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ABSTRACT

Identifying the specific substrates of memory deficits in early Alzheimer's disease would help to develop clinically-relevant therapies. The present study assesses the relationships between encoding versus retrieval deficits in patients with amnestic Mild Cognitive Impairment (aMCI) and atrophy specifically within the hippocampus and throughout white matter. Twenty-two aMCI patients underwent T1-weighted MRI scans and neuropsychological testing. Grey matter and white matter segments obtained from the MRI images were each entered in correlation analyses, assessed only in the hippocampus for grey matter segments, with encoding and retrieval memory performances. For the grey matter segments, the resulting spmT correlation maps were then superimposed onto a 3D surface view of the hippocampus to identify the relative involvement of the different subfields, a method already used and validated elsewhere. Memory encoding deficits specifically correlated with CA1 subfield atrophy, while no relationship was found with white matter atrophy. In contrast, retrieval deficits were weakly related to hippocampal atrophy and did not involve a particular subfield, while they strongly correlated with loss of white matter, specifically in medial parietal and frontal areas. In aMCI patients, encoding impairment appears specifically related to atrophy of the CA1 hippocampal subfield, consistent with the predominance of encoding deficits and CA1 atrophy in aMCI. In contrast, episodic retrieval deficits seem to be underlain by more distributed tissue losses, consistent with a disruption of a hippocampo-parieto-frontal network.

Abbreviations: Alzheimer's disease (AD); amnestic Mild Cognitive Impairment (aMCI); Cornu Ammonis (CA); dentate gyrus (DG); HIppocampal Encoding/Retrieval Pattern (HIPER); grey matter (GM); white matter (WM); small volume correction (SVC); three-dimensional (3D); transient global amnesia (TGA); neurofibrillary tangles (NFTs); diffusion tensor imaging (DTI)

Key words: amnestic Mild Cognitive Impairment; CA1; hippocampus; MRI; encoding; episodic memory

INTRODUCTION

For the development of new therapeutic agents for Alzheimer's disease (AD), the identification of clinically relevant targets is essential. Along this line, it is important to further our knowledge of the brain structures specifically involved in the deficit in episodic memory that characterizes the disease, especially at its pre-dementia stage, i.e. when neuropathological processes are still limited and cognitive deficits still partly reversible.

In patients with amnestic Mild Cognitive Impairment (aMCI), the clinical entity that best represents the pre-dementia stage of AD (Petersen, 2005), previous studies have consistently reported a relationship between episodic memory impairment and hippocampal atrophy (Convit et al., 1997; Fjell et al., 2008; Leube et al., 2008; Schmidt-Wilcke et al., 2009; Jhoo et al., 2010; Serra et al., 2010; Hanseeuw et al., 2011). However, episodic memory on the one hand involves several distinct processes, notably encoding and retrieval of the information, while, on the other hand, the hippocampus is a complex cytoarchitectonic structure made up of four Cornu Ammonis subregions (CA1, 2, 3 and 4, respectively), the dentate gyrus (DG) and the subiculum (Duvernoy, 1998). These hippocampal subfields differ in terms of their cellular nature and organization, as well as their connectivity with the rest of the brain (Teyler and DiScenna, 1984; Amaral, 1993). It is thus possible that these subfields have a differential role in episodic encoding and retrieval deficits in aMCI patients. In healthy subjects, the regional specialisation of encoding and retrieval processes within the hippocampus has been the topic of intensive investigations. An antero-posterior gradient has been posited as part of the HIppocampal Encoding/Retrieval Pattern (HIPER) model (Lepage et al., 1998), and a specific role for the different hippocampal subfields has been more recently proposed (Eldridge et al., 2005), though there is no clear-cut evidence to date as regards the specific

relationships between each hippocampal subfield and memory processes (see (Carr et al., 2010) for review).

In aMCI patients, we previously reported that both encoding and retrieval deficits were related to hippocampal grey matter (GM) atrophy (Chételat et al., 2003). Nevertheless, in early AD, encoding deficits tend to predominate over retrieval deficits (Wang and Zhou, 2002; Pike and Savage, 2008; see (Belleville et al., 2008) for review) while hippocampal atrophy preferentially affects the CA1 subfield (Apostolova et al., 2006; Apostolova et al., 2006; Becker et al., 2006; Wang et al., 2006; Chételat et al., 2008; Apostolova et al., 2010; Mueller et al., 2010; Yassa et al., 2010; Atienza et al., 2011); even if atrophy of CA3/DG (Yassa et al., 2010; Atienza et al., 2011) and subiculum (Apostolova, et al., 2010) has also been reported in aMCI. Otherwise, previous studies have reported a specific link between neuronal loss in CA1 and episodic memory impairment in AD (Zarow et al., 2005) or atrophy in CA1 and episodic memory deficits in mild AD (Sarazin et al., 2010), but in these studies encoding was not distinguished from retrieval. Taken altogether, these results raise the hypothesis of a specific role for CA1 atrophy in the encoding deficits of aMCI.

With respect to retrieval deficits in aMCI, although also broadly related to hippocampal atrophy, they are thought to involve dysfunction within a wider network. For instance, a role for posterior cingulate hypometabolism has previously been suggested (Chételat et al., 2003). Moreover, when using free recall tasks, which mainly depend on retrieval capacities in contrast to recognition tasks, episodic memory impairment in AD has been related to damage at multiple sites of a functionally integrated network comprising medial temporal lobe and related limbic–diencephalic circuitry (namely, the posterior cingulate cortex, thalamus and mammillary bodies (Nestor et al., 2006)), as well as the anterior cingulate (Desgranges et al.,

1998) and frontal cortex (Eustache et al., 2004); see (Salmon et al., 2008) for review). Overall, therefore, retrieval deficits in aMCI patients are believed to result from disruption of this network and are thus expected to depend on integrity of the connectivity within this network, rather than on damage to a specific hippocampal subfield.

The present study aims to test these hypotheses regarding both encoding and retrieval deficits, by assessing the specific relationships between these deficits in aMCI patients and both hippocampal subfields GM atrophy and white matter (WM) atrophy across the brain as a reflection of structural connectivity integrity.

MATERIALS AND METHODS

Patients

The present sample of aMCI patients partly overlaps with that used in our previous publications using MRI data (Chételat et al., 2003, 2005, 2008; Villain et al., 2010), although only those patients in whom both MRI data and scores at the 'Encoding Storage Retrieval' (ESR; (Eustache et al., 1998)) memory task were available were included in the present study. Briefly, twenty-two aMCI patients were recruited through a memory clinic, which they attended for a memory complaint. They were all right-handed, aged over 55 years and had at least 7 years of education (see Table 1 for their demographic and clinical data). They underwent medical, neurological, neuropsychological, and neuroradiological examinations, and were selected according to current criteria for aMCI, i.e. isolated episodic memory deficits (<1.5 SD of the normal mean matched for age and education), normal performance in other areas of cognition and in global cognition (assessed with the MMSE scale (Folstein et al., 1975)), and NINCDS-ADRDA criteria for probable AD (McKhann et al., 1984) not met

(see (Chételat et al., 2005) for details). According to the Declaration of Helsinki, each patient gave written informed consent to participate in the study, which was approved by the regional ethics committee.

Encoding and retrieval episodic memory capacities were evaluated using the ESR task already used in a previous study showing decreased performances in both processes in a partially overlapping sample of aMCI patients as compared to age-matched controls (see (Chételat et al., 2003) for details on the task and Table 1 for their scores). Briefly, the ESR task includes two learning phases (one superficial and one deep) of two different lists. Each list comprised 16 words, belonging to 16 different semantic categories. For the first list, patients had to say whether the first and last letters of each orally presented word were in alphabetical order, without any instruction to memorize. At the end of this incidental superficial encoding phase, a recognition phase was carried out where patients had to recognize the 16 target words among distractors. Each target word was presented visually, one by one, with three distractors, one semantically linked, one phonetically linked, and the third with no link with the target word. For each of these 16 presentations, patients were systematically required to point to a word with their finger, the one they recognized, or otherwise the one they chose at random. For the second list, patients were asked to memorize the words. In order to induce a semantic processing, they had to generate orally a sentence that defined or described the orally presented word. Every two words, an immediate cued recall task was performed using a semantic category cue, in order to ensure that encoding was made and to reinforce its semantic nature. If the patient failed, he was reminded of the word, and again requested to make a sentence containing the target, and to recall it in response to its categorical cue. At the end of this 16-word intentional deep encoding, patients were asked to recall as many words as possible, in any order and without time limitation. Performance in recognition after incidental superficial encoding from the first list is assumed to mainly reflect encoding capacity, as

recognition is supposed to compensate for potential retrieval deficits. In contrast, performance in free recall after intentional deep encoding is assumed to preferentially reflect retrieval capacity as encoding is supported, thereby compensating for potential deficits in spontaneous encoding capacities. Note that psychometric scores necessarily reflect both encoding and retrieval capacities, so that there is no measurement that would only reflect one of these two processes. The ESR task has been especially designed to place maximal demand on encoding and minimal demand on retrieval to assess encoding processes and conversely. Thus, although they are not pure measurements of each process, they will be designated in what follows by the process they preferentially tap, i.e. encoding and retrieval scores, for the sake of simplicity (Gabrieli et al., 1997).

MRI data acquisition and processing

Within a few days after inclusion, each patient underwent a 1.5Tesla T1-weighted MRI volume scan, all on the same scanner and using the same acquisition parameters. A set of 128 adjacent axial cuts parallel to the anterior-posterior commissure (AC-PC) line and with slice thickness 1.5 mm and pixel size 1x1 mm was obtained using the SPGR (spin gradient recalled) sequence (TR=10.3 ms; TE=2.1 ms; FOV=24x18 cm; matrix=256x192).

All data pre-processing steps were performed using VBM5.18 toolbox (Structural Brain Mapping Group, Christian Gaser, Department of Psychiatry, University of Jena, Germany), implemented in the SPM5 software (Wellcome Department of Imaging Neuroscience, Institute of Neurology, London, England) running on MATLAB 7.1.

Briefly, the MRI data were iteratively segmented and normalized with the bias correction option and the application of Hidden Markov Field weighting to enhance the accuracy of segmentation. The resulting spatially normalized GM and WM segments were then modulated. Note that, by contrast to the initial method of modulation that compensated for the

effects of both affine transformation (global scaling) and non-linear warping (local volume change), the modulation applied in the present study only corrects for the latter so that brain size variation is already taken into account and correction for Total Intracranial Volume (TIV) is not required. Resulting images were then smoothed using a Gaussian kernel of 4 mm for GM and 8mm for WM, and finally entered into the correlation analyses described below.

Statistical analyses

Correlations with encoding and retrieval deficits

Correlations were then computed between episodic memory encoding or retrieval scores, and the smoothed modulated normalised GM or WM segments, with age as a covariate, using the multiple regression voxelwise analysis of SPM5.

According to our hypotheses (see Introduction) correlations were assessed in the biologically meaningful direction only, i.e. higher GM or WM volume values being related to greater performance.

Regarding correlations with GM, we previously showed that both encoding and retrieval deficits in aMCI correlated only with hippocampal atrophy when assessing the whole GM (Chételat et al., 2003). In line with these findings, the objective of the present study was to specify the topography of these relationships within the hippocampus. For this purpose, the statistical maps resulting from the GM VBM-based correlation analysis described above were assessed only within the hippocampus using the small volume correction (SVC) tool of SPM and the hippocampal mask described below. The resulting spmT correlation maps were then directly superimposed onto the surface of a three-dimensional (3D) rendering of the hippocampi (see below for the delineation of the hippocampi). This approach has already been used in our laboratory to assess subregional hippocampal atrophy contrasting the effect of normal aging to those of aMCI and AD (Chételat et al., 2008). Moreover, this method has

been validated against manual delineation of hippocampal subfields on high resolution MRI, showing high reliability especially for distinguishing the CA1 versus the subiculum (La Joie et al., 2010), and allowing to obtain a representation of hippocampal subfields on the 3D surface view of the hippocampus (see Figure 1 – middle panel).

The right and left hippocampi were manually delineated using the publicly available Anatomist/BrainVISA software (www.brainvisa.info) on each coronal section of a customized template corresponding to the mean of the spatially normalized MRI of all aMCI patients. The 3D representation of the hippocampi was then obtained by converting the right and left hippocampal binary masks onto 3D meshes using the same Anatomist/BrainVISA software (see (Chételat et al., 2008) for further details). The hippocampal mask used for the SVC corresponded to the manually delineated mask dilated by two voxels.

Regarding correlations with WM, analyses were thresholded to p (uncorrected) < 0.005 for the voxels and cluster size k>500 voxels.

Complementary analyses

For the sake of completeness, we also included data from age-matched healthy controls. First, we compared the memory profile of the aMCI patients included in the present study to those of a group of healthy controls included in the previous study by Chételat et al. (2003; see Table 1 for their demographic and clinical data and scores) using a general linear model implemented in the JMP7 statistic software with score as the dependant variable, subject as a random factor, group (aMCI patients or healthy controls) and process (encoding or retrieval) as categorical independent variables, and age as independent quantitative variable, specifying a group*process interaction.

Second, to assess whether the correlations between brain structure and memory performance were specific to aMCI patients or were also present in healthy elderly, we repeated the same regression analyses including an additional group of 21 age-matched controls who had the

same memory task together with an MRI scan on the same scanner than the aMCI. Details on these analyses can be found in the Supplementary material.

RESULTS

Memory scores in aMCI patients

Consistent with our previous work on an overlapping sample of aMCI patients (Chételat et al., 2008), the difference between aMCI patients and matched controls was more significant for encoding ($F_{[1,40]}=13.8126$; $p=0.0003$) than for retrieval ($F_{[1,40]}= 6.4889$; $p=0.0125$), though the group*process interaction ($F_{[1,40]}=0.8287$; $p=0.367$) was not significant.

Correlations between hippocampal GM volume and encoding/retrieval scores

The statistics of the correlations within the hippocampus using the SVC approach are reported in Table 1. The spmT map of the correlations between lower GM volume and lower encoding score projected onto the hippocampal 3D surface rendering is illustrated in Figure 1 – left panel. Lowest P-values (corresponding to p (uncorrected) <0.005 in red) involved the external half of the superior aspect, and the external side of the inferior aspect of both hippocampi. With reference to the MRI atlas obtained from the manual delineation of the hippocampal subfields (La Joie et al., 2010) and depicted in Figure 1 – middle panel, significant correlations with encoding scores were mainly located in the CA1 subfield.

As illustrated in Figure 1 – right panel, the correlations between lower GM volume and lower retrieval scores were weaker and more diffuse than those with encoding scores, not matching any particular hippocampal subfield.

Correlations between whole brain WM volume and encoding/retrieval scores

Encoding scores were not found to correlate to WM volume in any brain area (Figure 2 – left panel). In contrast, significant correlations were found between lower retrieval score and lower WM volume, involving postero-medial aspects of the brain including the splenium of the corpus callosum, and the posterior part of the cingulum bundle, as well as the frontal tracts of the corpus callosum and the rostral part of the latter (Figure 2 – right panel).

Specificity of the correlations compared to healthy controls

The results described above were found to be specific to the aMCI patients as i) they were not significant within the healthy elderly and ii) all correlations were found to be significantly greater in the aMCI patients than in the healthy controls (see Supplementary materials).

DISCUSSION

In the present study, VBM and hippocampal surface mapping methods were used to test the hypothesis of a role for specific hippocampal subfields and regional WM damage in episodic memory encoding versus retrieval deficits in aMCI patients. As per our hypothesis, specific relationship was found between encoding deficits and atrophy in the most lateral part of the hippocampus bilaterally, corresponding to the CA1 subfield, but not with any WM region. By contrast, the relationship with retrieval deficits was weaker within the hippocampus and not specific to a particular subfield, but a strong relationship was found with atrophy of medial posterior and frontal WM tracts. Note that the present study is limited by the use of proxies to assess encoding and retrieval deficits as there is no direct, pure measurement of each process as detailed in the Materials and methods section.

A specific role for CA1 in episodic encoding deficit was first suggested in 1986 based on a case report (Zola-Morgan et al., 1986). The patient described in this study had circumscribed damage to the entire CA1 subfield and suffered from persistent anterograde amnesia in the face of preserved old memories, non-mnemonic functions and IQ. The isolated deficit of this patient in the ability to encode new information, while still capable of retrieving the information encoded before brain damage occurred was taken as evidence for a specific involvement of CA1 in episodic memory encoding. Moreover, some patients suffering from transient global amnesia (TGA) are characterized by encoding deficits (Eustache et al., 1999; Quinette et al., 2006) and, when present, focal MRI lesions are almost all selectively located within CA1 (see (Bartsch and Deuschl, 2010) for Review). Finally, spatial learning task performances, mainly involving encoding processes, have been recently shown to relate to CA1 lesion size in TGA (Bartsch et al., 2010).

As mentioned in the Introduction, a functional specialisation within the hippocampus for episodic encoding and retrieval processes in healthy young subjects was initially proposed as part of the HIPER model, with the anterior part of the hippocampus being preferentially involved in encoding, and retrieval mainly depending on its posterior portion (Lepage et al., 1998). In aMCI patients, a specific link between encoding deficits and atrophy of the anterior hippocampus has been reported, consistent with the HIPER model (Leube et al., 2008). Unlike this rostrocaudal gradient, Schacter & Wagner (Schacter and Wagner, 1999) emphasized the involvement of both the anterior and posterior parts of the hippocampus in encoding. Given that the CA1 subfield predominates in the anterior hippocampus but extends throughout its antero-posterior axis, the specific role of CA1 structural damage in episodic encoding deficits evidenced here in aMCI is therefore consistent with both hypotheses of an anterior (Lepage et al., 1998) and an antero-posterior (Schacter and Wagner, 1999)

hippocampal involvement in episodic encoding. More recently, a specific involvement of the different subfields of the hippocampus in encoding versus retrieval, as opposed to a specialization along its longitudinal axis, has been hypothesized (Eldridge et al., 2005). When testing this concept using high-resolution functional MRI focusing on the hippocampus in healthy young subjects, inconsistent findings have been reported regarding episodic encoding (Carr et al., 2010). More precisely, changes in functional activity related to encoding were found in different hippocampal subfields according to the particular material being used, namely CA23DG for faces (Zeineh et al., 2003) and objects (Eldridge et al., 2005; Carr et al., 2010), CA1 for spatial representations (Preston et al., 2010; Suthana et al., 2010), and the subiculum for scenes (Preston et al., 2010). There is thus uncertainty as regards the involvement of a particular hippocampal subfield during encoding in healthy young subjects. The present study was not designed to assess this question but to show the specific structural substrates of encoding deficits for verbal material in aMCI patients, i.e. sites that are necessary for encoding instead of any structure simply involved in this cognitive process. It is thus not surprising that our findings in aMCI using structural data do not perfectly match those obtained in healthy young subjects using functional MRI. Similarly, the fact that we found our results to be specific to aMCI patients (when contrasted to healthy controls) does not imply that the CA1 subfield is not useful to encoding process in healthy elderly for instance, but rather suggests that the variability in encoding performances is not explained by the variability in CA1 volume in the elderly.

The specific role of CA1 atrophy in episodic encoding deficits in aMCI reported here is however consistent with a large body of neuropathological data in AD. Atrophy in AD matches the topographical distribution of neurofibrillary tangles (NFTs; (Braak and Braak, 1991)) and is considered as an *in vivo* surrogate for NFTs (Vemuri et al., 2008; Whitwell et

al., 2008). NFTs were found to correlate to episodic memory deficits (Mitchell et al., 2002), especially those located in CA1 in aMCI patients (Markesbery et al., 2006). Furthermore, NFTs (Braak and Braak, 1997) as well as neuronal degeneration (Scheff et al., 2007) mostly affect the apical dendrites of CA1 neurons, themselves shown to correlate with episodic memory deficits in mild AD (Scheff et al., 2007). Given that the main input to CA1 originates from CA3 through Schaffer's collaterals (Amaral and Witter, 1989; Duvernoy, 1998), the specific relationships between encoding deficits and CA1 atrophy highlighted here in aMCI could reflect a disruption of the connection between CA3 and CA1, and the failure of information transfer from CA3 to CA1, critical to create an episodic trace (Rolls, 1996, 2007). This interpretation would fit with a previous report of changes in functional MRI activity during a memory encoding task in aMCI patients in CA3/DG, although these changes themselves correlated to memory performances only when sampling healthy controls and aMCI patients together but not within the aMCI patient sample (Yassa et al., 2010). Altogether, the intra-hippocampal CA3 – CA1 communication appears as a relevant target for future therapeutic intervention.

Regarding retrieval deficits of aMCI, there was no evidence from the available literature to predict a relationship with specific hippocampal subfield(s). In healthy young subjects, high resolution functional MRI focusing on the hippocampus pointed to an involvement of the subiculum in episodic retrieval (Carr et al., 2010). As mentioned above, the lack of a specific relationship between retrieval deficits and atrophy of a particular hippocampal subfield in the present study does not contradict the functional involvement of a specific subfield in retrieval processes in healthy controls. In other words, it is possible that subiculum activity has a predominant role in retrieval capacity, but is not responsible for the retrieval deficits of aMCI patients, which would be subtended by the disruption of a larger network (see Introduction).

Consistent with this notion, we found a strong relationship between WM tract alteration and retrieval, but not encoding, deficits in aMCI patients. More specifically, this relationship involved the medial parietal and frontal WM tracts, namely the posterior part of the cingulum bundle, as well as the splenium and the anterior part of the corpus callosum. Although VBM of WM (see for example (Villain et al., 2008, 2010) for a similar approach) is not as precise and specific to axonal damage as diffusion tensor imaging (DTI; (Gouw et al., 2008)), both methods have been shown to provide highly correlated assessments of WM damage (Gouw et al., 2008). Moreover, the cingulum bundle, as well as both the anterior and posterior parts of the corpus callosum, were previously reported to be altered in aMCI patients (see (Chua et al., 2008; Di Paola et al., 2010) for reviews), and together form a medial parieto-frontal network assumed to be involved in episodic retrieval (see (Buckner and Wheeler, 2001) for review).

Our findings are also consistent with previous studies using DTI in AD and/or aMCI that showed a correlation between performance in recall tasks and alterations in the posterior part of the cingulum bundle (Fellgiebel et al., 2005; Sexton et al., 2010) and the posterior part of the corpus callosum (Serra et al., 2010). Regarding the corpus callosum, its posterior part is thought to be involved in retrieval (see (Gazzaniga, 2000) for review) and patients with circumscribed splenial lesions exhibit recall deficits (Jeong et al., 2009). Finally, the relationship found here with the anterior and frontal tracts of the corpus callosum agree with the role of the frontal cortex in retrieval deficits in AD (see (Salmon et al., 2008; Schwindt and Black, 2009) for reviews).

CONCLUSION

In sum, this study highlights the specific involvement of atrophy of the CA1 hippocampal subfield in episodic memory encoding deficits in aMCI patients, while retrieval deficits would be subtended by disruption of a wider network through alteration of connecting WM tracts. Given the predominance of encoding deficits in the pre-dementia stage of AD, our findings emphasize the CA1 hippocampal subfield as a potential target in therapeutic research.

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FIGURE CAPTIONS

Figure 1: Illustration of the correlations between encoding or retrieval deficits and GM hippocampal atrophy in aMCI. Superimposition of the spmT maps of the correlations between GM volume and encoding (left) or retrieval (right) performances in aMCI patients. The middle panel shows a schematic representation of the hippocampal subfields on 3D surface superior and inferior views obtained from manual delineation (La Joie et al., 2010).

Figure 2: Illustration of the correlations between encoding or retrieval deficits and WM atrophy in aMCI. Representation of the correlations between WM volume and encoding (left) or retrieval (right) scores in aMCI patients thresholded at $p<0.005$ and $k>500$.