Original Research Article

Structural Neuroimaging of Concomitant Depressive Symptoms in Amnestic Mild Cognitive Impairment: A Pilot Study

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Key Words

Aging · Alzheimer's disease · Depression · Entorhinal cortex · Hippocampus · Mild cognitive impairment · Prodromal phase · Magnetic resonance imaging · Medial temporal lobe

Abstract

Late-life depression (LLD) and amnestic mild cognitive impairment (aMCI) can both denote prodromal Alzheimer's disease. While the two concepts share common clinical features, differential diagnosis between them is crucial. The objective of this pilot study was to explore differences in terms of the hippocampal (HC) and entorhinal cortex (EC) volume reduction between LLD and aMCI patients with (aMCI/D+ group) or without (aMCI group) depressive symptoms. Six LLD, 6 aMCI, and 6 aMCI/D+ participants were assessed using a structural magnetic resonance imaging protocol. Manual segmentation of HC and EC was carried out. The results of volumetric comparisons suggest that the HC was larger in aMCI/D+ and LLD subjects compared to aMCI participants. The left EC mean volume was slightly lower in aMCI/D+ subjects. Power analyses revealed that 36 participants per group would suffice to confirm these findings. Overall, these pilot findings suggest that aMCI can be distinguished from LLD based on cerebral atrophy measures, and that HC and EC atrophy in aMCI varies according to the presence or absence of depressive symptoms.

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Introduction

Alzheimer's disease (AD) has become a major public health issue, given that age is a primary risk factor and life expectancy is increasing in developed countries worldwide [1]. There is evidence that AD pathophysiological processes begin years before the diagnosis of clinical dementia [2]. Consequently, much research has focused on the transitional state between normal aging and early AD [3–5], often referred to as prodromal AD. Findings have shown that prodromal AD can be identified in older adults with amnestic mild cognitive impairment (aMCI) or patients with late-life depression (LLD).

The concept of aMCI generally applies to older adults showing cognitive decline that is greater than that expected for age and education level. Specifically, persons with aMCI present a cognitive complaint and show impaired episodic memory (with or without deficit in another cognitive domain) as indicated by age- and education-stratified norms. As a rule, cognitive symptoms are not severe enough to meet the criteria for dementia or to significantly interfere with activities of daily living [6, 7]. Nevertheless, several studies showed that aMCI is closely related to AD. In fact, it is generally assumed that elders with aMCI have approximately a tenfold increased risk of developing AD compared to healthy older adults [7, 8].

LLD refers to a mood disorder occurring in aging, the diagnosis of which is generally based on DSM-IV-TR [9] criteria for major depressive episode. LLD encompasses both late-onset and early-onset cases [10]. The neuropsychiatric symptoms of this syndrome can include depressed mood, anhedonia, sleep disturbances, psychomotor agitation or retardation, fatigue or loss of energy, feeling of worthlessness or guilt, diminished ability to think, and thoughts of death. Many patients with LLD also have cognitive deficits, and these can affect episodic memory, executive functions, information processing speed, and visuospatial skills [11, 12]. Similar to aMCI, research has shown that LLD is associated with subsequent dementia [13]. More precisely, Byers and Yaffe [14] reported that, of 12 prospective studies, 6 found evidence supporting a two- to fivefold increased risk of dementia associated with LLD [15–20].

There are several associations between aMCI and LLD. As mentioned above, both conditions may denote prodromal AD. Further, beside their cognitive deficits, up to 75% of elders with aMCI have concomitant neuropsychiatric symptoms, the most prevalent being depression, apathy, anxiety, irritability, and sleep disturbances [21, 22]. In addition, persons with aMCI or LLD may have similar cognitive and neuropsychiatric symptoms. That being said, differential diagnosis between aMCI and LLD is imperative because the pathophysiological mechanisms involved in each syndrome likely differ [10]. Surprisingly, and as emphasized by experts convened by the National Institute of Mental Health [23], investigations of these conditions have long proceeded along separate tracks; thus, there is a crucial need to carry out more studies comparing aMCI and LLD patients. These kinds of studies will help clarifying the common and distinct mechanisms involved in these two conditions [23], and this, in turn, will put forward some sources of heterogeneity of the prodromal phase of AD.

Some authors attempted to differentiate the cognitive profile of aMCI and LLD patients. Research on this topic revealed that, to some extent, LLD patients can encode, consolidate, and recognize items, but their self-retrieval processes are significantly impaired [24]. On the other hand, the memory impairment in persons with aMCI alters virtually all memory processes [25]. Overall, the phenotypic differences that were evidenced in previous studies suggest the existence of distinct underlying pathophysiological mechanisms between aMCI and LLD syndromes. More precisely, considering that memory processes are not equally affected in aMCI and LLD, there could be differences between these conditions regarding the integrity of medial temporal lobe (MTL) structures. A recent literature review has revealed that no study has yet addressed this issue [26].

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Besides the need for studies comparing aMCI and LLD patients, it is also necessary to clarify the role of depressive symptoms in older adults meeting the aMCI criteria. At this time, it is uncertain whether aMCI with concomitant depressive symptoms (aMCI/D+) should be considered as subclinical LLD or if it corresponds to a particular aMCI condition with higher risk of progression to AD [10, 27]. This question can hardly be answered as most previous studies on aMCI excluded persons with aMCI/D+. Thus, knowledge on the nosological status of elders with aMCI/D+ is actually very scarce. Systematic investigation of these patients and their comparison with LLD or aMCI patients with no, or few, depressive symptoms (hereafter named aMCI) could help clarifying the importance of assessing depressive symptoms in the diagnosis of prodromal AD [23].

Two studies have demonstrated that depression was a potentially useful clinical marker for identifying MCI subjects who are more likely to progress to AD [28, 29]. To date, however, few studies compared aMCI and aMCI/D+ patients. One work revealed that the risk of developing AD is doubled in persons with aMCI/D+ compared to their aMCI counterparts [30]. A recent 2-year study revealed that subjects with aMCI/D+ stable over time demonstrated a decline on select neuropsychological tests and had higher rates of conversion to AD (62%) compared with stable aMCI subjects [31]. At the semiological level, our studies revealed that aMCI and aMCI/D+ subgroups can be distinguished from each other on tasks assessing episodic memory, semantic memory, and executive functions [32, 33]. An important question is whether the differences between the episodic memory impairment of aMCI/D+ and aMCI patients are associated with neurobiological differences. A related question is to what extent aMCI/D+ and LLD are similar or different from a neurobiological perspective.

Neuroimaging could further elucidate the underlying neurobiological correlates of aMCI, aMCI/D+, and LLD semiology. The strong correlation between MTL volumes and episodic memory performance is well known [34]. Furthermore, the earliest AD-associated brain alterations, according to histopathological staging [35], occur in MTL structures such as the hippocampus (HC) and the entorhinal cortex (EC). Atrophy of HC and EC is present in aMCI patients [36–40] and has been associated to memory loss in these subjects [36, 37, 41]. In aMCI, the HC helps predicting progression to dementia [37, 42]. However, the EC is a better predictor of AD-related neurodegeneration [36, 43, 44]. In comparison to the HC, the EC appears to be less affected by normal aging [45]. The EC thus is a crucial structure to evaluate. In LLD subjects, atrophy of HC has also been documented [46], but no study measured the EC volume in these patients yet [47].

It is important to emphasize that all magnetic resonance imaging (MRI) studies assessing MTL volumes in aMCI or LLD have been conducted independently. Thus, it is difficult to estimate whether or not the degree of HC and atrophy is comparable between aMCI and LLD patients. Furthermore, to our knowledge, no study has evaluated EC atrophy in LLD and aMCI/D+. Taking into consideration that the EC is a better predictor of cognitive decline than the HC [48, 49], it could represent an opportunity to differentiate prodromal AD syndromes, especially as neuropsychological differences exist between them. Henceforth, there exist no comparative MRI data between these groups. As the neurobiological mechanisms relating to depression and cognitive impairment in older adults are poorly understood [23], it is critical to obtain accurate biomarker data such as the HC and EC to compare aMCI, aMCI/D+, and LLD patients. Differentiating these subgroups at high risk of developing dementia at the neurobiological level could help in the development (or adaptation) of more personalized pharmacological and non-pharmacological therapies [50].

The principal objective of this study is to investigate differences in HC and EC volumes between aMCI, aMCI/D+, and LLD individuals. We hypothesized that HC and EC volumes were less reduced in aMCI/D+ and LLD versus aMCI patients as aMCI/D+ appears to be closer to LLD and aMCI closer to AD from a nosological point of view. In this article, we re-

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port our results from a pilot study aimed at providing evidence towards larger-scale feasibility. Our secondary objective is to formulate recommendations in order to improve the design of future MRI studies in aMCI, aMCI/D+, and LLD populations.

Methods

Participants

This study included 6 aMCI, 6 aMCI/D+, and 6 LLD patients. All subjects gave informed written consent to participate in the study. The Ethics Research Committee of the Institut universitaire en santé mentale de Québec approved the study.

Experienced clinicians (general practitioners, neurologists, geriatricians, or psychiatrists) from Québec City (Qué., Canada) referred the patients. The diagnoses of aMCI or LLD were made by the referring clinician and confirmed by the research team based on the results from clinical and cognitive instruments (see below).

Participants were 59–80 years old and their mother tongue was French. Patients with LLD were diagnosed using the DSM-IV-TR [9] criteria for major depression disorder. Participants from the aMCI and aMCI/D+ groups all met the following criteria for single- or multiple-domain aMCI as proposed by Petersen [6]: (1) memory complaint, preferably corroborated by an informant; (2) objective memory impairment for age; (3) essentially preserved general cognitive function; (4) largely intact functional activities, and (5) not demented. None of the participants had dementia based on clinical assessment and the referring clinician judgment. The two aMCI subgroups were identified based on the participants' score on the Geriatric Depression Scale (GDS) [51]. In aMCI, the GDS is a reliable screening tool for depression, with sensitivity and specificity values of 95 and 67%, respectively, when a cut-off score of 8 is applied [52]. We identified participants as having aMCI/D+ if they had a score of 8 or more on the GDS. Participants were identified as aMCI (with few or no depressive symptoms) when the GDS score was below 8. Finally, one must note that in the current study depression in aMCI/D+ patients was subclinical (i.e. it did not meet any DSM-IV mood disorder criteria).

For all participants, the exclusion criteria were: (1) history of traumatic brain injury; (2) presence of significant vascular risk factors (i.e. score higher than 7 on the Hachinski scale [53]); (3) former intracranial surgery; (4) history of neurological disorder of cerebral origin, including dementia, or associated with another demented state (e.g. multiple sclerosis, parkinsonism, frontotemporal dementia); (5) unstable metabolic or medical condition (e.g. uncontrolled diabetes, hypothyroidism); (6) general anesthesia in the last 12 months, and (7) contraindications to MRI. A specific exclusion criterion for aMCI/D+ and aMCI was a history or actual diagnosis of major depression disorder [9].

During the study, aMCI participants took neither antidepressants nor benzodiazepines. Antidepressants were taken by 5 aMCI/D+ subjects (3 selective serotonin reuptake inhibitor, 1 serotonin-norepinephrine reuptake inhibitor, and 1 serotonin antagonist and reuptake inhibitor) and 5 LLD subjects (4 selective serotonin reuptake inhibitor and 1 tricyclic antidepressant). Benzodiazepines were taken only by 1 aMCI/D+ and 2 LLD subjects. Antipsychotic medication was taken by 1 LLD participant.

Neuropsychological and Clinical Assessment

Senior neuropsychology research assistants, supervised by one of the authors (C.H.), evaluated the participants over a 120-min session to provide quantification of clinical characteristics, cognitive functioning, and functional status.

Following a semi-structured interview to document medical history, drug prescriptions, and sociodemographic data, we used the Montreal Cognitive Assessment (MoCA) [54] to

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evaluate general cognitive functioning. The Hachinski ischemic scale [53] was used to assess vascular risk factors. We administered the Questionnaire de plainte cognitive [55] and the GDS [51] to assess cognitive complaints and depressive symptoms, respectively. We examined episodic memory using the Rappel libre/rappel indicé à 16 items [56], a free/cued word recall test used as a measure of verbal learning in French-speaking populations; the procedure of the Rappel libre/rappel indicé à 16 items is similar to the Free and Cued Selective Reminding Test [57]. Visuoconstructional abilities were evaluated by the copy of the Rey-Osterrieth Complex Figure Test [58], and early visuoperceptual processes were assessed with the size-match task of the Birmingham Object Recognition Battery [59]. Subjects also performed the Coding subtest of the Wechsler Adult Intelligence Scale [60] to estimate information processing speed. To examine language capabilities, participants performed a verbal fluency task using Letter (T-N-P) and Category (animals) conditions [61] as well as the 15-item version of the Boston Naming Test [62]. Semantic memory and executive functions were assessed using the picture version of the Pyramids and Palm Trees Test [63] and the California Stroop Test [64], respectively. Finally, participants were administered the Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory [65] to measure activities of daily living.

MRI Protocol

One aMCI/D+ patient was diagnosed with AD by a medical doctor 2 months after his MRI examination. This participant was not excluded from this study because he was still considered in the prodromal phase of AD at the time of the MRI exam.

All MR images were acquired on a 3.0-Tesla Phillips at IRM Québec in Québec City (Qué., Canada). A standardized ADNI imaging protocol [66], including T1-weighted 3D MP-RAGE sagittal volumetric acquisition (repetition time 69 ms, echo time 3.13 ms, flip angle 8°, slice thickness 1 mm, in-plane size 1×1 mm, no inversion, whole head coverage), was used. We co-registered the images to the ICBM152 pseudo-Talairach template space [67]. Then, an experienced tracer (S.P.) manually segmented the HC and EC on coronal slices using validated protocols by Pruessner et al. [68, 69]. The operator was blinded to all clinical data and diagnostic categories. Reported inter- and intrarater intraclass reliability coefficients for this protocol are as follows: right HC 0.94/0.91, left HC 0.86/0.94, right EC 0.93/0.91, and left EC 0.95/0.96.

Statistical Analyses

We performed statistical analyses using SAS 9.2 for Windows (SAS/STAT and SAS/Graph software; SAS, Cary, N.C., USA). First, parametric testing (ANOVA) was done to compare the sociodemographic and clinical characteristics of the aMCI, aMCI/D+, and LLD groups, and was further confirmed by non-parametric testing (Wilcoxon). Second, we considered a one-way ANOVA (parametric and non-parametric) design to evaluate volumetric differences of the left and right HC and EC between the groups. Third, in order to study the effect of certain variables on volumetric measurements, we used a regression model. The fitted model was: $\hat{Y} = b_0 + b_1.age + b_2.education + b_3.hachinski + b_4.sex$, where b_0, b_1, b_2, b_3, and b_4 are the estimated regression coefficients. Variables in this model (i.e. age, education, Hachinski score, and sex) were included because of their significant impact on HC and EC volumetry. Given the small number of subjects, we used classical and bootstrap regression. For bootstrap regression, a model based on 10,000 re-sample drawings with replacement from the original data was created to estimate regression coefficients. We then obtained predicted and residual values from both classical and bootstrap regressions. Finally, within the framework of a pilot study, we calculated the number of subjects necessary to detect significant differences between groups using an alpha value of 5% and a nominal power of 80%.

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Table 1. Means ± SD and significance levels of the demographic and clinical characteristics of the participants

Measure	aMCI (n = 6)	aMCI/D+ (n = 6)	LLD (n = 6)	p value
Participant characteristics				
Gender (female/male)	1/5	5/1	5/1	0.023
Age, years	70.7 ± 3.3	71.7 ± 7.7	71.5 ± 8.0	0.962
Education, years	16.0 ± 5.0	13.3 ± 5.6	15.8 ± 4.3	0.557
Depressive symptoms				
GDS	4.8 ± 1.9[b, c]	11.2 ± 1.5[a]	14.2 ± 4.3[b]	0.0001
IADLs				
ADCS-ADL patients	40.0 ± 2.8	41.0 ± 2.7	38.40 ± 3.05	0.492
ADCS-ADL caregivers	62.5 ± 3.5	56.2 ± 10.1	60.8 ± 5.2	0.586
Vascular risk factors				
Hachinski	1.7 ± 2.0	1.5 ± 1.4	2.5 ± 0.8	0.597
General cognitive state				
MoCA	24.7 ± 2.9	22.5 ± 3.8[c]	27.0 ± 1.2	0.045
Executive functions				
Stroop D-KEFS (errors)	1.7 ± 2.2	3.2 ± 4.7	1.7 ± 1.9	0.649
Information processing speed				
Digit Symbol score (WAIS-III)	56.7 ± 16.7	47.2 ± 13.7	49.3 ± 15.5	0.546
Visuoconstruction				
Rey-Osterrieth Complex Figure copy score	28.5 ± 5.4	28.7 ± 5.5	31.2 ± 3.6	0.619
Language				
Boston Naming Test score (15 items)	13.0 ± 1.3	12.0 ± 1.4	12.3 ± 1.75	0.512
Lexical evocation	33.0 ± 10.6	23.8 ± 6.5	32.5 ± 9.5	0.223
Semantic evocation	14.8 ± 6.0	14.8 ± 2.3	13.8 ± 6.2	0.928
Semantic memory				
Pyramids and Palm Trees Test	48.7 ± 1.9	48.0 ± 2.2	49.0 ± 1.3	0.659
Episodic memory				
RL/RI-16 free recall[1]	6.5 ± 3.2	5.4 ± 2.3	8.9 ± 2.1	0.089
RL/RI-16 total recall[2]	11.3 ± 3.6	11.7 ± 1.7	14.1 ± 2.5	0.205
RL/RI-16 delayed free recall	5.7 ± 4.4	6.2 ± 2.0	9.8 ± 2.7	0.078
RL/RI-16 total delayed recall	11.5 ± 4.9	11.8 ± 2.2	14.3 ± 1.8	0.284

IADLs = Instrumental activities of daily living; ADCS-ADL = Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory; WAIS-III = Wechsler Adult Intelligence Scale-third edition; RL/RI-16 = épreuve de rappel libre/rappel indicé à 16 items. [1] This score was calculated as the mean number of words retrieved over the three free-recall trials. [2] This score was calculated as the mean total number of words retrieved on all free-recall plus cued-recall trials.

[a] p < 0.05 compared to aMCI; [b] p < 0.05 compared to aMCI/D+; [c] p < 0.05 compared to LLD.

Results

Sample Characteristics

Table 1 reports the means (±SD) and significance levels of the demographic and clinical characteristics of the participants. The groups did not differ regarding age and education level. The aMCI/D+ and LLD groups did not differ in sex distribution (5 women vs. 1 man) but did differ from the aMCI group (5 men vs. 1 woman). As expected, GDS scores were significantly higher in LLD and aMCI/D+ subjects than in aMCI participants (p = 0.0001). With regard to instrumental activities of daily living and vascular risk factors (Hachinski score), all three groups were similar. Participants with LLD had a higher mean MoCA score
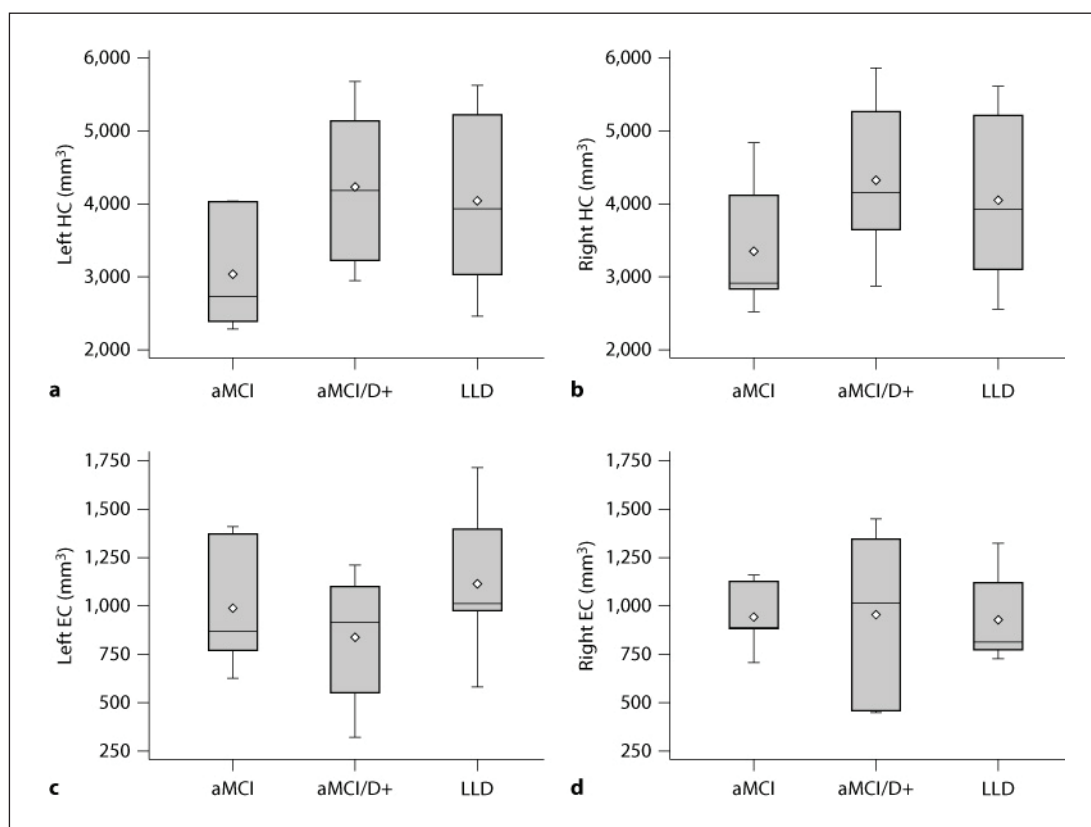
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Fig. 1. Boxplots of mean HC and EC volumes. **a** Boxplots of mean right HC volumes. **b** Boxplots of mean left HC volumes. **c** Boxplots of mean left EC volumes. **d** Boxplots of mean left EC volumes.

compared to aMCI and aMCI/D+ participants[1]. However, the groups did not differ in executive, information processing speed, visuoconstructive, language, and memory (semantic, episodic) measures.

Volumetric Measurements

Figure 1 depicts the mean (±SD) volumes (in mm^3) of the left (fig. 1a) and right (fig. 1b) HC, and left (fig. 1c) and right (fig. 1d) EC in aMCI, aMCI/D+, and LLD patients. Inspection of data indicates that the left HC was smaller in aMCI patients (3,039 ± 794) than in aMCI/D+ (4,232 ± 1,063) and LLD (4,041 ± 1,290) patients. Similarly, the right HC was smaller in aMCI patients (3,357 ± 905) than in aMCI/D+ (4,327 ± 1,084) and LLD (4,058 ± 1,236) patients. The mean left EC volume was slightly lower in aMCI/D+ patients (838 ± 336) compared to aMCI (987 ± 330) and LLD (1,118 ± 390) patients, whereas the mean right EC volume appeared to be approximately equal between aMCI/D+ (957 ± 447), aMCI (943 ± 170), and LLD (927 ± 240) patients (table 2).

The one-way ANOVAs (parametric and non-parametric) did not reveal any group effect regarding the different volumetric measurements ($F_{2, 15 \, LHC}$ = 2.16, p = 0.150; $F_{2, 15 \, RHC}$ = 1.28,

[1] The MoCA total score was not included in the fitted regression model (results below). By adding the MoCA to the other independent variables (age, sex, education, and Hachinski score), we obtained a p value higher than 0.85. Moreover, when a stepwise regression was applied, the MoCA was not retained as an important variable for its impact on HC and EC volumes.

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Table 2. Mean volumes ($\pm$SD) of MTL structures of interest (in mm^3)

Volume	aMCI	aMCI/D+	LLD
LHC	$3,039.2 \pm 794.2$	$4,232.7 \pm 1,063.0$	$4,041.8 \pm 1,289.5$
RHC	$3,357.2 \pm 905.0$	$4,326.5 \pm 1,083.9$	$4,058.3 \pm 1,236.0$
LEC	987.2 ± 329.7	838.2 ± 336.2	$1,117.8 \pm 390.0$
REC	943.2 ± 170.2	956.7 ± 447.1	926.8 ± 239.7

LHC = Left HC; RHC = right HC; LEC = left EC; REC = right EC.

Table 3. Necessary number of subjects to detect a significant difference between groups given an alpha level of 5% and a nominal power of 80%

Variable	Alpha	Nominal power	Power	Size
LHC	0.05	0.80	0.889	54
RHC	0.05	0.80	0.807	72
LEC	0.05	0.80	0.852	108
REC	0.05	0.80	0.801	6,192

LHC = Left HC; RHC = right HC; LEC = left EC; REC = right EC.

p = 0.307; $F_{2, 15 \text{ LEC}}$ = 0.94, p = 0.411; $F_{2, 15 \text{ REC}}$ = 0.01, p = 0.986). Using the t test, a gender effect was found for the left and right HC (t_2 = 3.07, p = 0.007; t_2 = 2.79, p = 0.013) but not for the left and right EC. Moreover, a classical regression did not reveal any significant association between independent variables (groups) and volumetric measurements; this was further confirmed by bootstrap regression, i.e. the probability of obtaining a significant association using multiple estimates coming from the same distribution was not significant.

Sample Sizes

Within the framework of a pilot study, we estimated the number of subjects needed to detect significant volumetric differences between groups using an alpha value of 5% and a nominal power of 80% (table 3). We found that the group size (i.e. total number of aMCI, aMCI/D+, and LLD participants) for left and right HC measurements should be at least 54 and 72, respectively. For left and right EC volume measurements, 108 and 6,192 participants should be recruited, respectively. In other words, results above should be confirmed with 36 participants per group.

Discussion

As emphasized in the Introduction, there is a need to elucidate the common and distinct mechanisms involved in aMCI and LLD [23]. It is also important to investigate aMCI/D+ patients more systematically because there is uncertainty whether these individuals actually present subclinical LLD or if they correspond to a particular aMCI subtype [10, 27]. With these considerations in mind, the present study aimed to provide preliminary evidence of differences in HC and EC volumes between aMCI, aMCI/D+, and LLD patients. Given the pilot status of the study, volume differences between groups did not reach statistical signifi-

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cance. Nonetheless, we observed a smaller HC volume in aMCI than in aMCI/D+ and LLD patients, which was in accordance with our hypothesis. Regarding the EC volume, the left EC was slightly smaller in aMCI/D+ compared to LLD patients, while no right EC volume difference was apparent between the groups. In the future, these findings will need to be confirmed with larger sample sizes (i.e. 36 participants per group).

Hippocampal atrophy was less important in subjects with depression features (aMCI/D+ and LLD groups) compared to those with no, or few, depressive symptoms (aMCI group). This finding corroborates previous studies that investigated the association between depressive symptoms and episodic memory impairment in older adults at risk of developing AD [32, 70]. That is to say, knowing that episodic memory in aMCI/D+ patients is somewhat less severely impaired than in aMCI patients [32], and bearing in mind that virtually all memory processes are altered in aMCI [25] but not in LLD [24], it was not surprising to find less HC atrophy in aMCI/D+ and LLD subjects compared to aMCI patients. A recent study using tensor-based morphometry showed that aMCI/D+ patients exhibited significantly more frontal, parietal, and temporal white matter atrophy bilaterally over 2 years compared with aMCI subjects [31]. This could be a result of separate degenerative processes that would corroborate the clinical phenotype.

The EC volume was not largely investigated in the literature on prodromal AD. In fact, our previous literature review [26] identified only 3 aMCI studies providing data for lateralized EC volumes [36, 71, 72], and no LLD studies has evaluated EC atrophy. Thus, to our knowledge, the present work is in fact the first to investigate EC volumetry in LLD. Interestingly, the left EC appeared to have a lower mean volume in aMCI/D+ subjects compared to aMCI and LLD subjects, while the right EC volume appeared to be approximately equal between all groups. Again, these findings need to be confirmed with larger samples. Investigation of the EC volume should be of use in studies interested in the differentiation of pre-AD syndromes knowing the EC is a better predictor of AD-related neurodegeneration [36, 43, 44] and of cognitive decline than the HC [48, 49].

The fact that HC and EC volumes differed between groups underlines the variability of prodromal AD biomarkers. These preliminary differences could rely on various complex mechanisms. For instance, multiple biological pathways potentially link depression to dementia neuropathology, such as vascular disease, alterations in glucocorticoid levels and hippocampal atrophy, increased deposition of amyloid-β, inflammatory changes, and deficits of nerve growth factors or neurotrophins [14]. Further longitudinal work is necessary to elucidate these mechanisms in relation to AD development.

From a nosological point of view and based only on the present HC volume data, one could argue that aMCI/D+ is closer to LLD than aMCI. However, the left EC data and previous neuropsychological findings [33] suggest that the semiology and pathophysiology of aMCI/D+ differ from those of LLD. Of note, our neurobiological findings and previous neuropsychological data [32] also suggest the importance of considering aMCI/D+ as a separate entity from aMCI. In the latter group, the more important HC atrophy could be accounted for by particular pathophysiological mechanisms (e.g. higher deposition of amyloid-β in aMCI compared to aMCI/D+ patients). Of course, this hypothesis remains speculative at this point. Nevertheless, we believe that our findings provide satisfactory evidence to support further investigations on that matter. Ultimately, such investigation could bring the development of more personalized interventions for the prodromal phase of AD.

Another finding of this study is that the left HC appeared smaller than the right HC in aMCI subjects only. Regarding aMCI/D+ and LLD patients, right and left HC volumes were fairly similar. Again, this can be viewed as additional evidence that aMCI and aMCI/D+ involve, to some extent, distinct pathophysiological mechanisms. Moreover, if we refer to our literature review [73], our results are consistent with the fact that, in 66% of previous

aMCI studies [36, 71, 72, 74, 75], volume reduction in the left HC was more important than in the right HC (for similar conclusions, see also the review by Ries et al. [39] and a meta-analysis by Shi et al. [38]). As for LLD patients, evidence for HC atrophy lateralization is controversial [73], with studies reporting either slightly more important right HC volume reduction [46, 76–78] or no bilateral differences [79–81], as in the current work. Additional LLD studies are required to clarify whether there is asymmetrical atrophy of the HC in these patients.

In our study, the aMCI/D+ group had a lower mean MoCA score than aMCI and LLD patients. This difference could first be attributable to the small sample size. It could also be explained by the fact that aMCI/D+ patients have more severe executive deficits [32], and this could have impacted the total MoCA score given the executive load of several items in this instrument. The pathophysiological correlates of executive deficits in aMCI/D+ could involve the presence of cerebrovascular lesions. As a matter of fact, white matter hyperintensities (WMH) are significantly associated with the diagnosis and extent of cerebrovascular lesions [82]. Furthermore, WMH are related to a noticeable decline in global cognitive function [83–87] and to rapid changes in executive function or processing speed [85, 87–89]. Thus, we could make the hypothesis that aMCI/D+ subjects have more WMH than aMCI patients (and possibly LLD patients too). This hypothesis would need to be verified in future studies.

One of the goals of this pilot study was to provide recommendations in order to improve the design of future research aiming to compare the neurobiological characteristics of aMCI, aMCI/D+, and LLD patients. Hence, in our opinion, the following points should be carefully considered in the future: (1) increase the number of participants in each group to detect significant volumetric differences for the right HC, left HC, and right EC; (2) include measures of WMH; (3) include other MRI measures (e.g. parahippocampal or amygdala atrophy, cortical thickness, or diffusion tensor imaging); (4) collect precise information about medications that can have an impact on cognition and brain structures (e.g. selective serotonin reuptake inhibitors); (5) evaluate APOE ε4 status as we know there is an association between APOE ε4 and emergent deficits in episodic memory [90]; we could suspect that APOE ε4 status has an impact on MTL structures; (6) obtain more detailed information about the nature of depressive symptoms in aMCI/D+ in order to clarify their similarities and differences with those of LLD; (7) consider the possibility for LLD patients to meet criteria for aMCI in order to compare 4 groups in a larger study (i.e. aMCI, aMCI/D+, LLD, and LLD/MCI+ patients); (8) investigate, in each group, other biomarkers of AD such as CSF dosage of β-amyloid and tau proteins or PET imaging of amyloid load, and (9) conduct longitudinal studies to verify whether the groups of patients differ with regard to the type of dementia (e.g. AD, vascular, or mixed) they eventually develop. Any demonstration of prognostic differences between these groups would reinforce the need to differentiate these syndromes in clinical practice and to develop adapted interventions for each category of patients.

Limitations

The first limitation of this study relates to the small number of participants, which could explain why our results were not statistically significant. Though, the main findings emphasize the need to investigate aMCI, aMCI/D+, and LLD simultaneously. The second limitation relates to the medication of participants. Five LLD and 5 aMCI/D+ subjects were taking antidepressants, and 1 aMCI/D+ and 2 LLD subjects took benzodiazepines while participating in the study. One should note that benzodiazepines have prominent central effects such as sedation, sleep induction, anxiety reduction, and anterograde amnesia [91, 92]. Moreover, the amnestic effects of benzodiazepines are thought to be mediated by GABA-A receptors containing α5 subunits that are highly expressed in the HC and related regions [91]. Therefore,

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it appears important to assess benzodiazepine use with more accuracy in future studies because of its possible impact on cognitive functions and, hypothetically, on the classification of subjects. As for antidepressants, about 80% of aMCI/D+ and LLD participants were taking this medication in the present study. There is growing evidence that long-term antidepressant use may have a positive impact on the HC volume in patients with depression and, therefore, may have a neuroprotective role [93, 94]. In our study, larger HC volumes were observed in participants taking antidepressant, i.e. most aMCI/D+ and LLD subjects. Therefore, antidepressants could have partly explained HC volumetric differences between the groups (aMCI/D+ and LLD vs. aMCI). The third limitation is that delays between neuropsychological evaluation and MRI examination varied from a couple of weeks to several months in certain cases. In future studies, this delay should be reduced as much as possible to diminish the risk of including participants who developed dementia at the time of the MRI examination.

Conclusions

Previous studies have indicated that aMCI, aMCI/D+, and LLD patients can be distinguished, to a certain extent, by their neuropsychological profiles [32, 33]. To our knowledge, this study is the first to focus on brain volumetric differentiation of these groups. Pre-AD syndromes have heterogeneous presentations and represent an opportunity for potential intervention with disease-modifying therapy [95]. It thus appears critical to further explore the heterogeneous presentations of prodromal AD syndromes and identify biomarkers (such as MTL volumetry and PET imaging of amyloid load and WMH) that could help differentiating and treating prodromal AD conditions.

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Disclosure Statement

The authors have no actual or potential conflicts of interest to declare.

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