



## Associative memory and its cerebral correlates in Alzheimer's disease: Evidence for distinct deficits of relational and conjunctive memory



Christine Bastin<sup>a,\*</sup>, Mohamed Ali Bahri<sup>a</sup>, Frédéric Miévis<sup>a</sup>, Christian Lemaire<sup>a</sup>, Fabienne Collette<sup>a</sup>, Sarah Genon<sup>a</sup>, Jessica Simon<sup>a</sup>, Bénédicte Guillaume<sup>b</sup>, Rachel A. Diana<sup>c</sup>, Andrew P. Yonelinas<sup>d,1</sup>, Eric Salmon<sup>a,e,1</sup>

<sup>a</sup> Cyclotron Research Center, University of Liège, Allée du 6 Août, B30, 4000 Liège, Belgium

<sup>b</sup> Centre Hospitalier du Bois de l'Abbaye et de Hesbaye, 4000 Liège, Belgium

<sup>c</sup> Department of Psychology, Virginia Tech, Blacksburg, VA 24061, USA

<sup>d</sup> Department of Psychology, University of California Davis, Davis, CA 95616, USA

<sup>e</sup> Memory Clinic, CHU Liège, 4000 Liège, Belgium

### ARTICLE INFO

#### Article history:

Received 28 May 2014

Received in revised form

14 August 2014

Accepted 19 August 2014

Available online 27 August 2014

#### Keywords:

Associative memory

Binding

Alzheimer's disease

FDG-PET

### ABSTRACT

This study investigated the impact of Alzheimer's disease (AD) on conjunctive and relational binding in episodic memory. Mild AD patients and controls had to remember item–color associations by imagining color either as a contextual association (relational memory) or as a feature of the item to be encoded (conjunctive memory). Patients' performance in each condition was correlated with cerebral metabolism measured by FDG-PET. The results showed that AD patients had an impaired capacity to remember item–color associations, with deficits in both relational and conjunctive memory. However, performance in the two kinds of associative memory varied independently across patients. Partial Least Square analyses revealed that poor conjunctive memory was related to hypometabolism in an anterior temporal-posterior fusiform brain network, whereas relational memory correlated with metabolism in regions of the default mode network. These findings support the hypothesis of distinct neural systems specialized in different types of associative memory and point to heterogeneous profiles of memory alteration in Alzheimer's disease as a function of damage to the respective neural networks.

© 2014 Elsevier Ltd. All rights reserved.

### 1. Introduction

Binding processes in memory can create an associative link between independent items or between items and context into episodic memories (relational memory) (Cohen et al., 1999). An alternative process, conjunctive binding, allows associations to be encoded as a united representation of features or a single entity (Mayes, Montaldi, & Migo, 2007; O'Reilly & Rudy, 2001). Whereas memory for novel relational associations relies on the hippocampus, parahippocampal cortex and regions of the default mode network (posterior cingulate cortex/precuneus, lateral parietal and medial prefrontal cortex) (Diana, Yonelinas, & Ranganath, 2007; Mayes et al., 2007; Ranganath & Ritchey, 2012), conjunctive memory involves the perirhinal cortex (Diana, Yonelinas, & Ranganath, 2010; Haskins, Yonelinas, Quamme, & Ranganath, 2008; Staresina & Davachi, 2008).

Probable Alzheimer's disease (AD) is characterized by gradually progressive cognitive deficits typically starting with severe impairment of episodic memory (McKhann et al., 2011). Given that binding of information is a key feature of episodic memory, characterization of the memory deficit in AD should consider whether this crucial mechanism is compromised. Current evidence indicates that patients with Alzheimer's disease (AD) show impaired long-term relational memory, as evidenced by decreased ability to remember novel associations between words or pictures (Algarabel et al., 2012; Duchek, Cheney, Ferraro, & Storandt, 1991; Gallo, Sullivan, Daffner, Schacter, & Budson, 2004; Lindeboom, Schmand, Tulner, Walstra, & Jonker, 2002; Lowndes et al., 2008; Wolk, Dunfee, Dickerson, Aizenstein, & DeKosky, 2011), between objects and locations (Bucks and Willison, 1997; Fowler, Saling, Conway, Semple, & Louis, 2002; Hanaki et al., 2011; Huijbers, Bergmann, Olde Rikkert, & Kessels, 2011; Kessels, Feijen, & Postma, 2005; Lee, Rahman, Hodges, Sahakian, & Graham, 2003; Swainson et al., 2001), between verbal information and their source (Dalla Barba, Nedjam, & Dubois, 1999; Multhaup and Balota, 1997) and between faces and names (Pariente et al., 2005; Sperling et al., 2003). In contrast, little is known with regard to the effect of AD on

\* Corresponding author. Tel.: +32 4 366 23 69; fax: +32 4 366 29 46.

E-mail address: [Christine.Bastin@ulg.ac.be](mailto:Christine.Bastin@ulg.ac.be) (C. Bastin).

<sup>1</sup> Equal contribution.

conjunctive memory (i.e., object–feature associations). Studies of short term memory have indicated that AD patients are impaired at remembering conjunctions of visual features (i.e., shape and color) (Della Sala, Parra, Fabi, Luzzi, & Abraham, 2012; Parra et al., 2009; Parra, Abrahams, Logie, & Della Sala, 2010a; Parra et al., 2010b). In long-term memory, two studies indicated that AD patients make more errors than controls when recalling the color of studied objects (Della Sala, Kinneer, Spinnler, & Stangalino, 2000; Lloyd-Jones, 2005).

However, as no study directly contrasted long-term conjunctive and relational memory in AD, it is not known whether patients are differentially impaired on these forms of associative memory. Based on known patterns of cerebral changes in the course of AD, particularly early atrophy and dysfunction of the entorhinal and perirhinal cortices (Gour et al., 2011; Juottonen et al., 1998), we predict impaired conjunctive memory in AD (Didic et al., 2011; Wolk, Mancuso, Kliot, Arnold, & Dickerson, 2013). Additionally, altered functional connectivity within the default mode network in AD (Pievani, de Haan, Wu, Seeley, & Frisoni, 2011) may be associated with the disturbance of relational processes in episodic memory. Interestingly, healthy older adults retain the capacity to learn new conjunctions, but demonstrate impairment on relational memory tasks (Bastin et al., 2013). If AD affects both kinds of associative memory, behavioral performance profiles might differentiate AD from normal aging. In particular, if conjunctive binding is disproportionately impaired in patients, this may represent a signature of AD.

We assessed the impact of mild stage AD on long-term relational and conjunctive memory by testing memory for novel word–color associations encoded under two conditions. The context detail condition was designed to create an arbitrary, relational, association between separate entities such that color becomes a contextual detail related to the item. In contrast, the item detail condition was designed to create a unified, conjunctive, representation such that color is integrated as a feature of the item (Diana et al., 2010). Patients' brain metabolic activity at rest (FDG-PET) was analyzed with spatio-temporal Partial Least Squares (McIntosh, Bookstein, Haxby, & Grady, 1996) in order to assess the relation of behavioral performance and activity in functional cerebral networks. We expect that the neural correlates of conjunctive and relational memory will dissociate. Given heterogeneity in cognitive and metabolic profiles in AD (Davidson et al., 2010; Salmon et al., 2009), we hypothesized that both relational and conjunctive memory may be variably compromised across patients due to variable amount of hypometabolism in distinct networks even if, as a group, the patients may present with deficits in both kinds of associative memory. Impaired performance in the item detail condition may be associated with hypometabolism in a temporal network encompassing the perirhinal cortex, whereas deficits in the context detail condition would be related to dysfunction within the default mode network.

## 2. Materials and methods

### 2.1. Participants

The participants in this study were 30 patients with a diagnosis of probable Alzheimer's disease (19 women) (McKhann et al., 2011) and 24 healthy older adults (14 women). All participants were community-dwelling, were native French speakers and had normal or corrected-to-normal vision. Patients with probable AD were recruited in memory clinics in the Liège area and were selected on the basis of general examination, neurological and neuropsychological assessments, and neuroimaging. Temporoparietal hypometabolism (FDG-PET) and cortical and/or hippocampal atrophy on structural magnetic resonance image (MRI) were taken as biomarkers. Structural MRI showed mild leukoariosis consistent with aging and degenerative processes. Patients were included if their symptoms corresponded to a mild stage of AD, as indicated by a MMSE score above 20 (Folstein, Folstein, & McHugh, 1975; Hugonot-Diener, 2001). Healthy older participants had no global cognitive decline (as confirmed by their score superior to 132/144 on the Mattis Dementia Rating Scale (Mattis, 1973)) or psychiatric problems, were free of medication that could affect cognitive functioning, and reported being in good health.

**Table 1**  
Demographic and clinical characteristics of the participants.

	AD (n=30)	Controls (n=24)	p-Value
Age (years)	77.1 (6.4)	75.9 (8.1)	.56
Education (years)	12.1 (3.6)	11.6 (2.7)	.62
Gender F/M <sup>a</sup>	19/11	14/10	.70
Mattis DRS	125.9 (8.1)	140.5 (3.1)	<.001
MMSE	23.9 (2.0)	–	
GDS	2.9 (2.3)	2.6 (1.5)	.58

Standard deviations in brackets. DRS Dementia Rating Scale. GDS Geriatric Depression Scale.

<sup>a</sup> Chi-square test; other analyses used *t*-tests.

Table 1 presents the demographic and clinical characteristics of both groups. Patients and healthy controls were comparable in terms of age, years of education and gender distribution. Patients showed a significant cognitive decline as assessed by the Mattis Dementia Rating Scale (Mattis, 1973) when compared to controls. There was no group difference on the Geriatric Depression Scale (Yesavage et al., 1983).

Written informed consent was obtained from all participants according to the declaration of Helsinki. The study was approved by the Ethics Committee of the University Hospital of Liège.

### 2.2. Materials and procedure

Mild AD patients and healthy older adults performed a source memory task where word items were associated with one of two background colors (red or green) under two conditions. In the context detail condition, participants were asked to imagine the item in a situation with a green 100-euro bill if the background was green or with a red stop sign if the background was red. In the item detail condition, participants were asked to imagine the item as though it were the same color as the background.

A list of 40 concrete nouns, as well as the associated descriptive sentences, were selected from the materials used by Diana, Yonelinas, and Ranganath (2008) and Diana et al. (2010) and translated into French. Each sentence provided an explanation as to why the word item might be associated with a stop sign or a 100-euro bill (context detail condition) or why the item might be green or red (item detail condition). The words were randomly divided in two sets of 20 items. Each word had a sentence for both the item detail and context detail conditions such that assignment of the words to the two conditions could be counterbalanced across participants. The descriptive sentences were selected based on a pilot study in young adults that matched performance between conditions (Diana et al., 2010). Examples of sentences in the item detail condition are "The turtle is red because kids at the beach painted the shell so it would stand out amongst the other turtles" for the association "turtle-red", and "The cloth is green because the waiter used it to clean up spilled pea soup" for the association "cloth-green". Examples of sentences in the context detail condition are "The monkey is on the stop sign to show people that they should turn right to get to the zoo" for the association "monkey-red", and "The sock has a 100-euro bill in it because the traveler put the bill in his sock to keep it safe" for the association "sock-green".

Participants were tested individually in two sessions about 1 week apart. Each participant performed both conditions, which were administered in distinct sessions in order to minimize the contamination of one encoding condition on the other. Half of the participants started with the item detail condition, while the other half were first given the context detail condition. Stimuli were presented on a laptop computer. Each trial consisted of the presentation of a word against a background color (either green or red), with a sentence at the bottom of the screen. Before each task, participants were informed that their memory for the association between each word and the background color would be subsequently tested. In the item detail condition, they were asked to imagine the item as if it were the same color as the background, to read the sentence explaining why the item is that color, and to report whether this explanation was easy or difficult to imagine. In the context detail condition, participants were asked to imagine the item interacting with a stop sign (red background) or with a 100-euro bill (green background), to read the sentence explaining why the item is associated with the stop sign or the 100-euro bill, and to report whether that explanation was easy or difficult to imagine. Pictures of a stop sign and a 100-euro bill were shown before the task. The stimulus remained on the screen until a response was made. After a 20 s interval filled with conversation, the test phase began in which the participants were presented with a randomized list of the studied words shown one at a time. For each word, they were asked to indicate whether the associated background was red or green. The test phase was also self-paced.

### 2.3. Neuroimaging data acquisition

#### 2.3.1. Cerebral metabolism

At the end of the first session, AD patients' brain metabolic activity was measured during quiet wakefulness with eyes closed and ears unplugged after

متن کامل مقاله

دریافت فوری ←

**ISI**Articles

مرجع مقالات تخصصی ایران

- ✓ امکان دانلود نسخه تمام متن مقالات انگلیسی
- ✓ امکان دانلود نسخه ترجمه شده مقالات
- ✓ پذیرش سفارش ترجمه تخصصی
- ✓ امکان جستجو در آرشیو جامعی از صدها موضوع و هزاران مقاله
- ✓ امکان دانلود رایگان ۲ صفحه اول هر مقاله
- ✓ امکان پرداخت اینترنتی با کلیه کارت های عضو شتاب
- ✓ دانلود فوری مقاله پس از پرداخت آنلاین
- ✓ پشتیبانی کامل خرید با بهره مندی از سیستم هوشمند رهگیری سفارشات