, Cluster 2 included dysexecutive items, and Cluster 3 loadings were apathy, inattention and loss of insight (table 2). Reliability analysis confirmed the consistency of the disinhibited/hostile (α=0.86) and dysexecutive (α=0.71) profiles, but not the third cluster (α=0.45). Reliability analysis was applied also to the ALSbi group (n=26) confirming the consistency of the disinhibited/hostile (α=0.82) and dysexecutive (α=0.70) profiles, but not the third cluster (α=0.41). Only the FBI apathy item was then used for further analysis.

### Correlation analyses

Clinical variables and progression rate were not related to any specific behavioural profile. Lower performance in delayed recall of Rey Auditory Verbal Learning test was associated with higher rates of apathetic (r = −0.333, p = 0.015, CIs −0.524 to −0.113) and disinhibited/hostile behaviours (r = −0.298, p = 0.030, CIs −0.541 to −0.017). These associations, however, were not confirmed within the ALSbi patient subgroup (n=26), in which there was a strong association between the severity of disinhibited/hostile behaviours and impairment of inhibitory control abilities (Stroop test: r = −0.681, p < 0.001, CIs 0.074 to 0.880).

### Neuroimaging correlates

The study of the cortical correlates of behavioural profiles revealed that the severity of disinhibited/hostile behaviours was associated with the thinning of the temporal and cingular regions of the right hemisphere. Severe apathetic symptoms were related to CT reduction in bilateral orbitofrontal lobes and left precentral gyrus. Both profiles were related to thinning of the right superior frontal gyrus. Dysexecutive behaviours were associated with the thinning of the left precuneus. See figure 2 and table 3 for further details. CT measures of these regions were not related to disease duration, whereas the right superior temporal gyrus was related to poor verbal fluency (F index: r = −0.555, p = 0.003, CI −0.782 to −0.125) and emotion recognition abilities (Ekman test: r = 0.522, p = 0.011, CI 0.094 to 0.781). Low performances at the digit span backward task were related to the thinning of the right marginal cingular sulcus (r = 0.491, p = 0.013, CI 0.118 to 0.797) and to the left precuneus (r = 0.462, p = 0.020, CI 0.109 to 0.782).

### Reliability analysis of bvFTD behavioural phenotypes

The reliability analysis performed with clustering pattern of FBI, based on the classification of behavioural disturbance in bvFTD, revealed that only the aggressive profile, characterised by mental rigidity, irritability and aggression, was reliable (α=0.82) in our sample of 60 non-demented patients with ALS with FBI total score ≥1. The FBI clustering patterns reflecting the FTD-associated apathetic (α=0.26) and disinhibited (α=0.44) profiles were not reliable. The same pattern of results was found in the ALSbi group (aggressive phenotype: α=0.78; apathetic: α=0.47; disinhibited: α=0.63). In the group of patients with ALS-FTD, the bvFTD-associated disinhibited (α=0.73) and aggressive (α=0.74) profiles were reliable, whereas the apathetic profile approached reliability (α=0.67).

### DISCUSSION

In the present work, we have characterised the behavioural profiles in a sample of non-demented patients with ALS using the FBI questionnaire. The spectrum of ALS behavioural abnormalities is heterogeneous. More than half of patients with ALS (58%) had behavioural changes, and only 25% satisfied criteria for behavioural impairment (ALSbi). In line with previous reports, we found that the most common behavioural symptom in ALS was irritability, occurring in 40% of patients, followed by apathy (22%) and inflexibility (20%). Behavioural profiles were determined by means of PCA, an unbiased data driven approach identifying clusters of highly correlated variables (FBI item-scores). PCA has been previously used in ALS.
to examine primary components of measurement tools. We detected three distinct behavioural patterns: the disinhibited/hostile, the dysexecutive and a cluster including apathetic, inattentive and hypocritical behaviours. Our findings support the notion of specific behavioural subphenotypes in ALS. Consistently, a similar data-driven approach identified five behavioural profiles in a large ALS population. These included disinhibition as the emotional consequences of a diagnosis of a neurodegenerative disease, mild disinhibition in non-demented patients with ALS without behavioural changes. This is in line with those of a previous study, which found orbitofrontal cortex thinning has been previously associated with multiple behavioural features, that is, apathy and disinhibition/agression, suggesting a link between the severity of behavioural symptoms and cortical thinning of the right hemisphere. This is consistent with previous studies supporting the notion that the right hemisphere has a critical role in complex social behaviours. It is interesting to note that the right superior frontal gyrus involvement has been found in motor neuron disease with comorbid FTD, suggesting that its early involvement in patients with ALS might be marker for the development of bvFTD.

The apathetic profile was linked to bilateral orbitofrontal cortex. Despite methodological discrepancies, our results are in line with those of a previous study, which found orbitofrontal atrophy in patients with ALS showing higher rates of apathy. Consistently, several studies have found early orbital degeneration in patients with FTD with high apathy scores. Surprisingly, the thinning of the left precentral gyrus was also related to apathy. The interpretation of this finding is unclear. In ALS, motor cortex thinning has been previously associated with cognitive performance. We cannot exclude that this association might be influenced by the inclusion of patients with P90R-ALS. Atrophy in bilateral precentral gyrus, however, has been reported in apathetic patients with Parkinson’s disease and in apathetic elderly subjects, suggesting a possible association between apathy/inertia and the motor cortex.

The disinhibited/hostile profile was related to the right superior temporal and cingular sulci. Even if there is no indication for the anatomical substrate of disinhibition in ALS, the selective involvement of the right temporal lobe in non-demented patients with ALS with disinhibited/hostile behavioural profile is not consistent. Therefore, we used the FBI apathy score to measure disinhibited/hostile behaviour score, the lower the cognitive performances in a highly demanding cognitive task assessing verbal episodic memory. This finding confirms that behavioural changes might be accompanied by cognitive deficits. Within the ALSbi group, however, the severity of disinhibition was related with difficulties in performing the Stroop task, suggesting a more general impairment of the inhibitory control system for these patients.

The study of the cortical correlates revealed that the behavioural deficit broadly reflects differential impairment within the cortical circuits which are compromised in ALS. Specifically, we found that the right superior frontal lobe was related to multiple behavioural features, that is, apathy and disinhibition/agression, suggesting a link between the severity of behavioural symptoms and cortical thinning of the right hemisphere. This is consistent with previous studies supporting the notion that the right hemisphere has a critical role in complex social behaviours. It is interesting to note that the right superior frontal gyrus involvement has been found in motor neuron disease with comorbid FTD, suggesting that its early involvement in patients with ALS might be marker for the development of bvFTD.
The involvement of the superior temporal sulcus is related to the degree of disinhibited symptoms measured with the Frontal System Behaviour Scale in patients with bvFTD. In addition, the right middle temporal gyrus has been found to be critical for the development of disinhibition in bvFTD. In our sample of non-demented patients with ALS, the thinning of this cortical region is also related to poor verbal fluency and emotion recognition impairment, two features occurring frequently in patients with ALS with frontotemporal symptoms. Thus, considering this specific anatomical region, a possible anatomical correlates underpinning the ALSbi phenotype, ie, patients with ALS with cognitive and behavioural impairment. More controversial is the association between disinhibited/hostile profile and the marginal part of the cingular sulcus. This region has been considered the termination of the cingulate sulcus and separates the paracentral lobule anteriorly and the precuneus posteriorly. Selective cortical thinning has been found in this region in both hemispheres in patients with ALS. We found that it is associated also with working memory abilities in our sample, suggesting its involvement in extramotor degeneration in ALS.

Finally, the left precuneus was related to the dysexecutive profile, qualifying easily distractible patients, showing insensitivity, inability to complete a task, restlessness/roaming and requiring prompting to initiate activities. Bilateral precuneus has already been found to be involved in patients with cognitive impairment. Accordingly, we found that working memory impairment is associated to the thinning of the left precuneus. Studies on resting-state fMRI in ALS have shown a reduced level of functional communication in the default-mode network, in which precuneus and posterior cingulate regions are key regions.

Overall, our findings support the notion of specific behavioural phenotypes in non-demented patients with ALS involving distinct cerebral networks. Whether the ALS-associated behavioural dysfunctions overlap those described in bvFTD remains an open question. The concept of ALS-FTD continuum predicts that a comparable spectrum of behavioural involvement should be present in ALS and bvFTD. To address this issue, we thus tested if the behavioural profiles of patients with bvFTD were reliable in our non-demented ALS sample. To our knowledge, there is only one study using the FBI questionnaire to characterise behavioural disturbances of patients with bvFTD. In this study, FBI items could be grouped into distinct clusters. The ‘disinhibited’ profile was defined by loss of insight, perseveration, hoarding, excessive jocularity, impulsivity, roaming, hyperorality and utilisation behaviour; the ‘apathetic’ by apathy and aspontaneity; the ‘aggressive’ by mental rigidity, irritability and aggression. We found that only the aggressive profile reliably applied to our cohort of non-demented ALS patients. The use of the FBI may be considered as a limitation of the study. Even if we took great care in excluding behavioural alterations that could be due to motor impairment, the questionnaire does not take into account the impact of physical disability on the determination of behavioural changes. Apathy and irritability might reflect emotional reactions to the progressive physical disability. In our sample, only irritability might actually represent an emotional reaction. It was indeed related to depressive mood (r=0.312, p=0.024, CI 0.041 to 0.057). However, irritability does not constitute, per se, a requirement for the diagnosis of ALSbi. A systematic evaluation of delusions, hallucinations, anxiety, would have also enhanced the strength of the results. The evaluation of anxiety, for instance, could have helped in better discriminating behavioural alterations suggestive of frontotemporal damage from those due to emotional reactions.

In conclusion, our findings provide evidence of distinct ALS behavioural phenotypes partially overlapping with those of bvFTD. ALS-associated apathy had specific neuroanatomical patterns related to bilateral orbitofrontal thinning, whereas hostile/disinhibited and dysexecutive behavioural patterns were associated with temporal, cingular and parietal cortical thinning. These results underline the need for further investigation of the prognostic value that the different patterns of behavioural dysfunction may have on ALS course as well as on the risk of progression towards the spectrum of FTD.

Contributors MC, EDB and VEC collected data. VEC acquired and analysed neuromaging data. MC designed the study and performed statistical analyses. MC, SFC and GL gave important intellectual content in data interpretation. MC, EDB and VEC wrote a draft of the manuscript. SFC and GL revised the final version of the manuscript for intellectual content.
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