Case report of complex Amyotrophic Latera Sclerosis with cogntitive impairment and cortical amyloid deposition.

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Journal of Alzheimer's Disease

Dear Dr. Perry,

We sincerely thank the positive response and the additional minor comments received from the reviewers.

We have revised the manuscript according to the reviewers' suggestions. Below please find our point-by-point responses.

REVIEWER 1
There are a few typographical errors/edits which probably could be corrected during the proof stage:
1) 3rd to the last sentence in the "case history" section and 3rd and 2nd sentences in the 2nd to the last paragraph in the "discussion" section: clinical"ly" [add ly]

Answer: The text has been corrected.

2) 2nd sentence in "results" section: while the other"s" [delete s] tests were normal

Answer: The text has been corrected.

3) 1st sentence in last paragraph of "discussion" section: additional text in front of MCI seems superfluous

Answer: We appreciate the reviewer's comment. However, we have not modified the text as we believe it helps understanding the patient's condition before he underwent the first clinical assessment.

4) last sentence in "discussion" section: outmost to "utmost"
Answer: The text has been corrected.

5) a reference for the El Escorial criteria may be indicated

Answer: The reference Brooks et al. J Neurol Sci 1994; 124: 96-107 has been added to the text

REVIEWER 2
Many thanks for a diligent revision. The title is more apt, and the presentation and discussion are nuanced. One also appreciates the new data included here. This is better,

by far, than the earlier version.

We highly appreciate the reviewer's positive perception of our revised manuscript.

My comments follow:
The first is that there is no explanation of how the patient met NINDS-ADRDA criteria for Alzheimer disease. Give isolated memory impairment, with normal scores on all non-memory psychometric measures, and no cognition-related functional impairments, I am not sure how the criteria were met. By the way, the change in FSIQe can not be construed as a functional measure.

Answer: As described in the revised manuscript there was a progression in cognition impairment with no possibility to work and need of help from family members.

What constitutes a "pathological" CSF beta-amyloid assay? I do not believe that any cut-off has been defined. If you disagree, present the evidence for your position. It is not obvious that elevated amyloid is, in itself, evidence of AD. Furthermore, this paper does not address the uncertainties/controversies in the interpretation of CSF amyloid and tau data in relation to AD diagnosis.

The normal levels of CSF beta-amyloid, as well as T-tau and P-tau are indicated in the manuscript under "CSF biochemical data" section (page 7):

"T-tau [497pg/ml, normal (N)<400pg/ml] and P-tau (85pg/ml, N<60pg/ml) CSF levels were slightly elevated at baseline, whereas the Aβ42 level was normal (692pg/ml, N>450pg/ml). Two years later, the Aβ42 level was pathological (152pg/ml), and both T-tau (202pg/ml) and P-tau (42 pg/ml) were within the normal range."

Therefore the CSF beta-amyloid assay was normal at baseline and pathological at follow-up.

Answer: We agree with the reviewer that the detection of brain amyloid plaques alone is not sufficient evidence for an AD diagnosis. The CSF data offers complementary information that is helpful especially in complex cases like the one we are reporting on. It is also true that PIB and CSF beta-amyloid assay are not always in agreement and there are discordant cases, where a patient might be PIB positive and CSF amyloid-beta negative, as well as the inverse.

The most important oversight here, however, is that there is no consideration that a large proportion of asymptomatic (i.e., cognitively, behaviorally, and functionally) mid-life adults and elders have "positive" PiB scans, this being the primary reason the technology cannot yet be used in clinical settings. This paper does not touch on this issue at all. It is very pertinent to the interpretation of the data - the possibility that, in this case, and the ALS-FTLD one cited, that cortical amyloid has no bearing on the cognitive state.

Answer: We agree that amyloid PET imaging using compounds as 11C-PIB or18F-amyloid compounds alone cannot be used for diagnosis of AD, but the 18F amyloid PET tracers are approved to be used in clinical setting for memory assessment to exclude AD (negative

amyloid PET scans). For this case the patient had MRI changes, FDG changes as well as cognitive problems which resulted that the patient was not able to work and together this talked forward prodromal AD/clinical AD. It is of course quite possible that amyloid plaque might be present in large amount in brain at the same time as a patient may have an additional disease as ALS.

The reference to the literature is rather narrow. This paper is overly reliant on citation #1, which is the only paper cited in the introduction. Yet there is a much more established link between ALS and FTLD, with a literature that dates back more than 50 years. It is in this literature that a link between initial cognitive impairment and ALS is fully described. Furthermore, I am not sure that the report that 30% of ALS subjects show AD pathology has been replicated. I think most studies find much less - even in subjects with dementia.

Answer: We agree with the reviewer that there is an extensive literature about ALS and FTLD and we have in the revised manuscript added some recent references (Gallister et al. 2014, Millicamps et al. 2014, Peters et al. 2015).

What about the apolipoprotein E data? What is the pertinence here?
For completeness in this case report, we have included the APOE genotype of the patient (the patient is APOE 3/4). Being only one case it is not possible to derive further conclusions from this information but APOE 4 being a risk factor for AD.

What visual system is used to rate cortical atrophy?

Answer: Scheltens visual scale as described in Scheltens et al. J Neurol Neurosurg Psychiatry 1992:55: 967-972 and the reference has been added to the revised manuscript

Include citations for the NINDS-ADRDA and El Escorial criteria.

Answer: The references to NINDS-ADRDA and El Escorial criteria have been added in the revised version of the manuscript.

REVIEWER 3
The present revision is substantially better, and the authors advanced numerous aspects of the manuscript. Although this case report lacks postmortem data and crucial genetic information, the manuscript presented here brings important discussions regarding applications of biomarkers in clinical settings.

First, this case shows an interesting coexistence between FTD/ALS and AD pathophysiology. Multiple pathologies have been highlighted by recent neuropathology research as frequent finding in normal and abnormal aging. In fact, this case report represents an interesting observation supporting this novel conceptual framework.

Answer: We sincerely appreciate the reviewer's positive appraisal of our study.

Second, the report highlights neuroinflammation as active pathological processes in AD and ALS. As shown in figure 6, it looks like the binding of [11C]DED PET is increased in the frontal, central, temporal cortices as well as subcortical areas. Unfortunately, the authors didn't discuss the overlapping between neuroinflammation, hypometabolism and amyloidosis in the context of this case. In fact, a more detailed description of the distribution of brain abnormalities in this case report would increase that quality on the manuscript. Finally, the present case report illustrates that interpretation of biomarker data in clinical settings can be challenging.

Answer: We appreciate the reviewer's comments of the multi-tracer PET imaging results for this patient. Given that this is only a single case, it is somewhat challenging to comment upon the spatial overlaps between neuroinflammation, hypometabolism and amyloidosis. From our ongoing multi-tracer studies in MCI and AD, there seems to be increasing evidence that astrocytosis, amyloid deposition and hypometabolism are independent processes affecting different brain regions at different times along disease progression.

We have however updated the manuscript to elaborate a bit further on the main regions (mainly fronto-temporal) showing astrocytosis, however any further conclusions on regional overlaps derived from only this case would be highly speculative. We agree with the reviewer that the interpretation of biomarker data in the clinic can be challenging, especially in complex cases like the one reported in our study.

The text has been updated now, as follows:

"^{11}C-DED binding was high in cortical regions especially in fronto-parietal lobes, consistent with astrocytosis (Figure-5C)." (page 7)

Case report of complex ALS with cognitive impairment and cortical amyloid deposition

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Key words: Amyotrophic lateral sclerosis; Frontotemporal dementia; Alzheimer's disease; PET imaging, ^{11}C-PIB, ^{11}C-~~deprnyl~~deprenyl, ^{18}F-FDG, CSF biomarkers~~.~~, MRI.

Abstract (<245 word)

Purpose: Amyotrophic lateral sclerosis (ALS), a fatal disease of unknown origin, affects motor neurons in the primary motor cortex, brainstem and spinal cord. Cognitive impairment may occur before the motor symptoms.

We present a patient who was initially diagnosed with mild cognitive impairment (MCI) due to Alzheimer's disease (AD) but who developed ALS-like symptoms during follow-up and died shortly thereafter.

Methods: A 60-year-old subject with cognitive impairment underwent neuropsychological testing, cerebrospinal fluid (CSF) analysis, structural imaging (computed tomography and magnetic resonance imaging) and functional imaging [^{11}C-Pittsburgh compound B (PIB) positron emission tomography (PET), ^{18}F-fludeoxyglucose (FDG) PET and ^{11}C-deuterium-L-deprenyl (^{11}C-DED) PET].

Results: Neuropsychological testing showed episodic memory impairment. CSF P-tau and T-tau ~~l~~ levels were elevated. CSF amyloid beta $(A\beta)_{42}$ levels were initially normal but became pathological during follow-up. MCI was diagnosed. ^{18}F-FDG PET showed hypometabolism in the left hippocampus and prefrontal cortices and ^{11}C-PIB PET showed amyloid plaque deposition in the prefrontal, posterior cingulate and parietal cortices. ^{11}C-DED PET showed high brain accumulation consistent with astrocytosis. The memory impairment progressed and AD was diagnosed. Motor impairments developed subsequently and, following additional neurological evaluation, ALS was diagnosed. The disease progressed rapidly and the patient died with pronounced motor symptoms three years after the initial cognitive assessment. Since relatives refused autopsy, post-mortem analysis was not possible.

Conclusions: Imaging abnormalities overlapping with those of other neurodegenerative diseases have been described in ALS patients. Prospective multi-tracer studies could be of clinical value to ~~conductto~~ clarify this still unexplored ~~-~~ area.

Introduction:

Cognitive impairment that does not cross the diagnosis threshold for dementia is described as mild cognitive impairment (MCI). The heterogeneous presentation of MCI makes diagnosis difficult because the symptoms may precede development of Alzheimer's disease (AD) or frontotemporal lobar degeneration (FTLD) but could also precede or coexist with other neurological disorders such as amyotrophic lateral sclerosis (ALS). ALS affects motor neurons in the primary motor cortex, brainstem and spinal cord, but cognitive impairment can appear before the motor symptoms [1]. Some studies suggest overlapping pathology, mostly between ALS and FTLD but also between Parkinson's and AD [1]. Amyloid deposition can occur in ALS patients, although the relationship between these histopathological findings and clinical manifestations remains unclear [1, 2]. Cognitive impairment may be more common in ALS patients than previously acknowledged [1]. In addition, 30% of ALS patients with dementia have AD pathology and some ALS patients without dementia have significant AD pathology [1]. The early identification of disease could be improved with research into better monitoring and/or screening.

We report the imaging findings for a patient with overlapping AD/ALS symptoms and discuss how biomarker analysis could help to explain the complex underlying pathophysiological neurodegenerative process.

Case history (Figure-1)

A 60-year-old, highly educated patient experiencing memory problems that were also observed by his family was referred to the Memory clinic, Department of Geriatric Medicine at Karolinska University Hospital Huddinge, Stockholm and underwent clinical assessment including brain computed tomography (CT), blood sample collection including APOE

genotyping (APOE ε 3/4~~) ,~~), psychiatric and neurological examinations, neuropsychology testing and cerebrospinal fluid (CSF) biomarker analysis. MCI was diagnosed following the clinical criteria as defined by Winblad *et al*.[3] with memory complaint, objective memory impairment (1.5 standard deviations (SD) below age-matched controls) and intact daily living~~,~~. The patient was recruited to a longitudinal MCI study in which he underwent multi-tracer positron emission tomography (PET) imaging [^{11}C-Pittsburgh compound B (PIB), ^{18}F-fludeoxyglucose (FDG) and ^{11}C-deuterium-L-deprenyl (DED)] and brain magnetic resonance imaging (MRI). Since the cognitive~~-~~ impairment progressed AD was diagnosed one year later (NINCDS-ADRDA criteria). The patient started to develop very soon after AD diagnosis motor impairment, with weakness in the left bicep muscle. The patient ~~clinical~~clinically showed bilateral ~~tenar~~thenar atrophy with bilateral reduced muscle volume and strengths in both arms. No fasciculations were observed. A reduction in body weight of 3 kg was observed. Sign for denervation was observed on electromyography. MRI showed no spinal cord ~~atrophyThe~~atrophy. The patient was ~~clinical~~clinically diagnosed with ALS according to El Escorial criteria. After 1.5 years of rapid progression, the patient died with pronounced motor symptoms but still with high mini mental state examination (MMSE) score (26/30), three years after the initial neuropsychological assessment. The family refused brain autopsy for confirmation of final brain pathology.

Methods:

Clinical examination (CT scan, CSF analysis and neuropsychological testing)

Neuropsychological assessment at baseline and at follow-up two years later included the full-scale intelligence quotient (FSIQ) test and evaluation of five neuropsychological domains: verbal (similarities), visuospatial (block design and Rey–Osterrieth copying), short-term memory (digit span), episodic memory (Rey auditory verbal learning and retention after

30min; Rey-Osterrieth retention after 30min) and attention and executive function (digit symbol and trail-making tests A and B).

CT scan and CSF mass spectrometry (MS) were performed and *CSF was analysed* according to routine clinical procedures.

Imaging research study (MRI, multi-tracer PET imaging)

Brain MRI was performed twice, approximately one and two years after the memory assessments, using a 1.5T scanner (Magnetom Vision-Plus, Siemens, Germany) with T1-weighted 3D images. Cortical atrophy was rated visually.

The brain PET investigations with ^{18}F-FDG, ^{11}C-PIB and ^{11}C-DED were performed six months after the initial memory assessments at the PET centre at Uppsala Academic Hospital, Sweden. These examinations were part of a longitudinal MCI multi-tracer research study. All PET scans were performed on ECAT EXACT-HR+ scanners (Siemens/CTI). The PET data were acquired in 3D mode. The patient fasted for 4h preceding the ^{18}F-FDG scan. The injected doses were 313, 195 and 254 MBq for ^{11}C-DED, ^{11}C-PIB, and ^{18}F-FDG, respectively. All PET image processing and analyses were performed according to previously reported methods [4].

Voxel-based analysis with statistical parametric mapping (SPM5; Wellcome Department of Cognitive Neurology, London, UK), which was implemented using MATLAB 7.8 (MathWorks Inc., Sherborn, MA), was used to compare the patient's ^{18}F-FDG and ^{11}C-PIB uptake with those of five age-matched healthy controls (HCs; mean age 60.4±3.6 SD). The acquisition protocol for the HCs was the same as that in the multi-tracer study. All reconstructed PET images were spatially normalised to the MNI standard template (McGill University, Montreal, Canada) to remove inter-scan and inter-subject anatomical variability. Then, images were smoothed by convolution, using an isotropic Gaussian kernel with 8mm

full-width at half maximum. The voxel-wise two-sample t-test for comparison between patient and HCs was computed, with p values uncorrected for multiple comparisons. Differences in glucose metabolism or PIB uptake in comparison with the HC group (threshold: p=0.0001; extent threshold: 50 voxels) were considered significant and projected onto the 3D-rendered brain to assist anatomical identification.

CSF analysis

The CSF was collected by lumbar puncture twice, at baseline and two years later into polypropylene tubes, centrifuged and aliquoted. One aliquot was sent on dry ice for analysis at the Clinical Neurochemistry Laboratory at the Sahlgrenska University Hospital. CSF T-tau (a marker of neuroaxonal degeneration), P-tau (a marker of tau hyperphosphorylation) and Aβ42 (a marker of Aβ pathology; low levels in lumbar CSF indicate retention of the protein in the brain) were determined by INNOTEST ELISAs. CSF Aβ isoforms were also analysed by immunoprecipitation (IP) MS as previously described [5]. CSF neurofilament light (NFL) protein (a marker of injury to large calibre myelinated axons) was measured as previously described [6].

Results:

Clinical memory assessment

At baseline, the ~~RAVL~~Rey auditory verbal learning (RAVL) test result for episodic memory was abnormal compared to the population reference data; all other test results including the MMSE (29/30) were normal (Figure-2). At follow-up, the results for two tests of episodic memory were abnormal, while the ~~others~~ other tests were normal compared to population data except for the MMSE score, which had dropped to 26/30. However, for this patient, five tests were abnormal at baseline in comparison with the estimated premorbid cognitive function

(FSIQe).

CSF biochemical data

T-tau [497pg/ml, normal (N)<400pg/ml] and P-tau (85pg/ml, N<60pg/ml) CSF levels were slightly elevated at baseline, whereas the Aβ42 level was normal (692pg/ml, N>450pg/ml). Two years later, the Aβ42 level was pathological (152pg/ml), and both T-tau (202pg/ml) and P-tau (42 pg/ml) were within the normal range. The MS Aβ42:Aβ40 ratio was low (Figure-3), verifying the second ELISA result. The CSF NFL protein levels were elevated (4700 ng/L, N<1850 ng/L).

Imaging research study

CT and MRI imaging showed slight atrophy of the frontal and parietal cortices and the bilateral hippocampus, which were more pronounced at the two-year follow-up (Figure-4).

^{18}F-FDG PET demonstrated hypometabolism in the left temporal and prefrontal cortices, consistent with neurodegeneration (Figure 5A). ^{11}C-PIB retention was significantly increased in the prefrontal, posterior cingulate and parietal cortices, consistent with high fibrillar amyloid plaque deposition (Figure-5B). In comparison with the HC data, the ~~voxle~~voxel-wise analysis confirmed that~~,~~ hypometabolism was especially pronounced in the left temporal and prefrontal cortices (Figure-6A), and that ^{11}C-PIB retention was increased in the prefrontal, posterior cingulate and parietal cortices (Figure-6B). ^{11}C-DED binding was high in cortical regions especially in fronto-parietal lobes, consistent with astrocytosis (Figure-5C).

Discussion:

This report describes a highly educated patient with estimated high premorbid cognitive

function who after some shorter period of episodic memory problems underwent extensive memory assessment and was initially diagnosed with MCI. Due to further decline in episodic memory, pathological CSF biomarker and positive amyloid PIB PET judged as prodromal AD, and who then rapidly developed symptoms of ALS. Advanced neuroimaging methods reveal structural, biochemical, metabolic and receptor alterations in the brain. To our knowledge, this is the first case of AD/ALS where PET imaging results are consistent with neurodegeneration, cerebral amyloidosis and astrocytosis. Several imaging abnormalities have been described in ALS patients, including many incompletely understood patterns overlapping with images from other neurodegenerative diseases such as FTLD and AD. Neuroimaging findings corroborate brain changes in ALS, in that many of the imaging features correlate with cognitive test scores. MRI studies have found grey matter atrophy in the motor cortex in patients with ALS but few researchers have mentioned the usefulness of molecular imaging in ALS [7]. ^{18}F-FDG PET results showing frontal hypometabolism and negative ^{11}C-PIB PET results have been reported in patients with ALS/FTLD [7]. In this study, we found slight frontal hypometabolism and positive ^{11}C-PIB PET results. Previous studies have reported that astrocytes can play an active role in the neurodegenerative process, particularly in the induction and propagation of motor-neuron loss in ALS [8]. PET studies have also shown increased uptake of ^{11}C-DED in patients with ALS [9] or AD [4], providing support for involvement of astrocytosis in the pathogenesis of both [3, 8]. To our knowledge, no positive ^{11}C-DED PET results have been reported in patients with FTLD.

In this study, the CSF Aβ42 level was initially normal while CSF T-tau and P-tau were elevated. However, during follow-up, CSF Aβ42 levels became highly abnormal, in agreement with amyloid PET and verified by MS, whereas T-tau and P-tau returned to normal levels. In the follow-up examination, CSF NFL protein levels were elevated, as commonly seen in ALS as a sign of long tract degeneration. Decreasing CSF P-tau levels during

progression of ALS has been reported [10]. The patient had high levels of NFL protein in the CSF, which is typically found in ALS and FTLD, while levels are usually normal in AD [11]. This CSF biomarker could thus be used to guide clinical differentiation between these disorders. In the present study the patient was not screened for C90RF72 mutation on chromosome 9p21 and while ALS is often associated with cognitive decline in the pattern of FTLD it can be ~~clinical~~clinically similar to AD [12]. It is thus plausible that what was ~~clinical~~clinically judged as MCI/prodromal –AD– in the present study might clinically have been early signs for FTLD with ALS. A patient with positive PET amyloid but with frequent frontal and temporal TDP43 positive histopathology was recently reported [13] suggesting the presence of amyloid plaque pathology also in non-AD.

~~In~~It is a ~~clinical~~clinically important observation that MCI could be an early sign of different neurological disorders, including ALS. Molecular imaging and CSF biomarker analysis illustrate the complexity of analysing clinically the underlying pathological mechanisms and possible interrelationships between different brain disorders. It will be of ~~outmost~~utmost importance to use different CSF and imaging biomarkers in cases where the diagnosis is uncertain but also important to follow-up with confirmatory histopathological investigations.

Acknowledgements

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Figure legends

Figure 1: Schematic representation of the time course for this patient.

Figure 2: Summary of neuropsychological test results at baseline and at follow-up assessments, demonstrating impairment in and deterioration of cognitive function. Assess = assessment; p5 = Fifth percentile; pop = general population.

FSIQ: full-scale intelligence quotient, Sim: similarities, BD: block design, Roc: Rey–Osterrieth copying, DSp: digit span, RAVL: Rey auditory verbal learning, RAVLd: Rey auditory verbal learning delay (after 30min), ROd: Rey-Osterrieth delay (after 30min)), DiSy: digit symbol, TMT A: trail-making test A, TMT B: trail-making test B).

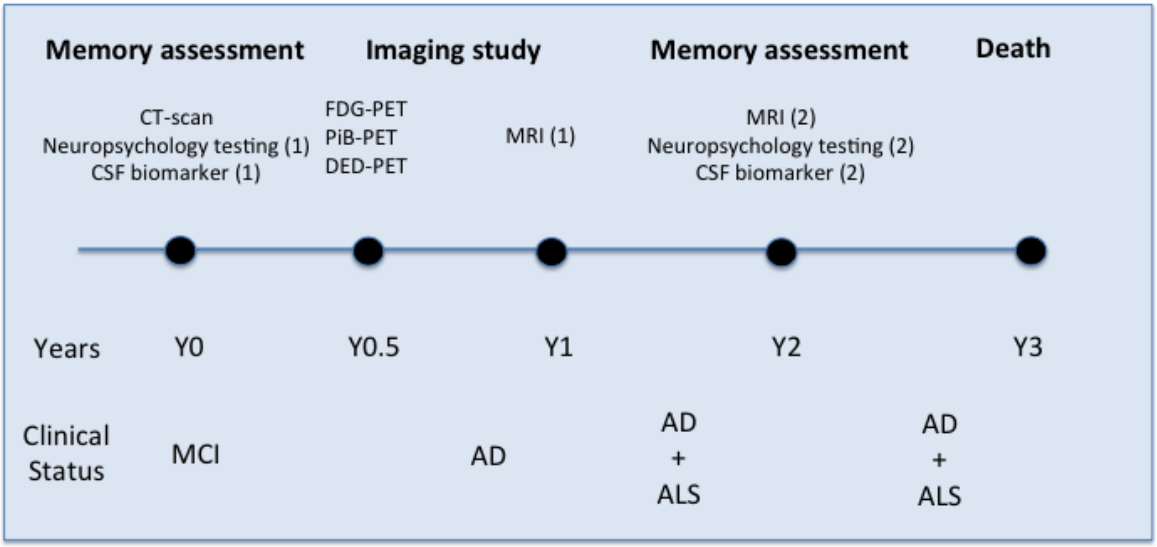
Figure 3: Mass spectra displaying the Aβ isoform pattern from (A) the AD/ALS patient and (B) a control subject. The major Aβ peptides are indicated. (C) Scatter plot showing the Aβ42/40 ratio in control subjects (n = 7) and the patient. The data are presented as means +/- SD.

Figure 4: Co-registered T1-weighted MRI results at five months and after two years of follow-up, showing bilateral hippocampal atrophy more marked on the left side (A), left frontal atrophy (B) and left parietal atrophy (C). Atrophy was more pronounced in the follow-up images (right column).

Figure 5: A) Brain ^{18}F-FDG PET results at six months, demonstrating non-specific hypometabolism in the left temporal and prefrontal cortices. B) Brain ^{11}C-PIB PET at five months, showing high cortical uptake in the prefrontal, posterior cingulate and parietal

cortices consistent with amyloid brain deposition. C) ^{11}C-DED PET at five months, showing high brain accumulation consistent with astrocytosis. The colour scale on the left indicates the index (A and B: relative to the cerebellum, C: Patlak slope).

Figure 6: 3D representation of statistical parametric mapping (SPM5) of ^{18}F-FDG (A) and ^{11}C-PIB (B) PET images in the brain. The red areas show hypometabolism, especially in the left temporal and prefrontal cortices (A), and increased ^{11}C-PIB retention, especially in the prefrontal, posterior cingulate and parietal cortices (B), in the ALS/AD patient, compared to a group of five age-matched healthy controls (p = 0.0001, uncorrected, k = 50 voxels).


Memory assessment
Imaging study
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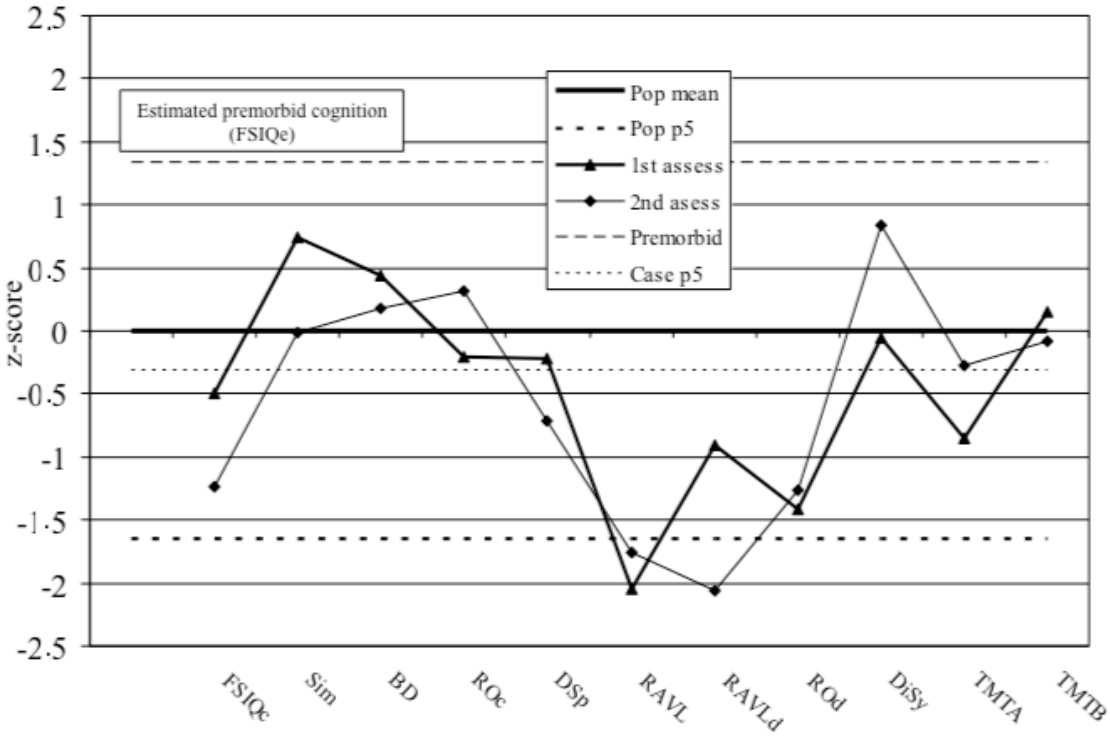
AD + ALS

Figure 1

Figure 2


Estimated premorbid cognition (FSIQe)
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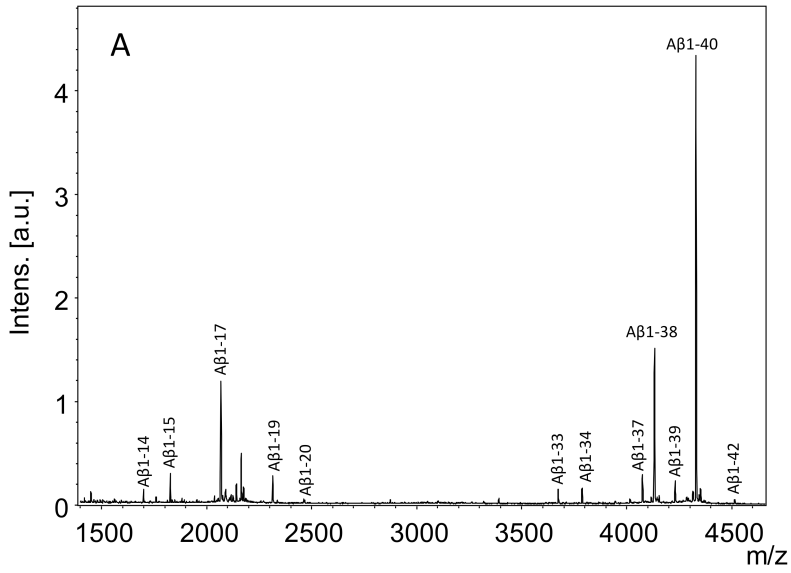
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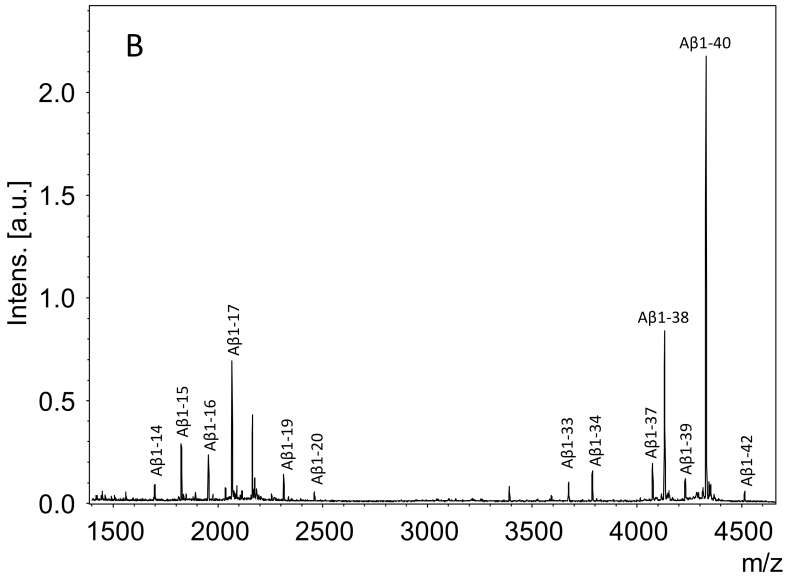
Aβ1-40
Aβ1-42


B
Intens. [a.u.]
m/z
Aβ1-14
Aβ1-15
Aβ1-16
Aβ1-17
Aβ1-19
Aβ1-20
Aβ1-33
Aβ1-34
Aβ1-37
Aβ1-38
Aβ1-39
Aβ1-40
Aβ1-42

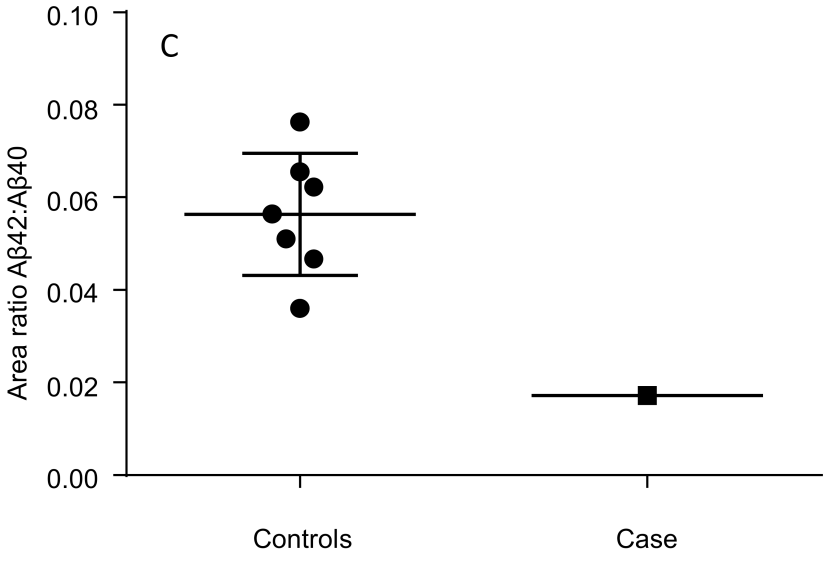

C
Area ratio Aβ42:Aβ40
Controls
Case

Figure 3

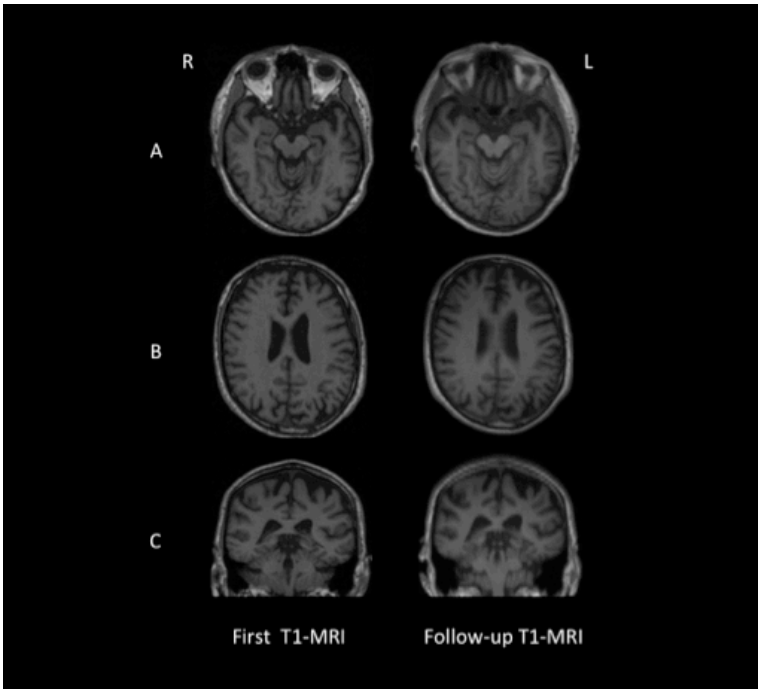


figure 4

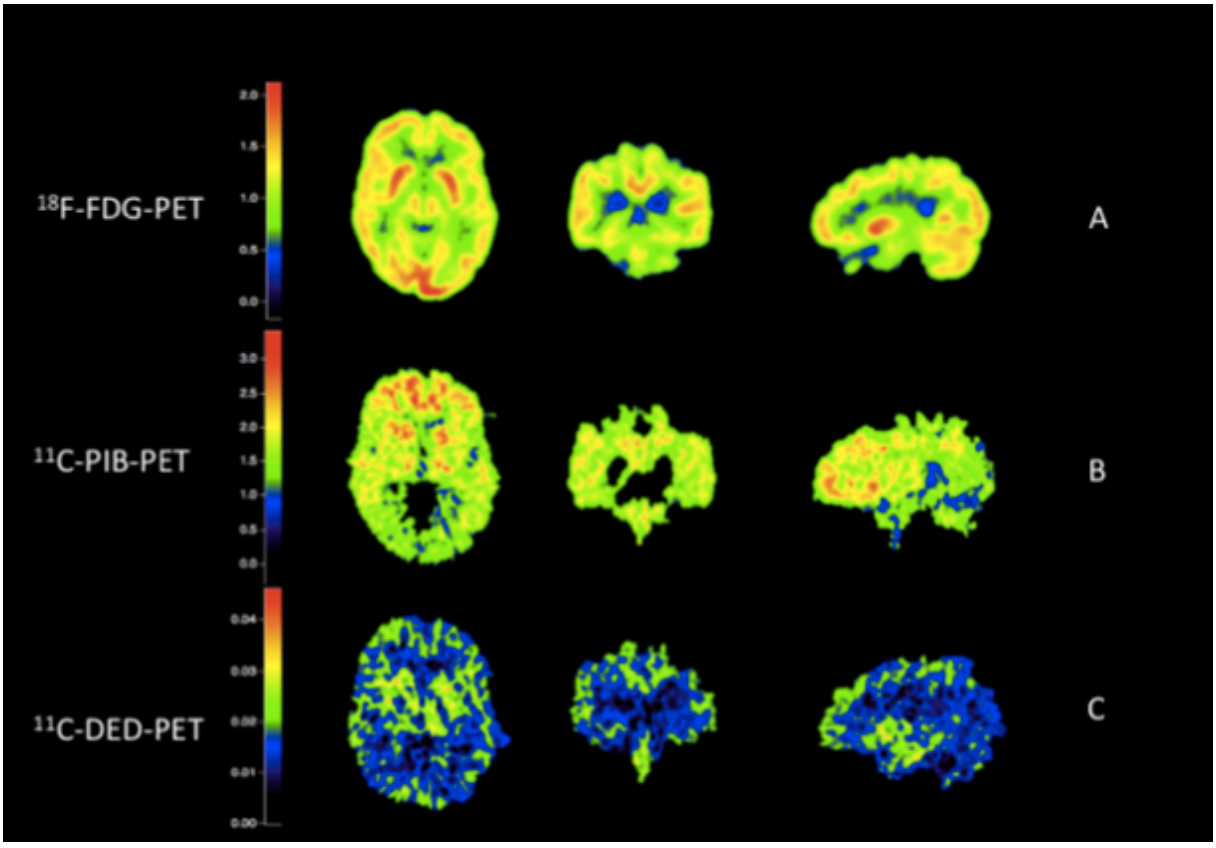


figure 5

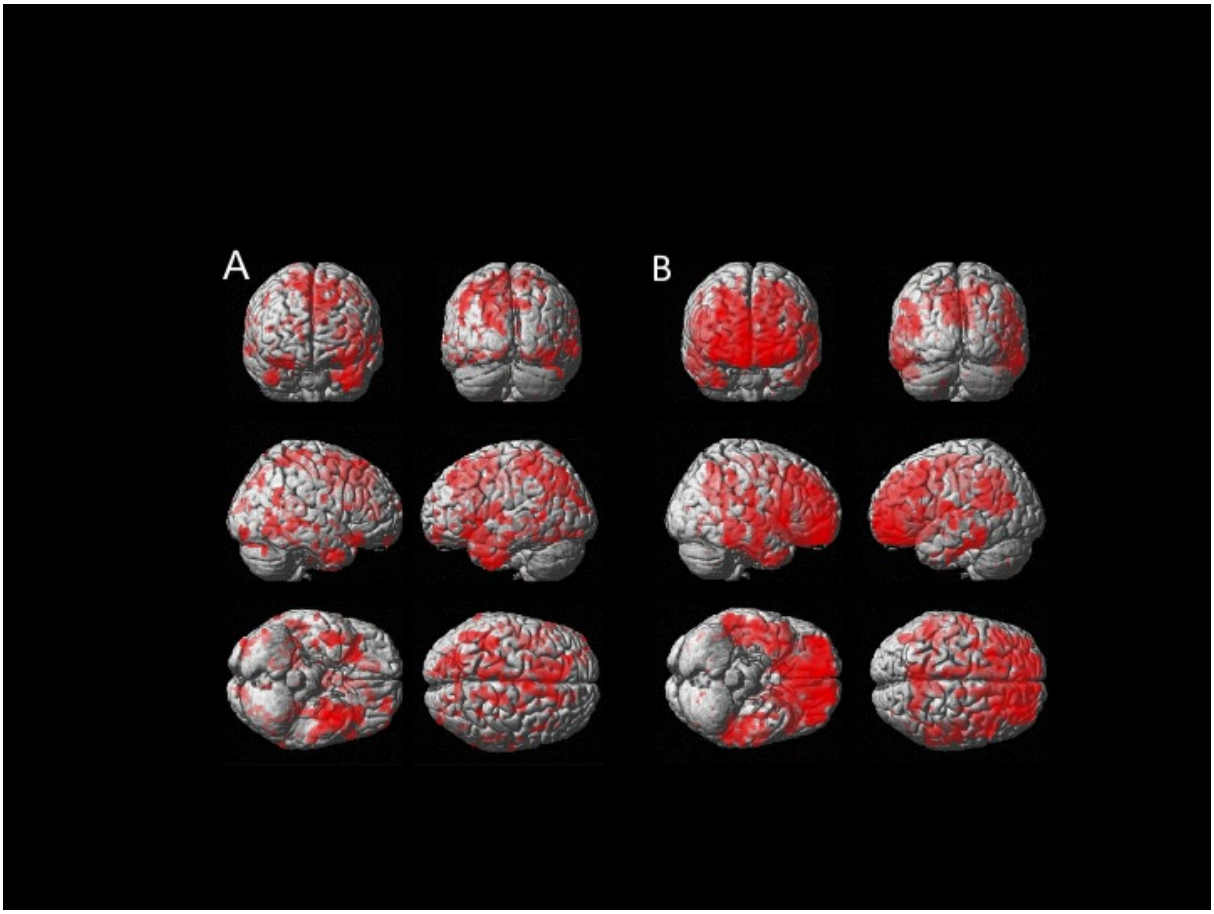


Figure 6