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Neurobiology of Aging 34 (2013) 361–373

NEUROBIOLOGY OF AGING

www.elsevier.com/locate/neuaging

Regular articles

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

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Received 19 August 2011; received in revised form 6 April 2012; accepted 8 April 2012

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.

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http://dx.doi.org/10.1016/j.neurobiolaging.2012.04.004

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-