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Increased sensitivity to proactive interference in amnestic mild cognitive impairment is independent of associative and semantic impairment

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ABSTRACT

Episodic memory deficit is the hallmark of amnestic mild cognitive impairment (aMCI). There is, however, an overlap in performance among patients with aMCI and elderly controls (EC). The memory deficit in aMCI therefore needs to be better characterized. Studies have shown that associative memory is selectively impaired in aMCI, and recent work suggested that aMCI may be hypersensitive to semantic proactive interference (PI). It is not known whether this increased PI is related to associative or semantic impairment. EC ($n = 44$) and patients with aMCI ($n = 30$) performed two tasks presenting a gradually increasing PI effect across four lists. One task used semantic cueing, the other phonological cueing. We controlled for associative memory by introducing it as a covariate and by matching our subjects for it. Patients with aMCI had a greater PI effect than EC matched for associative memory, regardless of the type of cueing. The increased PI effect in patients with aMCI is independent of their associative and semantic impairment.

1. Introduction

Early memory impairment is required for a diagnosis of dementia, particularly of Alzheimer type (McKhann et al., 1984; Small, Fratiglioni, Viitanen, Winblad, & Backman, 2000). Amnestic mild cognitive impairment (aMCI) – a condition believed to be, in most cases, a pre-demential stage of Alzheimer's disease (AD) – is characterized by selective deficits in episodic memory as its most prominent feature (Morris, 2006; Petersen, 2004). Most of the patients with aMCI have, however, a memory performance on tests that is still in the normal range (i.e., above −2SD or 2.5 percentiles). Therefore, the memory deficit needs to be better characterized to allow clearer identification of those aMCI patients who are at risk of evolving to AD (Dubois et al., 2007). Cued recall tests into which a semantic cue was presented at both encoding and recall have been shown to be more specific in diagnosing dementia (Buschke, Sliwinski, Kuslansky, & Lipton, 1997) and aMCI (Ivanoiu et al., 2005) than the more classical tests based on free encoding and delayed recall. One of these tests, the Rappel indicé 48 items (RI-48) (Adam et al., 2007), appeared particularly suitable for distinguishing patients with aMCI from elderly controls (EC) and for identifying those aMCI patients with the strongest risk of evolving to AD (Ivanoiu et al., 2005). These cued recall tests do not rely only on item memory (i.e., memory of the word itself) but also on associative or relational memory (i.e., memory of the association or the relationship existing between the item and its cue). It was recently shown that associative memory was impaired even more than item memory in patients with aMCI (Troyer et al., 2008). The higher specificity of the RI-48 for detecting the AD type of memory deficit has been explained by the fact that aMCI patients find it difficult to encode the relation between cues and items (Adam et al., 2007). However, this test also includes a proactive interference (PI) effect related to the way in which the items are presented. At the encoding phase of the RI-48, each item is presented with a categorical cue; but the same semantic category is used on four different, randomly distributed occasions (e.g., the category 'fruit' is used to cue the items 'cheer', 'melon', 'grape' and 'raspberry'). In such a paired-associates paradigm, PI is induced at encoding when an item (e.g., 'melon') is cued by a word (e.g., 'fruit') which has previously been associated with another item (e.g., 'cheer'). It is expected that recall of the second item will be worse than recall of the first because the first learned association will disturb the encoding of the second association. The importance of the PI effect in patients with aMCI and in EC has not been studied using this test. However, two studies have already shown that patients with aMCI are more sensitive to PI than EC (Ebert & Anderson, 2009; Loewenstein et al., 2004). And it has been suggested that a high sensitivity to PI could be an early marker of the evolution to dementia (Loewenstein, Acevedo, Agron, & Duara, 2007). Nevertheless, these studies have two shortcomings: first, they did not specifically analyse the

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relationship between the PI effect and associative memory. PI disturbs the formation of new associations in memory and associative impairment may explain variations in the sensitivity to the PI effect. To our best knowledge, this aspect has not been studied in aMCI. Second, the relationship between items was semantic in nature in these two studies (Ebert & Anderson, 2009; Loewenstein et al., 2004), making it difficult to rule out that an early semantic deficit (Hodges, Erzinclioglu, & Patterson, 2006) may have contributed to the results (Backman, 1998).

We aimed to analyse the specific (if any) contribution of PI to the memory impairment of patients with aMCI. We also wanted to find out whether the associative impairment and PI hypersensitivity were restricted to the use of semantic association or not. For these purposes, we evaluated the PI effect by controlling for associative memory and by using both semantic and non-semantic cueing.

2. Methods and subjects

2.1. Subjects

Forty-four EC and thirty patients with aMCI took part in this study. Patients with aMCI were recruited from patients attending the Memory Clinic at the Saint-Luc University Hospital in Brussels, and all fulfilled Petersen's criteria for aMCI (Petersen, 2004):

- Memory complaints corroborated by an informant.
- Objective memory impairment for age.
- Essentially preserved general cognitive function.
- Largely intact functional activities (not demented).

All aMCI patients undertook a magnetic resonance (MRI), including axial slices (FLAIR and Diffusion Sequences) and coronal slices (T2) perpendicular to the long axis of the hippocampus. The MRI scan ruled out vascular or other focal causes of cognitive impairment. EC were recruited from the patients' spouses and through advertisements. We excluded from the study subjects aged more than 85, who fulfilled criteria of dementia (DSM IV), or who had other neurological or psychiatric conditions (particularly depression) as well as those subjects that were taking antidepressive drugs for less than 3 months before the screening date. We obtained informed consent for each subject. The study has been approved by the Ethical Committee of the University of Louvain and the Saint-Luc University Hospital under the number 2007/176.

2.2. Material

Two types of material were used to create a semantic task and a phonological task, each including two runs of four lists (L1–L4).

2.2.1. Semantic task (S-task)

Ninety-six French words were cued by 24 different semantic categories (e.g., the words 'pigeon', 'crow', 'nightingale' and 'tit' were cued by the category 'BIRD'). We created two runs, each with four lists (=L1S–4S) of 12 words. Word typicality (Marchal, 2003), written and oral frequencies (New, Ferrand, & Matos, 2001), and length (number of syllables and number of letters) were controlled between runs and between lists.

2.2.2. Phonological task (P-task)

Sixty-four French words were cued by 16 different trigrams which corresponded to the first three letters of the word to be remembered (e.g., the words 'salaire' [salary], 'salade' [salad], 'saleté' [dirt] and 'salive' [saliva] were cued by the trigram 'SAL-'). We created two runs, each with four lists (=L1P–L4P) of eight words. Written and oral frequencies (New et al., 2001), length and the words' 4th letter were controlled.

2.3. Procedure

The words were presented randomly on a computer screen (15 in.), using MATLAB 6.5. The categorical or phonological cue appeared first on the screen and was followed after one second by the correspondent item. The cue–item association was displayed for 2 s in the S-task and for 3.5 s in the P-task, making the total time to encode one list equal to 36 s for both tasks. At the end of each list, a fixation cross was shown for 6 s. The cues were then shown again followed by the word 'answer', leaving 6 s for the subject to answer. Subjects were asked to respond verbally. The percentage of correct answers per list was noted. This procedure was repeated for the four lists of the two runs in each task. The orders of tasks, runs, lists and words were randomized across subjects.

The number of items per list and the duration to encode an item was controlled in each task to equate the level of difficulty of the two tasks. This procedure was adopted in order to be able to compare phonological and semantic cueing with the same level of memory performance. Since the six first EC had a different version of the P-task, we excluded them from the P-task analyses.

2.4. Neuropsychological assessment

The neuropsychological assessment included tests evaluating global cognitive functions (MMSE) (Folstein, Folstein, & McHugh, 1975), episodic memory (French adaptation by our team (Ivanoiu et al., 2005) of the Ten Words List Learning and Recall from the Consortium to Establish a Registry for Alzheimer's disease (=CERAD) battery (Morris, Mohs, Rogers, Fillenbaum, & Heyman, 1988) – sum of trials 1–3 to freely recall 10 words), visuospatial processing (the "praxis" part of the CERAD battery (Morris et al., 1988)), executive function (The Letter Fluency Test for the letter P in 1 min (de Partz, De Wilde, Seron, & Pillon, 2001)) and the Trail Making Test (TMT); language and semantic memory (The Category Fluency Test – names of animals evoked in 1 min – and a short version of the LEXIS naming test (de Partz et al., 2001)).

2.5. Statistical analysis

In order to evaluate if there was a hypersensitivity to PI independent of the associative deficit in aMCI, we had to control for associative memory. We considered the percentage of correct answers at L1 as a measure of the associative memory. The decrease in performance across lists from L1 to L4 was taken as a measure of the PI effect. We performed all our statistical analyses in SPSS 16.0. To achieve our purpose, we used two different methods: first we introduced L1 as a covariate in an ANOVA comparing L2, L3 and L4 between our groups. This method allows taking into account the variation of L4 which is due to L1 differences. A significant difference of performance between our groups in L4 (or L2 or L3) when L1 is introduced as a covariate, indicates that the PI effect is independent from associative memory. We aimed to double-check our results using another technique. Therefore, we performed a bootstrap procedure (Howell, 2006, chap. 18). The bootstrap procedure is a computational method which allows perfect matching between subjects of two groups according to one of their characteristics and then to compare the matched groups. In our study, we implemented in MATLAB 6.5 a bootstrap which chose randomly matched subjects from each group (17 aMCI-EC pairs in the S-task and 22 in the P-task). These pairs had exactly the same L1 performance. This procedure was repeated for 100,000