RAPID COMMUNICATION

A Medial Temporal Lobe Division of Labor: Insights From Memory in Aging and Early Alzheimer Disease

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ABSTRACT: **Dual process theories of recognition memory posit that recollection and familiarity represent dissociable processes. Animal studies and human functional imaging experiments support an anatomic dissociation of these processes in the medial temporal lobes (MTL). By this hypothesis, recollection may be dependent on the hippocampus, while familiarity appears to rely on extrahippocampal MTL (ehMTL) structures, particularly perirhinal and lateral entorhinal cortices. Despite these findings, the dual process model and these anatomic mappings remain controversial, in part because the study of patients with lesions to the MTL has been limited and has revealed predominantly single dissociations. We examined measures of recollection and familiarity in three groups (normal older adults, amnesic-mild cognitive impairment, Alzheimer's disease) in which these memory measures and the relative integrity of MTL structures are variable, thus enhancing our power to detect MTL-memory relationships. Recollection and familiarity and volumes of hippocampus and ehMTL, defined as a region including entorhinal/perirhinal cortices and parahippocampus, were measured. Regression analyses revealed a stronger relationship of recollection with the hippocampus compared to ehMTL, while familiarity was more highly related to ehMTL compared to hippocampus. These results are consistent with a division of labor in the MTL and the dual process model.** © 2010 Wiley-Liss, Inc.

KEY WORDS: **memory; recollection; familiarity; Alzheimer's disease; medial temporal lobe**

One major theory of episodic memory, the "Dual Process Model," proposes that recognition memory may be subserved by the dissociable processes of recollection and familiarity (Mandler, 1980; Jacoby, 1991; Eichenbaum et al., 1994; Brown and Aggleton, 2001; Yonelinas, 2002). Recollection is conceived of as reflecting conscious, contextual retrieval of a prior episode or event, while familiarity is described as an acontextual sense of prior exposure. Several lines of evidence using different methodologies have supported this dissociation and a possible anatomic segregation of these processes within the medial temporal lobe [MTL; (Yonelinas, 2002; Aggleton and Brown, 2006; Eichenbaum et al., 2007)]. Specifically, the hippocampus has been linked to recollection while surrounding anterior extrahippocampal medial temporal lobe regions (ehMTL) are hypothesized to be related to familiarity. In particular, the lateral entorhinal and perirhinal cortices have been associated with familiarity-based memory. However, these anatomic mappings and the dual process construct remain a contentious area of debate (Squire et al., 2007).

Functional imaging studies in humans have generally supported this dissociation (Davachi et al., 2003; Henson et al., 2003; Montaldi et al., 2006), but work in patients with MTL brain lesions has been somewhat less clear. Much of this work has come from relatively small case series of individuals in which single-dissociations have been reported. Hippocampal lesions are associated with selective loss of recollection, whereas more widespread MTL injury is associated with impairment of both recollection and familiarity (Holdstock et al., 2002; Yonelinas et al., 2002); however, conflicting results and interpretations have been reported (Manns et al., 2003; Squire et al., 2007). Stronger support for the hypothesis would come from a double dissociation in which recollection covaries with measures of hippocampal integrity and familiarity with ehMTL. Recently, two reports have provided the first neuropsychological evidence of this double dissociation. Bowles et al. (2007) described a single patient with a unilateral anterior MTL resection, including perirhinal/entorhinal cortex (EC) but sparing the hippocampus, who had disproportionate impairment of familiarity. Yonelinas et al. (2007)

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found that derived measures of recollection and familiarity were associated with hippocampal and entorhinal volumes, respectively, in older adults.

This study sought to expand these findings in a population chosen for its varying levels of recollection and familiarity: older adults, subjects with amnesic-MCI (a-MCI), and patients with Alzheimer's Disease (AD). Measures of these memory processes were investigated in relation to hippocampal and ehMTL (including entorhinal, perirhinal, and parahippocampal cortices) volumes. We predicted that verbal measures of recollection and familiarity would correlate more strongly with the left hippocampus and ehMTL, respectively. A related picture task was also employed to provide another assessment of these relationships and verify previously described modality-specificity effects (de Toledo-Morrell et al., 2000), with the expectation of larger correlation with right medial temporal structures.

Twenty-two older adult (OA) controls [mean: 71.7 ± 9.1 (SD) years; mean education: 16.7 ± 2.9 (SD) years; mean MMSE: 29.7 ± 0.7] and 23 patients with either a-MCI (n = 14) or mild AD (n = 9) [mean: 73.8 ± 7.5 (SD) years; mean education: 16.0 ± 3.1 (SD) years; mean MMSE: 26.4 ± 2.6] were recruited from the University of Pittsburgh's Alzheimer's Disease Research Center. The extensive evaluation process and clinical criteria applied has been described (Lopez et al., 2000). Many of the current cohort represent a subset of patients from whom behavioral data on the below experimental measures of recollection and familiarity were reported previously [18 OA, 12 a-MCI, and 0 patients with AD were included in the prior study (Wolk et al., 2008)].

All participants completed two memory tests that allowed for estimation of recollection and familiarity using a variation of the process dissociation procedure. These tasks have been described in detail (Wolk et al., 2008). Briefly, in one task subjects studied unrelated word pairs. At test they were shown intact pairs, rearranged pairs in which each word was previously studied, and novel pairs in which neither word was previously studied. They were instructed to make an "Old/New" decision, but to only endorse intact pairs as "Old." The rearranged pairs produce a condition in which recollection opposed familiarity. As each word of the rearranged pair had been studied previously, these items would be associated with familiarity, driving the subject to incorrectly endorse the pair as Old. However, the contextual retrieval of recollection would allow the subject to recall that the words had a different associate at study and correctly endorse the pair as "New."

On the basis of the rate of Old endorsements for these classes of items one can calculate estimates of recollection (R) and familiarity (F) based on the following: $R = p$ (intact) – p (rearranged); $F = p$ (rearranged)/(1 – R). To account for differences in base rates of false alarms (Old responses to novel pairs), familiarity was calculated using a measure of discrimination (d') derived from signal detection theory (Yonelinas et al., 1995; Davidson et al., 2006). The second task was identical conceptually; subjects studied words presented in red or green and at test were told to endorse only items studied in one of the two colors as Old. In an attempt to provide more stability to these measures, as well as to assess recollection with more than one form of contextual detail (word-pair and color), performance was collapsed across these two tests for each participant. Additionally, all but one patient performed a visual source memory task in which pictures were studied in one of four quadrants. At test, participants had to make an Old/New judgment (i.e., item memory) and then recall the quadrant of study (i.e., source memory) (Wolk et al., 2008). This paradigm represents a form of "task dissociation" in which the source judgments are thought dependent on recollection while the item judgment is likely dependent on a combination of recollection and familiarity, but may be performed accurately in the absence of recollection (Yonelinas, 2002).

MR imaging was performed using a 1.5 Tesla G.E. Signa scanner. A volumetric spoiled gradient recalled (SPGR) sequence was used to acquire T1-weighted images optimized for contrast among gray matter, white matter, and CSF (TE/TR = 5/25, flip angle = 40°). Images were acquired in the coronal plane, with 1 mm × 1 mm in plane resolution and 1.5 mm slice thickness/0 mm interslice. A total of 120 contiguous slices were acquired. Hippocampal and ehMTL volumes were calculated using the automated labeling pathway (ALP), an atlas-based segmentation technique utilizing a fully deformable registration approach to measure predefined regions of interest (Wu et al., 2006; Andreescu et al., 2007). The ALP technique registers the standard brain image to each individual subject, using a series of progressively more deformable registrations, including an affine linear registration, a hierarchical linear model, and demons-based model. The software was written using the Insight Segmentation and Registration Toolkit [ITK, (Yoo, 2004)]. ALP and related fully deformable registration techniques for hippocampal measurement have been applied successfully to scans of patients with AD and MCI and yielded high agreement with manual tracings (Carmichael et al., 2005; Wu et al., 2006). Anatomic regions of interest (ROIs) were from the automated anatomic labeling (AAL) atlas in which the ehMTL volume, referred to as parahippocampus in this atlas, included entorhinal and perirhinal cortices in addition to parahippocampus proper (Tzourio-Mazoyer et al., 2002). These ROIs were defined on the reference brain (MNI colin27) and transformed to fit each individual's anatomic image, and then entire brain was segmented into gray, white, and cerebrospinal fluid tissue types. Voxel counts of gray matter were automatically obtained from the ROIs of interest (Zhang et al., 2001).

Measures of recollection and familiarity for the three groups are presented in Table 1. Consistent with our prior report, a-MCI and patients with AD displayed an impairment of both recollection and familiarity relative to controls [a-MCI recollection: $t(33) = 2.4$, $P < 0.05$); a-MCI familiarity: $t(33) = 4.5$, $P < 0.01$; AD recollection: $t(28) = 3.4$, $P < 0.01$; AD familiarity: $t(28) = 5.9$, $P < 0.01$]. As expected, ICV-normalized hippocampal and ehMTL volumes were smallest in patients with AD, intermediate in a-MCI, and largest in OA (Fig. 1).

For measures of recollection and familiarity, we examined the relationship of ICV-normalized left hippocampal and ehMTL volumes, controlled for age and group status (entered

TABLE 1.

Demographic and Memory Data for Older Adults, Amnesic-Mild Cognitive Impairment Patients, and Alzheimer's Disease Patients

	OA (n = 21)	a-MCI (n = 14)	AD (n = 9)
MMSE	29.7 (0.7)	28.0 (1.7)[a]	24.0 (1.9)[a,b]
Age (years)	71.7 (9.1)	71.2 (8.0)	77.8 (4.4)[b]
Education (years)	16.7 (2.9)	16.6 (3.1)	15.0 (3.0)
Recollection	0.36 (0.23)	0.21 (0.12)[a]	0.10 (0.09)[a,b]
Familiarity (d')	1.86 (0.50)	1.12 (0.42)[a]	0.73 (0.40)[a,b]
Source/total studied	0.58 (0.17)	0.37 (0.16)[a]	0.30 (0.15)[a]
Source/hits	0.73 (0.15)	0.54 (0.19)[a]	0.36 (0.13)[a,b]
Item (d')	2.93 (0.57)	2.13 (0.60)[a]	1.74 (0.75)[a]

OA, older adult controls; a-MCI, amnesic-mild cognitive impairment; AD: Alzheimer's disease.
[a]$P < 0.05$ relative to controls.
[b]$P < 0.05$ relative to a-MCI.

as dummy variables), using several separate linear regressions. In each case, the model included either recollection or familiarity as the dependent variable and one of the above anatomic regions as the independent variable, along with the two covariates. Left hippocampal volume ($\beta = 0.37$, $P < 0.05$), but not left ehMTL ($\beta = 0.13$, $P > 0.1$), significantly predicted recollection. Conversely, familiarity was predicted by left ehMTL volume ($\beta = 0.35$, $P = 0.01$), but not significantly by left hippocampus ($\beta = 0.21$, $P > 0.1$; Fig. 1). Note that the significant associations (hippocampus with recollection and ehMTL with familiarity) were somewhat greater for left than right medial temporal structures consistent with a modality specific effect (recollection: $\beta = 0.37$ vs. $\beta = 0.26$; familiarity: $\beta = 0.35$ vs. $\beta = 0.31$, left vs. right, respectively). Alternatively, item memory, a form of memory thought relatively dependent on familiarity, was predicted by right ehMTL ($\beta = 0.35$, $P < 0.05$), but not hippocampus ($\beta = 0.16$, $P > 0.1$) or the left ehMTL ($\beta = 0.10$, $P > 0.1$), for the picture task. Source memory, a form of memory thought dependent on recollection, was not predicted by hippocampal or ehMTL volumes (β's < 0.19, P's > 0.1), regardless of whether calculated over the total number of studied items or hits.

To follow-up on the above-mentioned dissociation, a hierarchical regression model was developed in which the covariates of age and group were entered first and then both left

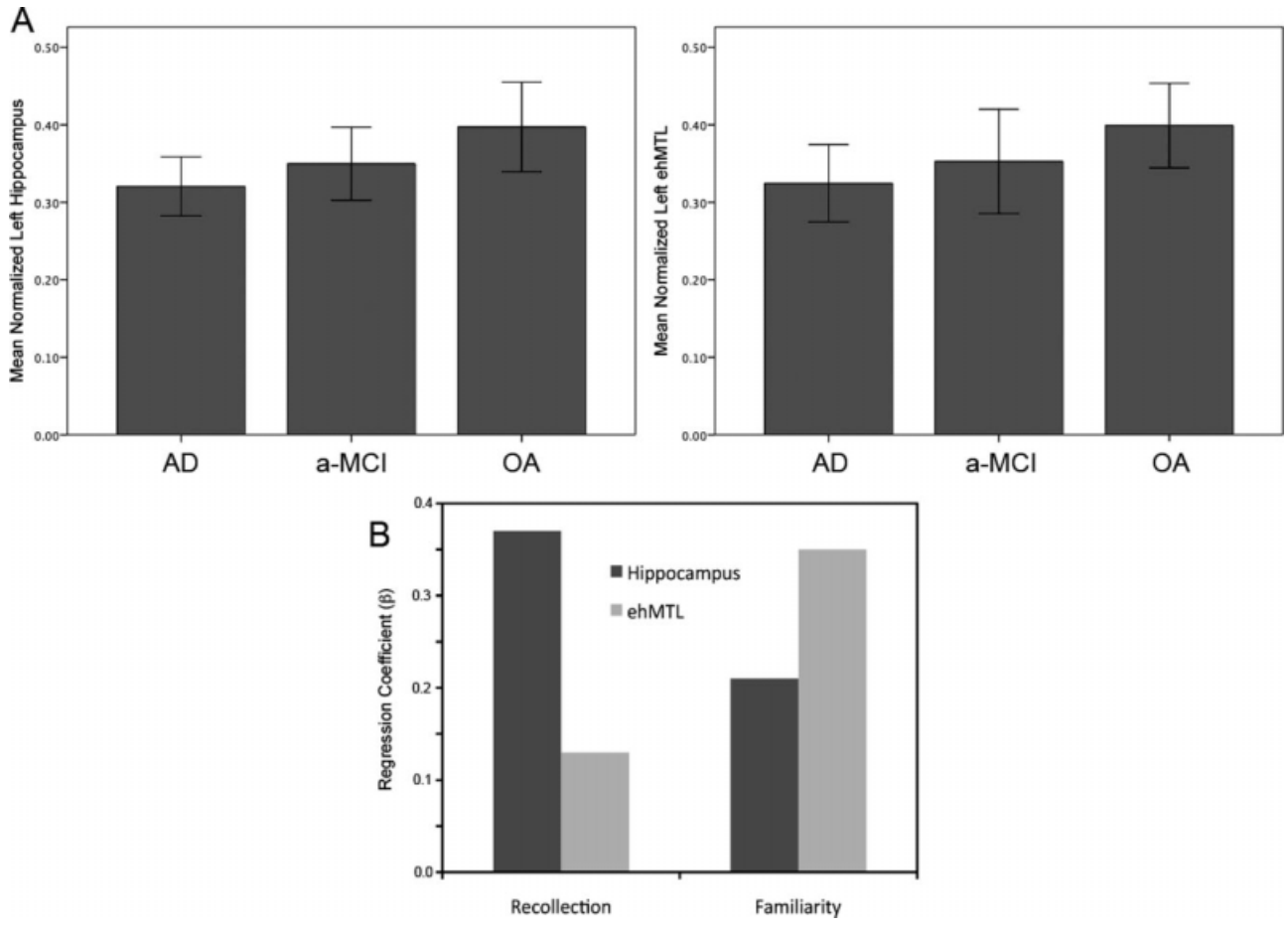

FIGURE 1. (A) Mean left hippocampal and extrahippocampal medial temporal lobe (ehMTL) ICV-normalized volumes for Alzheimer's disease (AD), amnesic-mild cognitive impairment (a-MCI), and older adults (OA). Error bars represent 1 standard deviation (SD). (B) Relationship (β) of left hippocampus and ehMTL with recollection and familiarity, respectively.

TABLE 2.

Predictors of Recollection and Familiarity in Hierarchical, Step-Wise Regression Model

Predictor	β	*t*	R^2	*F*	Model *P*
Recollection					
Model 1			0.36	5.6	0.001
Age	0.06	0.41			
D1 (AD = 1, MCI/control = 0)	−0.17	−1.1			
D2 (control = 1, AD/MCI = 0)	0.24	1.5			
Left hippocampus	0.37[a]	2.08			
Left extrahippocampal MTL	0.03	0.18			
Model 2			0.28	7.8	0.001
Age	0.09	0.54			
Left hippocampus	0.56[a]	3.6			
Left extrahippocampal MTL	0.13	0.73			
Familiarity					
Model 1			0.62	15.9	<0.001
Age	−0.01	−0.07			
D1 (AD = 1, MCI/control = 0)	−0.18	−1.53			
D2 (control = 1, AD/MCI = 0)	0.44[a]	3.61			
Left hippocampus	0.11	0.75			
Left extrahippocampal MTL	0.35[a]	2.70			
Model 2			0.45	10.8	<0.001
Age	0.12	0.82			
Left hippocampus	0.34[a]	2.18			
Left extrahippocampus MTL	0.47[a]	3.05			

For both recollection and familiarity, Model 1 was the most predictive model from the step-wise regression, controlling for group. Likewise, Model 2 was the most predictive model without controlling for group. Shaded rows represent variables not included in the model.

[a]$P < 0.05$; D1 and D2 represent group dummy variables.

hippocampal and ehMTL normalized volumes were regressed in a step-wise fashion. With recollection as the dependent variable, left hippocampal volume ($\beta = 0.37$, $P < 0.05$), but not ehMTL ($\beta = 0.03$, $P > 0.1$), was included in the model with the highest explanatory power. For familiarity, left ehMTL volume ($\beta = 0.35$, $P = 0.01$) was retained in the model, but not hippocampus ($\beta = 0.11$, $P > 0.1$). In other words, the ehMTL and hippocampus offered no additional explanatory information for recollection and familiarity, respectively (Table 2). Not including group in these models increased the predictive value of the anatomic regions, but did not change the qualitative pattern of these relationships (Table 2).

This study provides further evidence that recollection and familiarity are anatomically dissociable processes within the MTL, supporting dual process models of recognition memory (Yonelinas, 2002; Aggleton and Brown, 2006; Eichenbaum et al., 2007). Specifically, we found a double dissociation between these memory measures and their relative relationship with the hippocampus and ehMTL structures. This finding argues against the potential confounds of floor effects or the relative sensitivity of the memory measures, which are potential considerations for single dissociations that constitute the majority of reports in the neuropsychological literature on this topic.

Some, but not all (Stark et al., 2002; Manns et al., 2003), prior neuropsychological work has reported that isolated hippocampal lesions result in impaired recollection, but sparing of familiarity (Holdstock et al., 2002; Yonelinas et al., 2002). Alternatively, lesions that include both hippocampal and ehMTL structures result in impairment of both memory processes. The sparing of familiarity after isolated hippocampal lesions, but its sensitivity to more extensive ehMTL injury, has been taken as evidence of the dependence of this memory process on the latter region. While supportive, the lack of a clear double dissociation limits inference from such studies (Shallice, 1988).

The ability to study the memory effects of ehMTL lesions directly is limited by the rarity of injury sparing the hippocampus. In the literature, there is only one reported case of a patient with an isolated left perirhinal surgical resection, which included portions of amygdala and entorhinal cortex, but not hippocampus (Bowles et al., 2007), who was studied from the dual process perspective. This patient displayed a selective impairment of familiarity and, in effect, "completes" the double dissociation with the above-noted neuropsychological studies; however, it is only a single case.

This study population may be ideal for further defining and verifying the relationship between MTL structures and these memory processes, as there is significant variability in both recollection and familiarity (Table 1) and the relative volumes of these brain regions (Fig. 1) in the continuum from healthy aging to early AD. Considerable evidence supports that in aging and early AD, volumetric magnetic resonance imaging (MRI) of the medial temporal lobe is a good surrogate for the degree of neurodegenerative change, including neuronal loss and neuropathology [e.g., (Jack et al., 2002)]. Thus, this population affords the possibility of examining the relative effects of "lesions" to different medial temporal structures on measures of recollection and familiarity. Although there is significant correlation between pathology in early AD in hippocampal and extrahippocampal medial temporal structures, entorhinal and perirhinal regions tend to show greater earlier pathology than the hippocampus (Delacourte et al., 1999). Nonetheless, there is some variability in this pattern and it is impressive that despite correlation between these regions and their significant interconnectedness, we were still able to observe a dissociation in their relative strength of association with recollection and familiarity.

The current result conforms well with one other neuropsychological study of aging which also found a neuroanatomical dissociation between these memory processes (Yonelinas et al., 2007). Yonelinas et al. examined the relative correlations of hippocampus and EC with performance on a recall and item recognition memory task. They found that recall measures, dependent on recollection, correlated more highly with hippocampal than entorhinal volume, while the opposite pattern was found for item recognition measures; the latter is more likely dependent on familiarity. Structural equation modeling of recollection and familiarity further supported this dissociation.

The present data extend these findings by studying a population with a greater range of both memory impairment and

medial temporal degeneration. Further, direct estimations of recollection and familiarity were obtained using the process dissociation procedure, a method that has displayed significant convergence with other estimation techniques (Yonelinas, 2002). Finally, the ehMTL measure of this work also included perirhinal cortex, which has played a central role in most anatomical accounts of the dual process model (Yonelinas, 2002; Aggleton and Brown, 2006; Eichenbaum et al., 2007). Nonetheless, given the inherent assumptions of different methods for estimating recollection and familiarity, convergence with the Yonelinas et al. findings in a different dataset provides critical support for the anatomical dissociation of these memory processes. This neuropsychological support is an important complement to functional imaging studies, which have reported similar mappings of recollection and familiarity (Davachi et al., 2003).

Some caveats bear mention. First, while regression coefficients were stronger for one medial temporal region than the other for both recollection and familiarity, there were still positive, nonsignificant correlations with the other region. Whether this is simply a reflection of the correlation between these structures in individuals, as suggested by the step-wise regression, or evidence that these regions also contribute to a lesser degree to these memory processes cannot be resolved with the current analysis. Second, while ehMTL measurement included perirhinal and entorhinal regions in addition to the parahippocampus, one obviously cannot determine whether any of these regions were specifically more associated with familiarity; further work with more precise anatomic boundaries will be needed. Also, while the picture task produced a similar result (right ehMTL $>$ hippocampus) for a memory measure thought relatively dependent on familiarity (i.e., item memory), we did not observe a concomitant relationship between the hippocampus and the spatial source memory judgment. The reason for this is unclear, but could be related to the nature of study material, the task design, or even the relative dependence on frontal lobe function for source judgments (Johnson et al., 1997), which could weaken the relationship with hippocampal volume. Future studies will also need to examine the relationship of specific types of recollection (source vs. associative, etc) with brain structure.

Finally, one could also fit this data with some accounts of a "single-process," strength-based memory system. While the process dissociation tasks used here sort memory performance qualitatively, ostensibly on the basis of associative/relational vs. item retrieval, it has been argued that such process estimation techniques may be confounded by the orthogonal dimension of memory strength (Squire et al., 2007). Indeed, Squire et al. have argued that the anatomic mappings of recollection and familiarity may more accurately relate to strong and weak memories. While further research will be needed to disentangle these notions, this study strongly supports the more general idea that the hippocampus and ehMTL structures differentially represent specific memory states.

In conclusion, the current results offer important support of an anatomic dissociation of MTL structures and their relationship to measures of recollection and familiarity, and provide strong neuropsychological evidence consistent with the dual process model. Regardless of the proposed theoretical model, the fact that these memory measures appear to have differential sensitivity for the integrity of extra-hippocampal vs. hippocampal MTL structures also has important clinical implications, as different disease processes may involve these regions differentially.

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