

Distinct medial temporal contributions to different forms of recognition in amnesic mild cognitive impairment and Alzheimer's disease



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ARTICLE INFO

Available online 4 July 2013

Keywords:

Familiarity
Episodic memory
Recognition memory
Amnesic mild cognitive impairment
Alzheimer's disease

ABSTRACT

The simplest expression of episodic memory is the experience of familiarity, the isolated recognition that something has been encountered previously. Brain structures of the medial temporal lobe (MTL) make essential contributions to episodic memory, but the distinct contributions from each MTL structure to familiarity are debatable. Here we used specialized tests to assess recognition impairments and their relationship to MTL integrity in people with amnesic mild cognitive impairment (aMCI, $n=19$), people with probable Alzheimer's disease (AD; $n=10$), and age-matched individuals without any neurological disorder ($n=20$). Recognition of previously presented silhouette objects was tested in two formats—forced-choice recognition with four concurrent choices (one target and three foils) and yes/no recognition with individually presented targets and foils. Every foil was extremely similar to a corresponding target, such that forced-choice recognition could be based on differential familiarity among the choices, whereas yes/no recognition necessitated additional memory and decision factors. Only yes/no recognition was impaired in the aMCI group, whereas both forced-choice and yes/no recognition were impaired in the AD group. Magnetic resonance imaging showed differential brain atrophy, as MTL volume was reduced in the AD group but not in the aMCI group. Pulsed arterial spin-labeled scans demonstrated that MTL blood flow was abnormally increased in aMCI, which could indicate physiological dysfunction prior to the emergence of significant atrophy. Regression analyses with data from all patients revealed that regional patterns of MTL integrity were differentially related to forced-choice and yes/no recognition. Smaller perirhinal cortex volume was associated with lower forced-choice recognition accuracy, but not with lower yes/no recognition accuracy. Instead, smaller hippocampal volumes were associated with lower yes/no recognition accuracy. In sum, familiarity memory can be specifically assessed using the forced-choice recognition test, it declines later than other MTL-dependent memory functions as AD progresses, and it has distinct anatomical substrates.

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1. Introduction

Episodic memory, the ability to consciously recognize and recall previously experienced events, critically depends on the medial temporal lobe (Scoville & Milner, 1957). These MTL regions

include the hippocampus and adjacent cortical structures—entorhinal cortex and perirhinal cortex at the anterior end and parahippocampal cortex at the posterior end. The MTL is the most prominently affected brain area in Alzheimer's disease and first shows signs of disruption in the transitional stage known as mild cognitive impairment (MCI). Deficits at the MCI stage can impact one or more cognitive domains, often including episodic memory (amnesic subtype, aMCI). Patients with aMCI experience episodic memory deficits greater than those expected with healthy aging, but their cognitive deficits do not meet criteria for dementia

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(Petersen, 2007). Many individuals diagnosed with MCI never develop Alzheimer's disease, but all patients with Alzheimer's disease pass through an MCI stage.

In both AD and aMCI, histopathological studies have revealed increased neurofibrillary tangle density and neuron loss in MTL regions (Braak & Braak, 1991; Delacourte et al., 1999; Gomez-Isla et al., 1996; Guillozet, Weintraub, Mash, & Mesulam, 2003; Hyman, Van Hoesen, Damasio, & Barnes, 1984; Kordower et al., 2001; Mesulam, 1999), and various antemortem neuroimaging methods have indicated atrophy and reduced function in the MTL (Dickerson et al., 2001; Du et al., 2001; Jack et al., 2002; Kesslak, Nalcioglu, & Cotman, 1991; Killiany et al., 1993; Pannanen et al., 2004; Seab et al., 1988). Whereas pathological signs in postmortem brain tissue are needed for the formal diagnosis of Alzheimer's disease, typically there is no confirmation of pathology in patients under study—so the diagnosis given is “probable Alzheimer's disease” (here abbreviated as AD). Pathological and imaging studies have generally documented a greater extent of MTL damage in AD compared with aMCI.

A common assumption is that the progressive episodic memory deficits in aMCI and AD primarily arise from progressive MTL dysfunction. Yet, current theories suggest that episodic memory is not a unitary phenomenon. Thus, AD-related pathology may disrupt some phenomena more than others. The distinction between recollection and familiarity (Jacoby, 1991; Mandler, 1980; Yonelinas, 2002) may be particularly relevant. Recollection refers to the full-blown experience of recalling attended information and its contextual setting. Familiarity refers to the unsubstantiated sense that something has been experienced previously, without remembering associated contextual details. There is general agreement that both recollection and familiarity are disrupted in AD patients (e.g., Smith & Knight, 2002). In aMCI patients, recollection is typically disrupted but results have been mixed with regard to familiarity. Some studies reported preserved familiarity in aMCI (Anderson et al., 2008; Hudon, Belleville, & Gauthier, 2009; Serra et al., 2010; Westerberg et al., 2006), whereas others reported impaired familiarity in aMCI (Ally, Gold, & Budson, 2009; Wolk, Dunfee, Dickerson, Aizenstein, & DeKosky, 2011; Wolk, Signoff, & DeKosky, 2008). Our aim is to further examine how aMCI and AD pathology may impact familiarity in unique ways.

A pervasive hypothesis common to many current memory models is that a significant contribution from the hippocampus is not necessary for familiarity (Aggleton & Brown, 1999; Davachi, 2006; Diana, Yonelinas, & Ranganath, 2007; Montaldi & Mayes, 2010; Norman & O'Reilly, 2003; Shimamura, 2010). Consistent with these theories, several studies have shown intact item recognition despite impaired recall in neurological patients with circumscribed hippocampal damage (Aggleton & Brown, 1999; Holdstock et al., 2002; Mayes, Holdstock, Isaac, Hunkin, & Roberts, 2002; Vargha-Khadem et al., 1997; Yonelinas et al., 2002), and some of these have confirmed that item familiarity was intact (see Montaldi & Mayes, 2010). Additionally, in fMRI studies with young healthy adults, a lack of apparent hippocampal activity but robust changes in perirhinal activity have been associated with item familiarity (Davachi, Mitchell, & Wagner, 2003; Montaldi, Spencer, Roberts, & Mayes, 2006; Ranganath, Heller, Cohen, Brozinsky, & Rissman, 2005; Staresina & Davachi, 2008). There is general agreement across these models that perirhinal cortex is sufficient to support item familiarity, whereas the role that entorhinal cortex and parahippocampal cortex may play in familiarity is somewhat unclear. Some investigators have speculated that parahippocampal cortex may be involved in contextual representations (Davachi, 2006; Diana et al., 2007), and Montaldi and Mayes (2010) have suggested it may mediate familiarity for context.

Nonetheless, an alternative view is that functional dissociations between MTL regions are not so clear-cut, and that a hippocampal contribution to familiarity can be operative (Smith, Wixted, & Squire, 2011; Song, Wixted, Hopkins, & Squire, 2011). In patients with circumscribed hippocampal damage, for example, recall and recognition were similarly impaired (Manns, Hopkins, Reed, Kitchener, & Squire, 2003; Wixted & Squire, 2004). In fMRI experiments, perirhinal cortex has been implicated in inter-item associative recognition, which presumably cannot be completed based on familiarity alone (Düzel et al., 2003; Kirwan & Stark, 2004; Tendolkar et al., 2007). Furthermore, Squire and colleagues argue that methods that purport to separate familiarity from other memory expressions fail to avoid confounding differences in memory strength (Squire, Wixted, & Clark, 2007). This view thus acknowledges possibilities for functional heterogeneity across MTL regions, but it argues against the strong position that familiarity memory can be highly localized to perirhinal cortex. These arguments underscore the fact that a key challenge for this research is in measuring valid deficits in familiarity memory independently from allied memory functions.

Important advantages for interpreting memory dysfunction can be achieved when the number of available strategies people can use to reach an accurate memory decision is small. Holdstock et al. (2002) took advantage of this view by using two recognition tests in which foils were highly similar to studied objects. One test entailed a four-alternative forced-choice format wherein the participant attempted to select the studied object from among four highly similar objects (Fig. 1). The other test required standard yes/no decisions for studied objects and their similar foils, with one object presented at a time. Responding on the forced-choice but not the yes/no test can primarily rely on familiarity. For both the forced-choice and yes/no formats, recollecting conceptual information is unhelpful, given the high similarity among a target and its corresponding foils. For example, remembering a verbal label for a studied object will not yield accurate target-foil discrimination, nor will remembering contextual features from the study episode. Recollecting a specific visual feature can be helpful, but the large overlap in features present between the foils and corresponding targets makes it very difficult to recollect the critically distinguishing features. In the forced-choice format, when targets are grouped with their corresponding foils, recollecting distinguishing features may occasionally be effective, but a dominant strategy could be to determine the familiarity of each of the four highly similar choices and then select the one most

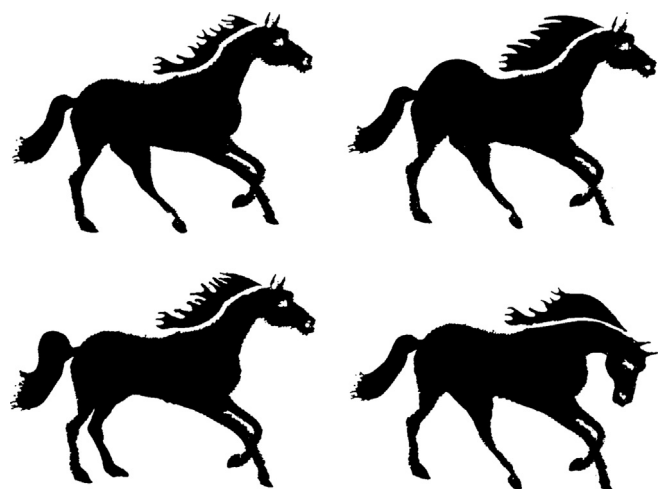


Fig. 1. Stimuli used for testing recognition. This is an example of one forced-choice recognition test trial. Only one of the four highly similar objects was previously studied.

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