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Verbal learning in Alzheimer's disease and mild cognitive impairment: fine-grained acquisition and short-delay consolidation performance and neural correlates

Sarah Genon[a], Fabienne Collette[a], Chris J.A. Moulin[b], Françoise Lekeu[c], Mohamed Ali Bahri[a], Eric Salmon[a,c,1], Christine Bastin[a,1,*]

[a] *Cyclotron Research Centre, Université of Liège, Liège, Belgium*
[b] *Leeds Memory Group, University of Leeds, Leeds, UK*
[c] *Memory Centre, CHU Liège, Liège, Belgium*

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Abstract

The aim of this study was to examine correlations between acquisition and short-delay consolidation and brain metabolism at rest measured by fluorodeoxyglucose positron emission tomography (FDG-PET) in 44 Alzheimer's disease (AD) patients, 16 patients with mild cognitive impairment (MCI) who progressed to dementia (MCI-AD), 15 MCI patients who remained stable (MCI-S, 4–8 years of follow-up), and 20 healthy older participants. Acquisition and short-delay consolidation were calculated respectively as mean gained (MG) and lost (ML) access to items of the California Verbal Learning Task. MG performance suggests that acquisition is impaired in AD patients even at predementia stage (MCI-AD). ML performance suggests that short-delay consolidation is deficient only in confirmed AD patients. Variations in acquisition performance in control participants are related to metabolic activity in the anterior parietal cortex, an area supporting task-positive attentional processes. In contrast, the acquisition deficit is related to decreased activity in the lateral temporal cortex, an area supporting semantic processes, in patients at an early stage of AD and is related to metabolic activity in the hippocampus, an area supporting associative processes, in confirmed AD patients.

Keywords: Alzheimer's disease; Mild cognitive impairment; Verbal learning; Verbal acquisition; Short-delay consolidation; Brain imaging

1. Introduction

Episodic memory impairment is a key feature of cognitive decline in Alzheimer's disease (AD). Indeed, episodic memory is generally the first cognitive function to be altered even at a predementia stage of the disease. Episodic learning performance can consequently be used to distinguish between normal aging and early impairment in AD (e.g., Grober and Kawas, 1997; Petersen et al., 1994, 1997; Swainson et al., 2001). Typically, episodic learning is assessed with multitrial list-learning tasks. According to a survey carried out in Canada and the United States (Rabin et al., 2005), one of the most frequently used learning tasks in clinical assessment is the California Verbal Learning Test (CVLT; Delis et al., 2000). It has been found to distinguish patients with AD and mild cognitive impairment (MCI) from healthy older adults (Delis et al., 1991; Deweer et al., 1995; Fox et al., 1998; Greenaway et al., 2006; Libon et al., 1998).

In the CVLT, participants are presented with five study-test trials of a target list, followed by one study-test trial of a distractor list, which in turn is followed by immediate and delayed recall trials of the target list. The target list comprises 16 words that can be classified into four semantic categories and is introduced to participants as a grocery list.

* Corresponding author at: Cyclotron Research Centre, University of Liège, Allée du 6 Août, B30, 4000 Liège, Belgium. Tel.: +32 4 366 23 27; fax: +32 4 366 29 46.
E-mail address: Christine.Bastin@ulg.ac.be (C. Bastin).
[1] These authors contributed equally to this manuscript.

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Traditional learning tasks, like the CVLT, can provide separate measures of acquisition and retention. Acquisition performance generally corresponds to the number of words recalled at the last immediate trial or the total number of words recalled across study-test trials. Retention performance usually refers to the score at delayed free/cued recall or at recognition, sometimes compared with the last immediate trial. Learning can be assessed by examining the increase in number of words recalled across study-test trials.

Impaired performance on most of these measures has been frequently reported in AD patients and interpreted as a global verbal learning impairment (see notably Fox et al., 1998). However, these measures only provide a rough estimation of learning abilities. Standard measures of acquisition, such as the number of words recalled at each trial or the total number of words recalled across all trials, overlook subtle changes in the content of the recall, like the gain of items that happens at the expense of loss of other items. For example, a participant may recall "apricot," "plum," "tie," and "jacket" on trial 3 and "apricot," "plum," "chive," and "basil" on trial 4. In this case, a "classical" learning measure indicates that the number of recalled items is four at both trial 3 and trial 4, leading to the interpretation that the participant did not learn any items between trial 3 and trial 4. In contrast, an intertrial analysis of recall reveals that the participant has acquired two words and lost two words. In this case, the participant's learning curve may be flat because the number of gained items compensates for the lost ones, but not because there is an acquisition deficit. This conclusion can only be achieved by performing a fine-grained analysis, based on the content recalled on each trial.

In turn, there may be a bias in the way that the retention performance is traditionally measured because it is based on delayed recall that is mostly dependent on performance on the last study-test trial. For these two reasons, learning measures based on gained and lost items across trials are particularly interesting in AD. Gained access refers to the proportion of items that were not recalled at the previous trial, but that are recalled at the current trial. Total gained access reflects the proportion of words added at each trial and is considered as a measure of acquisition. In free recall, gained access is likely to reflect engagement of several processes such as efficient encoding and controlled access to the trace of the item in memory. Lost access refers to the proportion of items that are not recalled on the current trial, but that were recalled on the previous trial. Lost access reflects an intertrial short-delay consolidation deficit that leads to forgetting of items from one trial to the next (Woodard et al., 1999). Memory consolidation is not a new notion, and it has been widely examined previously (Sara and Hars, 2006), but most of the research on memory consolidation has focused on long-lasting consolidation, which is measured in hours or days, whereas initial consolidation, which is supposed to occur within the first few seconds or minutes after encoding, has received less attention in the scientific literature (Miller and Matzel, 2006). Indeed, initial (i.e., short-delay) consolidation has been rarely investigated in multitrial learning tasks, although such tasks are ideally suited for such an investigation.

Woodard et al. (1999) measured gained and lost access in AD patients, using the Rey Auditory Verbal Learning Test (RAVLT; Rey, 1964). They showed that patients' performance in a list-learning task is characterized by both an acquisition deficit and a consolidation deficit. These results were replicated by Moulin et al. (2004), who used the CERAD verbal episodic memory test (Consortium to Establish a Registry for Alzheimer's Disease; Welsh et al., 1991), reinforcing the idea of a double deficit in learning tasks in AD patients. Moulin et al. also measured gained and lost access in patients with MCI. Their results indicated that these patients already have deficient acquisition and consolidation processes, but as a group, outperform the AD sample.

More recently, Chang et al. (2010) calculated a Learning Efficiency Index (LEI) and a Percent Retention Index (PRI) in MCI patients on the RAVLT. The LEI is derived from the sum of words recalled across the study-test trials, and the authors consider it a measure of acquisition. The PRI reflects the amount of data remembered after the short and long delay, relative to the original recall of words, and is considered as a measure of retention. Thus, these measures reflect standard means to fractionate recall into acquisition and consolidation but do not offer the fine-grained examination of separate contributions of gained and lost access across trials. Nonetheless, Chang et al. showed that some patients with MCI have a specific deficit in acquisition or a specific deficit in retention, whereas others have both deficits. Moreover, by examining the progression rate to AD after 2 years, they found that either impaired acquisition or impaired retention increased the likelihood of future diagnosis of AD and that patients with both impaired learning and retention abilities showed the highest risk of AD conversion. In summary, there has been some attempt in the literature to consider the separate contributions of acquisition and retention of materials in standard learning tasks to better classify and diagnose patients—particularly because they seem to have predictive power. As opposed to typical aggregate measures, such as those reported by Chang et al., others have argued for fine-grained item-by-item analyses of recall that consider patterns of data overlooked in aggregate measures. The novel focus of the current article was to see how such fine-grained analyses of impairment relate to brain function according to neuropsychological models of memory functioning.

At present, the brain alterations underlying deficient acquisition and consolidation processes in AD are unknown. Moulin et al. (2004) hypothesized that the acquisition deficit might be associated with changes in frontal areas supporting executive function, whereas impaired consolidation might be related to hippocampal damage. However, these hypoth-

eses have not yet been tested. In fact, various cerebral alterations might underlie acquisition and consolidation deficits in AD even at an early stage. Regarding the brain correlates of consolidation, according to McClelland et al. (1995), the hippocampus plays a crucial role in learning of new information by providing a site of initial storage of this information. In their complementary-learning-systems (CLS) framework, these authors suggest that the hippocampus is necessary to learning because it allows initial storage of information in a way that avoids interference with the knowledge already acquired in the neocortical system. These assumptions are congruent with the findings of Kramer et al. (2004) that, in AD patients, the hippocampal volume is the best predictor of how well studied words are maintained in memory and recalled after a delay of a few minutes in a list-learning task, even after controlling for initial performance. Accordingly, Kramer et al. suggested that the role of the hippocampus might be specific to the consolidation of new memories.

With regard to acquisition, one is faced with a more complex learning process implicating distinct memory processes. Thus, it is more likely to be supported by a wide brain network commonly associated with episodic memory processes, including prefrontal, parietal, and temporal areas (Spaniol et al., 2009), than by one particular area. In their study, Chang et al. (2010) found that MCI patients with impaired acquisition showed a more widespread pattern of gray matter loss including frontal, temporal, and other cortical regions relative to those with impaired retention. Contemporary views of the neuropsychology of memory posit that, broadly speaking, acquisition involves the recruitment of frontotemporal circuits, with possibly more anterior regions involved in conceptual and strategic processing, and more sensory-affective elements supported by temporal-occipital networks (e.g., Conway, 2009).

The present study concerned fine-grained acquisition and short-delay consolidation in patients at early stages of AD compared with that in control populations and examined correlation with regional brain metabolism at rest. In this context, one objective of this study was to confirm the existence of acquisition and short-delay consolidation deficits in patients with MCI, as shown by Moulin et al. (2004). Patients with MCI are either those at a very early stage of AD that will subsequently convert to dementia or older adults who have relatively isolated cognitive deficits that remain stable across time because they are caused by various factors other than the AD pathological process (Petersen et al., 2001). One criticism of this previous work is that Moulin et al. did not split their MCI patients according to information at follow-up. Therefore, the deficits found by Moulin et al. in MCI cannot be interpreted strictly in terms of predementia characteristics of memory profile in AD. To determine whether both the acquisition and short-delay consolidation processes are impaired at the very early stage of the disease, we compared gained and lost access profiles at the predementia stage of the disease, at stable MCI (after a minimal follow-up of 4 years), at early dementia stage of the disease, and at normal aging. On the basis of the results obtained by Moulin et al. and Woodard et al. (1999), we predicted that acquisition and short-delay consolidation processes should be impaired in AD patients and in patients at a very early stage of AD, whereas these processes might be intact in patients with MCI who will not subsequently meet criteria for AD in comparison with healthy control (HC) subjects.

The second objective of this study was to investigate the brain areas related to gained and lost access performance in each group and more precisely to better understand the cerebral modifications underlying deficient learning in AD. Our hypothesis was that acquisition processes are supported by a brain network comprising prefrontal, temporal (including medial temporal), and parietal regions, and that deficient acquisition in AD would be related to dysfunction in prefrontal and temporal areas, whereas deficient short-delay consolidation processes might preferentially be linked to impaired activity of the hippocampal formation.

To achieve these objectives, we first analyzed gained and lost access applied to the CVLT in patients with MCI who fulfilled or did not fulfill criteria of AD after a minimal follow-up of 4 years, in patients who were diagnosed as AD patients, and in healthy participants. To explore whether gained and lost access performance may be influenced by short-term memory process (i.e., working memory or primary memory), corrected gained and lost access scores were calculated. Corrected gained and lost access scores refer to gained and lost access proportions computed only on items that are part of long-term (secondary) memory, according to the procedure developed by Tulving and Colotla (1970). Second, we mapped standard correlations between resting-state brain ^{18}F-fluorodeoxyglucose (^{18}F-FDG) uptake measured with fluorodeoxyglucose positron emission tomography (FDG-PET) and corrected gained/lost access scores reflecting long-term acquisition and short-delay consolidation, respectively, in the groups of patients and healthy participants, looking at, in each population, which precise region would be preferentially related to memory performance reflected by our measures.

2. Methods

2.1. Participants

Participants were included in a multicenter European study (Network for Efficiency and Standardisation of Dementia Diagnosis or NEST-DD). Participants' data analyzed in this study were all collected in Liège. The sample coming from the NEST-DD study included 44 AD patients, 31 MCI patients, and 12 healthy older adult control subjects. Behavioral data of eight healthy older control subjects were further collected to reach a sufficient number of control participants for statistical analyses. Patients were sent from

Table 1
Demographic and clinical data in studied groups

Demographic and clinical variables	AD	MCI-AD	MCI-S	*Control*
n (M/F)	44 (19/25)	16 (5/11)	15 (11/4)	*20 (10/10)*
Age (years)	71.9 (8.6)	71.4 (5.6)	65.7 (7.4)	*68.5 (7.4)*
Years of education	9.3 (4.0)	11.6 (4.1)	11.9 (4.6)	*10.9 (2.9)*
MMSE score	*19.9 (4.9)*[a]	*24.1 (2.3)*[a]	*25.8 (2.1)*	*29.4 (0.9)*

Key: AD, Alzheimer disease; MCI-AD, patients with very early AD; MCI-S, patients with stable mild cognitive impairment; M, male; F, female; *n*, size. Values are expressed as mean (standard deviation) for age, years of education, and total MMSE score. [a] Significantly lower in patients group than in Control group, $p < .05$.

memory clinics to participate in the study at the Cyclotron Research Centre. Neuropsychological variables collected for the study were not used in the diagnostic process, which was confirmed using clinical interview with the patient and a relative and using documents provided by the memory clinics. AD patients were diagnosed according to the NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association)criteria for AD (McKhann et al., 1984), and FDG-PET was used as a biomarker in the current study. Differential diagnosis was conducted using clinical criteria for frontotemporal dementia (Neary et al., 1998), Lewy body dementia (McKeith et al., 1996), Parkinson disease (Gelb et al., 1999), and depression (APA, 1994). AD patients suffered from mild-to-moderate dementia. Mean disease duration of AD patients was 35.3 ± 25.0 months. MCI patients were diagnosed according to Petersen et al.'s criteria (1999). Follow-up of these MCI patients 4 to 8 years after entry revealed that 15 patients remained stable (MCI-S), whereas 16 met criteria for AD (MCI-AD). Therefore, MCI patients have been "a posteriori" classified in two separate groups (MCI-S and MCI-AD) according to the clinical diagnosis made more than 4 years after the initial cognitive and FDG-PET data acquisition. Control participants had no history of neuropsychiatric problems or memory difficulty. In all participants, vascular risk factors were estimated by the Hachinski score (Hachinski et al., 1975), and major vascular lesions were ruled out by examining neuroanatomical imaging data. Participants who showed mild signs of leukoaraiosis were not excluded. The most frequently used medications, distributed across groups, were antihypertensive treatments (n = 34), benzodiazepines (n = 29), platelet antiaggregants (n = 24), hypolipemiants (n = 19), and antidepressants (mainly serotonin reuptake inhibitors; n = 14). Sixteen AD patients received an acetylcholinesterase inhibitor. All participants had language capacities sufficient for test administration.

In the sample of participants coming from NEST-DD study, a 1-way analysis of variance (ANOVA) showed that groups differed in terms of age ($F(3,83) = 5.1$; $p < .005$). A post hoc analysis (Tukey's test for N different) revealed that the higher age in AD patients compared with control participants accounted for this effect, despite the fact that the difference was not significant ($p = .066$). In the same way, a 1-way ANOVA showed that groups differed in terms of years of education ($F(3,83) = 2.7$; $p < .05$), whereas a post hoc analysis (Tukey's test for N different) did not reveal significant difference between groups. AD patients had poorer Mini-Mental State Examination (MMSE) scores than MCI-AD patients ($p < .05$), MCI-S patients ($p < .005$), and control participants ($p < .0005$). MCI-AD patients differed in terms of MMSE score from control participants ($p < .05$). Other differences in MMSE score were not significant. In the whole sample of participants (i.e., including the data of the eight healthy older control subjects collected "a posteriori"), Student *t* test revealed that control and AD groups did not differ with regard to age ($t(62) = 1.55$; $p = .13$), and a 1-way ANOVA revealed that groups did not differ in terms of education ($F(3,91) = 2.45$; $p = .069$). A post hoc analysis (Tukey's test for N different) confirmed that there was no significant difference between groups regarding education. Each participant (or a close relative) gave informed consent to participate in the NEST-DD study, in line with the Declaration of Helsinki, after approval by the ethics committee of the University Hospital of Liège.

Main demographic and clinical data of the whole sample of participants are summarized in Table 1.

2.2. Cognitive measures

This study is a retrospective analysis of data collected as part of neuropsychological assessment. The episodic learning task is the CVLT (Delis et al., 2000), which was embedded in a longer battery of tests. In this task, participants were first presented orally with a list of 16 words from four semantic categories (list A). Immediately after the list presentation, participants were asked to recall as many words as possible in any order. This procedure was repeated four times. The fifth trial was then followed by a study-test trial of a distracter list, list B, which shared two semantic categories with the critical list. Recall of the distracter list was in turn followed by immediate and delay recall of the critical list A. All participants selected in this study had recalled at least one word at each of the five study-test trials.

To compare corrected gained and lost access measures with other standard measures of learning, three types of

measures were performed on the CVLT data: gained and lost access scores, traditional acquisition and retention scores, and learning scores, as used by Chang et al. (2010).

2.2.1. Gained and lost access measures

In a first time and in line with previous studies, gained access was calculated as the proportion of items correctly recalled on trial *n+1* that had not been recalled on trial *n*, whereas lost access was calculated as the proportion of items not recalled on trial *n+1* that had been correctly recalled on trial *n* (Dunlosky and Salthouse, 1996; Moulin et al., 2004; Woodard et al., 1999). Gained access is a ratio in which the numerator is the number of items gained at trial *n* and the denominator is the number of items that were not recalled on trial *n−1*, which are items that the participant might potentially gain at trial *n*. Lost access is a ratio in which the numerator is the number of items lost at trial *n* and the denominator is the number of items that were recalled on trial *n−1*. Gained access and lost access were calculated for each of the critical study-test trials, starting with trial 2. However, when all 16 words were recalled at one of the five critical study-test trials, gained access to the next trial was equal to 0. In this rare case (n = 1), gained access was calculated only for trials performed before reaching maximum recall to avoid ceiling effects. For this reason, while mean lost access was calculated as the sum of lost access for each trial divided by 5 (the number of study-test trials), mean gained access was calculated as the sum of gained access for each trial taken into account divided by the number of trials taken into account.

In a second time, gained access and lost access were calculated only on items that are considered as part of the secondary memory (SM), according to the procedure used by Tulving and Colotla (1970). Concretely, the length of the intratrial retention interval (ITRI) was first calculated for each recalled item. The ITRI of an item is defined by the number of items presented plus the number of items recalled between the presentation and the recall of the given item. Secondly, each recalled item was classified as part of the short-term memory or the long-term memory component on the basis of the length of its ITRI. That is, if the ITRI of an item is inferior or equal to 7, the given item is considered to be part of the short-term memory component. Conversely, if the ITRI of an item is superior to 7, the given item is considered to be part of the long-term memory component. This method is considered to provide a relatively "pure" measure of the long-term memory part in recall (Watkins, 1974). Gained and lost access scores were then calculated only on the part of the recall that is considered to be based on long-term memory. These scores are called "corrected" gained and lost scores, as opposed to "traditional" gained and lost access scores.

2.2.2. Standard measures of learning

Acquisition is traditionally assessed as the total number of words recalled across trials 1–5. Retention is traditionally assessed as the proportion of words recalled after a delay of a few minutes relative to the number of words recalled at trial 5 (in percentages).

In line with the study by Chang et al. (2010), the LEI and the PRI were also computed. The LEI is the sum of the "learning over trials" (LOT = the sum of words recalled across trials 1–5 minus the number of words recalled at the first trial multiplied by the number of trials) and the number of words recalled at the first trial. To obtain an acquisition score that was independent of short-term memory as corrected gained access, the LEI index was computed only on items that were considered to be part of long-term memory. The PRI is the sum of the short-term percent retention index (STPR = the proportion of words recalled after a short delay relative to the number of words recalled at trial 5) and the long-term percent retention index (LTPR = the proportion of words recalled after a delay of a few minutes relative to the number of words recalled at trial 5).

Correlations between lost and gained access were carried out separately for each group to examine independency of these two measures. ANOVAs were conducted separately for gained access, lost access, traditional acquisition index, traditional retention index, LEI, and PRI to examine differences between groups.

2.3. PET acquisition method

PET examination was performed at entry on all participants included in the NEST-DD study. Data were acquired using a Siemens CTI 951 R 16/31 scanner (Community Tectonics Inc., Knoxville, TN, USA).[18]F-FDG uptake was measured in the resting condition, with eyes closed and ears unplugged, in a quiet and dark environment. Radiotracer (110 to 370 MBq) was administered intravenously by bolus injection. PET data acquisition began 30 minutes postinjection. Scan duration was 20 minutes. Images were reconstructed using filtered back projection, including correction for measured attenuation and scatter using standard software. PET data were not available for the eight supplementary control participants who were not included in the NEST-DD study.

2.4. Image processing

First, the PET images' origins were set using statistical parametric mapping (SPM99, Welcome Department of Cognitive Neurology, London, UK), and those images were manually reoriented with the Montreal Neurological Institute (MNI) PET template in SPM8 (SPM8, Welcome Department of Cognitive Neurology, London, UK). Then, PET data were subjected to an affine and nonlinear spatial normalization onto the SPM8 standard PET brain template. Normalized images were represented on a 79 × 95 × 68 matrix with 2 × 2 × 2-mm voxel size. A mean image was generated from all the normalized images. This mean image served as a brain template specific to the sample of participants. Each PET image was then spatially normalized onto

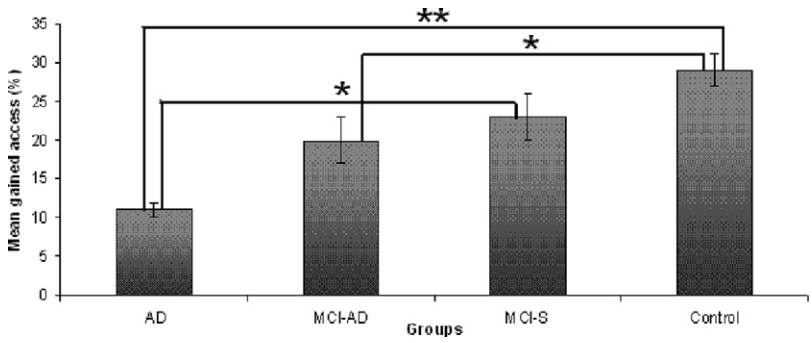

Fig. 1. Mean gained access expressed as proportions in patients and control groups. Error bars represent ±1 standard error of the corresponding mean. Post hoc mean comparisons were conducted using Tukey's test for N different. * $p < .01$, ** $p < .001$.

the brain template created. Finally, images were smoothed with a 12-mm isotropic Gaussian filter. Except origin setting, all image processing steps were carried out using SPM8.

Global activity adjustment was performed using proportional scaling (global activity was chosen because the PET scanner had a limited field of view, and reference regions, such as cerebellum or sensorimotor cortex, were not adequately sampled in all participants). The correlation analyses between learning measures and resting brain ^{18}F-FDG uptake were performed using SPM8. The influence of age and overall dementia severity was controlled by including age and the MMSE score as confounding variables in a single-design matrix. Cognitive–metabolic correlations were performed not only between corrected gained/lost access and brain metabolism but also between LEI/PRI scores and brain metabolism. Only the correlations in the neurobiologically expected direction were conducted, that is, positive correlation for corrected gained access, LEI, and PRI and negative correlation for corrected lost access. The (high) threshold was set at $p < .05$ corrected for multiple comparisons or $p < .001$, uncorrected for multiple comparisons for regions on which we had a priori hypotheses (i.e., temporal and prefrontal regions for corrected gained access and the hippocampus for corrected lost access).

3. Results

3.1. Behavioral data

The main objective of this study was to examine acquisition and short-delay performance and their neural correlates in AD, MCI, and control population. Therefore, statistical analyses have not been performed on other indices of the CVLT to avoid type 1 errors. However, these scores have been calculated and are reported in Table S1 in supplemental data for information.

3.1.1. Traditional gained and lost access scores

Correlation analysis revealed that gained and lost accesses were not significantly correlated (all $p > 0.5$), except in the AD group ($r(44) = 0.54$; $p < .001$). Owing to this correlation in the AD group, lost access was introduced as a nuisance variable in the ANCOVA (analysis of covariance) for gained access and vice versa. ANCOVA revealed a highly significant effect of group ($F(3,90) = 21.48$; $p < .000001$) for mean gained access. A post hoc analysis (Tukey's test for N different) showed that gained access was significantly lower in the AD group than in the control and MCI-S groups, and that it was significantly lower in the MCI-AD group than in the control group. An ANCOVA performed on mean lost access demonstrated a significant effect of group ($F(3,90) = 4.06$; $p < .01$). Post hoc analyses (Tukey's test for N different) showed that marginally significantly greater lost access in AD patients compared with control participants ($p = .052$) accounted for this result.

3.1.2. Corrected gained and lost access scores (calculated on long-term memory items)

Correlation analysis revealed that corrected gained and lost accesses were not significantly correlated (all $P > 0.5$). ANOVA revealed a highly significant effect of group ($F(3,87) = 21.23$; $p < .000001$) for mean corrected gained access. A post hoc analysis (Tukey's test for N different) showed that corrected gained access was significantly lower in the AD group than in the control ($p < .001$) and MCI-S groups ($p < .01$), and that it was significantly lower in the MCI-AD group than in the control group ($p < .01$). Mean corrected gained access scores for each group are illustrated in Fig. 1. An ANOVA performed on mean corrected lost access revealed a significant effect of group ($F(3,87) = 7.07$; $p < .001$). Post hoc analyses (Tukey's test for N different) showed that significantly greater lost access in AD patients compared with control participants ($p < .01$) accounted for this result. Mean corrected lost access scores for each group are illustrated in Fig. 2.

3.1.3. Standard measures of acquisition and retention

An ANOVA revealed a highly significant effect of group ($F(3,91) = 39.30$; $p < .000001$) on traditional acquisition scores. A post hoc analysis (Tukey's test for N different) showed that the traditional acquisition score was significantly lower in the AD group than in the control ($p < .001$) and MCI-S groups ($p < .001$), and that it was significantly

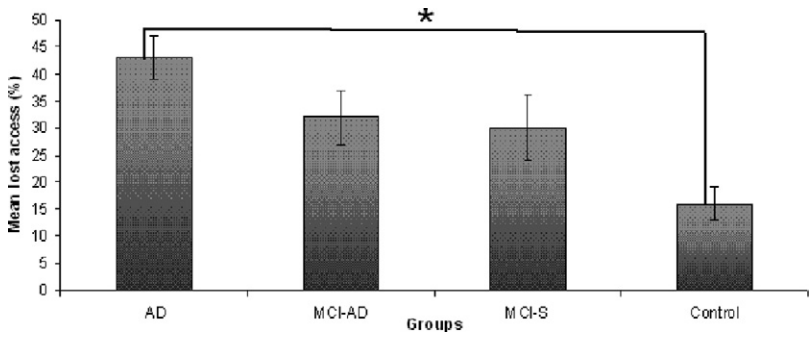

Fig. 2. Mean lost access expressed as proportions in patients and control groups. Error bars represent ±1 standard error of the corresponding mean. Post hoc mean comparisons were conducted using Tukey's test for N different. * $p < .01$.

lower in the MCI-AD ($p < .001$) and MCI-S ($p < .01$) groups than in the control group. An ANOVA on traditional retention scores revealed a highly significant effect of group ($F(3,89) = 20.32$; $p < .000001$). A post hoc analysis (Tukey's test for N different) showed that the traditional retention score was significantly lower in the AD group than in the control ($p < .001$) and MCI-S groups ($p < .01$), and that it was significantly lower in the MCI-AD ($p < .001$) group than in the control group.

An ANOVA revealed a highly significant effect of group ($F(3,87) = 22.02$; $p < .000001$) on LEI scores. A post hoc analysis (Tukey's test for N different) showed that the LEI score was significantly lower in the AD group than in the control ($p < .001$) and MCI-S groups ($p < .01$), and that it was significantly lower in the MCI-AD ($p < .01$) and MCI-S ($p < .01$) groups than in the control group. An ANOVA on PRI score revealed a highly significant effect of group ($F(3,87) = 24.84$; $p < .000001$). A post hoc analysis (Tukey's test for N different) showed that the PRI score was significantly lower in the AD group than in the control ($p < .001$) and MCI-S groups ($p < .001$), and that it was significantly lower in the MCI-AD group than in the control group ($p < .05$).

3.2. Cognitive and metabolic correlations

3.2.1. Corrected gained and lost access

In the control group, the mean corrected gained access proportion was preferentially correlated to metabolism in the anterior part of the left parietal cortex ($Pcor < .05$). In the MCI-AD group, the mean corrected gained access proportion was significantly correlated to metabolism in the right lateral temporal cortex ($Pcor < .05$). In the AD group, the mean corrected gained access proportion was significantly correlated to metabolism in the left posterior hippocampus ($Puncor < .001$) and the left ventral pallidum ($Pcor < .05$). In the MCI-S group, there was no significant correlation between mean corrected gained access proportion and brain metabolism. These results are presented in Table 2 and Fig. 3. In contrast, there was no significant correlation between mean corrected lost access proportion and brain metabolism in any group at the selected threshold.

3.2.2. LEI and PRI

There was no significant correlation between the LEI scores and brain metabolism in our groups. Similarly, there was no significant correlation between the PRI scores and brain metabolism in the AD group, in the HC group, and in the MCI-S group. However, in the MCI-AD group, the PRI score was significantly correlated with brain metabolism in the right lateral temporal cortex ($Pcor < .05$). This result is presented in Table 3 and Fig. 4.

Table 2
Brain metabolic correlates of mean corrected gained access proportion

Participant group	Regions	x	y	z	*z score*
Control	Left anterior parietal cortex	−62	−30	48	*4.49*[a]
MCI-AD	Right lateral temporal cortex	48	−6	−22	*4.96*[a]
		54	−2	2	*4.41*[a]
		58	−12	2	*4.24*[a]
AD	Left posterior hippocampus	−30	−32	−4	*3.52*
	Left ventral pallidum	−4	−2	−8	*4.47*[a]

x, y, z: MNI space stereotactic coordinates of the peaks in mm; $p < .001$ uncorrected; [a] $p < .05$ corrected.

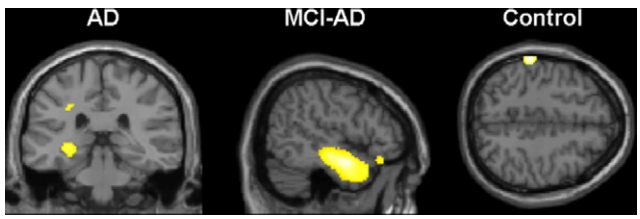

Fig. 3. SPM8 T-map of significant correlations between the mean proportion of corrected gained access and FDG uptake, controlling for the confounding effects of age and dementia severity (MMSE score). The significant correlations are shown as colored voxels superimposed on the MNI template. The right side of the figure corresponds to the right hemisphere. For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.

Table 3
Brain metabolic correlates of PRI scores

Participant group	Regions	x	y	z	*z score*
MCI-AD	Right lateral temporal cortex	66	−4	−14	*5.38*[a]
		58	10	−20	*5.26*[a]
		52	*−10*	*−10*	*4.61*[a]

x, y, z: MNI space stereotactic coordinates of the peaks in mm; [a] $p < .05$ corrected.

4. Discussion

One aim of this study was to examine memory acquisition and short-delay consolidation by means of a novel gained and lost access analysis, obtained in a widely used multitrial list-learning task (CVLT) in normal aging (control) subjects, in patients with stable MCI (MCI-S), in patients at the predementia stage of AD (MCI-AD), and in patients at the dementia stage of the disease (AD). The second aim of this study was to investigate the preferential brain correlates of memory acquisition and short-delay consolidation in each of these groups.

As expected, acquisition, as measured by gained access scores, is impaired in AD and MCI-AD patients relative to HC subjects. This result is congruent with previous studies (Moulin et al., 2004; Woodard et al., 1999). However, the results of the present study go further by showing that impaired acquisition, as measured by gained access scores, is not general in patients with MCI but is specific to those patients who subsequently convert to dementia. In contrast, acquisition, as measured by the traditional acquisition and LEI scores, is impaired in all groups of participants, including MCI-S participants, when compared with the healthy older control subjects. The fact that the LEI and the traditional acquisition measures are sensitive to memory impairment of both the early AD patients and the normal older participants with MCI suggests that these measures are sensitive to heterogeneous cognitive impairments. It is not surprising that the LEI and the traditional acquisition measures yield similar findings because the LEI computation is close to the computation of the traditional acquisition measure in that both measures are aggregation measures. Altogether, these findings argue in favor of gained access as a finer measure of acquisition than traditional acquisition scores, particularly in AD pathology.

In our study, greater lost access was found only in AD patients at the dementia stage of the disease. Previous studies using lost access have reported deficient consolidation in both AD (Woodard et al., 1999) and MCI patients (Moulin et al., 2004). In these studies, gained access and lost access have been calculated on all recalled items (i.e., items recalled from primary memory and items recalled from secondary memory). Therefore, differences in lost access scores might be influenced by the proportion of items that are recalled based on primary memory in the MCI patients. In contrast, retention, as assessed by the traditional retention measure and the PRI, appeared deficient in both the AD and MCI-AD patients but not in the MCI-S participants when compared with the healthy older participants. These findings suggest that lost access and traditional acquisition measures reflect different memory processes. In this view, Woodard et al. (1999) and Moulin et al. (2004) have both shown that although gained access and traditional acquisition scores were correlated in both HC and AD groups, lost access and traditional retention scores were not. For years, confusion has been reigning in the literature about the definition, the measure, and the nature of the memory consolidation process. As mentioned in the introduction, we suggest that lost access refers to initial consolidation, that is, an immediate short-delay consolidation, as opposed to the more frequently discussed long-lasting consolidation process (for a review on the distinction between initial and subsequent consolidation, see Miller and Matzel, 2006). The traditional retention concept seems to refer to different processes, which may be closer to the concept of storage and long-delay consolidation and which are intrinsically linked to the delay retrieval process. In this view, an important issue in the assessment of consolidation after a delay with traditional retention measures is that we cannot distinguish memory loss from retrieval failure of the information in the form in which it has been stored or represented (for details on the changes of the representation system across the consolidation process and preparation for later retrieval, see McClelland et al., 1995 and Miller and Matzel, 2006, respectively). Consequently, the deficit on the traditional retention measures of the AD and MCI-AD patients cannot be interpreted with certainty in terms of decay of the memory trace or memory loss.

In summary, acquisition, as measured by gained access, is impaired severely and very early in AD, whereas initial (i.e., short-delay) consolidation of acquired items, as measured by lost access, seems to be impaired only in the patients at the dementia stage of the disease. The preservation of initial consolidation in the AD patients at a very early stage of the disease, as measured by lost access, contrasts with the deficient retention scores in these patients. According to Chang et al.'s (2010) findings, both acquisi-

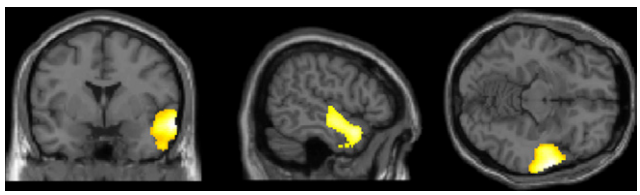

Fig. 4. SPM8 T-map of significant correlations between the PRI score and FDG uptake in MCI-AD participants, when controlling for the confounding effects of age and dementia severity (MMSE score). The significant correlations are shown as colored voxels superimposed on the MNI template. The right side of the figure corresponds to the right hemisphere. For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.

tion and retention measures in people with MCI provide good predictive value of progression to AD, although impaired acquisition had somewhat better predictive power than impaired retention. Altogether, the findings of the present study, combined with existing findings, suggest that the acquisition deficit in list-learning tasks is a robust characteristic of the early cognitive profile in AD.

In the AD group, acquisition was positively correlated to metabolic activity in the left medial temporal structure. This finding is congruent with our hypothesis that the acquisition process would engage a wide network comprising the medial temporal region. Indeed, in AD patients, the volume of the hippocampus has been found to be related to diverse measures of memory in learning tasks, such as immediate recall, learning scores, delayed recall, intrusions, and discriminability (Deweer et al., 1995; Kramer et al., 2004; Laakso et al., 1995; Libon et al., 1998; Petersen et al., 2000). In functional magnetic resonance imaging (fMRI) studies, hippocampal activation is frequently reported in healthy participants both during encoding and retrieval of items (for a review, see Spaniol et al., 2009). Thus, it seems that the hippocampus is the site of a cognitive function that plays a critical role in the different stages of episodic memory tasks.

Contemporary theories of episodic memory, such as those of Conway (2009) and Moscovitch et al. (2005), center on the hippocampus for the formation of episodic memories. In addition, the hippocampus is seen as having a "binding" function in memory (Cohen et al., 1999; Squire, 1992). This hypothesis has been recently reinforced by fMRI data showing that the activation of the hippocampus is modulated by the extent to which relational processing is needed in a retrieval task (Giovanello et al., 2004), and that activation in the hippocampus is related to the relational load of the items (Addis and McAndrews, 2006) and the number of details successfully bound with the memories (Staresina and Davachi, 2008). In the CVLT, many episodic links can be made to optimize the performance at free recall. First, the items must be linked to the context of the list, which is a grocery list. Second, links can be set between the different semantic categories (e.g., fruits and aromatic herbs). Finally, according to their self-memories and knowledge, participants may form arbitrary associations, thus helping to acquire a variable number of the list items into long-term memory. In our study, the preferential relationship between acquisition performance and metabolism in the hippocampus is possibly mediated by the variable ability to arbitrarily link many elements to each other in our AD sample, that is, the decrease of hippocampal metabolism in AD patients with lower rates of acquisition possibly relates to a failure to integrate the items to episodic memory by an associative mechanism. This hypothesis is consistent with the findings that while the hippocampus is a critical structure for successful associative memory in young and healthy subjects, AD patients activate the hippocampus to a significantly lesser extent than healthy subjects during encoding of new associations (Sperling et al., 2003; Sperling, 2007). Thus, decreased metabolism in the hippocampus in AD patients might lead to impaired creation and/or retrieval of associations in memory, accounting for the acquisition deficit of AD patients in list-learning tasks.

In the AD group, acquisition was also positively correlated with metabolism in the left ventral pallidum. This region is an integrative structure in which different neurotransmitters converge. The stimulation and inhibition of these systems in animals have been found to have implications on motivation (Smith et al., 2009). For example, rats in which this structure is chemically inactivated showed diminished willingness to work hard on an instrumental task (Farrar et al., 2008). In addition, the modifications of the neurotransmitter systems that converge in the ventral pallidum have also deleterious effect on learning in animals (Kretschmer, 2000). In humans, patients who underwent left ventral pallidotomy showed acquisition deficits in the CVLT (Riordan et al., 1997; Trépanier et al., 1998) and the RAVLT (Crowe et al., 1998). In addition, left pallidotomy typically results in a decline in verbal fluency (Cahn et al., 1998; Junqué et al., 1999; Lacritz et al., 2000; Riordan et al., 1997; Schmand et al., 2000; Trépanier et al., 1998). More precisely, these patients seem to have difficulties with set shifting and cognitive flexibility in the verbal fluency task (Demakis et al., 2003). Taken together, these findings suggest that the ventral pallidum, as a part of a frontosubcortical system, may be important for normal mental flexibility and initiation. Therefore, the correlation we found between left pallidum and acquisition performance in the CVLT in AD patients might reflect the fact that acquisition performance is modulated either by motivation or by flexibility and initiation abilities in patients at the dementia stage of AD. However, the actual knowledge on the role of basal ganglia in human cognition is too poor to allow us to assume the exact implication of their alteration in AD patients' impaired acquisition.

In MCI-AD patients, significant positive correlations were found between a large part of the right lateral temporal cortex (including the temporal pole) and acquisition performance. The left lateral temporal cortex has been found to be activated not only during semantic processes but also during accurate episodic memory retrieval in healthy adults (Menon et al., 2002). It has also been associated with autobiographical retrieval in young adults (Nyberg et al., 2002), healthy older participants, and AD patients (Meulenbroek et al., 2010). Right lateral temporal cortex has been similarly associated with episodic autobiographical retrieval. Indeed, Bastin et al.(in press) found that the amount of episodic details retrieved for recent autobiographic memories correlated with brain metabolism in the right lateral temporal cortex in both healthy older and MCI participants. Clément et al. (2010) found that during encoding of words, MCI patients showed less activation than healthy older

participants in lateral temporal cortex. Moreover, the authors found that increased pathology severity was associated with smaller activation of this region in MCI patients (Clément et al., 2010). According to Burianova et al. (2010), the middle and the superior temporal gyri are part of a network common to autobiographical, episodic, and semantic retrieval that supports the processing of necessary semantic representations during declarative retrieval. Therefore, on the basis of these previous findings, one may assume that the association between acquisition performance and the metabolism in right lateral temporal cortex in the AD patients at a very early stage of the disease may reflect the fact that the acquisition performance is related to the generation, recovery, and manipulation of semantic information that helps to encode and retrieve target items.

In MCI-S participants, there was no significant correlation between acquisition performance and brain metabolism at the selected threshold. This lack of significant correlation in this group is not surprising because the nature and etiology of cognitive troubles in older people with MCI that remain stable across time are certainly heterogeneous. Indeed, if MCI-S participants differ between each other with respect to their cognitive profile and the locus and nature of their brain modifications, a pattern of association between variations of the metabolism and variations of the learning performance can probably not be found.

Finally, in control participants, our data revealed that acquisition was preferentially related to anterior parietal metabolism. This region is part of a "task positive" attentional cerebral network reported by Fox et al. (2005). The task-positive network refers to areas that routinely exhibit activity increase during attention-demanding cognitive tasks. It is opposed to the task-negative network, which refers to areas that routinely decrease their activities during attention-demanding cognitive tasks. The task-positive regions may support task execution. Fox et al. reported that fluctuations in neural activity in both networks in the resting human brain are roughly anticorrelated, reinforcing the hypothesis that these two networks subserve opposite goals or competing representations. The task-positive network comprises regions in the intraparietal sulcus, inferior parietal lobule, and the precentral area, including the frontal eyes field (FEF), the dorsal lateral prefrontal cortex, the middle temporal cortex, the insula/frontal operculum, and the supplementary motor area (SMA). As the anterior parietal regions are part of the task-positive network, the association between metabolism at rest in this region and the acquisition in control participants can be interpreted in terms of attentional processes. Variations of performance in control participants may be predominantly associated with the ability to engage attention to perform the memory task. In summary, our data in the healthy older participant group suggest that in this population, the acquisition performance in a list-learning task is modulated by abilities that are not specific to episodic memory processes but rely on "basic" attentional resources that are engaged in a range of cognitive tasks.

Surprisingly, the short-delay consolidation process, as measured here by lost access, was not correlated with brain metabolism at the selected threshold in any group. According to Miller and Matzel (2006), the initial consolidation occurs at a synaptic or molecular level. For example, they suggest that the brain-derived neurotrophic factor (BDNF) might play a role in the molecular cascade that underlies initial consolidation. If the initial consolidation consists, indeed at the brain level, in a complex molecular process in which various proteins, such as the BDNF, are involved, it is possible that deficient initial consolidation process cannot be approached by cognitive–metabolic correlations. Further studies using different methodologies would be necessary to determine the neural substrates of this process in AD.

No significant correlations could be found between the LEI scores and brain metabolism in our groups. The fact that the correlation analysis between gained access scores and brain metabolism yielded significant results, whereas the correlation analysis between LEI scores and brain metabolism did not yield any significant results, brings additional evidence that gained access is a finer measure of the acquisition process than the acquisition scores that are computed on the total number of recalled items. Similarly, no significant correlation could be found between PRI scores and brain metabolism in the AD, MCI-S, and control groups. However, in the MCI-AD group, the PRI scores were found to be related to brain metabolism in the right lateral temporal cortex. The metabolism in the right lateral temporal cortex has also been found to be correlated with the gained access scores in these patients. As mentioned previously, the lateral temporal cortex seems to support the manipulation of semantic concepts or representations. The fact that the proportion of items recalled after a delay correlated with metabolism in this region in the patients at an early stage of AD suggests that their performance is related to the ability to manipulate the semantic concepts. Because, as mentioned earlier, the retention score is not a "pure" measure of the consolidation process, the relation between semantic abilities and PRI scores can be interpreted in various ways. First, one may assume that the retention performance is related to the ability to store the information according to the semantic concepts inherent to the information. Second, one may assume that the retention score is related to the ability to retrieve the information by using semantic representation at the time of the recall. Because the semantic manipulation seems to be already involved at the time of acquisition, it is likely that it plays a role in all stages of the learning process: acquisition of new information, storage/consolidation, and retrieval of stored information. The presence of significant correlations between metabolism in the lateral temporal cortex and the acquisition and retention performance in the MCI-AD group does not mean that learning performance and lateral temporal metabolism

are related only in these patients, but rather suggests that the learning performance of these patients is prominently related to their lateral temporal metabolism and therefore to their abilities to engage semantic manipulation.

In conclusion, we characterized the learning profile of AD patients before and during the dementia stage by using fine-grained intertrial analysis of recall. In addition, we showed that acquisition, measured by gained access, was related to metabolism in different brain areas, depending on the population. Our behavioral data of gained access confirm that acquisition is impaired in AD, even at a very early stage. We anticipated acquisition to be related to temporal and prefrontal brain areas, which participate in an episodic memory network (Spaniol et al., 2009). As expected, impaired acquisition in demented patients was preferentially related to metabolic changes in the hippocampal formation, possibly suggesting an impairment of binding processes in the dementia stage of the disease. Moreover, in AD patients at a very early stage of the disease (MCI-AD), acquisition performance was related to the metabolism in the lateral temporal cortex, a region supporting manipulation of semantic concepts. Our data also revealed that brain areas positively associated with gain access in control participants were predominantly the anterior parietal regions, which participate in a "task-positive" attentional cerebral network. Thus, these results suggest that deficient acquisition in AD patients is primarily related to damage to the hippocampus, a vital structure in the creation of memory traces in episodic memory. In these patients, the variations in the metabolic activity in the lateral temporal and parietal areas may be less associated to acquisition scores because these regions cannot play their role in semantic monitoring and attentional/executive functioning, respectively, when the prerequisite of an acquisition process is not met (i.e., the integrity of the memory trace). In contrast, in AD patients at a very early stage of the disease, the hippocampus might support minimal associative process and thus variations of acquisition performance would be related to the semantic manipulation abilities. Finally, in normal aging, the hippocampus would be sufficiently efficient in its associative role, leading to normal acquisition performance, which varies predominantly according to attentional processes.

Disclosure statement

There is no actual or potential conflict of interest for any author concerning this manuscript.

None of the reported data have been published. Additionally, they are not under current consideration by another editor and will not be before an editorial decision is made.

Appropriate approval and procedures were used concerning human subjects. Indeed, according to the Declaration of Helsinki, all participants gave their written consent to participate in the study, which was approved by the ethics committee of the University Hospital of Liège.

All authors of the article have read and approved the final version of the manuscript and validated the accuracy of the data.

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Appendix. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neurobiolaging.2012.04.004.

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