

Early-onset and late-onset Alzheimer's disease are associated with distinct patterns of memory impairment

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Key words: early-onset Alzheimer's disease, late-onset Alzheimer's disease, cognition, memory, semantic memory, neuropsychological tests

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Number of words: 7783

Short title (running head): Memory impairment in EOAD and LOAD

Abstract

The goal of this study was to investigate the specific patterns of memory breakdown in patients suffering from early-onset Alzheimer's disease (EOAD) and late-onset Alzheimer's disease (LOAD). Twenty EOAD patients, twenty LOAD patients, twenty matched younger controls, and twenty matched older controls participated in this study. All participants underwent a detailed neuropsychological assessment, an MRI scan, an FDG-PET scan, and AD patients had biomarkers as supporting evidence of both amyloidopathy and neuronal injury. Results of the neuropsychological assessment showed that both EOAD and LOAD groups were impaired in the domains of memory, executive functions, language, praxis, and visuoconstructional abilities, when compared to their respective control groups. EOAD and LOAD groups, however, showed distinct patterns of memory impairment. Even though both groups were similarly affected on measures of episodic, short term and working memory, in contrast semantic memory was significantly more impaired in LOAD than in EOAD patients. The EOAD group was not more affected than the LOAD group in any memory domain. EOAD patients, however, showed significantly poorer performance in other cognitive domains including executive functions and visuoconstructional abilities. A more detailed analysis of the pattern of semantic memory performance among patient groups revealed that the LOAD was more profoundly impaired, in tasks of both spontaneous recall and semantic recognition. Voxel-Based Morphometry (VBM) analyses showed that impaired semantic performance in patients was associated with reduced gray matter volume in the anterior temporal lobe region, while PET-FDG analyses revealed that poorer semantic performance was associated with greater hypometabolism in the left temporoparietal region, both areas reflecting key regions of the semantic network. Results of this study indicate that EOAD and LOAD patients present with distinct patterns of memory impairment, and that a genuine semantic impairment may represent one of the clinical hallmarks of LOAD.

1. Introduction

Alzheimer's disease (AD) accounts for approximately 60% of all dementia cases. Typically memory is the cognitive domain that is affected foremost and that remains impaired most severely throughout the course of AD. Episodic memory impairment is considered as the core clinical feature of AD and begins in the earliest stages of the disease, although semantic memory and working memory are also impaired. Deficits in episodic memory can be evidenced using neuropsychological tests that require remembering word lists, figures and faces over a period of time ranging from several minutes to one week. Impairment in delayed recall seems to be one of the best predictors of future dementia (Small *et al.*, 2000; Ivanoiu *et al.*, 2005). Semantic memory, which concerns general world knowledge, is also impaired in AD, even at the pre-dementia stages of the disease (Chertkow and Bub, 1990; Duong *et al.*, 2006; Joubert *et al.*, 2010). Semantic deficits have been documented in AD using a variety of standard clinical neuropsychological tests (Huff *et al.*, 1986; Rosser and Hodges, 1994; Hodges and Patterson, 1995; Adlam *et al.*, 2006) and using more specific measures (Chertkow and Bub, 1990; Hodges *et al.*, 1992; Greene and Hodges, 1996; Fung *et al.*, 2001; Thompson *et al.*, 2002; Whatmough *et al.*, 2003; Joubert *et al.*, 2010). Working memory deficits are also frequently reported in AD and involve reduced span for words, digits, letters and spatial locations (Grossi *et al.*, 1993; Belleville *et al.*, 1996). Beyond the memory impairment, other aspects of cognitive function are also altered in the clinical course of AD. For instance, executive dysfunction is an early manifestation of AD (Binetti *et al.*, 1996). It affects inhibition (Collette *et al.*, 1999), mental flexibility and set-shifting (Haxby *et al.*, 1988; Lafleche and Albert, 1995; Albert *et al.*, 2001), planning abilities, and attention (Pate *et al.*, 1994; Perry and Hodges, 1999; Rizzo *et al.*, 2000; Baddeley *et al.*, 2001; Slavin *et al.*, 2002; Pignatti *et al.*, 2005). Specific language deficits including anomia are also common in AD and become exacerbated as the disease advances (Kempler, 2005). Other cognitive deficits such as visuoconstructional apraxia also occur in AD (Ajurriaguerra *et al.*, 1960; Edwards *et al.*, 1991; Rosen *et al.*, 2005), although they are usually less important than memory impairment and executive dysfunction. In terms of the staging of cognitive deficits in AD, it is commonly accepted that episodic memory is first impaired in AD, followed by semantic, executive and attentional deficits,

and later on by linguistic and visuospatial impairments (Perry *et al.*, 2000; Lambon Ralph *et al.*, 2003; Joubert *et al.*, 2007).

Even though age is the primary risk factor for developing AD, the disease can occur at different stages of life. The concept of early-onset AD (EOAD) commonly refers to AD patients who develop the first symptoms before the age of 65. Although early-onset and late-onset AD (>65) (LOAD) are assumed to share common neuropathological features (Braak and Braak, 1991), refer to a common disease and are diagnosed on the same clinical grounds (McKhann *et al.*, 1984), there is increasing evidence that EOAD patients present with distinct patterns of cognitive impairment relative to LOAD patients. The variability in clinical presentation between EOAD and LOAD patients may be due to in part to inherently subtle differences in the underlying topological distribution of atrophy within the medial temporal lobe and neocortical structures. In fact, atrophy may not be as prevalent within medial temporal lobe structures in EOAD as in LOAD but may be over-represented in neocortical structures, including the parietal cortex, the prefrontal cortex and the anterior temporal lobes (Poncet *et al.*, 2006). This has been confirmed by recent studies which have shown that early and late-onset AD patients show different patterns of cortical atrophy, brain metabolism, and functional connectivity, likely due to differences in the distribution of underlying pathological changes (Felician and Pellissier, 2005; Gour *et al.*, 2013).

It was first reported (Delay and Brion, 1962) that younger AD patients presented with an inaugural memory impairment, rapidly followed by a severe deficits of cortical functions (aphasia, apraxia, and agnosia), the latter reflecting the more striking clinical feature in these patients. The authors also insisted on the relatively brief evolution of the disease (2-4 years from onset of dementia). In contrast, they reported that older AD patients showed a slower overall decline and deficits predominated in the memory domain, while functions such as language and praxis usually remained preserved. Briefer evolution in early-onset patients was later confirmed (Jacobs *et al.*, 1994), but there have been conflicting results in the literature regarding the nature of the cognitive decline. Several studies did not find any distinctive differences between EOAD and LOAD patients (Cummings *et al.*, 1985; Bayles *et al.*, 1987; Grady *et al.*, 1987; Selnes *et al.*, 1988; Toyota *et al.*, 2007) or have attributed such differences to dementia severity

(Jacobs *et al.*, 1994; Smits *et al.*, 2012). Regarding memory, a relative sparing of memory in EOAD has been reported (Binetti *et al.*, 1996; Smits *et al.*, 2012), while several studies have found that LOAD patients present primarily with memory difficulties (Jacobs *et al.*, 1994; Imamura *et al.*, 1998). Several studies also found that language function was more altered in early-onset patients (Chui *et al.*, 1985; Filley *et al.*, 1986; Becker *et al.*, 1988; Faber-Langendoen *et al.*, 1988; Binetti *et al.*, 1996; Imamura *et al.*, 1998), even when factors such as education and severity of dementia were controlled for, while variable findings were reported regarding the presence of apraxia (Seltzer and Sherwin, 1983; Reid *et al.*, 1996). A more recent neuropsychological study reported that mildly demented EOAD patients performed worse than LOAD patients on visuospatial functioning, executive functioning, and attention, while memory was remarkably preserved (Smits *et al.*, 2012). Other studies have also reported that early-onset patients have significant visuospatial difficulties when compared to late-onset patients (Fujimori *et al.*, 1998; Koedam *et al.*, 2010). In summary, there have been conflicting results in the literature regarding the patterns of cognitive dysfunction in EOAD and LOAD, but taken together results of these studies seem to suggest that EOAD patients have more prominent difficulties in non-memory domains which include language, visuospatial skills, and executive functions. The absence of consensus may be due to several factors: 1) cognitive evaluations of EOAD and LOAD patients in previous studies were often brief and limited to general domains such as memory and executive functions, while other domains were often not tested (Smits *et al.*, 2012); 2) differences in disease stage may not have been taken into account; 3) variability in the tests used to evaluate specific cognitive domains; 4) specific subdomains were not considered (e.g. memory), possibly eluding differences between EOAD and LOAD groups.

One question of critical importance is whether EOAD and LOAD patients show distinct patterns of impairment within different memory domains. To our knowledge, the question of whether memory subdomains such as episodic memory, semantic memory, short-term memory, and working memory, are affected differently in EOAD and LOAD has never been investigated previously. Therefore, the main objective of this study is to investigate different memory subdomains in EOAD and LOAD using a detailed battery of neuropsychological tests, in order to gain a better understanding of the precise nature

of the memory deficits in these groups. A secondary objective is also to assess neuropsychological performance of patients and age-matched controls across a number of other cognitive domains including executive functions, language, visuo-perceptual abilities, visuospatial abilities, visuo-constructional abilities, and praxis. This may allow gaining a clearer picture of the nature of the cognitive impairment in the early stage of EOAD and LOAD. It is hypothesized that LOAD patients will present with more important deficits in working memory, episodic memory and semantic memory when compared to EOAD patients, while the latter group will show more important deficits in non-memory domains such as language and visuospatial abilities. Finally, a corollary goal of this study is to better pinpoint the brain regions associated with decline in specific memory subsystems by investigating relationships between patterns of cortical atrophy and brain metabolism, using Voxel-based Morphometry (VBM) and Positron emission tomography (PET-FDG), and patterns of memory impairment emerging in EOAD and LOAD patients.

2. Material and Methods

2.1. Subjects

Eighty subjects participated in the current study: twenty EOAD patients, twenty LOAD patients, and two groups of twenty healthy controls matched for age and education to each of the patient groups. All subjects provided informed consent to participate in the study. The research protocol was approved by the local Research Ethics Committee.

EOAD and LOAD patients were recruited at the Memory clinic of the Neurology and Neuropsychology Unit in the Timone Hospital, Marseille. All patients underwent a neurological examination, a neuropsychological assessment, a brain MRI and laboratory workup to rule out nondegenerative causes of cognitive impairment. The diagnosis of probable AD was established by a team of trained neurologists and neuropsychologists following consensus meetings based on past and recent recommendations (McKhann *et al.*, 1984; McKhann *et al.*, 2011). Age of onset was estimated using a structured interview of the patient and caregiver. All patients had dementia of mild severity, with deficits involving memory and other cognitive domains. In order to avoid misdiagnosis in

early and late-onset AD, only probable AD patients with a high level of supporting evidence in favor of a pathophysiological process were included (i.e. clinical criteria for probable AD and biomarkers showing evidence of both amyloidopathy and neuronal injury) (McKhann *et al.*, 2011). Consequently, Cerebro Spinal Fluid (CSF) analysis was performed in all patients prior to inclusion. CSF was subjected to usual procedures (cell counts, total protein levels, CSF / serum albumin ratio and oligoclonal bands). Total Tau, P-Tau 181 and A β 42 peptide levels were determined using ELISA, the Innotech-h Tau-Ag-kit, the Innotech Phospho-Tau (181P) kit and the Innotech A β 42 kit respectively (Innogenetics, Ghent, Belgium).

Clinical inclusion criteria were probable amnesic AD with high level of evidence of AD pathophysiological process, such as determined by Innotech Amyloid Tau Index (IATI) < 0.8 and P-Tau > 60 (an optimal combination of CSF biomarkers that predicts AD with a specificity of 95% and a sensitivity of 85%) (Vanderstichele *et al.*, 2006); presence of a reliable informant; mild dementia severity (Clinical Dementia Rating – CDR of 1) (Morris, 1993); onset of symptoms ranging from 1 to 5 years prior to inclusion; no personal history of neurological or psychiatric disorder; no family history of AD that could suggest autosomal dominant inheritance; no abnormal feature on brain MRI including stroke, more than one ischemic lacuna, and white matter changes on FLAIR, above grade 2 at the Fazecas scale (Fazekas *et al.*, 1987; Gour *et al.*, 2013). Patients with non-amnesic clinical presentations of AD such as logopenic aphasia or posterior cortical atrophy were excluded. The subgroups of AD patients were classified based on a determined cut-off of 65 years of age at onset, based on previous studies comparing features of EOAD and LOAD patients (Kemp *et al.*, 2003; Kim *et al.*, 2005; Shiino *et al.*, 2006; Frisoni *et al.*, 2007; Rabinovici *et al.*, 2010; Canu *et al.*, 2012; Sa *et al.*, 2012; Smits *et al.*, 2012; Cho *et al.*, 2013), as well as on clinical grounds (Amaducci *et al.*, 1986). This cut-off is also used in the DSM-IV TR nomenclature to specify subtypes (American Psychiatric Association, 2000). See Table 1 for details on the results of biomarkers in this study.

INSERT TABLE 1 ABOUT HERE

The group of EOAD patients included twelve females and eight males (CDR = 1; MMSE = 21 (3.7), mean age: 60.6 (5.2), mean number of years since onset of disease: 2.9 (1.0); mean number of years of education: 11.6 (2.7)) and the group of LOAD included twelve females and eight males (CDR = 1, MMSE = 22 (3.2), mean age: 77.9 (4.7), mean number of years since onset: 2.8 (1.2); mean number of years of education: 11.3 (3.5)). Two groups of twenty healthy control participants were matched for age and education with the two patient groups (Younger controls: 14 females/6 males; CDR = 0, MMSE = 29 (0.9), mean age = 57.1 (6.4), mean number of years of education: 13.1 (2.1); Older controls: 13 females/7 males; CDR = 0, MMSE = 29 (0.6), mean age = 75.6 (5.7), mean number of years of education: 11.3 (3.5)). Controls had no history of neurological or psychiatric disorder, no cognitive complaint, normal neuropsychological performance and no abnormal feature on structural brain MRI and 18-FDG-PET imaging. Patients and controls underwent a full neurological examination, a detailed neuropsychological assessment, brain MRI and 18-PET-FDG. Apo E genotype was obtained in all subjects using Hha 1 digestion and electrophoresis analysis. Within the context of a functional connectivity study, part of the neuroimaging and clinical data of a subgroup of participants from the current study were published recently (Gour *et al.*, 2013).

Statistical analyses showed that the EOAD and LOAD groups did not differ between each other in terms of general cognitive level such as assessed by MMSE score (t-test, $t = 1.23$, $p = 0.22$), number of years of education ($t = 0.30$, $p = 0.76$), number of years since onset of disease ($t = 0.42$, $p = 0.67$), and gender (Fischer's exact test, $p = 1.0$). In addition, the EOAD and LOAD groups did not differ significantly from their respective control group in terms of age and education (LOAD vs. older controls: age, $t = 1.48$, $p = 0.15$; education, $t = 0.45$, $p = 0.96$; gender, Fischer's exact test, $p = 1.0$; EOAD vs. younger controls: age, $t = 1.87$, $p = 0.07$; education, $t = 1.96$, $p = 0.06$; gender, Fischer's exact test, $p = 0.74$). As expected, however, both AD groups differed from their respective control group in terms of MMSE score (EOAD: $t = 9.95$, $p < 0.01$; LOAD: $t = 9.9$, $p < 0.01$). Regarding biomarkers, there were no significant differences between EOAD and LOAD groups with respect to total Tau ($t = 0.40$, $p = 0.69$), P-Tau 181 ($t = 1.52$, $p = 0.14$), A β 42 ($t = 1.08$, $p = 0.29$), IATI ($t = 0.53$, $p = 0.60$), nor were there differences in terms of Apo E4 status (Fischer's exact test, $p = 0.69$). Results therefore

confirm that there were no significant differences in terms of biomarkers between EOAD and LOAD patients, that both groups present with a similar high frequency of Apo E4 carriers, and that there is a high level of supporting evidence in favor of a diagnosis of AD in early-onset and late-onset patients.

2.2. Neuropsychology

All three groups of participants underwent a comprehensive neuropsychological assessment, which included neuropsychological measures of memory, attention and executive functions, language, visuoperceptual skills, visuospatial skills, visuo-constructional skills, and praxis. General cognitive abilities were assessed using the Minimal State Examination (MMSE)(Folstein *et al.*, 1975) and the Batterie rapide d'évaluation frontale (BREF/FAB)(Dubois *et al.*, 2000). In terms of memory, episodic memory (anterograde memory) was assessed both in the verbal and visual domains. Verbal memory was assessed with the RL/RI 16 (Van der Linden *et al.*, 2004), a free/cued word recall test widely used as a measure of verbal learning in French similar to the free and cued selective reminding test (FCSRT) (Grober *et al.*, 1988). Visual memory was assessed using the Delayed Matching to Sample test (DMS48), a visual recognition memory test widely used in the assessment of MCI and dementia (Barbeau *et al.*, 2004). Semantic memory (retrograde memory) was assessed using the TOP 10 (Thomas-Anterion and Puel, 2006). The TOP 10 is a standardized test evaluating famous person knowledge of 10 celebrities who were famous between the 1950s and 2000s. This semantic test comprises several sections, including spontaneous recall of biographical knowledge about famous persons (name and occupation), recognition such as assessed through multiple choice questions (name and occupation), specific questions about each individual, and assessing the approximate epoch of fame for each famous person. Tests of famous person knowledge have been shown to be very sensitive to assess semantic breakdown in patients suffering from AD and amnesic MCI (Estevez-Gonzalez *et al.*, 2004; Vogel *et al.*, 2005; Joubert *et al.*, 2008; Joubert *et al.*, 2010; Barbeau *et al.*, 2012; Brambati *et al.*, 2012). Short term memory was assessed in the verbal and spatial domains using respectively the forward digit span of the Wechsler Adult Intelligence scale (Wechsler, 1997) and the forward visuospatial span of the Wechsler Memory Scale

(Wechsler, 2001). Working memory was assessed in the verbal and spatial domains using respectively the backward digit span of the Wechsler Adult Intelligence scale (Wechsler, 1997) and the backward visuospatial span of the Wechsler Memory Scale (Wechsler, 2001).

Executive functions were assessed using several tests which included the Trail Making Test part A (attention), the Trail Making Test part B (Reitan, 1955) and the modified Wisconsin Card Sorting Test (WCST) (Nelson, 1976) (cognitive flexibility and inhibition), as well as the Digit Symbol-Coding subtest of the Wechsler Adult Intelligence scale (processing speed) (Wechsler, 1997). Language tests included measures of naming, spontaneous speech, fluency, repetition, and comprehension. They included the DO80, a French standardized picture naming task (Deloche and Hannequin, 1997), the Letter (P) and Category (animals) fluency tests (Cardebat *et al.*, 1990), the Spontaneous speech subtest of the MEC (Joanette *et al.*, 2004), repetition of abstract and concrete sentences (Kaplan and Adaptation française Mazeau, 1972), as well as the Logic and reasoning, Verbal commands, and Verbal discrimination subtests of the HDAE (Kaplan and Adaptation française Mazeau, 1972). Praxis were evaluated using the Batterie brève d'évaluation des praxies gestuelles (Mahieux-Laurent *et al.*, 2009). The Benton line orientation test was employed to evaluate visuospatial abilities (Benton *et al.*, 1978), while the Benton Facial Recognition Test was used to assess visuoperceptual processing (Benton *et al.*, 1983). Visuoconstructional abilities were assessed using the copy of the Rey–Osterrieth figure (Rey, 1960).

2.3. Statistical analysis

In regards to the neuropsychological tests, as a first step the following comparisons were carried out: EOAD vs. younger controls, LOAD vs. older controls, and EOAD vs. LOAD. The Kolmogorov-Smirnov test was used to assess normality of distribution. When distribution was normal, Student t-tests were carried out on the neuropsychological tests for the three group comparisons. Appropriate Bonferroni correction was applied to control for multiple comparisons. Since there were 40 variables for each group comparison (EOAD vs. LOAD, EOAD vs. YCTR, LOAD vs. OCTR), the threshold of statistical significance was set at $p < 0.0013$ (Bonferroni correction, $p < 0.05/40$). If the

distribution was not normally distributed, significant differences were analyzed using non-parametric Kolmogorov-Smirnov Z tests. SPSS Statistics 20 Software was used.

As a second step, in order to address more specifically which memory subdomains and which cognitive domains were affected in each patient group when compared to their respective control group, composite z-scores were computed for the following memory subdomains: Verbal anterograde memory, visual anterograde memory, semantic retrograde memory, verbal short term memory, visuospatial short term memory, verbal working memory, and visuospatial working memory. In addition, composite z-scores were computed for the following cognitive domains: executive functions, language, praxis, visuospatial abilities, visuoconstructional abilities, and visuoperceptual abilities. Composite z-scores for verbal anterograde memory were derived from delayed free and total recall scores at the RL/RI 16 test, while composite z-scores for visual anterograde memory were derived from delayed recall scores at the DMS48. Composite z-scores for semantic memory were derived from total scores at the TOP 10. Composite z-scores for verbal short term and working memory were calculated from forward and backward digit span scores of the WAIS-III, respectively, while composite z-scores for visuospatial short term and working memory were calculated from forward and backward visuospatial span scores of the WMS-III. Moreover, additional analyses were carried out to investigate if specific patterns or cognitive impairment emerged between groups. Composite scores for language were computed from naming, category fluency, repetition, and comprehension scores. Composite z-scores for praxis were derived from scores on the symbolic, action, and abstract subtests of the Praxis test. Composite z-scores for executive functions were derived from WCST number of sets and total error scores and letter fluency. Composite z-scores for visuoperceptual abilities were derived from total scores on the Benton Facial Recognition Test. Composite z-scores for visuospatial abilities were derived from total scores on the Benton Line Orientation Test. Finally, composite z-scores for visuoconstructional abilities were derived from total scores on the copy of the Rey-Osterrieth Figure. Missing values on the cognitive tests included: Rey copy - one EOAD patient; BFRT - one EOAD; BLOT - one EOAD and one LOAD; RL/RI 16 - four LOAD and seven EOAD; DMS48 - one EOAD; TOP10 - two EOAD and two LOAD; WCST - five EOAD and four LOAD; HDAE comprehension – four

LOAD and two EOAD; Test of praxis - one LOAD. If a participant had not completed a specific test or subtest, cells were entered as missing values. If a participant had failed all trials of a test and was unable to complete this test, a score of zero was given. Individual z-scores were calculated as follows for each test: $z\text{-score} = [(\text{participant score} - \text{mean score for the age-matched control group}) / \text{standard deviation for the age-matched control group}]$. Individual patient z-scores were then averaged into a global patient group z-score (EOAD or LOAD) for each domain. Appropriate Bonferroni correction was applied to control for multiple comparisons. Concerning memory domains, the threshold of statistical significance was set at $p < 0.007$ (Bonferroni correction, $p < 0.05/7$). Concerning cognitive domains, the threshold of statistical significance was set at $p < 0.008$ (Bonferroni correction, $p < 0.05/6$).

2.4. MRI procedure and data processing

Imaging was performed on a 3T Magnetom Verio MR Scanner (Siemens, Erlangen, Germany) equipped with a 12 channel head coil. Foam padding and headphones were used to limit head motion and reduce scanner noise. Conventional MRI included 3D MPRAGE T1-weighted images (TE/TR 2.99 ms/2,3000 ms, 144 contiguous slices, 1.3mm slice thickness, field of view (FOV) 250 mm, matrix 256) acquired in the sagittal plane.

To obtain gray matter (GM) tissue probability maps, 3D-T1 weighted magnetic resonance images were postprocessed using the VBM 8 implemented in SPM8 software (Wellcome Trust Centre for Neuroimaging, London, UK). MRI data were spatially normalized (MNI space), segmented to isolate the GM partition, and modulated. The resulting images, expressed as GM volume corrected for brain size, were masked (75%) to remove remaining non-GM voxels and smoothed (FWHM 6 mm).

Regression analyses were performed at voxel-level, using SPM 8, to study correlations between gray matter volume of EOAD and LOAD subjects and memory performance (mean composite z-scores for memory subdomains: DMS 48; TOP 10 and RL/RI 16 tests). These regression were performed within patterns of atrophy in EAOD and LOAD relative to age-matched controls obtained from an ANOVA with two factors: Group (AD versus Controls) and Age (<65 years versus >65 years) (see supplementary Figure 1).

The SPM (T) maps were obtained at a threshold (voxel level significance) of $p < 0.005$, FDR corrected at the cluster level $p < 0.05$, and using age, gender education level and sex as nuisance variables. MNI coordinates were converted into Talairach coordinates, and brain structures were identified using Talairach Daemon database (<http://www.talairach.org/>).

2.5. FDG-PET procedure and data processing

PET scan was performed using an integrated PET/CT camera (Discovery ST, GE Healthcare, Waukesha, USA), with 6.2 mm axial resolution, allowing 47 contiguous transverse sections of the brain of 3.27 mm thickness. 150 MBq of ¹⁸F-FDG were injected intravenously in an awake and resting state, with eyes closed, in a quiet environment. Image acquisition started 30 min after injection and ended 15 min later. Images were reconstructed using ordered subsets expectation maximization algorithm, with 5 iterations and 32 subsets, and corrected for attenuation using CT transmission scan.

Whole-brain PET statistical analysis was performed at voxel-level using SPM8 software, to study correlations between cerebral metabolic rate of glucose of EOAD and LOAD subjects and memory performance (mean composite z-scores for memory subdomains: DMS 48; TOP 10 and RL/RI 16 tests). These regression were performed within patterns of hypometabolism in EOAD and LOAD relative to age-matched controls obtained from an ANOVA with two factors: Group (AD versus Controls) and Age (<65 years versus >65 years) (see supplementary Figure 2).

The PET images were spatially normalized onto the Montreal Neurological Institute atlas (MNI). The dimensions of the resulting voxel were 2 mm × 2 mm × 2 mm. The images were then smoothed with a Gaussian filter (8 mm FWHM) to blur individual variations anatomy and to increase signal-to-noise ratio. The “proportional scaling” routine was used to check for individual variations in global brain metabolism. The SPM (T) maps were obtained at a height threshold (voxel level significance) of $p < 0.005$, FDR corrected at the cluster level $p < 0.05$, and using age, gender education level as nuisance variables. MNI coordinates were converted into Talairach coordinates, and brain structures were identified using Talairach Daemon database (<http://www.talairach.org/>).

3. Results

3.1. Neuropsychological data

Results of the neuropsychological assessment are presented in Table 2. A legend at the bottom of Table 2 indicates when parametric and non-parametric tests were applied, as well as Bonferroni correction. Results show that when compared to their respective control group, both EOAD and LOAD groups were affected in most of the cognitive domains assessed, including episodic memory, semantic memory, short term memory, working memory, executive functions, language, praxis, and visuoconstructional abilities. When the EOAD and LOAD groups were compared to each other, however, the LOAD group was only found to be significantly more impaired than the EOAD group on the TOP 10, a test of semantic knowledge. Younger controls and older controls did not differ in terms of their performance on the TOP 10 ($t = 1.0$, $p = 0.3$), indicating that there was no significant effect of age on semantic performance.

INSERT TABLE 2 ABOUT HERE

In order to investigate more specifically the specific patterns of memory function in each patient group in relation to its respective control group, composite z-scores were computed for each memory domain. Results are presented in Figure 1. Results demonstrate that the LOAD group was significantly more impaired than the EOAD group in semantic memory (EOAD = -2.0 (1.0); LOAD = -3.7 (0.9); $t = 5.23$, $p < 0.0001$). There was also a trend toward significance regarding visual recognition memory (EOAD = -2.5 (3.3); LOAD = -5.3 (3.3); $t = 2.70$, $p = 0.01$). There were no differences between groups in verbal anterograde memory (EOAD = -15.4 (4.5); LOAD = -14.4 (4.6); $t = 0.55$, $p = 0.58$), verbal short term memory (EOAD = -0.4 (1.3); LOAD = 0.1 (1.1); $t = 1.22$, $p = 0.23$), verbal working memory (EOAD = -1.6 (1.5); LOAD = -1.2 (1.1); $t = 1.0$, $p = 0.33$), visuospatial short term memory (EOAD = -2.1 (1.0); LOAD = -1.3 (1.9); $t = 1.61$, $p = 0.12$), or visuospatial working memory (EOAD = -1.6 (1.2); LOAD = -1.8 (1.6); $t = 0.44$, $p = 0.67$). In conclusion, the most striking difference between patient groups concerned semantic memory which was found to be disproportionately impaired in the

LOAD group. When looking at the individual performance of patients within each group on the semantic test, it was found that 100% of LOAD patients were significantly impaired (such as determined by a cut-off z-score of < -1.96), while only 50% of EOAD patients exhibited significant semantic memory deficits.

INSERT FIG. 1 ABOUT HERE

Composite z-scores were also computed for cognitive domains other than memory so as to report the specific patterns of cognitive impairment found in each patient group relative to its control group. Results are presented in Figure 2. Results show that the EOAD group was significantly more impaired relative to the LOAD group in two cognitive domains: executive functions (EOAD = -3.9, (2.5); LOAD = -1.3 (1.1); $t = 3.7$, $p < 0.008$), and visuoconstructional abilities (EOAD = -16.3 (11.0); LOAD = -3.2 (3.8); $t = 5.01$, $p < 0.008$). In contrast, the LOAD group did not show significantly poorer performance than the EOAD group in any cognitive domain. Finally, the two groups of patients did not differ significantly in terms of praxis (EOAD = -6.0 (6.2); LOAD = -2.3 (3.1); $t = 2.30$, $p = 0.025$), language (EOAD = -10.5 (6.2); LOAD = -7.6 (6.5); $t = 1.33$, $p = 0.19$), visuospatial skills (EOAD = -2.2 (2.4); LOAD = -1.1 (2.0); $t = 1.55$, $p = 0.13$), or visuo perceptual skills (EOAD = -0.5 (1.5); LOAD = -0.1 (0.5); $t = 1.16$, $p = 0.25$).

INSERT FIG. 2 ABOUT HERE

Based on the finding that LOAD patients performed significantly worse than EOAD patients on the semantic memory test, a more in-depth investigation of the patterns of semantic performance of patients was performed. In order to better document the pattern of semantic impairment in both groups of patients, two separate aspects of semantic performance were examined, raw scores on spontaneous recall of semantic knowledge (free recall) and scores on semantic recognition (multiple choice questions). Spontaneous recall involves effortful retrieval of stored conceptual knowledge, while in semantic recognition maximum contextual information is provided through multiple choice questions, thereby guiding and facilitating semantic decision. Although

dissociations in free recall vs. recognition of semantic knowledge do not allow to directly answer the question of whether semantic deficits are due to difficulties in accessing knowledge vs. breakdown of this knowledge, as would be the case with a semantic priming task (Giffard *et al.*, 2002; Brambati *et al.*, 2012), deficits in semantic recognition are nonetheless typically considered to reflect a more genuine breakdown of semantic knowledge (Joubert *et al.*, 2010; Barbeau *et al.*, 2012). As illustrated in Figure 3, the main finding was that EOAD were significantly more impaired relative to younger controls on the free recall (EOAD = 10.1 (3.4); YCTR = 16.3 (3.4); $t = 5.58$, $p < 0.01$) but not on the semantic recognition task (EOAD = 9.2 (1.2); YCTR = 9.6 (0.8); $t = 1.39$, $p = 0.18$) of the TOP 10, while LOAD were impaired both on the free recall (LOAD = 4.5 (2.9); OCTR = 14.0 (3.6); $t = 8.88$, $p < 0.01$) and on the semantic recognition task (LOAD = 7.2 (1.5); OCTR = 9.4 (0.6); $t = 5.89$, $p < 0.01$) relative to their respective control group. LOAD patients were also overall more impaired than EOAD patients on the TOP 10 total score (EOAD = 31.9 (8.7); LOAD = 17.8 (6.8); $t = 5.44$, $p < 0.01$). Thus, these results support the notion that LOAD patients suffer from a more profound and genuine semantic impairment.

INSERT FIG. 3 ABOUT HERE

3.2. VBM results

Regression analyses revealed a positive correlation between performance on TOP 10 (total score) and gray matter volume of left inferior temporal gyrus (BA 21; $k = 345$; T-score=4.09; $p\text{-voxel} < 0.001$; Talairach coordinates $x = -40$, $y = -5$, $z = -29$) and left superior temporal pole (BA 38; $k = 568$; T-score= 4.35 $x = -40$, $y = 5$, $z = -14$). RL/RI 16 performance (verbal anterograde memory) and DMS48 performance (visual anterograde memory) were not significantly correlated with gray matter volume in any region. Results are presented in Figure 4A.

INSERT FIG. 4A ABOUT HERE

Further analyses were carried out to investigate correlations between free recall and recognition of semantic knowledge on the TOP 10 and gray matter volume. Regression analyses revealed a positive correlation between free recall performance on the TOP 10 and gray matter volume of the right inferior frontal cortex (BA47, Talairach coordinates $x=47, y=7, z=-42$), the right temporal pole (BA 38; Talairach coordinates $x=45, y=-4, z=-20$), and the right insula (Talairach coordinates $x=48, y=-4, z=-2$). Recognition on the TOP10, however, was not significantly correlated with gray matter volume in any region.

INSERT SUPPLEMENTARY FIG. S1, S2, S3A AND S3B ABOUT HERE

3.3. FDG-PET data

TOP10 total performance (semantic memory) was positively correlated with the PET metabolism of left posterior middle temporal gyrus (BA39; $k=215$; T-score=3.3; p -voxel=0.001; Talairach coordinates $x=-48, y=-63, z=25$) (Figure 4B). RL/RI16 performance (verbal anterograde memory) and DMS48 performance (visual anterograde memory) were not significantly correlated with PET metabolism in any brain region.

INSERT FIG. 4B ABOUT HERE

INSERT SUPPLEMENTARY FIG. S4 ABOUT HERE

4. Discussion

The principal goal of this study was to compare the neuropsychological profiles of early-onset and late-onset Alzheimer's disease patients in order to document the patterns of memory impairment specific to each group. A secondary goal was to compare group performance across cognitive domains, and to carry out VBM and FDG-PET analyses in order to investigate the relationships between patterns of cortical atrophy and brain metabolism and the memory impairment in these patients. Results indicate that when compared to their respective matched healthy control groups, EOAD and LOAD patients were significantly impaired in most cognitive domains examined, including episodic

memory, semantic memory, short term memory, working memory, executive functions, language, praxis and visuoconstructional abilities. A detailed analysis of functional integrity across memory subsystems showed common patterns of dysfunction as well as specific differences between groups. Verbal anterograde memory was very impaired in EOAD and LOAD, but the degree of impairment was equivalent in both groups. In contrast, a specific pattern of memory dysfunction emerged, revealing that semantic memory was significantly more affected in the LOAD than in the EOAD group. A more detailed analysis of the patterns of semantic impairment revealed that LOAD patients showed a more profound semantic impairment than EOAD patients, affecting both free recall and semantic recognition. No aspect of memory was more impaired in the EOAD than in the LOAD group, but results showed that the EOAD group showed significantly poorer performance in the domains of executive functions and visuoconstructional skills.

Overall, results of this study show that there are distinct profiles of memory impairment associated with EOAD and LOAD. Contrary to previous studies which have reported a relative sparing of memory in EOAD (Binetti *et al.*, 1996; Smits *et al.*, 2012), results of the current study showed that EOAD patients presented with an important verbal episodic memory impairment, similar to that found in LOAD patients, even though patients in both groups were in a mild stage of dementia. Therefore, our results do not support the view that EOAD patients show a remarkable preservation of memory in the early stage of the disease and develop difficulties at later stages of the disease (Smits *et al.*, 2012). Rather, they support the idea that the episodic memory impairment is present early in the disease process of EOAD, such as initially suggested by Delay and Brion (Adlam *et al.*, 2006). The most novel finding of this study, however, was that LOAD patients showed prominent semantic memory deficits. This breakdown affecting both recall and recognition was evidenced using a semantic test which probed biographical knowledge about famous persons who had been famous between the 1950s and 2000s. Tests of famous person knowledge have been particularly useful in demonstrating semantic breakdown in AD but also in amnesic Mild cognitive impairment (aMCI) (Estevez-Gonzalez *et al.*, 2004; Vogel *et al.*, 2005; Joubert *et al.*, 2008; Joubert *et al.*, 2010; Barbeau *et al.*, 2012; Brambati *et al.*, 2012). In fact, aMCI individuals have been found to be significantly more impaired at naming and providing information about

photographs of famous faces and famous monuments than about common objects (Ahmed *et al.*, 2008; Joubert *et al.*, 2010; Clague *et al.*, 2011). Moreover, some studies have shown that aMCI individuals whose semantic knowledge of famous persons was most impaired had a higher rate of conversion to AD relative to non-converters (Thompson *et al.*, 2002; Estevez-Gonzalez *et al.*, 2004). Therefore, results of the present study suggest that there is a genuine and widespread semantic impairment in LOAD patients. This is particularly true considering that 100% of the LOAD patients were considered to be clinically impaired on the semantic test, as determined by a pathological cut-off of -1.96 standard deviations below the mean of the young control group. In contrast, only 50% of the EOAD patients reached this clinically significant cut-off. These results indicate that semantic breakdown may represent a clinically relevant and characteristic feature of LOAD.

There was also a trend toward significance in regard to visual recognition memory (DMS48), LOAD patients performing more poorly than EOAD patients. It is worth to mention that the difference between EOAD and LOAD patients was marginally significant due to the severe correction of p values. Therefore, this difference may be genuine but lacking sufficient power. Visual recognition memory has been shown to be affected very early in AD and aMCI. The DMS48 specifically has been shown to be a very useful tool in the early detection of memory deficits in AD (Barbeau *et al.*, 2004). Visual recognition memory is considered to be a “context-free” form of memory since it concerns an individual’s ability to recognize previously seen objects and shapes out of their context and it relies on a sense of familiarity rather than on recollection. Therefore, this type of memory is ridded of the spatial and temporal contextual information, and visual recognition memory is believed to rely on the integrity of subhippocampal structures such as the perirhinal cortex (Barbeau *et al.*, 2004; Davies *et al.*, 2004). Despite the fact that the DMS48 is a test of anterograde memory while the TOP 10 is a test of retrograde memory, both tests share some similarities in terms of the underlying memory processes, since semantic memory can also be considered to be context-free. Indeed, semantic memory allows accessing and retrieving conceptual knowledge that is free of contextual elements such as spatial and temporal cues. Therefore, it is conceivable that visual recognition memory and semantic memory may share some at least partly

overlapping common neuroanatomical grounds, including a network of interconnected temporal regions such as the perirhinal and entorhinal cortices as well as the anterior temporal lobe region (ATL) (Barbeau *et al.*, 2012).

Associations of gray matter volume (VBM) and brain metabolism (PET-FDG) with performance of EOAD and LOAD patients (combined in a single group) in three memory subdomains (TOP 10, DMS48, and RL/RI16 tests) did not allow identifying common brain regions between semantic memory and visual recognition memory. In fact, visual recognition memory (DMS48) and verbal anterograde memory (RL/RI16) did not correlate with gray matter volume and metabolism of any specific brain regions. In contrast, VBM analyses showed that poorer semantic performance in patients correlated positively with reduced gray matter volume in the left anterior and inferior temporal lobe region as well as in the right anterior temporal lobe, while FDG-PET analyses showed that poorer semantic performance correlated with greater hypometabolism in the left posterior middle temporal gyrus. Both of these regions are considered to be key regions of the semantic network. The anterior temporal lobe region has been described as a critical site for the convergence and processing of semantic information at an abstract and amodal level (Patterson *et al.*, 2007; Lambon Ralph *et al.*, 2009), and damage to this region has been suggested to result in a central loss of conceptual knowledge, affecting the identification and recognition of objects, persons and other classes of concepts across all sensory modalities. Alternately, Gainotti (Gainotti, 2014, 2015) also highlights the importance of the ATL region in his influential model of semantic memory, but unlike the unitary semantic hub hypothesis, suggests that lexical-semantic representations rely to a greater extent on the left ATL while non-verbal representations depend mainly on the right ATL. Results of the current study seem to fit with both conceptions.

The left posterior middle temporal gyrus has also been identified as an important region of the semantic network (Whitney *et al.*, 2012; Jefferies, 2013; Noonan *et al.*, 2013). More specifically, it has been recently suggested that this region plays a major role in the executive aspects of semantic cognition, including the manipulation and selection of task relevant knowledge as well as the inhibition of task-irrelevant knowledge. Therefore, the anterior temporal lobe region plays a more central role in semantic memory, whereas the left temporoparietal region plays a more important role in the

executive aspects of semantic processing. In this study, both regions correlated significantly with semantic performance, which suggests that both central processes and semantic control processes are affected in Alzheimer's disease.

In summary, the patterns of memory impairment in EOAD and LOAD patients indicate that LOAD were more impaired than EOAD patients on measures of semantic memory. The LOAD group was not more impaired than the EOAD group in any other cognitive domain. The EOAD group, however, was more impaired than the LOAD group in other cognitive domains such as executive functions and visuoconstructional skills. The EOAD group also performed more poorly on praxis, even though the difference was not statistically significant. This difference, however, may be genuine but lacking sufficient power due to the strict Bonferroni correction applied. No significant differences between EOAD and LOAD groups were observed in terms of language abilities, visuospatial skills, and visuo-perceptual skills. One finding of this study which differs from previous reports is that visuospatial skills were not found to be disproportionately impaired in the EOAD group. This contrasts with several previous studies which have reported more important visuospatial deficits in EOAD patients (Fujimori *et al.*, 1998; Koedam *et al.*, 2010). In the present study, however, visuoconstructional skills were severely affected in EOAD patients when compared to LOAD patients, such as measured by performance on the copy of the Rey-Osterrieth Figure. Although this test involves the manipulation of spatial information and is often used as a measure of visuospatial integrity, it also involves motor skills as well as the implementation of executive functions (planning, structuring, coordination, and execution). The multifaceted nature of this test in terms of the underlying cognitive processes involved and the underlying executive function deficits in EOAD patients may therefore account for the severe difficulties encountered by the EOAD group on this test. This severely compromised performance in the EOAD group contrasted with preserved performance on another test of visuospatial function, the Benton line orientation test, which may be considered as a "purer" test of visuospatial integrity than the copy of the Rey-Osterrieth Figure. In summary, visuospatial skills may not be as severely compromised in EOAD as has been previously suggested in the literature.

In terms of language, our findings do not support the claim that EOAD patients present with significantly greater language impairment, such as has been suggested in previous studies (Chui *et al.*, 1985; Filley *et al.*, 1986; Becker *et al.*, 1988; Faber-Langendoen *et al.*, 1988; Binetti *et al.*, 1996; Imamura *et al.*, 1998). In this study, composite scores were derived from tests that covered several aspects of expressive and receptive language including picture naming, speech, category fluency, repetition, and comprehension. When looking at Figure 2, the EOAD group showed greater language impairment when compared to the LOAD group, such as expressed by the mean z-scores, but this difference was not statistically different. This is due to the important within-group variability (i.e. large standard deviations) in the EOAD group. Therefore, although some EOAD patients were clearly very impaired on language tasks, this was not the case for all EOAD patients. These results highlight the heterogeneity of language deficits in these patients.

5. Conclusion

In conclusion, this study provides new insights into the nature of the cognitive decline in young and late-onset Alzheimer's disease patients. EOAD and LOAD groups were strictly matched for disease severity and were recruited in an early stage of the disease. They were also matched for gender and education. EOAD and LOAD patients showed strong supporting evidence of Alzheimer's disease using biomarkers, and both groups did not differ significantly in terms of biomarker values or in terms of ApoE4 status. Results indicate that both groups of patients present with significant memory impairment, but that distinct patterns of memory deficits emerge. LOAD patients were found to be significantly more impaired than EOAD patients solely in the memory domain (Jacobs *et al.*, 1994; Koss *et al.*, 1996). More specifically, LOAD patients presented with greater semantic memory deficits. In contrast, EOAD were found to be significantly more affected in non-memory domains including executive functions and visuoconstructional abilities. Contrary to previous studies, however, EOAD patients were not found to be more impaired in the language and visuospatial domains. Semantic deficits in AD patients were found to be associated with gray matter volume reduction in the left

anterior temporal lobes and with greater hypometabolism in the left temporoparietal region, both key regions of the semantic network.

Acknowledgements

None of the authors have any actual or potential conflicts of interest in relation with the topic of the study. SJ is supported by a Chercheur-boursier Senior award from the Fonds de recherche du Québec – Santé (FRQS) and by the Alzheimer Society of Canada. This work was funded by the French Hospital Clinical Research Program (PHRC ADAGE 2008-A01213-52). The authors are indebted to the association “dechaine ton coeur” for its financial support. They are thankful to the patients, their families and healthy controls for their generous participation in this study. They are grateful to Dr Radka Gantcheva for clinical assessment of healthy subjects, Dr Raphaëlle Bernard for performing Apo E genotyping, Julie Pelat, Maryline Blanchon for their help with management of throughout the study including data managing, Mohamed Fattalah (Centre d’Investigation Clinique) for computational assistance, and Elisabeth Soulier, Sylviane Confort-Gouny and Patrick Viout for the MRI acquisitions.

Table 1. Patient characteristics, Apo E4 frequency and biomarker values (mean and SD).

<i>patient characteristics</i>	EOAD	LOAD
Age	60.6 (5.2)	77.9 (4.7)
Gender	12F/8M	12F/8M
Education	11.6 (2.7)	11.3 (3.5)
MMSE	21 (3.7)	22 (3.2)
Years since onset of disease	2.9 (1.0)	2.8 (1.2)
ApoE E4 homozygote	2	2
ApoE E4 heterozygote	14	8
<i>CSF biomarkers</i>		
Tau protein total	587.0 (278)	550.1 (267)
Phospho Tau 181	104.5 (35)	87.7 (31)
Amyloid	423.4 (122)	379.1 (122)
IAT1	0.543 (0.2)	0.485 (0.2)

Table 2. Neuropsychological assessment of EOAD, LOAD, and healthy controls.

	EOAD	LOAD	Young controls	Older controls	EOAD vs. LOAD	EOAD vs. YCTR	LOAD vs. OCTR
General cognitive functioning							
MMSE	20.7 (3.7)	22.0 (3.2)	29.2 (0.9)	29.2 (0.6)	n.s.	*	* †
FAB	12.7 (3.3)	13.1 (3.3)	17.5 (0.8)	17.5 (0.9)	n.s.	* †	* †
Memory							
Verbal anterograde memory							
RL/RI 16 Immediate Free Recall (48)	5.3 (5.8)	4.6 (4.9)	33.1 (5.6)	32.4 (5.1)	n.s.	*	*
RL/RI 16 Immediate Total Recall (48)	17.3 (11.7)	19.9 (12.2)	46.1 (2.6)	46.1 (1.5)	n.s.	* †	*
RL/RI 16 Delayed Free Recall (16)	0.9 (1.5)	1 (1.7)	13.4 (1.7)	12.9 (2.0)	n.s. †	*	* †
RL/RI 16 Delayed Total Recall (16)	4.4 (4.1)	6.4 (3.6)	15.9 (0.5)	15.8 (0.4)	n.s.	* †	* †
Visual anterograde memory							
DMS 48 Immediate (2 min)	82.9 (15.1)	78.4 (12.3)	96.2 (3.1)	94.9 (5.9)	n.s.	*	*
DMS 48 Delayed (1 hour)	82.2 (16.5)	72.7 (14.2)	95.7 (5.1)	95.6 (4.3)	n.s.	n.s.	*
Short term and working memory							
Verbal forward digit span (WAIS-III)	4.5 (1.2)	4.6 (1.2)	4.9 (0.9)	4.5 (1.1)	n.s.	n.s.	n.s.
Verbal backward digit span (WAIS-III)	2.5 (1.0)	2.8 (0.9)	3.6 (0.7)	3.7 (0.7)	n.s.	* †	n.s. †
Spatial forward span (WMS-III)	3.0 (0.8)	3.4 (1.0)	5.0 (1.0)	4.0 (0.7)	n.s.	*	n.s. †
Spatial backward span (WMS-III)	2.7 (1.0)	2.7 (0.8)	4.0 (0.9)	3.7 (0.7)	n.s. †	* †	*
Semantic retrograde memory							
TOP 10 picture naming (20)	10.1 (3.4)	4.5 (2.9)	16.3 (3.4)	14.0 (3.6)	*	*	*
TOP 10 semantic free recall (20)	8.8 (4.2)	3.6 (2.6)	16.2 (4.0)	16 (2.8)	*	*	*
TOP 10 semantic recognition (10)	9.2 (1.2)	7.2 (1.5)	9.6 (0.8)	9.4 (0.6)	* †	n.s. †	*
TOP 10 Time (10)	3.8 (1.7)	2.5 (1.8)	7.4 (2.6)	7.5 (2.4)	n.s.	*	*
TOP 10 Total (60)	31.9 (8.7)	17.8 (6.8)	49.5 (8.6)	46.7 (7.9)	*	*	*
Attention, speed of processing and executive functions							
Coding (WAIS-III)	40.9 (23.2)	29.5 (14.1)	65.8 (14.1)	54.0 (12.2)	n.s.	*	*
TMT Part A (Time in sec.)	77 (45)	121 (177)	35.8 (11.4)	51.0 (17.3)	n.s. †	*	n.s. †
TMT Part A (errors)	0	0	0.2 (0.4)	0.2 (0.4)	n.s. †	n.s. †	n.s. †
TMT Part B (Time in sec.)	268 (106)	191 (68)	74.9 (17.6)	115.4 (29.3)	n.s.	*	*
TMT Part B (errors)	3.0 (3.1)	1.2 (1.2)	0.3 (0.6)	0.8 (0.9)	n.s.	n.s. †	n.s.
WCST (Nelson) categories	3.5 (1.7)	3.5 (1.9)	5.9 (0.3)	5.4 (1.1)	n.s.	* †	n.s. †
WCST (Nelson) errors	15.6 (8.4)	15.0 (8.1)	4.8 (3.6)	6.7 (4.6)	n.s.	* †	*
Letter P fluency (2 min)	15.3 (6.2)	15.0 (6.5)	19.5 (4.9)	18.8 (5.3)	n.s.	n.s.	n.s.
Language							
Picture naming							
DO80 picture naming test (80)	73.7 (5.6)	71.3 (8.2)	79.9 (0.2)	79.9 (0.3)	n.s.	* †	* †
Fluency							
Animals (2 min)	13.6 (6.3)	15.4 (7.5)	30.2 (5.9)	28.4 (6.4)	n.s.	*	*
Speech							
MEC spontaneous speech (34)	27.8 (3.9)	27.0 (5.9)	34.0 (0.2)	33.9 (0.4)	n.s.	* †	* †
Repetition							
Concrete sentences (8)	7.4 (1.5)	7.3 (1.4)	8.0 (0.2)	7.9 (0.5)	n.s. †	n.s. †	n.s. †
Abstract sentences (8)	6.4 (1.8)	5.7 (2.5)	7.9 (0.3)	7.9 (0.3)	n.s.	n.s. †	n.s. †
Comprehension							
HDAE Logic and reasoning (12)	7.5 (3.2)	8.1 (3.1)	11.5 (0.6)	11.2 (0.9)	n.s.	* †	*
HDAE Verbal commands (15)	11.8 (4.1)	13.0 (3.7)	14.8 (0.6)	14.6 (0.9)	n.s.	n.s. †	n.s. †
HDAE Verbal discrimination (72)	66.4 (5.6)	66.8 (4.2)	71.9 (0.2)	71.7 (0.6)	n.s.	* †	* †
Praxis							
Symbolic (5)	4.1 (1.1)	4.5 (1.0)	5.0 (0.2)	4.9 (0.4)	n.s. †	n.s.	n.s. †
Actions (10)	8.2 (2.6)	8.8 (1.8)	10 (0.2)	9.9 (0.3)	n.s.	*	n.s. †
Abstract (8)	5.0 (2.4)	5.1 (1.6)	7.9 (0.5)	7.3 (0.9)	n.s.	* †	* †
Visuoconstructional abilities							
Rey Figure copy - score (36)	15.4 (14.7)	22.5 (12.4)	34.6 (1.3)	33.4 (3.2)	n.s.	*	*
Rey Figure copy - time (36)	234 (99)	268 (85)	139 (43)	190 (102)	n.s.	*	n.s.
Visuospatial abilities							
Benton Line Orientation Test (30)	15.6 (8.0)	18.4 (7.6)	22.9 (3.3)	22.5 (3.8)	n.s.	*	n.s.
Visuoperceptual abilities							
Benton Facial Recognition Test (27)	20.4 (2.7)	20.1 (1.8)	21.4 (1.8)	20.5 (3.3)	n.s.	n.s.	n.s.

values indicate mean scores and standard deviations in brackets

n.s. = non significant

* = statistically significant difference, $p < 0.0013$ (Bonferroni correction applied)

† = non-parametric tests were carried out due to non-normal distribution of sample (Kolmogorov-Smirnov Z)

Figure 1. Mean composite z-scores for memory subdomains in EOAD and LOAD groups. Semantic memory was found to be significantly more impaired in the LOAD group than in the EOAD group, while no memory subdomain was more impaired in the EOAD than in the LOAD group (significance was set at $p < 0.007$ after Bonferroni correction). Verbal anterograde memory was equally affected in both groups.

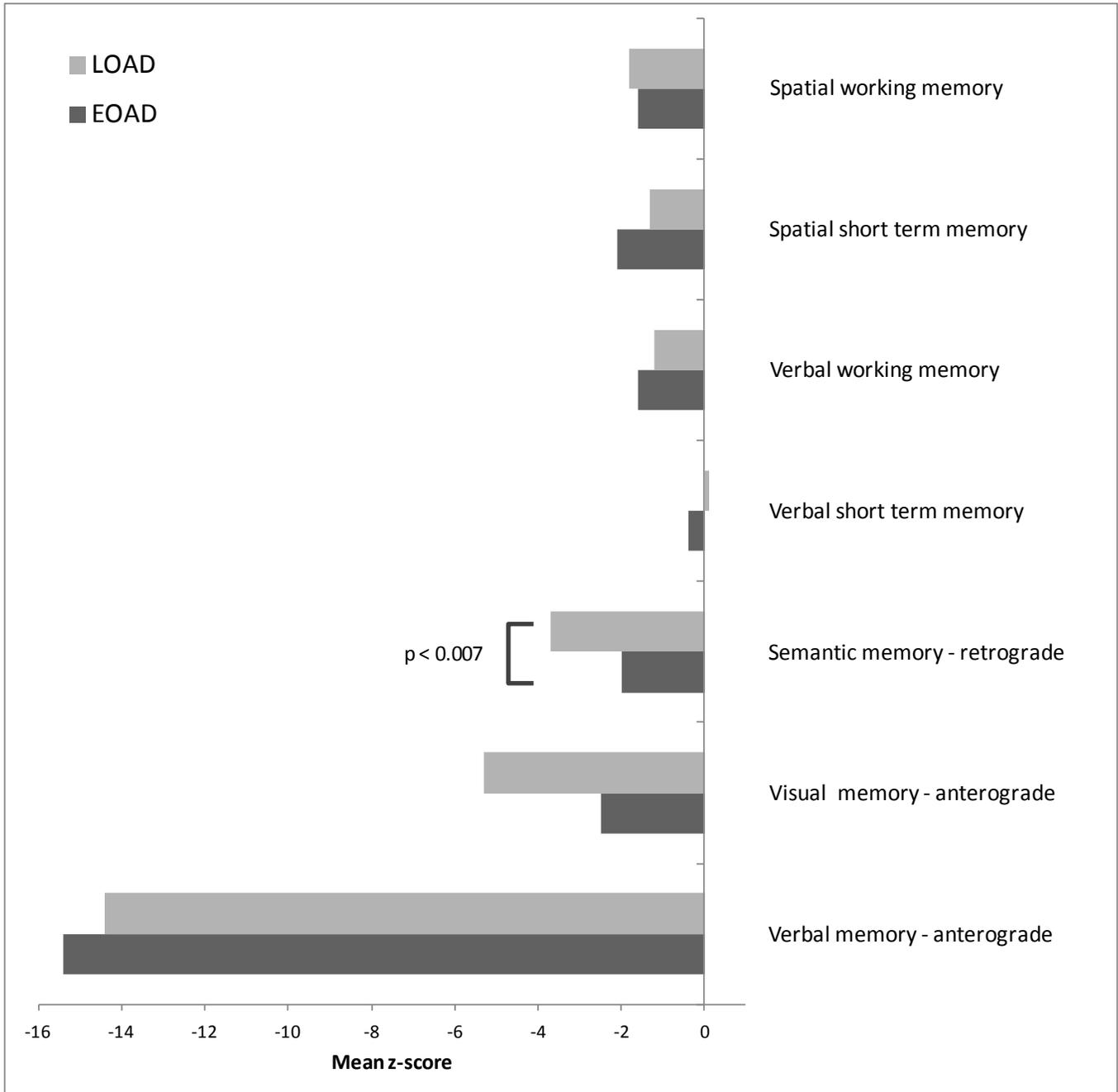


Figure 2. Mean composite z-scores for non-memory cognitive domains in EOAD and LOAD groups. The EOAD group was significantly more impaired than the LOAD group in executive functions and visuoconstructional abilities. The LOAD was not more impaired than the EOAD group in any cognitive domain (significance was set at $p < 0.008$ after Bonferroni correction).

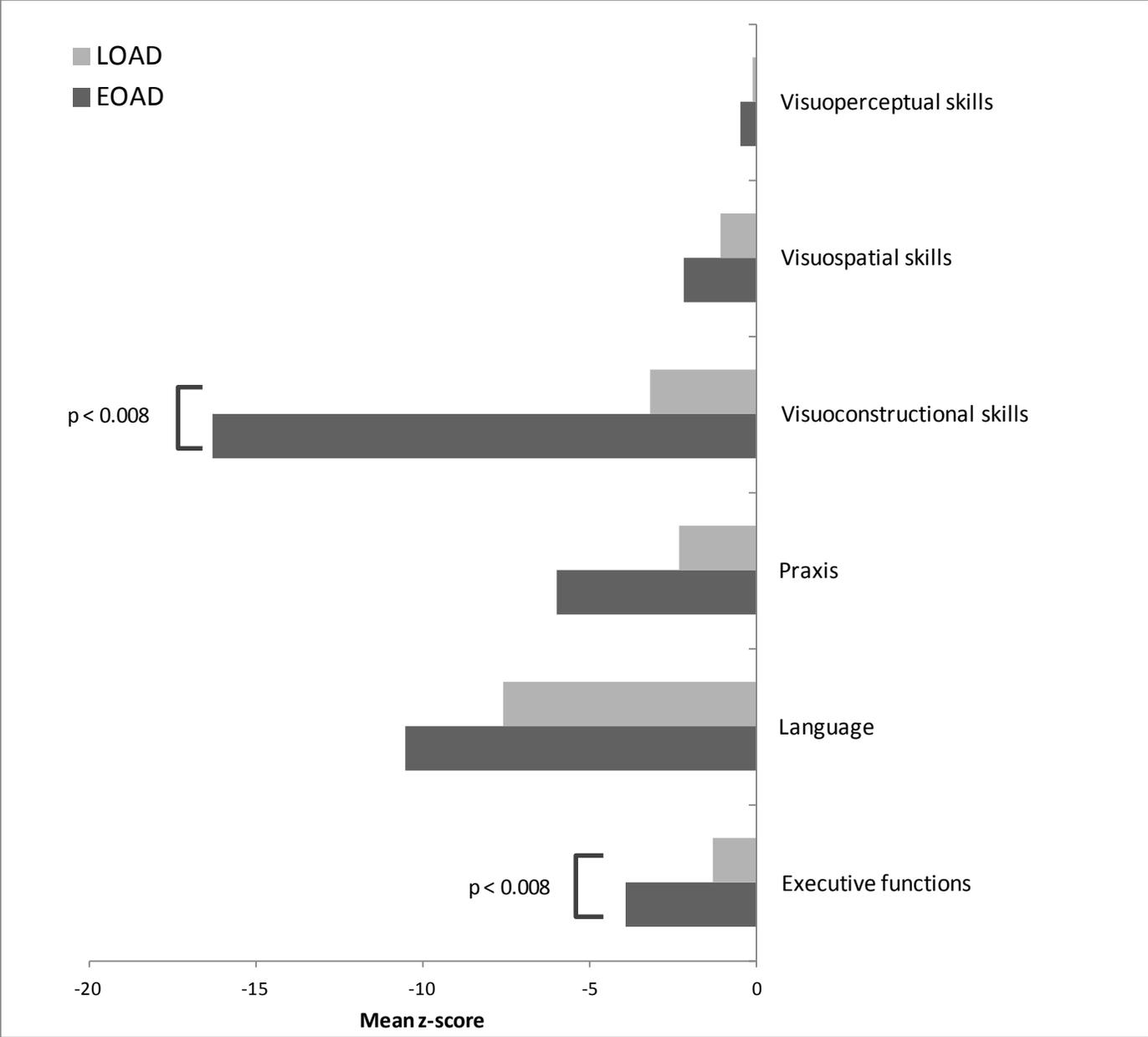


Figure 3. Semantic performance of EOAD (top row) and LOAD (bottom row) groups and their respective control groups on the TOP 10. Results show that LOAD patients were impaired both on the semantic free recall and recognition tasks, while EOAD were impaired only on the semantic free recall task. These results suggest a more profound semantic impairment in the LOAD group.

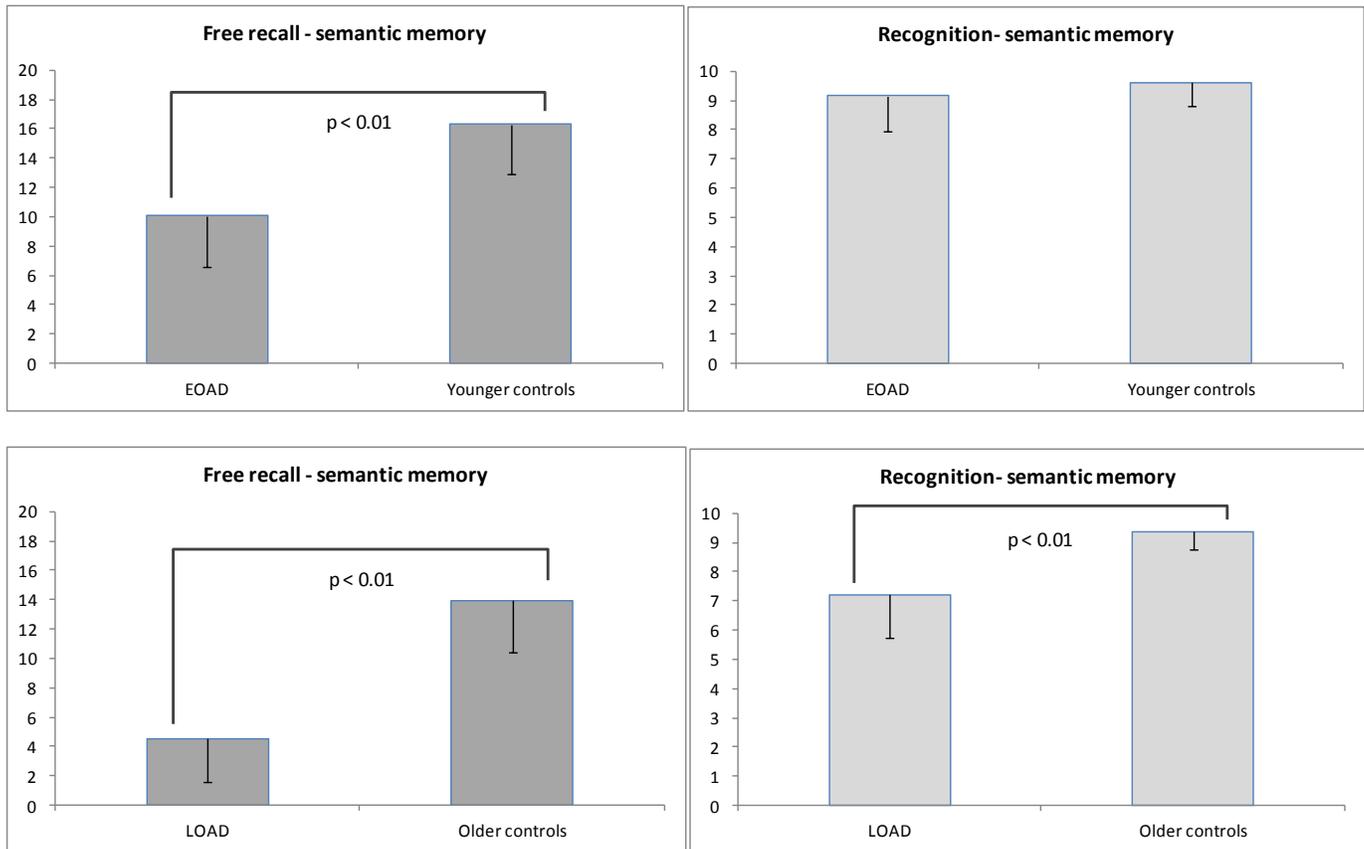


Figure 4A. Voxel-based Morphometry (VBM) results (multiple regression with age, educational level and gender as confounding variables ($p < 0.005$, FDR corrected at the cluster level $p < 0.05$) showing that semantic memory performance (TOP 10 total score) was positively correlated with gray matter volume of left inferior temporal gyrus (BA 21) and left superior temporal pole (BA 38).

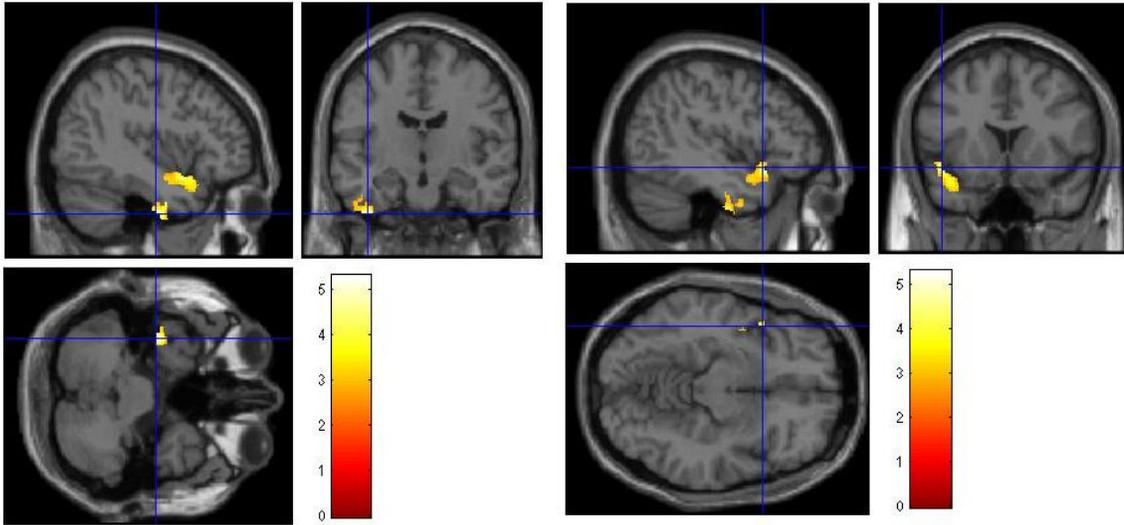
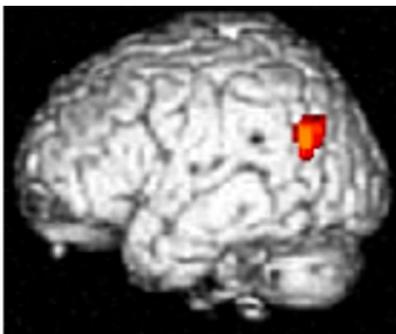


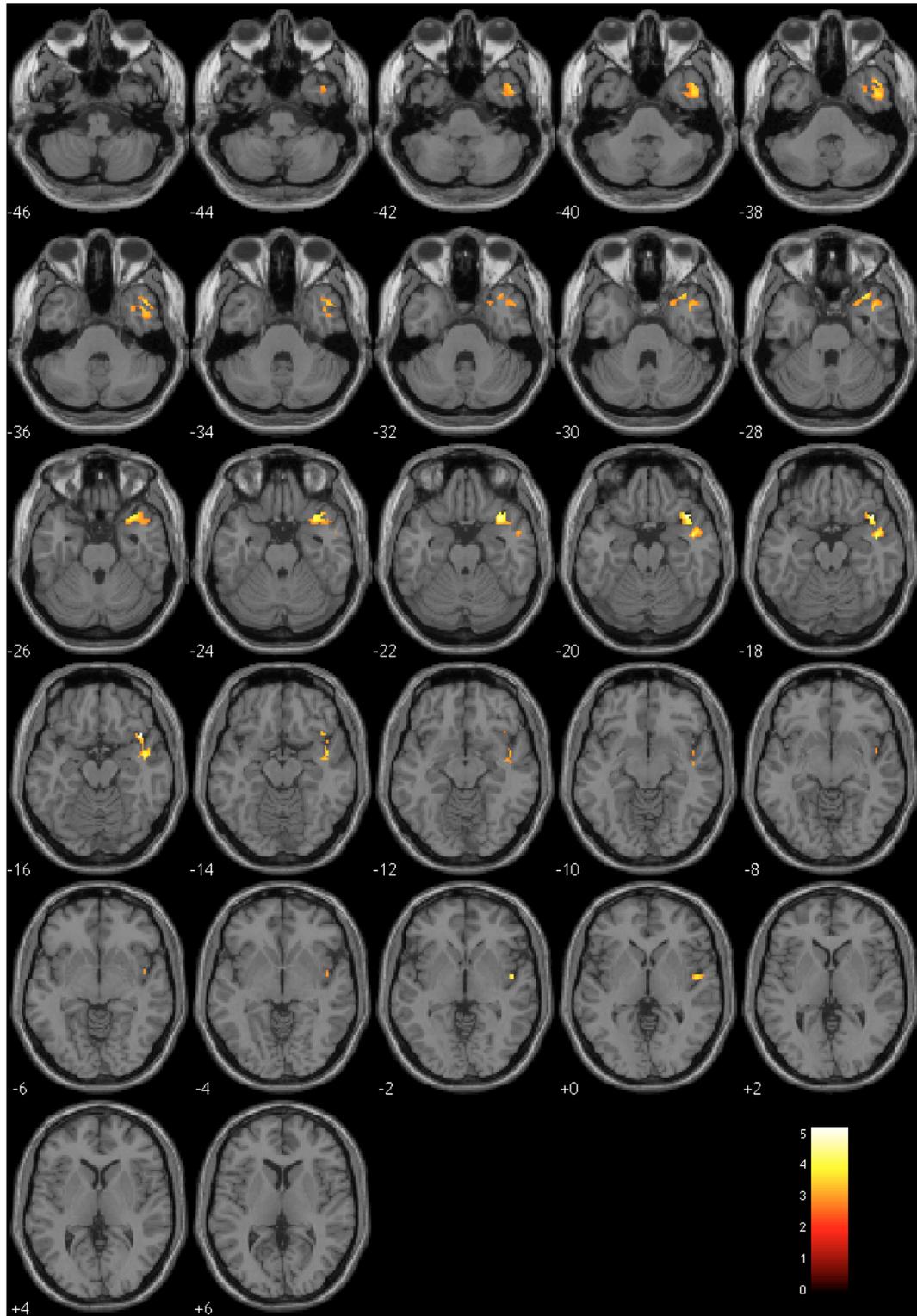
Figure 4B. Semantic memory performance (TOP10 total score) was positively correlated with the PET metabolism of left posterior middle temporal gyrus (Brodmann area 39), a key region of the semantic network.



Supplementary data

Figure S1

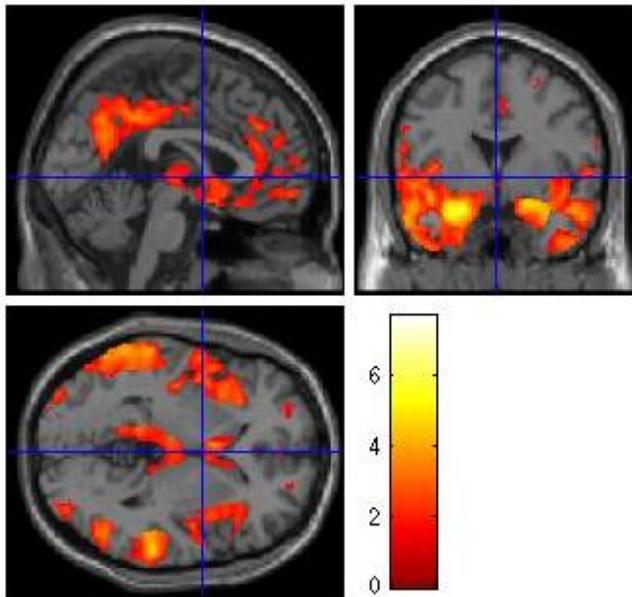
Voxel-based Morphometry (VBM) results ($p < 0.005$, FDR corrected at the cluster level $p < 0.05$) showing a positive correlation between free recall performance on the TOP 10 and gray matter volume of the right temporal pole (BA 38).



Supplementary data

Figure S2

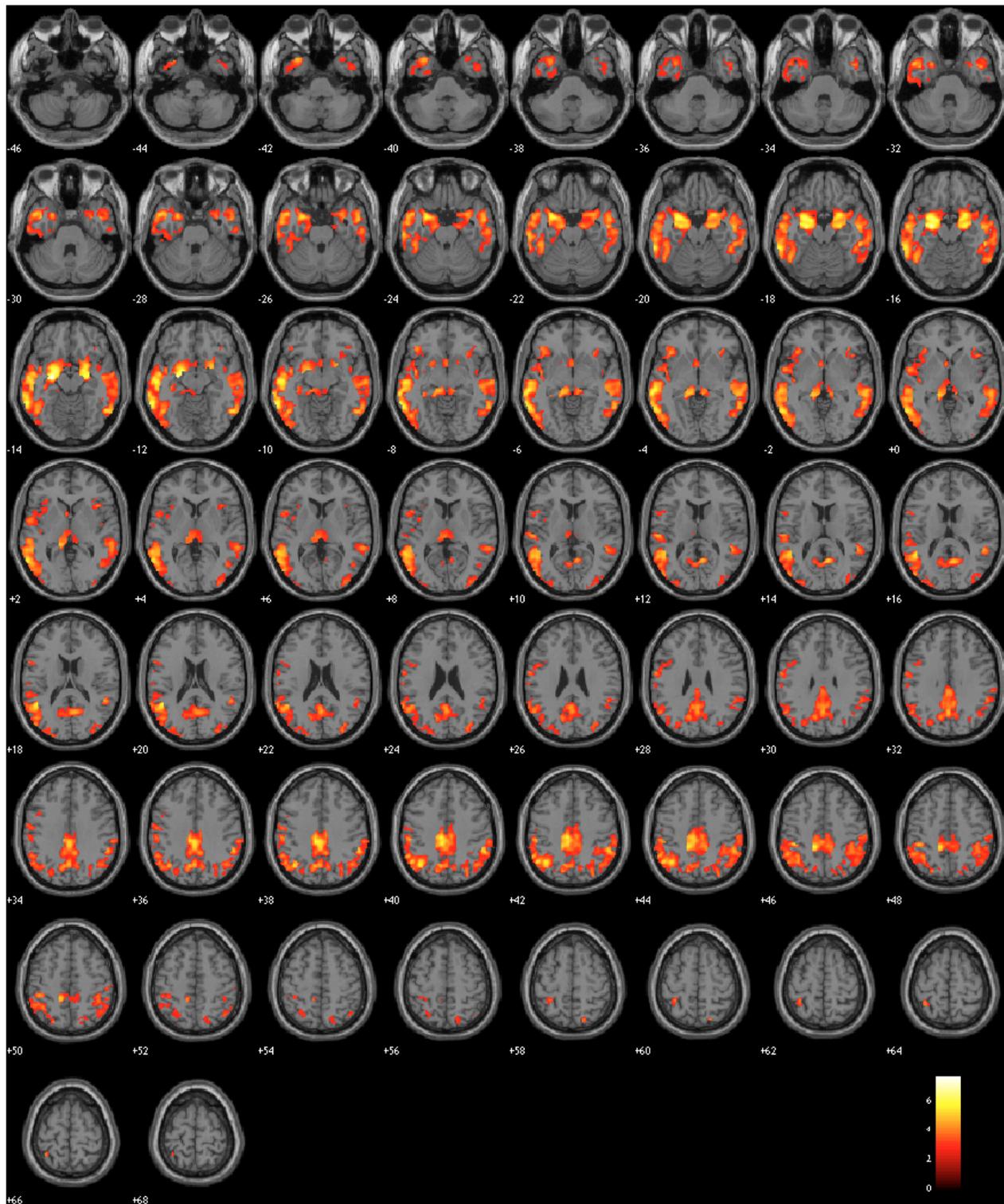
Voxel-based Morphometry (VBM) results (ANOVA with age, educational level and gender as confounding variables) ($p < 0.005$, FDR corrected at the cluster level $p < 0.05$) showing patterns of atrophy in EAOD and LOAD relative to age-matched controls.



Supplementary data

Figure S3A

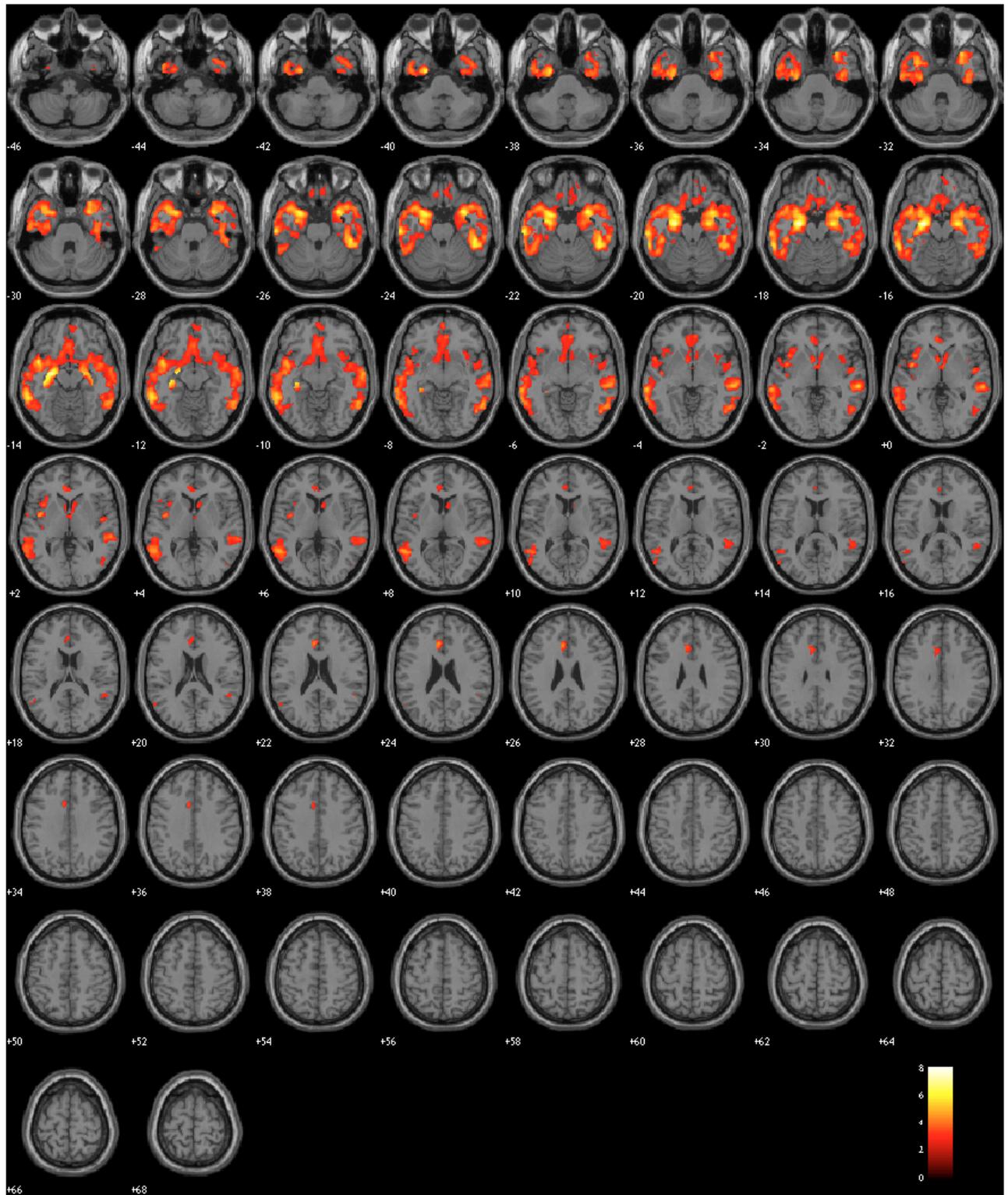
Voxel-based Morphometry (VBM) results ($p < 0.005$, FDR corrected at the cluster level $p < 0.05$) showing patterns of atrophy in EAOD relative to age- and education-matched younger controls. Patterns of atrophy in EOAD affect the temporal lobes, but largely extend into the parietal regions.



Supplementary data

Figure S3B

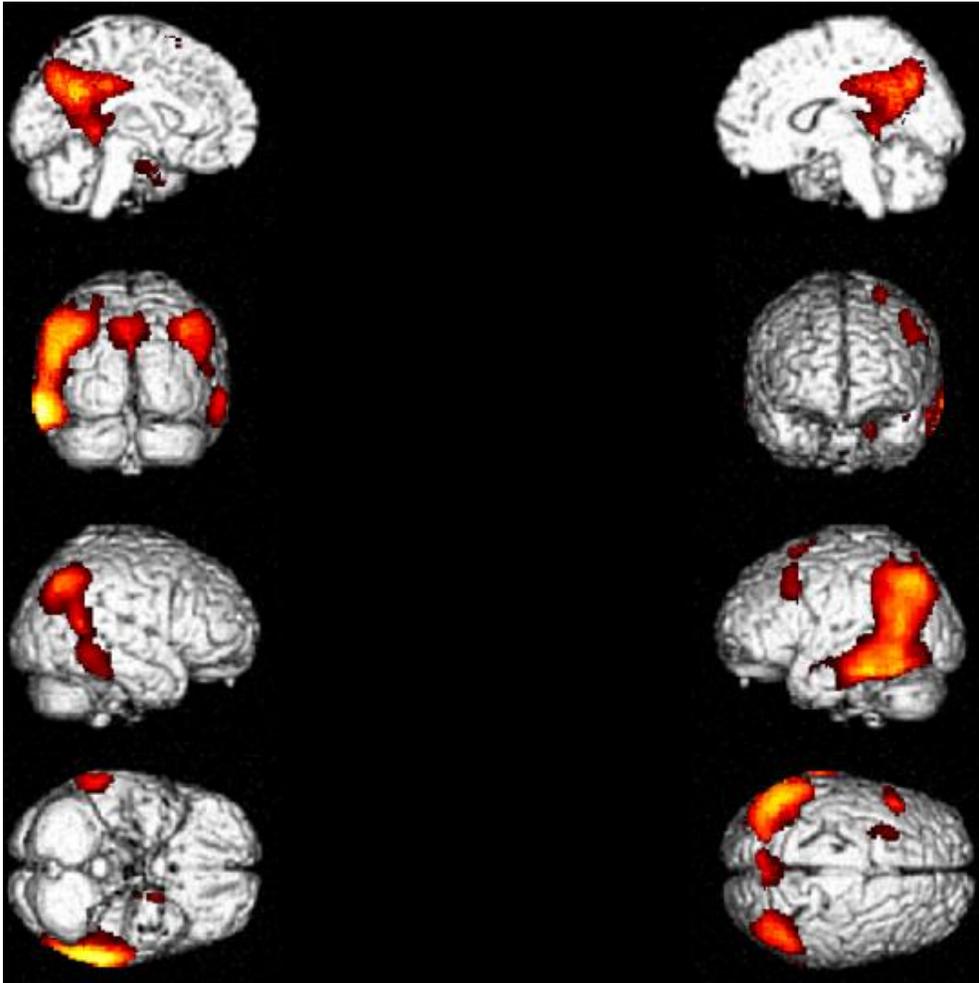
Voxel-based Morphometry (VBM) results ($p < 0.005$, FDR corrected at the cluster level $p < 0.05$) showing patterns of atrophy in LOAD relative to age- and education-matched older controls. Patterns of atrophy predominate mainly in the temporal lobes with a significant but moderate extension into the parietal lobes.



Supplementary data

Figure S4

Whole-brain PET statistical analysis (ANOVA with age, educational level and gender as confounding variables ($p < 0.005$, FDR corrected at the cluster level $p < 0.05$) showing patterns of hypometabolism in EAOD and LOAD relative to age-matched controls.



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