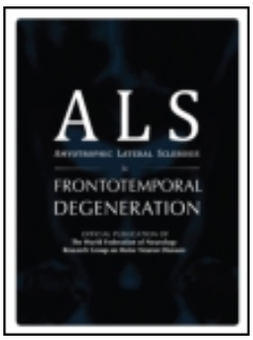

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ORIGINAL ARTICLE

A visual MRI atrophy rating scale for the amyotrophic lateral sclerosis-frontotemporal dementia continuum

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Abstract

Our objective was to distinguish ALS, ALS-FTD and bvFTD via a novel visual MRI cortical atrophy scale that can be employed in a clinical setting. MRI images of 100 participants (33 ALS, 11 ALS-FTD, 22 bvFTD and 34 controls) were rated in four brain areas: orbitofrontal cortex, anterior temporal pole, anterior cingulate, and motor cortex. Areas were rated on a 5- point Likert scale by two raters blinded to the diagnosis. Results demonstrated that bvFTD patients showed the highest levels of atrophy across all regions, while ALS patients had the lowest atrophy scores. ALS-FTD patients have higher atrophy ratings compared to ALS patients for the motor cortex, anterior cingulate and anterior temporal lobe, with a statistical trend for the orbitofrontal cortex. ALS-FTD patients were not significantly different from bvFTD for any of the brain regions. These findings were confirmed in a post hoc VBM analysis of the same participants. Our study demonstrates that a simple visual MRI rating scale can reliably distinguish ALS, ALS-FTD and bvFTD atrophy patterns in a clinical setting. Motor cortex, anterior cingulate and anterior temporal atrophy emerged as good diagnostic markers for ALS-FTD. Employment of this MRI rating scale can complement clinical diagnostics of patients in the ALS-FTD continuum.

Key words: *Visual atrophy rating scale, MRI, amyotrophic lateral sclerosis, frontotemporal dementia*

Introduction

There is increasing evidence that amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) overlap on clinical, genetic and pathological levels (1–6). Such strong overlap suggests that neural correlates of both syndromes should also be related. To date, many studies, utilizing various imaging techniques, have explored the ALS and ALS-FTD overlap. However, very few studies have investigated and compared grey matter changes across the whole ALS-FTD continuum (ALS, ALS-FTD and bvFTD).

Earlier studies mostly investigated overlap between ALS patients and ALS patients who show additional cognitive symptoms (ALS-FTD). For example, Chang et al. (7) found that ALS and ALS-FTD patients showed grey matter changes in motor and premotor areas, as well as frontal and temporal lobes (see also (8)). To our knowledge, only the recent study of Lillo et al. (9) investigated grey and white matter changes across the whole ALS-FTD continuum, which found that all clinical syndromes showed grey matter changes in motor cortical and anterior cingulate brain regions. By contrast, more substantial prefrontal and temporal cortex atrophy was indicative of bvFTD compared to ALS and ALS-FTD, while ALS-FTD showed substantially more anterior cingulate and anterior temporal lobe grey matter atrophy compared to ALS.

These findings highlight that, although the clinical syndromes show considerable atrophy overlap, there are also atrophy patterns specific to each subtype of the continuum. This is particularly relevant for the overlap syndrome (ALS-FTD) that presents with concurrent motor and behavioural/cognitive changes. The combination of motor and behavioural changes has been shown to detrimentally affect survival (10)

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as well as patient and carer well-being (11). Earliest detection of ALS-FTD is therefore paramount, as it informs disease management. The previously identified substantial anterior cingulate and anterior temporal lobe atrophy could be therefore a potential imaging biomarker to identify ALS-FTD and distinguish it from ALS and bvFTD.

Nevertheless, all neuroimaging studies investigating cortical atrophy in the ALS-FTD continuum to date have used techniques that are difficult to implement in everyday clinics due to time and cost restraints, such as voxel based morphometry (VBM). By contrast, a visual magnetic resonance imaging (MRI) rating scale is a less sophisticated technique, but has been shown to be very valuable to distinguish neurodegenerative patients (12–14). In this study we explore whether a simple coronal MRI atrophy rating scale distinguishes ALS, ALS-FTD, and bvFTD patients at first clinic presentation. Employment of such a scale would allow establishment of atrophy in everyday clinics and would allow corroborating clinical and cognitive assessment findings. Based on previous neuroimaging findings identified in the Lillo study (3), we selected four cortical grey matter regions for rating: motor cortex, anterior cingulate, anterior temporal lobe, and orbitofrontal cortex. We selected areas in which atrophy has been reported across the ALS-FTD continuum, in addition to areas that could discriminate between specific diagnoses, particularly ALS-FTD from ALS. We hypothesized a gradient of cortical atrophy across conditions, with bvFTD being worst affected, ALS least affected and ALS-FTD showing intermediate atrophy levels. We further hypothesized that ALS-FTD patients could be best distinguished from ALS based on anterior temporal lobe and anterior cingulate visual atrophy ratings.

Material and methods

Case selection

Patients were selected from the FRONTIER Dementia Clinic database resulting in a sample of 33 ALS, 11 ALS-FTD, 22 bvFTD patients and 34 controls. All ALS and bvFTD patients met current consensus criteria for ALS, ALS-FTD and bvFTD (15–17), respectively (see Table I for demographic details). All caregivers completed the Cambridge Behavioural Inventory (CBI, (18)), which assesses behavioural symptoms. ALS and ALS-FTD patients were further assessed using the Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS) – a validated measure of degree of functional impairment in ALS patients, with lower scores indicating higher degree of motor impairment. Age-matched healthy controls were selected from a healthy volunteer panel, or were spouses/carers of patients.

Patients underwent general cognitive screening using Addenbrooke's Cognitive Examination (ACE-R, (19)). Only data from the first assessment were included in analyses. Ethics approval for this study was obtained from the South Eastern Sydney and Illawarra Area Health Service and the University of New South Wales ethics committees. All participants, or their person responsible, provided informed written consent in accordance with the Declaration of Helsinki.

Behavioural analyses

Data were analysed using SPSS 20.0 (SPSS Inc., Chicago, Ill., USA). Parametric demographic (age, education), neuropsychological (general cognitive tests) and behavioural (CBI) data were compared across the four groups (ALS, ALS-FTD, bvFTD and controls) via one-way ANOVAs followed by Tukey post hoc tests. A priori, variables were plotted and checked for normality of distribution by Kolmogorov-Smirnov tests. Variables revealing non-normal distributions were log transformed and the appropriate log values were used in the analyses. Variables showing non-parametric distribution after log transformation were analysed via χ^2 and Kruskal-Wallis tests with post hoc pairwise comparisons performed using Dunn's (20) procedure.

Image acquisition and analysis

All patients and controls underwent the same imaging protocol with whole-brain T1-weighted images using a 3-Tesla Philips MRI scanner with standard quadrature head coil (coronal orientation, matrix 256×256, 200 slices, 1×1 mm^2 in-plane resolution, slice thickness 1 mm, TE/TR = 2.6/5.8 ms, flip angle $\alpha = 19$).

Two raters (AA, EF), blind to the clinical diagnosis, rated T1 coronal MRIs based on a rating scale developed by Davies et al. (21) using a standard template against which to judge atrophy. An inter-rater reliability analysis using the Kappa statistic was performed to determine consistency among raters for an MR training set of 100 scans. Inter-rater reliability for the raters was found to be Kappa = 0.91 ($p < .0.026$). Four brain regions were scored: orbitofrontal cortex, anterior cingulate, precentral gyrus, and anterior temporal pole. Three slices in the anterior-posterior position were identified. The orbitofrontal cortex was rated at the most anterior slice in which the temporal pole may be seen. The temporal pole and anterior cingulate were rated at the most anterior slice in which the internal capsule can be seen in the corpus striatum, and the motor cortex at the most anterior slice in which the medial opening of the intralimbic gyrus is seen.

Atrophy within each region was rated on a 5-point Likert scale ranging from 0 to 4 (0 = normal; 1 = borderline appearance but not definitely abnormal; 2 = definite abnormality with sulcal widening and gyri thinning; 3 = severe atrophy with loss of

Table I. Demographics, cognition and behaviour. Comparison on demographics and cognitive tests across ALS, bvFTD and ALS-FTD groups.

	bvFTD $n = 22$	ALS-FTD $n = 11$	ALS $n = 33$	Controls $n = 34$	*F*-values
Age (mean, SD) years	61.6 (10.3)	65.1 (8.1)	60.6 (11.3)	65.6 (6.5)	NS
Education (mean, SD) years	11.6 (3.0)	13.4 (3.3)	13 (3.5)	13.8 (2.4)	*
Gender (M/F)	14/8	7/4	18/15	17/17	NS
Disease duration, years (mean, SD)	3.4 (2.4)	3.4 (2.7)	2.9 (3.7)	–	NS
ACE-R (total score)	73.9(16.1)	61.6 (13.8)	88.7 (9.4)	94.7 (4)	***
CBI-R (total score)	72.5 (33.7)	50.8 (24.7)	32 (19.7)	7.1 (9.2)	***
ALSFRS (total score)	–	31.8 (5.9)	40.65 (4.9)	–	**

F-values indicate significant differences across groups; Tukey post hoc tests compare differences between group pairs.
Kruskal-Wallis test and Mann-Whitney *U*-test were applied for education, disease duration, ACE-R and CBI-R data.
ALS: amyotrophic lateral sclerosis; ALS-FTD: ALS with frontotemporal dementia; bvFTD: behavioural variant frontotemporal dementia.
ACE-R: Addenbrooke's Cognitive Examination revised; CBI-R: Cambridge Behavioural Inventory Revised; ALSFRS: ALS Functional Rating Scale.
$^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$; NS: non-significant.

grey/white matter differentiation but not as marked as a score of 4; 4 = severe atrophy, in the temporal pole there is no clear tissue present. For the remaining structures there are remnants of tissue present only) (see Figure 1). The structures were initially assessed individually for the left and right to account for variations in brain orientation. These were then averaged to give one score for the overall region. More detailed description of the rating method can be found in (21).

Voxel based morphometry (VBM) analysis

Voxel based morphometry (VBM) was conducted on the three-dimensional T1-weighted scans, using the FSL-VBM toolbox in the FMRIB software library package (http://www.fmrib.ox.ac.uk/fsl/). The first step involved extracting the brain from all scans using the BET algorithm in FSL, using a fractional intensity threshold of 0.22 (22). Each scan was visually checked after brain extraction, both to ensure that no brain matter was excluded, and no non-brain matter was included (e.g. skull, optic nerve, dura mater).

A grey matter template, specific to this study, was then built from canvassing 10 scans from each group (total $n = 40$). An equal number of scans across groups were used to ensure equal representation, and thus avoid potential bias toward any single group's topography during registration. Template scans were then registered to the Montreal Neurological Institute Standard space (MNI 152) using non-linear b-spline representation of the registration warp field, resulting in study-specific grey matter template at $2 \times 2 \times 2$ mm^3 resolution in standard space. Simultaneously, brain-extracted scans were also processed with the FMRIB's Automatic Segmentation Tool (FAST v4.0) (23) to achieve tissue segmentation into CSF, grey matter and white matter. Specifically, this was carried out via a hidden Markov random field model and an associated Expectation-Maximization algorithm. The FAST algorithm also corrected for spatial intensity variations such as bias field or radio-frequency inhomogeneities in the scans, resulting in partial volume maps of the scans. The following step saw grey matter partial volume maps then non-linearly registered to the study-specific template via non-lia b-spline representation of the registration warp. These maps were then modulated by dividing by the Jacobian of the warp field, to correct for any contraction/enlargement caused by the non-linear component of the transformation (24). After normalization and modulation, smoothing the grey matter maps occurred using an isotropic Gaussian kernel (standard deviation = 3 mm; full-width half maximum = 8 mm).

Statistical analysis was performed with a voxelwise general linear model. Significant clusters were formed by employing the threshold-free cluster enhancement (TFCE) method (25). TFCE is a cluster-based thresholding method that does not require the setting of an arbitrary cluster forming threshold (e.g. t, z). Instead, it takes a raw statistics image and produces an output image in which the voxelwise values represent the amount of cluster-like local spatial support. The TFCE image is then turned into voxelwise *p*-values via permutation testing. We employed a permutation-based non-parametric testing with 5000 permutations (26). A region-of-interest (ROI) mask was created for all visually rated regions: anterior temporal pole, orbitofrontal cortex, anterior cingulated, and precentral gyrus.

All patient-control group comparisons were tested for significance at $p < 0.05$, corrected for multiple comparisons via Family-wise Error (FWE) correction across space. The inter-patient comparisons did not survive FWE correction and was tested at a

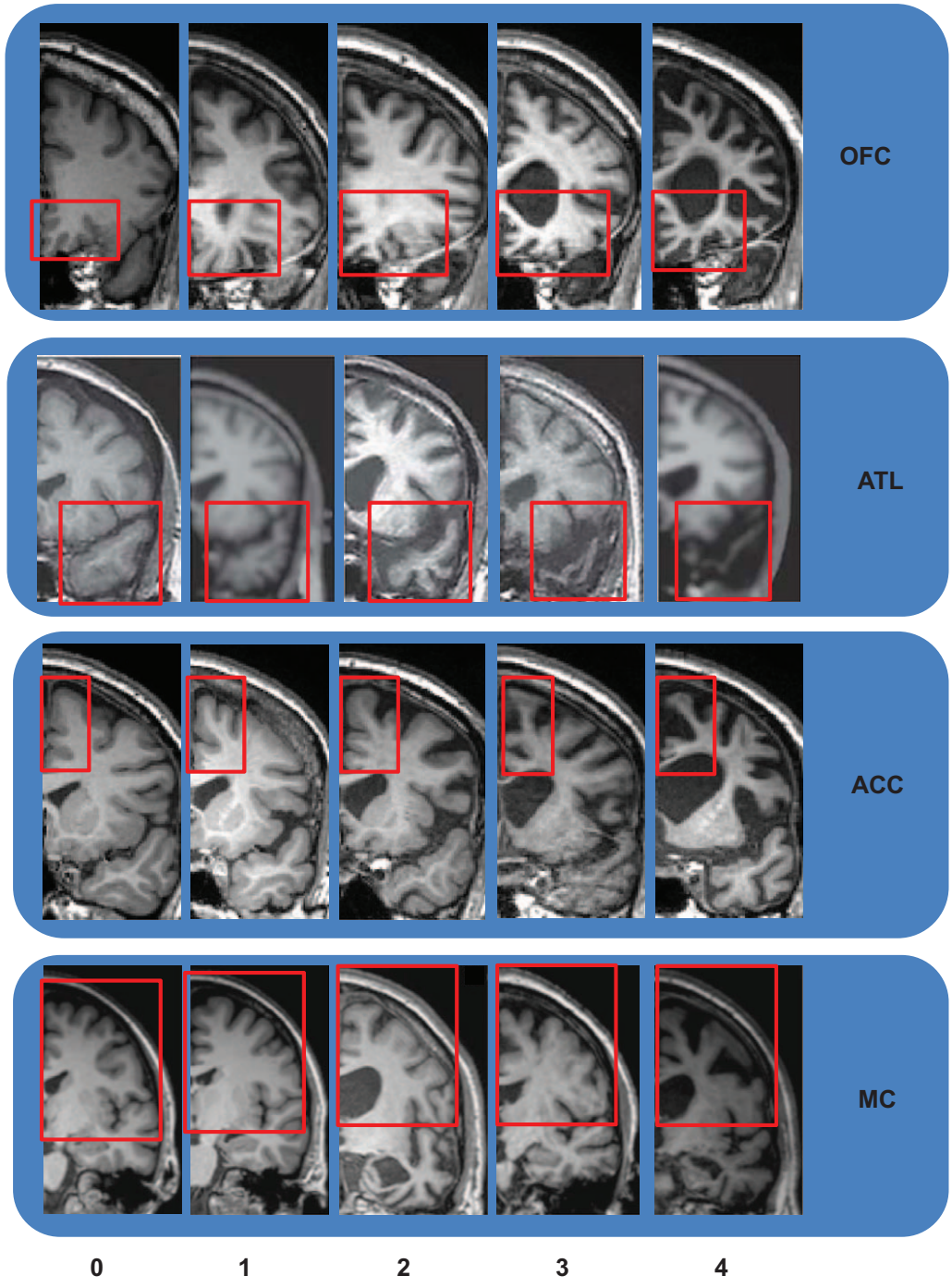

Figure 1. Figure 1 shows the array of MR reference images and rating criteria employed in judging atrophy in the frontal lobe brain regions. Rating criteria range from 0 = no atrophy to 4 = severe atrophy for the rated brain regions. OFC: orbitofrontal cortex; ATL: anterior temporal lobe; ACC: anterior cingulate cortex; MC: motor cortex.

significance level of $p < 0.01$, false discovery rate (FDR) corrected.

Results

Background and demographics

All participant groups did not differ significantly on age, gender or disease duration (all p's $> .1$; Table I). However, bvFTD and control groups differed on years of education, with the bvFTD patients undergoing fewer years of education ($p < .05$).

Scan ratings

Comparisons with controls. The scan rating results (Figure 2, Table II) show that ratings varied considerably across groups with significant group effects for all regions (all p's $< .001$). Controls were rated as having significantly less atrophy than bvFTD on all region ratings (all p's $< .05$). Similarly, ALS-FTD differed significantly from controls for all regions (p's < 0.01). Interestingly, ALS only differed from controls on OFC atrophy ratings ($p < .01$), but none of the other ratings (all p's $> .1$).

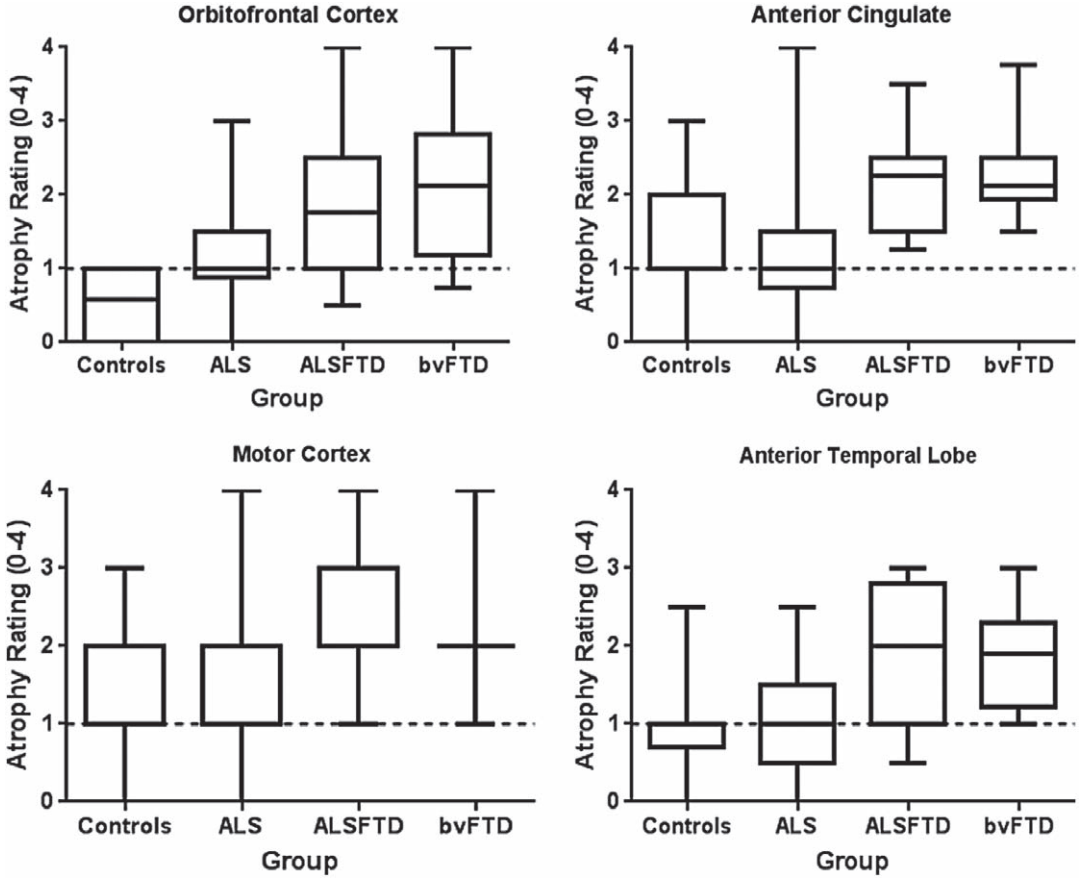

Figure 2. Figure 2 shows boxplots for atrophy ratings in orbitofrontal cortex, anterior cingulate cortex, motor cortex, and anterior temporal lobe across all participant groups. The dotted line indicates the threshold from which on a rating is considered to be abnormal. Boxplot whiskers indicate 5–95% confidence intervals.

Between-patient comparisons. Between-patient comparisons revealed that bvFTD had significantly higher ratings than ALS in all regions (all p's $<.01$). ALS-FTD did not differ from bvFTD for any brain region (all p's $>.05$). More importantly, the contrast of ALS vs. ALS-FTD showed that ALS-FTD had higher motor cortical, anterior cingulate, and anterior temporal lobe atrophy ratings than ALS ($p<.01$), with a statistical trend for more OFC atrophy in ALS-FTD ($p=.067$).

Lateralization results

When left and right regions were analysed separately, ALS-FTD now showed significantly higher ratings of atrophy than ALS for both the left and right OFC (p's $<.05$). Additionally, ALS no longer differed significantly from controls for either the left or the right OFC (p's $>.05$). For the motor cortex, the left and right motor cortex no longer differed significantly between bvFTD and controls when analysed separately (p's $>.05$). All other regions reflected the same patterns when lateralized as when averaged across left and right, for all group comparisons.

Logistic regression analysis

A similar continuum was also present in logistic regression analyses using the ENTER method. All regions showed excellent to very good discrimination of patient groups from controls (bvFTD vs. controls, 92.9% correct; ALS-FTD vs. controls, 80.6% correct; ALS vs. controls, 95.6% correct). Of the

Table II. Scan ratings: comparison of scan ratings (mean and standard deviation) across ALS, bvFTD and ALS-FTD groups.

	bvFTD	ALS-FTD	ALS	Controls	Kruskal-Wallis
Orbitofrontal cortex	2.1 (1)	1.8 (1.0)	1.1 (0.6)	0.5 (0.4)	***
Anterior cingulate	2.2 (0.6)	2.2 (0.7)	1.2 (0.8)	1.4 (0.7)	***
Motor cortex	1.9 (0.5)	2.3 (0.8)	1.4 (0.7)	1.5 (0.6)	***
Anterior temporal lobe	1.8 (0.6)	1.8 (0.8)	1.0 (0.6)	1.0 (0.6)	***

ALS: amyotrophic lateral sclerosis; ALS-FTD: ALS with frontotemporal dementia; bvFTD: behavioural variant frontotemporal dementia.
***$p<0.001$.

between-patient comparisons for atrophy ratings across all regions, the bvFTD patients could be best distinguished from ALS (83.6% correct), while bvFTD vs. ALS-FTD resulted in a lower discrimination rate (78.8%). ALS vs. ALS-FTD could be correctly classified in 75% of the cases.

Voxel based morphometry analysis

In a final step, we conducted a VBM analysis to confirm our visual atrophy rating findings. The VBM results (Supplementary Figures 1 and 2, which are only available in the online version of the journal. Please find this material with the following direct link to the article: http://www.informahealthcare.com/doi/abs/10.3109/21678421.2014.880180) replicated the visual rating results for all regions, except for the OFC atrophy in ALS vs. controls, which did not reach significance.

Discussion

Our results show that a simple visual MRI rating scale can reliably detect grey matter atrophy across the ALS-FTD continuum. In particular, the scale is very sensitive to commonly observed cortical atrophy in bvFTD and ALS-FTD. Our visual MRI ratings also replicated previous VBM findings in ALS by showing very variable cortical grey matter changes in this patient group. Finally, ALS-FTD could be best distinguished from ALS based on motor cortical, but also anterior temporal lobe and anterior cingulate atrophy ratings. These findings held true when left and right regions were considered separately. This lateralization analysis also strengthened the association with orbitofrontal cortex atrophy.

The distinction between ALS and ALS-FTD can be diagnostically challenging particularly in a clinical setting when little behavioural or cognitive information might be available. Our study found that atrophy of the motor cortex can be useful to aid this distinction with ALS-FTD patients showing significantly more atrophy in this region than ALS. This should be not surprising, as motor cortical atrophy has been only observed in around 25% of ALS patients in a recent meta-analysis (27). More importantly, our findings are corroborated by a recent study showing that the degree of cognitive/behavioural impairment in ALS determines the degree of motor cortical atrophy (28). ALS-FTD is diagnosed on the basis of having substantial cognitive and behavioural changes, which explains why they showed significantly more motor cortical atrophy than ALS alone in our study. In this regard it is also important to note that bvFTD patients who have substantial behavioural/cognitive changes also showed significantly more cortical atrophy than ALS patients, although were indistinguishable from ALS-FTD, which replicates previous findings (9). Unfortunately, this did not hold true when analysed laterally, which probably reflects the small sample size of bvFTD patients. Nonetheless, this raises the question as to how much the motor cortical atrophy actually contributes to the motor symptoms seen in ALS and whether the predominant white matter changes in ALS (9,29–32) are more critical in the generation of those symptoms, which clearly needs to be addressed in future studies.

The more substantial atrophy in ALS-FTD for the anterior cingulate is also of great interest. In general, the underlying white matter tracts of the anterior cingulate have been shown to be consistently affected in ALS (30). Our results indicate a significant difference between ALS and ALS-FTD in this region as well as between ALS and bvFTD. This pattern of anterior cingulate atrophy nicely replicates results of studies employing automized imaging analyses (9) and our VBM post hoc analysis. The reliability of this anterior cingulate atrophy makes it potentially an important diagnostic marker for the continuum, particularly because no cognitive or behavioural markers tap exclusively into this area to date. Previous findings have suggested that anterior cingulate region changes are associated with apathy in ALS (33), which is one of its most prevalent behavioural features (34). However, the functional specificity for this region has been questioned by functional neuroimaging studies in the healthy, which have attributed anterior cingulate function to a multitude of behavioural and cognitive changes, including social cognition, attention, emotion processing, motor learning but also more general executive function deficits (for a meta-analysis see (35)). Clearly, a delineation of those anterior cingulate contributions would be very beneficial for diagnosing ALS, ALS-FTD and bvFTD (9).

By contrast, orbitofrontal and temporal pole atrophies have been associated for a long time with particular symptoms and syndromes. Especially bvFTD patients show consistent OFC damage even from a very early disease stage onwards (14,36), which has been strongly linked with the prevalent disinhibition in this patient group (37,38). Our results confirm this notion by showing OFC atrophy being severely affected in bvFTD followed by ALS-FTD and ALS. A previous VBM study similarly showed OFC atrophy for bvFTD and ALS-FTD though did not show significant atrophy for ALS (9). Nevertheless, ALS patients have been shown to be impaired on OFC dependent tasks, tapping into inhibitory function (3,39,40) and gambling decision making (41), which suggests some degree of dysfunction in this brain region, albeit less than in ALS-FTD or bvFTD. Similarly, anterior temporal lobe atrophy is a consistent feature of bvFTD (42), which we replicate in this study. More importantly, ALS-FTD patients also showed significant anterior temporal lobe atrophy in our study compared to controls, whereas ALS patients were virtually unaffected in this region with significant differences between both patient groups for this region. This finding is in line with the Lillo et al. study showing that anterior temporal lobe atrophy is likely a good diagnostic marker to distinguish ALS

from ALS-FTD, with only the latter being affected in this region (3). Anterior temporal atrophy is usually attributed to mainly semantic language processing, such as the deficits seen in semantic dementia (43), although it has been also associated with certain degrees of behavioural dysfunction (37). This raises the question as to whether semantic impairments could corroborate the imaging findings in the groups. bvFTD patients have been shown to have semantic knowledge impairment, although not as severe as in semantic dementia (44). Similarly, semantic impairments and other language processing deficits have been reported in ALS-FTD (45–47). By contrast, in ALS fluency deficits have been observed; however, those deficits have been mostly associated with inferior frontal cortex dysfunction (48) and not temporal atrophy in this patient group. Surprisingly, no study to our knowledge has contrasted semantic impairments across all subtypes in the ALS-FTD continuum. The imaging findings that anterior temporal lobe atrophy is specific for ALS-FTD and bvFTD could thus become a potentially good diagnostic marker for both clinical subtypes.

On a clinical level, our findings have clear relevance for diagnostic procedures. Our visual rating scale is corroborated by more sophisticated but time-consuming automized imaging methods, such as our post hoc VBM analysis. Clinicians can reliably apply our novel scale in a clinical setting even when only hardcopies of coronal T1 scans are available. More importantly, the conjunction of clinical/cognitive/behavioural features and visual atrophy ratings in a patient will allow clinicians to corroborate the clinical diagnosis further. This might particularly affect the early identification of ALS-FTD patients, who are often seen either in an ALS specific clinic setup but requiring the liaison of both clinics. Early identification of ALS-FTD is critical to ensure appropriate disease management to alleviate the higher patient and carer distress in these patients. In addition, it will allow earlier intervention via disease modifying therapies in ALS-FTD patients who show the shortest survival rates across the continuum (10).

The flipside of our and previous findings is that cortical atrophy in ALS is not a consistent feature and therefore significant brain atrophy in an ALS patient might warrant further cognitive/behavioural investigations on a clinical level to exclude ALS-FTD as a diagnosis. This seems particularly prudent in the light of recent findings showing that ALS patients with cognitive and behavioural symptoms that do not reach the criterion for ALS-FTD diagnosis can critically influence cortical atrophy (28). Finally, motor cortical atrophy emerges as a poor indicator of motor impairment, as bvFTD patients show similar or more atrophy in this region than ALS-FTD and ALS, respectively, without having only minor clinical signs of upper motor dysfunction (49).

Despite these promising findings, our study had several shortcomings. In particular, the sample size for the ALS-FTD group was small compared to the other groups and therefore replication in a bigger sample seems advisable. There was also no pathological confirmation of diagnosis, particularly for our bvFTD sample, and we cannot exclude therefore the possibility that a percentage of patients might have a different underlying pathology. Although our findings replicate our VBM results, visual MRI ratings are subjective and therefore prone to greater variability both within and between raters. We carefully trained both raters (AA, EF) in this study on an independent set of scans and both showed high inter-rater reliability, but future studies replicating our findings would be important to corroborate the validity of this rating scale in the ALS-FTD continuum. Also, our study group presented relatively late in their disease course, which perhaps reflects referral practices to specialist centres or suggests that these patients had a milder disease course. It has been reported that up to 45% of ALS patients may not satisfy diagnostic criteria for probable ALS at first presentation (50). As a result, by strictly adhering to diagnostic criteria and therefore including only those with probable ALS, according to El Escorial criteria, the results may not be representative of ALS as seen by clinicians at presentation. A consideration for future studies may be to relax inclusion criteria to ensure a representative sample of ALS patients is studied.

Taken together, the presented visual atrophy rating scale has great clinical promise to detect cortical changes in the ALS-FTD continuum. The scale shows high correspondence with automized imaging findings and may therefore provide clinicians with an important tool for the assessment of ALS, ALS-FTD and bvFTD patients, particularly in conjunction with clinical and neuropsychological data. This may allow earlier detection of ALS-FTD subtypes, which may in turn provide better disease management for patients and their families in the future.

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Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Supplementary material available online

Supplementary Figures 1 and 2 available at http://informahealthcare.com/doi/abs/10.3109/21678421.2014.880180