## semantic deficits in amyotrophic lateral sclerosis

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**Abstract**

***Objective***: To investigate, and establish neuroanatomical correlates of, semantic deficits in amyotrophic lateral sclerosis (ALS) and amyotrophic lateral sclerosis-frontotemporal dementia (ALS-FTD), compared to semantic dementia (SD) and controls. ***Methods***:Semantic deficits were evaluated using a naming and semantic knowledge composite score, comprising of verbal and non-verbal neuropsychological measures of single-word processing (confrontational naming, comprehension, and semantic association) from the Sydney Language Battery (SYDBAT) and Addenbrooke’s Cognitive Examination - Revised (ACE-R). Voxel-based morphometry (VBM) analysis was conducted using the region of interest approach. ***Results***: In total, 84 participants were recruited from a multidisciplinary research clinic in Sydney. Participants included 17 patients with ALS, 19 patients with ALS-FTD, 22 patients with SD and 26 age- and education- matched healthy controls. Significant semantic deficits were observed in ALS and ALS-FTD compared to controls. The severity of semantic deficits varied across the clinical phenotypes; ALS patients were less impaired than ALS-FTD patients, who in turn were not as impaired as SD patients. Anterior temporal lobe atrophy significantly correlated with semantic deficits. ***Conclusion***: Semantic impairment is a feature of ALS and ALS-FTD, and reflects the severity of temporal lobe pathology.

**Keywords:** ALS-FTD; cognitive impairment; semantic

**Introduction**

Approximately one third of patients with amyotrophic lateral sclerosis (ALS) show mild to moderate cognitive changes, while at least 5% demonstrate more severe impairment, meeting criteria for frontotemporal dementia (FTD) ([1](#_ENREF_1), [2](#_ENREF_2)). Increasing clinical ([3](#_ENREF_3), [4](#_ENREF_4)), pathological ([5](#_ENREF_5), [6](#_ENREF_6)) and genetic ([7](#_ENREF_7), [8](#_ENREF_8)) evidence suggests that ALS and FTD overlap and form the two extremes of a disease continuum.

Language disturbance is characteristic of FTD language phenotypes, including Semantic Dementia (SD). SD is characterized by distinct loss of semantic knowledge, secondary to progressive atrophy of the anterior temporal poles, particularly on the left-hand side ([9](#_ENREF_9)). Specific instruments, such as the Sydney Language Battery (SYDBAT), have been developed to differentiate FTD language variants. The SYDBAT is sensitive to semantic loss in SD ([10](#_ENREF_10)).

Executive dysfunction is well established in ALS ([11](#_ENREF_11)) and ALS-FTD ([12](#_ENREF_12)), however, non-executive cognitive impairment may occur. Language disturbance has been reported in both ALS and ALS-FTD ([13](#_ENREF_13)), but remains poorly characterized. Interestingly, neuroimaging studies have described SD-like anterior temporal lobe changes in ALS-FTD and more recently in ALS ([14](#_ENREF_14)).

The present study investigated semantic deficits in ALS and ALS-FTD using the SYDBAT and compared the results to the SD phenotype of FTD. We hypothesized that semantic impairment would become more severe across the disease spectrum. Specifically, we hypothesized that ALS patients would have relatively mild semantic impairment compared to controls, whereas ALS-FTD patients would be more impaired, but not as impaired as SD patients. Furthermore, we hypothesized that the degree of semantic impairment across the disease spectrum would reflect the severity of anterior temporal lobe pathology.

**Method**

### 2.1 Participants

Patients were recruited from the multidisciplinary ForeFront clinics between January 2008 and May 2013. The diagnosis of ALS was made according to the Awaji and El Escorial Criteria Revised ([15](#_ENREF_15), [16](#_ENREF_16)). Alternate diagnoses were excluded on the basis of routine blood tests, magnetic resonance imaging of the brain and spinal cord and neurophysiological investigations. ALS-FTD patients fulfilled criteria for both FTD ([17](#_ENREF_17), [18](#_ENREF_18)) and ALS ([15](#_ENREF_15)). SD patients met current clinical consensus criteria ([19](#_ENREF_19)). All patient groups were matched for mood disturbance on the Depression, Anxiety and Stress Scale (DASS) ([20](#_ENREF_20)), 21-item version. Controls subjects were healthy volunteers recruited from the community. Exclusion criteria included: forced vital capacity (FVC) below 70%, nocturnal hypoventilation, other neurological conditions, and substance abuse.

### Standard Protocol Approvals, Registrations, and Patient Consents

Ethics approval was obtained from the Human Research Ethics Committee of South Eastern Sydney/Illawarra Area Health Service. Written informed consent was obtained from each participant, or their next of kin where necessary.

### 2.2 Measures

#### 2.2.1 *Disease severity and cognitive measures*

The ALS Functional Rating Scale Revised ALSFRS-R ([21](#_ENREF_21)) was used to document motor functional capacity. A reduced ALSFRS-R indicated impaired motor performance. Rate of disease progression was estimated using decline on the ALSFRS-R score after symptom onset (48 minus ALSFRS-R score divided by time in months from symptom onset to date of assessment).

The ACE-R is a brief cognitive screening tool that assesses five cognitive domains, including: attention (18 points), memory (26 points), language (26 points), visuospatial ability (16 points) and verbal fluency (14 points), calculated using a fluency index (11) to control for motor impairment. A score below 88/100 detects dementia with a sensitivity of 94% and specificity of 89% ([22](#_ENREF_22)).

#### 2.2.2 Measures of Semantic Processing

Semantic deficits were assessed using the Sydney Language Battery (SYDBAT)([10](#_ENREF_10)) and components of the Addenbrooke’s Cognitive Examination - Revised (ACE-R) ([22](#_ENREF_22)). The SYDBAT consists of four subtests including confrontational naming, word comprehension, semantic association, and single word repetition. Single word repetition was excluded in the final analysis to avoid potential confounding effects of dysarthria. Qualitatively responses were not reflective of inattention or impulsivity.

A naming composite score was calculated using the confrontational naming subtask of the SYDBAT and the confrontational naming component of the ACE-R. Errors were characterized as clear mispronunciations, including phonemic or semantic paraphasias and not included in the final score, although the former were extremely rare. Minor slurring was not penalized. To further mitigate any potential impact of dysarthria, a semantic knowledge composite score was calculated using non-verbal test scores, which required only pointing responses (word comprehension and semantic association from the SYDBAT; word comprehension from the ACE-R). Test scores were converted into percentages for comparison across groups. A cut-off of 2 standard deviations below the mean for controls was used to define impaired performance ([10](#_ENREF_10)).

#### 2.3 *Voxel-based Morphometry (VBM)*

Voxel-based morphometry (VBM) was conducted on three dimensional T1-weighted scans, using a previously described method ([23](#_ENREF_23)). Patient-control group comparisons were conducted on a whole brain level and tested for significance at p < 0.05, corrected for multiple comparisons via Family-wise Error correction. The semantic covariate analyses were conducted on a temporal lobe region of interest, due to a priori predictions that this region is most implicated with semantic processing. The covariate analyses were reported at p < 0.05, corrected for multiple comparisons via Family-wise Error correction (Further details in Appendix 1).

**2.4 *Behavioral data analyses***

Demographic data and neuropsychological performance were compared across the 4 groups (ALS, ALS-FTD, SD and controls). IBM SPSS version 20 was used for analyses. Kolmogorov-Smirnoff tests were used to check normality of continuous variables. The one-way analysis of variance, with Tukey tests for posthoc tests comparisons, was used when data was normally distributed. The Kruskal-Wallis Test, with the Mann-Whitney U Tests for posthoc pairwise comparisons, was used when data was non-normally distributed. Categorical data were analyzed using the Chi square test. Pearson’s (normally distributed) and Spearman’s (non-normally distributed) correlations were used to explore relationships between continuous data.

**Results**

* 1. **Demographic and clinical profiles**

In total, 84 participants were included in the study; 17 ALS (12 limb-ALS and 5 bulbar-ALS), 19 ALS-FTD, 22 SD, and 26 controls. Of the ALS-FTD patients, 12 presented with FTD and subsequently developed ALS, 6 presented with ALS and subsequently developed FTD, and 1 presented with ALS and FTD concomitantly. Patients and controls were matched for age and education. ALS and ALS-FTD patients were matched for disease duration, but SD patients had significantly longer disease duration compared to the ALS-FTD group (*U* = 93, *z* = -2.665, *p* = .007, Table 1).

As might be expected, both the ALS (*U* = 5, *z* = -3.003, *p* = .003) and ALS-FTD (*U* = 0, *z* = -3.051, *p* = 0.002) groups scored significantly below the SD group on the ALSFRS-R. No difference was observed between the ALS and ALS-FTD groups, suggesting a similar level of motor disability. Rate of disease progression, estimated using decline on the ALSFRS-R score, did not significantly differ between ALS and ALS-FTD groups.

The ALS group did not demonstrate general cognitive impairment, reflected by comparable performance on the ACE-R, compared to controls. The ALS group did, however, demonstrate subtle executive impairment, compared to controls (*U* = 106.5, *z* = -2.89, *p* = .004), indexed by verbal fluency. In contrast, both the SD and ALS-FTD group were significantly reduced (Table 1). Specifically, the SD group was the most cognitively impaired (*U* = 21.5, *z* = -5.52, *p* < .0001), followed by the ALS-FTD group (*U* = 10.5, *z* = -5.48, *p* < .0001).

\*\*insert Table 1\*\*

* 1. **Prevalence of semantic impairment and clinical correlation**

Analysis of the naming and semantic knowledge composite score (Table 2) revealed a gradation of impairment across the 4 groups in the following pattern: controls > ALS > ALS-FTD > SD (Figure 1). Significant semantic deficits were observed in ALS (naming *U* = 81.50, *z* = -2.87, *p* = .003; semantic knowledge *U* = 81.00, *z* = -2.374, *p* = .018), ALS-FTD (naming *U* = 27.5, *z* = -5.063, *p* < .0001; semantic knowledge *U* =35.50, *z* = -4.337*, p* < .0001) and SD (naming *U* = 0.00, *z* = -5.932, *p* < .0001; semantic knowledge *p* < .0001) compared to controls. The ALS-FTD group also performed significantly below the ALS group (naming *U* = 44.50, *z* = -3.227, *p* = .001; semantic knowledge *U* = 44.50, *z* = -2.223, *p* = .025), but performed significantly better than the SD group (naming *U* = 22.00, *z* = -4.89, *p* < .0001; semantic knowledge *U* = 55.00, *z* = -3.168, *p* < .0001). Naming and semantic knowledge composite scores were comparable in the control, ALS, and ALS-FTD groups. In SD, however, the semantic knowledge composite score was significantly higher than the naming composite score (*p* < .0001).

\*\*insert Table 2\*\*

Scores from almost all individual measures followed a similar gradation across groups: controls > ALS > ALS-FTD > SD. ALS patients were significantly impaired compared to controls on SYDBAT (naming *U* = 107, *z* = -2.149, *p* = .032; comprehension *U* = 118, *z* = -2.484, *p* = .013) and ACE-R tasks (naming *U* = 132.5, *z* = -2.974, *p* = .003; comprehension *U* = 146, *z* = -2.636, *p* = .008), with the exception of the SYDBAT semantic association task. The ALS-FTD group performed significantly below the ALS group on all SYDBAT tasks (naming *U* = 39.5, *z* = -3.434, *p* = .001, semantic association *U* = 50, *z* = -2.333, *p* = .02, comprehension *U* = 81, *z* = -1.996, *p* = .046) and ACE-R comprehension (*U* = 81, *z* = -2.333, *p* = .02). The SD group performed significantly below the ALS-FTD group on all semantic tasks including the SYDBAT (naming *U* = 25.5, *z* = -4.804, *p* < .0001, semantic association *U* = 70.5, *z* = -3.004, *p* = .002, comprehension *U* = 83.5, *z* = -2.938, *p* = .003) and ACE-R (naming *U* = 22.5, *z* = -4.911, *p* < .0001, comprehension *U* = 93.5, *z* = -2.71, *p* = .007).

Overall, 35.7% of ALS, 78.9% of ALS-FTD and 100% SD patients were impaired (more than 2 standard deviations below the control mean, *See Methods*) on the naming composite score. Similarly, 33.3% of ALS, 73.3% of ALS-FTD and 100% of SD were impaired on the semantic knowledge composite score. On the SYDBAT, 29.4% of ALS patients were impaired on 2 or more of the subtests, while 58.8% showed no impairment. Only 2 patients demonstrated impairment on 1 SYDBAT subtest. Specifically, 35% if ALS patients were impaired on naming, 29% on comprehension and 17.6% on semantic association.

\*\*insert Figure 1\*\*

Naming and semantic knowledge composite scores were not significantly associated with disease duration or disease severity, across the ALS and ALS-FTD groups. A significant negative association (*r* = -.497, *p* = .036) was observed between rate of disease progression and the naming composite score across the ALS and ALS-FTD groups. This negative association, however, did not remain significant when a partial correlation was performed to control for bulbar symptomology, as measured by combined bulbar scores on the ALSFRS-R.

**3.3 Voxel based morphometry**

The SD and ALS-FTD groups had significant atrophy compared to controls at corrected thresholds, but the ALS group did not differ significantly from controls (Supplemental Figure 1). Both the SD and ALS-FTD groups demonstrated atrophy of the anterior temporal lobes bilaterally. In addition, the SD group had mild prefrontal cortex and left-sided insular atrophy, whereas the ALS-FTD patients had more widespread and bilateral atrophy involving the prefrontal, insular, premotor, and superior parietal cortices.

The neuroanatomical correlates of semantic deficits were explored. Naming and semantic knowledge composite scores significantly correlated with bilateral temporal lobe atrophy in SD patients as well as ALS-FTD, however, to a lesser degree than SD (Figure 2). In ALS patients, the naming and semantic knowledge composite scores correlated with right-sided temporal lobe atrophy, as well as the right frontal pole.

\*\*insert Figure 2\*\*

**Discussion**

The present study has established that semantic deficits are common in ALS and ALS-FTD, independent of motor speech disturbances. Furthermore, the severity of semantic deficits increased across the ALS-FTD disease continuum, such that ALS patients were less impaired than ALS-FTD patients, who were in turn less impaired than patients with SD. Semantic deficits were correlated with anterior temporal lobe atrophy in all three disease groups. Overall, results from the present study emphasize the importance of performing detailed language assessments during cognitive screening of ALS patients.

Around one third of ALS patients in the present study demonstrated semantic deficits compared to controls, even when verbal tasks were excluded from the analysis. Although the deficits were relatively mild in the ALS group, they were consistently demonstrated through performance on several individual and both composite measures of semantic abilities, suggesting that semantic deficits are an important feature of ALS. A number of studies have previously documented language disturbance in ALS (1-2, [24-26](#_ENREF_24)), however, prevalence rates vary widely (9.1 - 43%) and very few studies have explicitly investigated semantic deficits. These differences may reflect multiple factors, including, differences in assessment approaches (e.g. confrontational naming or comprehension), lack of comprehensive semantic assessment, semantic deficits being poorly recognized by patients, carers, and clinicians alike, as they are in SD (27-[28](#_ENREF_28)) or samples including an admixture of ALS and ALS-FTD patients.

The first large population based-study of cognitive impairment in ALS ([1](#_ENREF_1)) reported non-executive cognitive impairment in 17.4% of non-demented ALS patients. Notably, only a single measure of semantics (confrontational naming) was used to evaluate general language abilities, on which the proportion of impaired patients did not differ between non-demented ALS patients and controls. Given the subtle nature of semantic impairment in ALS, as previously reported and observed in the current study, is it likely that utilizing one measure fails to provide sufficient sensitivity to detect impairment. Consistent with this interpretation, and in keeping with the findings of the present study, a recent study ([26](#_ENREF_26)) demonstrated language disturbance in 43% of ALS patients utilizing a composite of 12 general language measures. Of the 12 tasks, 5 tasks evaluated semantics, on which the proportion of impaired ALS patients ranged from 4-25% and patients performed poorer than controls on 2 of the 5 measures. This highlights the variable sensitivity of existing semantic measures and emphasizes the potential utility of the SYDBAT as a clinical tool, which provides a simple, comprehensive, and sensitive method for assessing verbal and non-verbal semantics in ALS.

Importantly, the current findings suggest that semantic impairment in ALS is not simply a reflection of more severe general cognitive impairment. This is evidenced by the fact that the ALS group performed below controls on both the naming and semantic knowledge composite scores, in the context of comparable general cognitive abilities, as measured by the ACE-R. Interestingly, semantic impairment was not associated with disease duration or disease severity, across ALS and ALS-FTD groups. Rather, semantic impairment was associated with faster disease progression. This association, however, was only significant with the naming composite and did not remain significant when controlling for bulbar symptomology. This suggests that the relationship may simply reflect more severe bulbar disability and requires further exploration.

Our results highlight several shortcomings of the current consensus criteria for the classification of cognitive impairment in ALS ([12](#_ENREF_12), [26](#_ENREF_26)). Specifically, the current guidelines recommend using executive dysfunction to define cognitive impairment in ALS, which in the context of the current findings may be problematic and suggest that current prevalence studies are underestimating cognitive dysfunction. Furthermore, the construct validity of one of the five executive measures identified as sensitive to executive dysfunction in ALS (i.e., animal fluency) is poor. Behavioral and imaging studies suggest that this task primarily evaluates semantic abilities and the integrity of the temporal lobes, rather than executive dysfunction ([29](#_ENREF_29)). Interestingly, in light of the current results, ALS patients may demonstrate difficulties on this semantic-based task, however, due to temporal rather than frontal lobe dysfunction. Revision of the current consensus criteria should be considered to include more comprehensive cognitive measures, including assessments of semantics (e.g., the SYDBAT).

The current study found that semantic impairment was more frequent and severe in patients with ALS-FTD compared to those with pure ALS and may be a sensitive cognitive marker for concomitant FTD. At least 73% of ALS-FTD compared to 33% of ALS patients reached clinical impairment levels. Interestingly, for many ALS-FTD patients, semantic disturbance was as marked as those patients with pure SD (naming composite; 21.1%; semantic knowledge composite = 46.7%). It is worth noting that 66.6% of the ALS-FTD group was initially diagnosed with FTD, however, none of these patients met criteria for SD and rather behavioral changes predominated. A recent study similarly reported a high prevalence (90%) of FTD-type language disturbance in patients with behavioral-dominant ALS-FTD at some point over the disease course ([30](#_ENREF_30)). It is also worth noting that the discrepancy between naming and semantic knowledge abilities in the SD group is not surprising, with disproportionately poorer anomia compared to comprehension, being a common clinical observation ([31](#_ENREF_31)), particularly for those SD patients with a predominance of left temporal atrophy ([32](#_ENREF_32)), present in 73% of the current sample.

A link between the anterior temporal lobe atrophy and semantic knowledge has been well established in SD ([33](#_ENREF_33)). Our results reinforce this relationship in the context of ALS and ALS-FTD, and suggest that the severity of semantic deficits in an individual patient may reflect the degree of temporal pathology. Interestingly, semantic deficits were lateralized to the right temporal lobe in the ALS group. One potential explanation for this finding is the use of visual stimuli (i.e. pictures) in the SYDBAT, and the fact that integrity of the right temporal lobe appears more important for non-verbal semantic storage ([34](#_ENREF_34)), and particularly recollection of visual features ([35](#_ENREF_35)). Alternatively, other MRI studies have reported asymmetric atrophy patterns in ALS ([36](#_ENREF_36)) and this lateralization may reflect more predominant right hemisphere atrophy in the ALS group, in the context of relatively mild left-sided atrophy. Of note, this does not necessarily mean that visual semantic measures such as the SYDBAT can only detect right hemisphere temporal lobe pathology. Rather it has been posited that anatomically the semantic system is highly connected and anterior temporal lobe pathology, regardless of hemisphere, can result in semantic impairment ([37](#_ENREF_37)).

 The ALS group in the present study did not demonstrate significant anterior temporal lobe differences compared to controls. This finding may have been driven by the severity of atrophy, which may vary significantly in ALS, according to the degree of cognitive impairment ([38](#_ENREF_38)). Reassuringly, poor performance on the SYBAT correlated with anterior temporal atrophy in ALS, albeit on the right hand side.

The current imaging results also demonstrate that ALS-FTD patients have significantly more pronounced temporal lobe atrophy compared to the ALS group. This is consistent with previous reports identifying the anterior temporal lobe as a potential pathological biomarker of ALS-FTD ([14](#_ENREF_14)) and further evidenced by the inclusion of anterior temporal lobe atrophy into a recently developed visual MRI rating scale to distinguish between ALS, ALS-FTD and FTD ([40](#_ENREF_40)). As the current findings also suggest this region as a biomarker for ALS-FTD, investigations should establish whether the prognosis for ALS patients with semantic deficits is poorer than those without.

Certain study limitations must be acknowledged. Firstly, ALSFRS-R data was unavailable for a considerable number of patients, especially ALS-FTD patients (ALS = 23%; ALS-FTD = 60%). This limited the power of the study to detect a relationship between severity of semantic impairment, disease severity, duration and progression. Secondly, the present study was cross-sectional in design, so the question of whether semantic deficits predict the subsequent development of ALS-FTD cannot be addressed. Also, while unlikely to be driving the results, executive impairment cannot be excluded as a contributory factor. Finally, the number of patients in the ALS and ALS-FTD groups did not allow a meaningful exploration of differences between limb- and bulbar-onset cases.

The present study demonstrates that semantic impairment is a feature of ALS and ALS-FTD and most likely reflects the degree of temporal lobe pathology. The high prevalence of semantic deficits in ALS and ALS-FTD suggest that the consensus criteria for cognitive impairment in ALS should be revised to account for non-executive deficits. Finally, the use of tasks sensitive to semantic deficits, such as the SYDBAT, should be considered when performing cognitive assessments of patients with ALS.

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**References**

1. Phukan J, Elamin M, Bede P, Jordan N, Gallagher L, Byrne S, et al. The syndrome of cognitive impairment in amyotrophic lateral sclerosis: a population-based study. Journal of neurology, neurosurgery, and psychiatry. 2012 Jan;83(1):102-8. PubMed PMID: 21836033.

2. Ringholz GM, Appel SH, Bradshaw M, Cooke NA, Mosnik DM, Schulz PE. Prevalence and patterns of cognitive impairment in sporadic ALS. Neurology. 2005 Aug 23;65(4):586-90. PubMed PMID: WOS:000231371600018. English.

3. Lillo P, Savage S, Mioshi E, Kiernan MC, Hodges JR. Amyotrophic lateral sclerosis and frontotemporal dementia: A behavioural and cognitive continuum. Amyotrophic lateral sclerosis : official publication of the World Federation of Neurology Research Group on Motor Neuron Diseases. 2012 Jan;13(1):102-9. PubMed PMID: 22214356.

4. Strong MJ, Lomen-Hoerth C, Caselli RJ, Bigio EH, Yang W. Cognitive impairment, frontotemporal dementia, and the motor neuron diseases. Annals of neurology. 2003;54 Suppl 5:S20-3. PubMed PMID: 12833364.

5. Lomen-Hoerth C. Clinical Phenomenology and Neuroimaging Correlates in ALS-FTD. J Mol Neurosci. 2011 Nov;45(3):656-62. PubMed PMID: WOS:000296518900043. English.

6. Murray ME, DeJesus-Hernandez M, Rutherford NJ, Baker M, Duara R, Graff-Radford NR, et al. Clinical and neuropathologic heterogeneity of c9FTD/ALS associated with hexanucleotide repeat expansion in C9ORF72. Acta Neuropathol. 2011 Dec;122(6):673-90. PubMed PMID: WOS:000297471200003. English.

7. Renton AE, Majounie E, Waite A, Simon-Sanchez J, Rollinson S, Gibbs JR, et al. A Hexanucleotide Repeat Expansion in C9ORF72 Is the Cause of Chromosome 9p21-Linked ALS-FTD. Neuron. 2011 Oct 20;72(2):257-68. PubMed PMID: WOS:000296224000009. English.

8. Brouwers N, Sleegers K, Engelborghs S, Maurer-Stroh S, Gijselinck I, van der Zee J, et al. Genetic variability in progranulin contributes to risk for clinically diagnosed Alzheimer disease. Neurology. 2008 Aug 26;71(9):656-64. PubMed PMID: WOS:000258725900008. English.

9. Hodges JR, Patterson K. Semantic dementia: a unique clinicopathological syndrome. Lancet neurology. 2007 Nov;6(11):1004-14. PubMed PMID: WOS:000250617700015. English.

10. Savage S, Hsieh S, Leslie F, Foxe D, Piguet O, Hodges JR. Distinguishing Subtypes in Primary Progressive Aphasia: Application of the Sydney Language Battery. Dementia and Geriatric Cognitive Disorders. 2013;35(3-4):208-18.

11. Abrahams S, Leigh PN, Harvey A, Vythelingum GN, Grise D, Goldstein LH. Verbal fluency and executive dysfunction in amyotrophic lateral sclerosis (ALS). Neuropsychologia. 2000;38(6):734-47. PubMed PMID: WOS:000086054500002. English.

12. Strong MJ, Grace GM, Freedman M, Lomen-Hoerth C, Woolley S, Goldstein LH, et al. Consensus criteria for the diagnosis of frontotemporal cognitive and behavioural syndromes in amyotrophic lateral sclerosis. Amyotrophic lateral sclerosis : official publication of the World Federation of Neurology Research Group on Motor Neuron Diseases. 2009 Jun;10(3):131-46. PubMed PMID: 19462523.

13. Bak TH, Hodges JR. Motor neurone disease, dementia and aphasia: coincidence, co-occurrence or continuum? Journal of neurology. 2001 Apr;248(4):260-+. PubMed PMID: WOS:000168385400002. English.

14. Lillo P, Mioshi E, Burrell JR, Kiernan MC, Hodges JR, Hornberger M. Grey and white matter changes across the amyotrophic lateral sclerosis-frontotemporal dementia continuum. PloS one. 2012;7(8):e43993. PubMed PMID: 22952843. Pubmed Central PMCID: 3430626.

15. Brooks BR, Miller RG, Swash M, Munsat TL, Gr WFNR. El Escorial revisited: Revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotroph Lateral Sc. 2000 Dec;1(5):293-9. PubMed PMID: WOS:000166007500002. English.

16. de Carvalho M, Dengler R, Eisen A, England JD, Kaji R, Kimura J, et al. Electrodiagnostic criteria for diagnosis of ALS. Clin Neurophysiol. 2008 Mar;119(3):497-503. PubMed PMID: WOS:000254253300002. English.

17. Rascovsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus J, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain. 2011 Sep;134(Pt 9):2456-77. PubMed PMID: 21810890. Pubmed Central PMCID: 3170532. Epub 2011/08/04. eng.

18. Neary D, Snowden JS, Gustafson L, Passant U, Stuss D, Black S, et al. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. Neurology. 1998 Dec;51(6):1546-54. PubMed PMID: 9855500.

19. Gorno-Tempini ML, Hillis AE, Weintraub S, Kertesz A, Mendez M, Cappa SF, et al. Classification of primary progressive aphasia and its variants. Neurology. 2011 Mar;76(11):1006-14. PubMed PMID: WOS:000288371800016. English.

20. Lovibond PF, Lovibond SH. The Structure of Negative Emotional States - Comparison of the Depression Anxiety Stress Scales (Dass) with the Beck Depression and Anxiety Inventories. Behav Res Ther. 1995 Mar;33(3):335-43. PubMed PMID: WOS:A1995QK93200011. English.

21. Cedarbaum JM, Stambler N, Malta E, Fuller C, Hilt D, Thurmond B, et al. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. Journal of the neurological sciences. 1999 Oct 31;169(1-2):13-21. PubMed PMID: WOS:000083655500003. English.

22. Mioshi E, Dawson K, Mitchell J, Arnold R, Hodges JR. The Addenbrooke's Cognitive Examination Revised (ACE-R): a brief cognitive test battery for dementia screening. Int J Geriatr Psych. 2006 Nov;21(11):1078-85. PubMed PMID: WOS:000242253400011. English.

23. Mioshi E, Lillo P, Yew B, Hsieh S, Savage S, Hodges JR, et al. Cortical atrophy in ALS is critically associated with neuropsychiatric and cognitive changes. Neurology. 2013 Mar;80(12):1117-23. PubMed PMID: WOS:000316674000013. English.

24. Rakowicz WP, Hodges JR. Dementia and aphasia in motor neuron disease: an underrecognised association? J Neurol Neurosur Ps. 1998 Dec;65(6):881-9. PubMed PMID: WOS:000077418200014. English.

25. Bak TH, Hodges JR. The effects of motor neurone disease on language: Further evidence. Brain Lang. 2004 May;89(2):354-61. PubMed PMID: WOS:000220944800010. English.

26. Taylor LJ, Brown RG, Tsermentseli S, Al-Chalabi A, Shaw CE, Ellis CM, et al. Is language impairment more common than executive dysfunction in amyotrophic lateral sclerosis? Journal of Neurology Neurosurgery and Psychiatry. 2013 May;84(5):494-8. PubMed PMID: WOS:000317388800007. English.

27. Godbolt AK, Josephs KA, Revesz T, Warrington EK, Lantos P, King A, et al. Sporadic and familial dementia with ubiquitin-positive tau-negative inclusions - Clinical features of one histopathological abnormality underlying frontotemporal lobar degeneration. Arch Neurol-Chicago. 2005 Jul;62(7):1097-101. PubMed PMID: WOS:000230508600012. English.

28. Snowden JS. Semantic dysfunction in frontotemporal lobar degeneration. Dement Geriatr Cogn. 1999;10:33-6. PubMed PMID: WOS:000081936600007. English.

29. Mummery CJ, Patterson K, Hodges JR, Wise RJ. Generating 'tiger' as an animal name or a word beginning with T: differences in brain activation. Proceedings Biological sciences / The Royal Society. 1996 Aug 22;263(1373):989-95. PubMed PMID: 8805836.

30. Coon EA, Sorenson EJ, Whitwell JL, Knopman DS, Josephs KA. Predicting survival in frontotemporal dementia with motor neuron disease. Neurology. 2011 May;76(22):1886-93. PubMed PMID: WOS:000291049100010. English.

31. Bozeat S, Ralph MAL, Patterson K, Garrard P, Hodges JR. Non-verbal semantic impairment in semantic dementia. Neuropsychologia. 2000;38(9):1207-15. PubMed PMID: WOS:000088396500001. English.

32. Ralph ML, McClelland J, Patterson K, Galton C, Hodges J. No right to speak? The relationship between object naming and semantic impairment: Neuropsychological evidence and a computational model. Journal of Cognitive Neuroscience. 2001;13(3):341-56.

33. Patterson K, Nestor PJ, Rogers TT. Where do you know what you know? The representation of semantic knowledge in the human brain. Nat Rev Neurosci. 2007 Dec;8(12):976-87. PubMed PMID: WOS:000251074900018. English.

34. Hsieh S, Hornberger M, Piguet O, Hodges JR. Neural basis of music knowledge: evidence from the dementias. Brain. 2011 Sep;134:2523-34. PubMed PMID: WOS:000294959800012. English.

35. Vandenbulcke M, Peeters R, Fannes K, Vandenberghe R. Knowledge of visual attributes in the right hemisphere. Nat Neurosci. 2006 Jul;9(7):964-70. PubMed PMID: WOS:000238590800024. English.

36. Kassubek J, Unrath A, Huppertz HJ, Lule D, Ethofer T, Sperfeld AD, et al. Global brain atrophy and corticospinal tract alterations in ALS, as investigated by voxel-based morphometry of 3-D MRI. Amyotroph Lateral Sc. 2005 Dec;6(4):213-20. PubMed PMID: WOS:000233617700004. English.

37. Rogers TT, Ralph MAL, Garrard P, Bozeat S, McClelland JL, Hodges JR, et al. Structure and deterioration of semantic memory: A neuropsychological and computational investigation. Psychol Rev. 2004 Jan;111(1):205-35. PubMed PMID: WOS:000188205300012. English.

38. Abrahams S, Goldstein LH, Suckling J, Ng V, Simmons A, Chitnis X, et al. Frontotemporal white matter changes in amyotrophic lateral sclerosis. J Neurol. 2005 Mar;252(3):321-31. PubMed PMID: WOS:000228232600009. English.

39. Abrahams S, Goldstein LH, Kew JJM, Brooks DJ, Lloyd CM, Frith CD, et al. Frontal lobe dysfunction in amyotrophic lateral sclerosis - A PET study. Brain. 1996 Dec;119:2105-20. PubMed PMID: WOS:A1996WE28000025. English.

40. Ambikairajah A, Devenney E, Flanagan E, Yew B, Mioshi E, Kiernan MC, et al. A visual MRI atrophy rating scale for the amyotrophic lateral sclerosis-frontotemporal dementia continuum. Amyotrophic lateral sclerosis & frontotemporal degeneration. 2014 Feb 18. PubMed PMID: 24533506.

41. Smith SM. Fast robust automated brain extraction. Human brain mapping. 2002 Nov;17(3):143-55. PubMed PMID: WOS:000178994100001. English.

42. Zhang YY, Brady M, Smith S. Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. Ieee T Med Imaging. 2001 Jan;20(1):45-57. PubMed PMID: WOS:000167324900005. English.

43. Andersson J L R J, M, Smith S. Non-linear registration aka FMRIB Technial Report TR07JA2 [http://www.fmrib.ox.ac.uk/analysis/techrep.:](http://www.fmrib.ox.ac.uk/analysis/techrep.%3A) Analysis Group of the University of Oxford; 2007 [cited 2007].

44. Smith SM, Nichols TE. Threshold-free cluster enhancement: Addressing problems of smoothing, threshold dependence and localisation in cluster inference. Neuroimage. 2009 Jan 1;44(1):83-98. PubMed PMID: WOS:000262300900010. English.

45. Nichols TE, Holmes AP. Nonparametric permutation tests for functional neuroimaging: A primer with examples. Human brain mapping. 2002 Jan;15(1):1-25. PubMed PMID: WOS:000172887500001. English.

**Table and Figure Legends**

**Table 1**

*Title:* Participants’ (ALS, ALS-FTD, SD, controls) demographics and information on disease duration, general cognition, behavioural changes and disease staging *(Mean +/- StDev).*

*Legend:* Abbreviations: ALS = amyotrophic lateral sclerosis; ALS-FTD = amyotrophic lateral sclerosis-frontotemporal dementia; SD = semantic dementia; ACE-R = Addenbrooke’s Cognitive Examination-Revised; ALSFRS-R = Amyotrophic Lateral Sclerosis Rating Scale-Revised

aALSFRS-R missing for 4 patients with ALS (2 with bulbar onset; 2 with limb onset), 12 with ALS-FTD, 16 with SD.

bH values indicate significant differences across groups; c = one-way analysis of variance (ANOVA), *F* test; NS = not significant; \*\*\*p<0.001; \*\*p<0.01; \*p<0.05

Tukey post hoc tests compare differences between group pairs; *p* < 0.05 vs. dcontrol group, eALS group, fALS-FTD group, gSD group

**Table 2**

*Title:* Behavioral and semantic test scores for ALS, ALS-FTD, SD and control participants. *(Mean +/- StDev)*

*Legend:* Abbreviations: ALS = amyotrophic lateral sclerosis; ALS-FTD = amyotrophic lateral sclerosis-frontotemporal dementia; SD = semantic dementia; SYDBAT = Sydney Language Battery; ACE-R = Addenbrooke’s Cognitive Examination-Revised

aNaming Composite Score missing for 3 patients with ALS

bSemantic knowledge Composite Score missing for 5 ALS patients, 4 with ALS-FTD, 2 with SD

cH values indicate significant differences across groups; \*\*\*p<0.001; \*\*p<0.01; \*p<0.05

Tukey post hoc tests compare differences between group pairs; *p* < 0.05 vs. dcontrol group, eALS group, fALS-FTD group, gSD group

**Figure 1**

*Title:* Composite total scores for all participant groups

*Legend:* Abbreviations: ALS = amyotrophic lateral sclerosis; ALS-FTD = amyotrophic lateral sclerosis-frontotemporal dementia; SD = semantic dementia

**Figure 2**

*Title:*Voxel-based morphometry analysis showing regions of temporal lobe atrophy that correlated with impaired semantic performance on the Naming Composite Score and Semantic Knowledge Composite score, for SD, ALS-FTD and ALS patients.

*Legend:*Abbreviations: ALS = amyotrophic lateral sclerosis; ALS-FTD = amyotrophic lateral sclerosis-frontotemporal dementia; SD = semantic dementia. Clusters are overlaid on the MNI standard brain (*t* > 2.50). Cultured voxels show regions which were significant in the analyses for *p* < .05 uncorrected and a cluster threshold of 40 contiguous voxels.

**Table 1**:

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **ALS****(N = 17)** | **ALS-FTD****(N = 19)** | **SD****(N = 22)** | **Controls****(N = 26)** | ***H* value** |
| **Sex (M:F)** | 9:8 | 14:5 | 14:8 | 14:12 | NS |
| **Age** | 62.6 ± 12 | 66 ± 8.8 | 62 ± 7.5 | 67.5 ± 5.7 | NS |
| **Education** | 13.3 ± 2.9 | 13.5 ± 3.7 | 12.3 ± 3.2 | 12.3 ± 2.3 | NS |
| **Disease Duration (months)** | 45.1g ± 61.5 | 34.5g ± 14.1 | 54.2 ± 25.9 | N/A | \*\* |
| **General Cognition (ACE-R Total)** | 89.1f, g ± 8.6 | 70.1d, e, g ± 14.1 | 58.5d, e, f ± 16.4 | 96 ± 2.8 | \*\*\* |
|  **Attention** | 97.2d, f, g ± 4.0 | 87.1d, e ± 12.6 | 84.6d, e ± 20.2 | 99.4 ± 1.8 | \*\*\* |
|  **Memory** | 83.0d, f, g ± 17.7 | 66.2d, e ± 25.9 | 52.4d, e ± 25.3 | 93.6 ± 7.0 | \*\*\* |
|  **Fluency** | 62.8d, f, g ± 34.7 | 29.8d, e ± 27.6 | 34.4d, e ± 27.7 | 89.6 ± 10.7 | \*\*\* |
|  **Language** | 85.1d, f, g ± 15.7 | 72.9d, e, g ± 15.9 | 50.0 d, e, f ± 18.5 | 98.1 ± 3.6 | \*\*\* |
|  **Visuospatial** | 88.3 ± 16.1 | 87.8d ± 11.5 | 92.6 ± 11.2 | 96.4 ± 6.4 | \* |
| **Disease Staging (ALSFRS-R)a** | 38.2g ± 8.6 | 37.9g ± 4.3 | 47.3 ± 0.5 | N/A | \*c |

**Table 2**:

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **ALS****(N = 17)** | **ALS-FTD****(N = 19)** | **SD****(N = 22)** | **Controls****(N = 26)** | ***H* value** |
| **SYDBAT** |  |  |  |  |  |
| **Naming (/30)** | 25 ± 2.9d, f, g | 17.1 ± 6.6d, e, g | 5.4 ± 3.9d, e, f | 27 ± 1.9 | \*\*\* |
| **Comprehension (/30)** | 27 ± 3.6d, f, g | 24.3 ± 4.5 d, e, g | 18 ± 6.6 d, e, f | 29.2 ± 1.5 | \*\*\* |
| **Semantic Assoc. (/30)** | 26.4 ± 2.8f, g | 22.1 ± 7.4 d, e, g | 17 ± 16.2 d, e, f | 27.6 ± 1.8 | \*\*\* |
| **ACE-R** |  |  |  |  |  |
| **Naming (/12)** | 11 ± 1.5d, g | 9.6 ± 2.9 d, e, g | 2.9 ± 2.4 d, e, f | 11.9 ± 0.4 | \*\*\* |
| **Comprehension (/4)** | 3.53± 0.6 d, f, g | 2.5 ± 1.3 d, e, g | 1.3 ± 1.2 d, e, f | 3.9 ± 0.3 | \*\*\* |
| **Naming Composite Score (% correct)** | 88.4 ± 8.1d, f, g | 68.6 ± 20.9 d, e, g | 20.9 ± 15.5 d, e, f | 94.5 ± 4.1 | \*\*\* |
| **Semantic knowledge Composite Score (% correct)** | 89.2 ± 2.6d, f, g | 75.6 ± 17.9 d, e, g | 51.3 ± 4.2 d, e, f | 95.7 ± 4.1 | \*\*\* |

#### Supplemental Material

#### Appendix 1. Voxel-based Morphometry (VBM) acquisition and analysis

Subjects were scanned using a 3T Philips MRI scanner. T1-weighted acquisition: coronal orientation, matrix 256x256x200, 161 mm2 in-plane resolution, slice thickness 1 mm, TE/TI = 2.6/5.8 ms.

Voxel-based morphometry (VBM) was conducted on the three dimensional T1-weighted scans, using the FLS-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 ([41](#_ENREF_41)). Each scan was visually checked after brain extraction, both to ensure that no brain matter was excluded, and no non-brain matter was included (eg. skull, optic nerve, dura mater). If non-brain matter was visually detected or brain matter was falsely excluded, the BET algorithm for that scan was repeated with a modified fractional intensity threshold, to give smaller or larger brain border estimates.

A grey matter template, specific to this study, was then built by canvassing 10 scans from each group (total n = 40). An equal number of scans across each group were used to ensure equal representation, thus avoiding potential bias during registration toward the pattern of atrophy in any single group. 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 2x2x2 mm3 resolution in standard space. Simultaneously, brain-extracted scans were also processed with the FMRIB’s Automatic Segmentation Tool (FAST v4.0) ([42](#_ENREF_42))to achieve tissue segmentation into CSF, grey matter and white matter. Specifically this was done 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. Grey matter partial volume maps were then non-linearly registered to the study-specific template via non-linear 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 ([43](#_ENREF_43)). 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). The statistical analysis was performed with a voxel-wise general linear model. Significant clusters were formed by employing the threshold-free cluster enhancement (TFCE) method([44](#_ENREF_44)). The TFCE method is a cluster-based thresholding method which does not require the setting of an arbitrary cluster forming threshold (e.g. t,z). Instead, it uses raw statistics to produce an output image in which the voxel-wise values represent the amount of cluster-like local spatial support. The TFCE image is then turned into voxel-wise p-values via permutation testing. We employed a permutation-based non-parametric testing with 5000 permutations ([45](#_ENREF_45))on the temporal lobe as a region-of-interest (ROI). The ROI mask was created by employing the temporal lobe region of the Harvard-Oxford probabilistic atlas.

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. Similarly, covariate analyses are reported at p < 0.05, corrected for multiple comparisons via Family-wise Error (FWE) correction across space, unless stated otherwise.

References

1. Smith SM. Fast robust automated brain extraction. Human brain mapping. 2002 Nov;17(3):143-55. PubMed PMID: WOS:000178994100001. English.

2. Zhang YY, Brady M, Smith S. Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. Ieee T Med Imaging. 2001 Jan;20(1):45-57. PubMed PMID: WOS:000167324900005. English.

3. Andersson J L R J, M, Smith S. Non-linear registration aka FMRIB Technial Report TR07JA2 [http://www.fmrib.ox.ac.uk/analysis/techrep.:](http://www.fmrib.ox.ac.uk/analysis/techrep.%3A) Analysis Group of the University of Oxford; 2007 [cited 2007].

4. Smith SM, Nichols TE. Threshold-free cluster enhancement: Addressing problems of smoothing, threshold dependence and localisation in cluster inference. Neuroimage. 2009 Jan 1;44(1):83-98. PubMed PMID: WOS:000262300900010. English.

5. Nichols TE, Holmes AP. Nonparametric permutation tests for functional neuroimaging: A primer with examples. Human brain mapping. 2002 Jan;15(1):1-25. PubMed PMID: WOS:000172887500001. English.

**Supplemental Figures**

**Figure 1**

*Title:* Grey matter atrophy of patients compared to controls**.**

*Legend:* Voxel-based morphometry analysis showing brain area atrophy for **i)** SemD vs. controls, **ii**) ALS-FTD vs. controls. No significant differences for ALS vs. Controls (Not shown). Clusters are overlaid on the MNI standard brain (t>2.41). Coloured voxels show regions that were significant in the analyses for p<0.05 FWE corrected.