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Working memory retrieval differences between medial temporal lobe epilepsy patients and controls: A three memory layer approach ☆

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ABSTRACT

Multi-store models of working memory (WM) have given way to more dynamic approaches that conceive WM as an activated subset of long-term memory (LTM). The resulting framework considers that memory representations are governed by a hierarchy of accessibility. The activated part of LTM holds representations in a heightened state of activation, some of which can reach a state of immediate accessibility according to task demands. Recent neuroimaging studies have studied the neural basis of retrieval information with different states of accessibility. It was found that the medial temporal lobe (MTL) was involved in retrieving information within immediate access store and outside this privileged zone. In the current study we further explored the contribution of MTL to WM retrieval by analyzing the consequences of MTL damage to this process considering the state of accessibility of memory representations. The performance of a group of epilepsy patients with left hippocampal sclerosis in a 12-item recognition task was compared with that of a healthy control group. We adopted an embedded model of WM that distinguishes three components: the activated LTM, the region of direct access, and a single-item focus of attention. Groups did not differ when retrieving information from single-item focus, but patients were less accurate retrieving information outside focal attention, either items from LTM or items expected to be in the WM range. Analyses focused on items held in the direct access buffer showed that consequences of MTL damage were modulated by the level of accessibility of memory representations, producing a reduced capacity.

1. Introduction

Conceptualization of memory as a complex entity comprising different forms or systems has relied on several criteria for establishing such distinctions. Among them, differences in principles that characterize their modes of operation, and differences in underlying neural substrate (Fuster, 1995; Schacter, Wagner, & Buckner, 2000). Accordingly, differentiation between long-term memory (LTM) and working memory (WM) has been a widely accepted dichotomy (Fuster, 1995). Contrary to this perspective, unitary models of memory has called into question the distinction between WM and LTM, and considered that both processes are governed by the same principles (Crowder, 1993; Nairne, 2002; for a review see Lustig et al., 2009). Likewise unitary models, an influential theoretical framework proposes that WM and LTM are not entirely separable, and conceives WM as an activated subset of LTM. Crucially, some of the representations in the activated LTM have immediate access, the so-called 'focus of attention' (Cowan, 1999, 2001), and are considered to be limited to about 4 items in normal adult humans (Cowan, 2001; Lewis-Peacock, Drysdale, Oberauer, & Postle, 2012; Luck & Vogel, 1997; Lustig et al., 2009; Matsukura & Hollingworth, 2011). This proposition has been further elaborated and complemented by a model postulating three embedded components (Oberauer, 2002), which are conceived as successive levels of selection of memory representations (Rerko & Oberauer, 2013). The narrowest level of selection is the focus of attention (FA), with a single-item capacity (Basak & Verhaeghen, 2011; Garavan, 1998; McElree, 2006; Rerko & Oberauer, 2013; Verhaeghen et al., 2007); a region of direct access (DA), holding approximately 3–4 additional items (Basak & Verhaeghen, 2011; Oberauer, 2002, 2006; Oberauer & Hein, 2012; Verhaeghen et al., 2007); and an activated subset of LTM

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(aLTM), that is not limited by capacity (Basak & Verhaeghen, 2011; Cowan, Rouder, Blume, & Saults, 2012). In this view, WM capacity is determined by the capacity of the DA region (Oberauer & Bialkova, 2009). Recently, several neuroimaging studies have tested the neural substrates associated with processing of representations posited to be in distinct accessibility states. With this aim, these studies used a recognition paradigm with a rapid visual presentation of verbal (i.e. words) (Nee & Jonides, 2008, 2011; Öztekin, Davachi, & McElree, 2010) or visual information (i.e. faces) (Nee & Jonides, 2013). By analyzing the neural activation associated with retrieval of items in different serial positions, this paradigm allows to explore whether or not different brain regions are associated with retrieval of information held in FA (last item of the list), DA (two–three items previous to the last one), and aLTM (rest items of the list). Crucially, it was found that medial temporal lobe (MTL), including the hippocampus, parahippocampus and entorhinal cortex, a brain region traditionally assumed to support exclusively LTM operations (Jeneson & Squire, 2011), was activated during all serial positions of the list other than the last. This is, items from LTM and items expected to be actively maintained (Nee & Jonides, 2008, 2011, 2013; Öztekin et al., 2010; see also Öztekin, McElree, Staresina, & Davachi, 2009). Furthermore, it was found that MTL was even more activated when processing items within the DA (Nee & Jonides, 2011, 2013; Öztekin et al., 2010). Likewise, a recent study on visual WM using a change detection paradigm (Luck & Vogel, 1997) showed that hippocampal activation emerged within memory capacity and dropped when capacity limit was exceeded (von Allmen, Wurmitzer, Martin, & Klaver, 2013). Thus, results from these studies provide support for a three-layer model (Oberauer, 2002), and align with accumulating evidence showing the involvement of MTL in WM operations (Axmacher, Elger, & Fell, 2009a; Campo et al., 2005, 2012; Finke, Bruehl, Duzel, Heekeren, & Ploner, 2013; Poch & Campo, 2012; Poch, Fuentemilla, Barnes, & Duzel, 2011; Race, Laroque, Keane, & Verfaellie, 2013; Stretton et al., 2012; Toepper et al., 2010; von Allmen et al., 2013). Interestingly, recent behavioral studies have raised reasons to hypothesize that not all the items held in WM are equally processed. Memory strength parameters of representations held in memory follow a power function of serial position, this is, the magnitude of the memory strengths decreases with increasing lag (Donkin & Nosofsky, 2012a). Further support comes from a shared-resource model (Bays & Husain, 2008), according to which "the proportion of resources allocated to each item determines the precision with which it is remembered" (Fougnie, Suchow, & Alvarez, 2012; Wei, Wang, & Wang, 2012). This is also accounted by Oberauer's model, which considers that increasing number of items in the DA interfere with each other and that the FA can only retrieve items from DA, (Oberauer & Hein, 2012; Pelegrina, Borella, Carretti, & Lechuga, 2012), what make correct item selection more difficult with increasing set size (Basak & Verhaeghen, 2011; Ecker, Lewandowsky, Oberauer, & Chee, 2010; Janczyk & Grabowski, 2011).

To test the causal role of MTL in retrieving items within the WM range we explored the differences in accuracy and reaction time between a group of patients with focal MTL damage and a control group using the word recognition paradigm described by Öztekin et al. (2010). Mesial temporal lobe epilepsy (mTLE) associated with hippocampal sclerosis (HS) can be considered a model disorder to investigate the role of MTL in those operations (Jokeit, Bosshardt, & Reed, 2011). Our experimental approach was based on Oberauer's concentric model (Oberauer, 2002). If activation findings from the above mentioned studies are reflecting an essential contribution of MTL to WM, then it would be expected to find that patients with mTLE will retrieve items from DA consistently worse than healthy controls. Considering 'power-law' models, if increasing number of items will compete for limited resources it could be hypothesized that MTL damage would be reflected in weaker strength of memory representations when more items have to be maintained, potentially leading to a reduced memory capacity (Pelegrina et al., 2012). As differences in WM capacity are related to the ability to hold relevant information in the DA buffer, and are unrelated to variations in parameters of the FA (Oberauer & Hein, 2012), lesion effect would be absent for the last presented item, and become evident as a function of serial position within the DA buffer (Basak & Verhaeghen, 2011; Ecker et al., 2010; Janczyk & Grabowski, 2011).

2. Method

2.1. Participants

Thirteen patients (four male) with mTLE undergoing evaluation at the "Hospital Universitario Clínico San Carlos" and 26 healthy volunteers (seven male) were enrolled in the study. Participants were right handed according to the Edinburgh Handedness Inventory (Oldfield, 1971), and Spanish was their primary language. All participants gave written informed consent to be included in this study, approved by the local Research Ethics committee of the Hospital Universitario Clínico San Carlos. There were no significant differences between groups in terms of age ($t_{37} = 1.59$, $p > .10$) (Mean = 37, SD = 7.13 for patients; Mean = 31.62, SD = 10.96 for controls) or level of education ($t_{37} = 0.74$, $p > .45$) (Mean = 14.38, SD = 1.61 for patients; Mean = 14.88, SD = 2.16 for controls).

Diagnosis was established according to clinical EEG and MRI data. All patients underwent neurological examination, EEG monitoring, and high resolution 1.5 T brain MRI. Patients were included in the study when clinical data and MRI and EEG findings were suggestive of unilateral mesial temporal lobe epilepsy related to left HS. All patients had; (i) seizures with typical temporal lobe semiology that were not controlled with antiepileptic drugs (AEDs) and (ii) decreased volume (and abnormally increased T2 and FLAIR signal) of the left hippocampus on brain MRI. No lesions were observed in other structures beyond left MTL. No seizure occurred within 24 h prior to the experiment. At the time of study patients were on AED treatment, including levetiracetam, lamotrigine, oxcarbazepine, carbamazepine, valproate, topiramate, zonisamide, clonazepam, lorazepam, either in monotherapy or multitherapy.

Control volunteers were interviewed and entered in the study if they met the following inclusion criteria: (i) absence of a previous history of neuropathological conditions or psychopathological diseases; and (ii) no antecedent of drug or alcohol abuse.

2.2. Materials and procedure

Experimental task was adapted from Öztekin et al. (2010), consisting on a rapid sequential presentation of a 12-word list (525 ms each). After the study list, a 450 ms visual mask was presented. This was followed by a single trial probe during which participants were presented with two words for 2250 ms, one from the study-list and one a new word. Participants were required to indicate, by button press, which word had been presented in the study-list, thus minimizing any issue of response bias (Cowan et al., 2012). The order of test probes was determined randomly. Target word was randomly presented 50% of the trials on the right side and 50% on the left side of the display. There was and intertrial interval of 4500 ms consisting on a fixation cross. Words were randomly selected (without replacement) from a set of 806 one- or two-syllable words (Algarabel, Ruiz, & Sanmartín, 1988). Mean values of the selected words on relevant characteristics were as follows: on imaginability was 4.6 (ranging 3.5–6.7), on familiarity was 4.4 (ranging 2–6.3), on concreteness was 4.2 (ranging 3.5–6.7), and