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Associative reinstatement: A novel approach to assessing associative memory in patients with unilateral temporal lobe excisions[☆]

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ABSTRACT

We investigated whether unilateral medial temporal lobe (MTL) damage disrupts associative reinstatement, which represents the gain in item memory when the studied associative information is reinstated at retrieval. We were interested to see whether associative reinstatement relies on the same relational binding operations that support other types of associative memory (associative identification and recollection) thought to be subserved by the MTL. In addition, we examined whether such damage affects the different types of associative memory to a greater extent than item memory and item familiarity, and whether a different pattern is seen in patients with language dominant relative to non-dominant temporal lobe resection when the studied material consists of verbal information. To do so, we used a word pair recognition paradigm composed of two tasks: (1) a pair recognition task that provides measures of associative reinstatement and item memory, and (2) an associative identification recognition task that provides a measure of associative identification memory. Estimates of item familiarity and recollection were derived from performance on both tasks using a variant of the process-dissociation procedure. Our results showed that associative reinstatement, like other types of associative memory measures, was impaired in patients with unilateral resection, irrespective of the side of damage. Item familiarity, however, was impaired solely following language dominant resection. The lack of a laterality effect in our relational measures was likely due to using an encoding task that promoted formation of both verbal and visual associations, whereas item-based familiarity could rely exclusively on verbal operations. We propose that associative reinstatement provides a sensitive measure of relational memory that is less dependent on strategic processing and therefore more appropriate for evaluating MTL function in patients.

Memories of newly experienced events are composed of single pieces of information (item memory) and links or associations between these elements (associative memory). Several dissociations have been documented between these types of memory using recognition memory tasks in which participants are required to discriminate between studied and novel items (item memory) or between studied and novel pairings of previously encountered items (associative identification). These dissociations pertain to the cognitive operations required at encoding and at retrieval, the underlying memory processes, and the neural substrate of these types of memory (see Eichenbaum, Yonelinas, & Ranganath, 2007; Yonelinas, 2002, for reviews). Notably, associative identification, to a greater extent than item memory, requires the creation of links between items during the encoding phase via relational binding operations, which have been shown to be dependent on the medial temporal lobes (MTL; see Davachi, 2006, for review). Furthermore, associative identification requires the instantiation of self-directed strategic operations at retrieval, which are thought to be more dependent upon frontal lobe regions (Achim & Lepage, 2005; Lepage, Brodeur, & Bourgouin, 2003). From the perspective of dual-process models of recognition memory (Mandler, 1980; see Yonelinas, 2002, for a review of these models), these strategic retrieval operations are strongly involved in supporting recollection-based memory. Recollection is typically defined as an effortful and slow process (but see Dewhurst, Holmes, Brandt, & Dean, 2006) that permits retrieval of contextual or associative information. In contrast, these operations are not as necessary to retrieve item information via familiarity, which is a fast process characterized by a decontextualized feeling of oldness.

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Importantly, we showed in previous behavioural studies that not all types of associative memory require these strategic retrieval operations or recollection (Cohn, Emrich, & Moscovitch, 2008; Cohn & Moscovitch, 2007). Specifically, associative reinstatement, which refers to gains in item memory seen when items are presented in their studied pairings relative to novel pairings (akin to cueing), clearly does not. In contrast to associative identification and in some cases item memory, associative reinstatement is not affected by conditions that prevent participants from undertaking elaborate retrieval operations (e.g., speeded retrieval, short response deadline, overlapping pairing condition in which a target word has several studied associates). It is also unaffected, along with item familiarity, in older adults who show deficits in associative identification and recollection, which can be attributed to suboptimal frontal lobe functioning. However, unlike item familiarity, associative reinstatement appears to require some kind of relational binding operations. Notably, it is reduced, as is associative identification, following dividing attention at encoding (Castel & Craik, 2003) and following shallow encoding of the relational information between items (Cohn & Moscovitch, 2007). In sum, associative reinstatement is like associative identification and recollection as it requires relational binding operations at encoding, but differs from these at retrieval as it does not necessitate elaborate retrieval operations. Therefore, we propose that associative reinstatement may provide a 'purer' index of relational binding ability and of MTL function than other associative memory tasks.

The main goal of the current study was to verify whether associative reinstatement and the relational binding operations that support it rely on the MTL, as do associative identification and recollection. While several studies have documented associative identification deficits following bilateral MTL lesions, either of greater (Giovanello, Verfaellie, & Keane, 2003; Giovanello, Keane, & Verfaellie, 2006; Holdstock, Mayes, Gong, Roberts, & Kapur, 2005; Mayes, Holdstock, Isaac, Hunkin, & Roberts, 2002; Mayes et al., 2004; Turriziani, Fadda, Caltagirone, & Carlesimo, 2004; Vargha-Khadem et al., 1997) or of equal magnitude than deficits in item memory (Cipolotti et al., 2006; Stark, Bayley, & Squire, 2002; Stark & Squire, 2003), only two studies have investigated associative reinstatement in these patients. In one study, associative reinstatement was impaired in amnesic patients despite intact associative priming, suggesting that the relational binding operations underlying reinstatement depend on MTL regions and were dissociable from those underlying associative priming subserved by the posterior neocortex (Goshen-Gottstein, Moscovitch, & Melo, 2000). In another study, amnesic patients also showed impaired reinstatement, even when item memory was equated with that of control participants (Kan, Giovanello, Schnyder, Makris, & Verfaeillie, 2007). The latter suggested that reinstatement is dissociable from item familiarity, though item memory is not a pure measure of this process as recollection also contributes to it.

These studies involved patients with bilateral MTL lesions or degeneration with severe functional memory deficits. In Kan et al. (2007), to equate performance between patients and controls and to avoid floor effects in patients or ceiling effects in controls, patients received six presentations of the study material, while controls received only one. A fundamental problem with this approach is that it assumes that this manipulation enhances all types of recognition memory and processes to the same extent. However, repetition at study in healthy participants enhances item memory but has little or no effect on associative identification (Cleary, Curran, & Greene, 2001). Thus, the difference between the tasks completed by patients and by controls creates confounds and makes interpretation difficult, especially if one argues for dissociations between memory types. It is thus preferable to use the same study procedure, but test patients with milder memory deficits. Such patients include individuals with unilateral MTL dysfunction (e.g., temporal lobe epilepsy) or lesion [e.g., unilateral temporal lobe excision (TLE) for the treatment of epilepsy]. These patients are not functionally amnesic, but typically show memory impairments on standardized neuropsychological tests that are specific to the material preferentially processed by the damaged hemisphere (e.g., left hemisphere for verbal material; Jones-Gotman, 1997; Milner, 1974; Morris, Abrahams, & Polkey, 1995).

To our knowledge, there are no studies investigating associative reinstatement or associative identification in these patients. There are only a few published studies that investigated recollection and familiarity for single items using other paradigms (e.g., remember-know procedure and source memory), but their findings are mixed. All studies showed recollective deficits in this population, which were interpreted as impaired relational binding operations, but some showed deficits only for material processed by the damaged hemisphere (Bird, Shallice, & Cipolotti, 2007; Moscovitch & McAndrews, 2002), only in dominant TLE patients irrespective of the type of material used (Blaxton & Theodore, 1997) or in all TLE patients regardless of side of lesion and material (Moran, Seidenberg, Sabsevitz, Swanson, & Hermann, 2005; Thaiss & Petrides, 2003). All studies also suggest that familiarity is intact for material processed by the undamaged hemisphere, but some suggest that it is impaired solely for material processed by the damaged hemisphere (Bird et al., 2007; Blaxton & Theodore, 1997; Thaiss & Petrides, 2003) whereas others report that it is intact regardless of the type of material or side of lesion (Moscovitch & McAndrews, 2002).

In the current study, our first goal was to verify whether associative reinstatement is impaired in memory-impaired but non-amnesic patients with unilateral TLE, and thus, verify whether this type of associative memory relies on relational binding operations subserved by MTL regions, as suggested by previous studies with amnesic patients (Goshen-Gottstein et al., 2000; Kan et al., 2007). Our second goal was to investigate potential differences in associative and non-associative memory between patients with language dominant and non-dominant hemisphere resections to help resolve some of the mixed results noted in the literature. To do so, we employed a word pair recognition paradigm previously used with young adults under various experimental conditions (Cohn & Moscovitch, 2007) and with older adults (Cohn et al., 2008). This paradigm includes two old–new recognition tasks: (1) a pair recognition task in which participants must discriminate between pairs containing at least one unstudied word (new and half-old pairs) from pairs composed of two studied words (intact pairs and rearranged pairs), and (2) an associative identification recognition task in which participants are required to endorse pairs that reinstate the studied pairings (intact pairs) and reject all other pairs (new, half-old and rearranged pairs). The associative reinstatement and item memory measures are derived from performance on the pair recognition task, the associative identification measure is derived from the associative identification recognition task, and estimates of familiarity and recollection are derived from performance on both tasks using a variant of the process-dissociation procedure (Jacoby, 1991; Yonelinas, Regehr, & Jacoby, 1995).

1. Method

1.1. Participants

1.1.1. Patients

Twenty-four patients with unilateral TLE were recruited from the Epilepsy Clinic at Toronto Western Hospital and participated in this study. The temporal excision typically included resection of the hippocampus (3 cm), parahippocampal gyri (including portions of perirhinal, entorhinal and parahippocampal cortices), amygdala and anterior portion of the inferior and middle temporal lobe gyri. Twelve patients underwent dominant TLE (all left hemisphere resections) and twelve underwent non-dominant TLE (three left hemisphere and nine right hemisphere resections). Hemispheric dominance was determined based on findings from clin-

Table 1
Demographic characteristics and neuropsychological test results.

	Male:female ratio	Age	Education (years)	Duration of illness (years)	Years since surgery	WASI VIQ	WRT words	WRT faces
Dominant-TLE	3:9	43.2 (7.4)	13.8 (2.3)	27.0 (16.4)	3.5 (2.8)	95.0 (12.2)	42.3 (4.0)	41.5 (5.9)
Non-dominant TLE	6:6	40.3 (10.0)	14.4 (1.8)	21.0 (14.0)	3.6 (3.3)	101.4 (10.4)	48.2 (0.9)	37.7 (5.5)
Controls	4:8	42.1 (12.9)	15.0 (2.2)	–	–	–	–	–

Note. WASI: Wechsler Abbreviated Scale of Intelligence and WRT: Warrington Recognition Test raw scores out of 50.

Table 2
Mean proportions and standard deviations of “old” responses per pair type in the pair recognition and associative identification tasks.

	Pair recognition task				Associative identification task			
	New (FA)	Half (FA)	Rearranged (hit)	Intact (hit)	New (FA)	Half (FA)	Rearranged (FA)	Intact (hit)
Dominant TLE	0.39 (0.21)	0.59 (0.21)	0.72 (0.15)	0.74 (0.14)	0.14 (0.13)	0.28 (0.19)	0.42 (0.16)	0.61 (0.18)
Non-dominant TLE	0.23 (0.19)	0.39 (0.19)	0.63 (0.16)	0.72 (0.16)	0.07 (0.10)	0.20 (0.18)	0.38 (0.23)	0.65 (0.14)
Controls	0.05 (0.06)	0.25 (0.14)	0.69 (0.11)	0.84 (0.11)	0.01 (0.02)	0.03 (0.04)	0.16 (0.11)	0.68 (0.11)

ical neuropsychological assessment including functional MRI and (in select cases including the three non-dominant TLE patients with exclusive right hemisphere language dominance) sodium amobarbital WADA procedure. Patients were tested at least 6 months post-operatively, were free of depression, were seizure free or had a 75% reduction in seizure frequency at the 6-month post-operative mark, and had verbal intellectual quotient (VIQ) greater than 75 as assessed on the Wechsler Abbreviated Scale of Intelligence (WASI; The Psychological Corporation, 1999). Demographic information and relevant psychometric data are presented in Table 1. There were no significant differences between the two patient groups with respect to age ($t < 1$), education ($t < 1$), duration of illness ($t < 1$), time since surgery ($t < 1$) or VIQ [$t\,(23) = 1.39$; $p = 0.18$; $d = 0.56$].

Importantly, the patient groups differed in terms of their performance on the Recognition Memory Test (Warrington, 1984), a standardized measures of recognition memory for verbal (words) and visual (faces) material. A 2 (Words, Faces) × 2 (groups) repeated measure ANOVA revealed a significant interaction [$F(1,22) = 17.69$; $p < 0.001$; *partial* $\eta^2 = 0.45$]. Language dominant TLE patients performed more poorly than the non-dominant TLE patients on the verbal version [$t(23) = 4.96$; $p < 0.001$; $d = 2.38$] and there was a trend suggesting that the non-dominant TLE patients performed more poorly on the visual version, but this comparison failed to reach significance [$t(23) = 1.64$; $p = 0.12$; $d = 0.67$]. These data support the documented material-specific memory deficit observed following unilateral damage to temporal lobe structures (Jones-Gotman, 1997; Milner, 1974; Morris et al., 1995).

1.1.2. Control participants

Twelve age and education matched neurologically intact control participants were recruited from research participant pools at the University of Toronto and received CAN$10.00/h compensation or a course credit for their participation. Demographic data are presented in Table 1.

1.2. Materials

Sixteen lists of twelve semantically unrelated word pairs were created by combining seven-letter and six-letter nouns, for a total of 192 word pairs. Each word had two possible pairings. This allowed the creation of the four types of retrieval test items described below. Lists were equated in terms of Kucera–Francis frequency ($M = 37.0$, range = 2–211) and each list was assigned, in a counterbalanced manner across participants, to one of two test types (pair and associative identification recognition tasks) and to one of four types of items at retrieval (new pairs, half-old pairs, rearranged pairs and intact pairs).

The study phase consisted of 120 word pairs plus six buffer pairs (three buffer pairs placed before and three placed after the 120 study pairs). At test, both the pair and associative identification recognition tasks included 24 *intact pairs*, which consisted of the previously studied pairs, 24 *rearranged pairs*, which were made of studied words rearranged to form new pairings, 24 *half-old pairs*, which were created by combining 24 words from 12 studied pairs with non-studied words, and 24 *new pairs*, which were composed of non-studied words. In total, each task was composed of 96 critical test pairs. At all phases, pairs were presented in a random order. E-Prime software was used for presentation and data collection.

1.3. Procedure

At study, participants were instructed to remember the words and their pairing for a later test, and were required to generate a complete sentence, aloud, that contained the two words and maintained both the form (i.e., singular noun) and order of the words as they appeared on the screen. Each pair was presented for 5 s followed by a fixation cross, which remained until the sentence was completed or until a reasonable delay elapsed but participants had not initiated or were unable to complete the sentence. The study phase lasted, on average, 17, 19 and 14 min for the dominant TLE, non-dominant TLE and control groups, respectively. The study phase was significantly shorter for the control group relative to both patient groups [dominant TLE: $t(22) = 3.10$, $p < 0.01$; $d = 1.30$; non-dominant TLE: $t(22) = 3.30$, $p < 0.01$; $d = 1.48$], but did not differ significantly between the two patient groups [$t(22) = 1.13$, $p = 0.27$; $d = 0.48$]. With respect to sentence generation, the dominant TLE, non-dominant TLE and control groups were successful in generating complete and accurate sentences with 83% (87% with one outlier removed), 89% and 91%, respectively. The three groups did not differ in terms of sentence generation success [dominant TLE vs. non-dominant TLE: $t(22) = 1.10$, $p = 0.29$; $d = 0.48$; non-dominant TLE vs. control: $t < 1$; dominant vs. control: $t(22) = 1.21$, $p = 0.24$; $d = 0.50$].[1]

At test, participants completed a pair old–new recognition test and an associative identification old–new recognition test in counterbalanced order, in which they were instructed to respond quickly and accurately. They completed practice items prior to each task to ensure that they understood the instructions. In the associative identification recognition task, participants were asked to endorse pairs presented in their studied pairings (intact pairs) and reject all other pairs (new, half-old and rearranged pairs). In the pair recognition task, participants were asked to endorse pairs composed of two studied words, regardless of their pairing (intact and rearranged pairs) and reject pairs composed of at least one unstudied word (new and half-old pairs). Participants keyed-in their “old” and “new” responses with their left and right index fingers using the “v” and “m” keys. The response-key mapping was counterbalanced across participants.

1.4. Results

The proportion of “old” responses to each pair type (new, half-old, rearranged and intact) in the pair and associative identification recognition tasks are presented in Table 2. The associative reinstatement, associative identification and item memory scores were calculated using signal detection theory (d'-scores). To calculate d'-scores, hit rates and false alarm rates of 0 or 1 were adjusted to 0.02 and 0.98, respectively. The associative reinstatement measure, was calculated by subtracting the d'-score derived from the proportion of old responses to rearranged and new pairs, from the d'-score derived from the proportion of old responses to intact and new pairs in the pair recognition task (Fig. 1). Associative identification was calculated by contrasting hits to intact pairs and false alarms to rearranged pairs in the associative identification task (Fig. 2). Item memory was calculated by contrasting hits to rearranged pairs and false alarms to new pairs in the pair recognition task (Fig. 3).

Indicators of item familiarity and recollection were also computed using a variant of the process-dissociation procedure (Jacoby, 1991; Yonelinas et al., 1995). The recollection indicator is presented in Fig. 4 and the item familiarity indicator is presented in Fig. 5. The specific algorithms used are presented in Appendix A. These estimates are derived using the hit rates to rearranged pairs in the pair recognition task, which result from recollection and item familiarity working together, the false alarm rates to the rearranged pairs in the associative recognition task, which result

[1] Intuitively, one may believe that the ability to successfully generate sentence with the studied pairs may impact participants' memory for these pairs and that participants with poorer language skills are at a disadvantage. However, this was not the case in the current experiment. In the three groups, sentence generation success was not significantly positively correlated with performance on the critical memory measures. Furthermore, the one outlier in the dominant TLE group who generated correct sentences with only 45% of the items performed within or slightly above the average of the dominant TLE group (who generated sentences with 86% of the items) on the critical memory measures. Lastly, the performance of the dominant TLE group was equivalent when the analyses pertained only to studied pairs for which an accurate sentence was provided relative to when the analyses were done on all items.

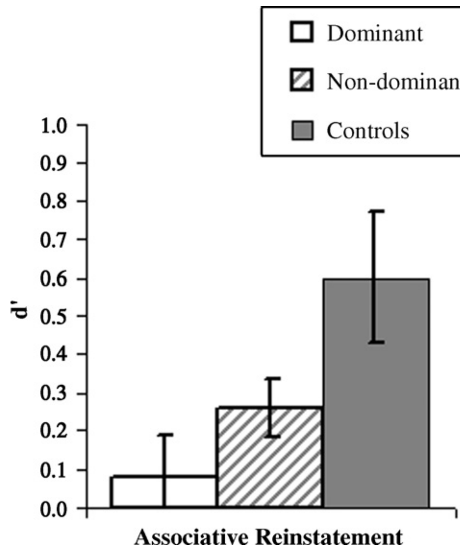

Fig. 1. Associative reinstatement.

from item familiarity in the absence of (or un-opposed by) recollection, and the baseline false alarm rates to new pairs in each task, which help control for potential differences in response bias across tasks. The recollection estimate is essentially the difference between the hit rates to rearranged pairs in the pair recognition task and the false alarm rate to rearranged pairs in the associative recognition task. In other words, the recollection estimate combines the two ways recollection contributes to recognition memory; (1) recollection can enhance hit rates in the pair recognition task (i.e., recall-to-accept), and (2) it can reduce false alarm rates to rearranged pairs in the associative recognition task by opposing a sense of item familiarity (i.e., recall-to-reject) assuming that the recollected information includes the studied pairing. In contrast, the item familiarity estimate, which is expressed in d', represents the ability to discriminate between rearranged and new pairs that is not due to recollection.

ANOVA and t-tests were conducted separately on the associative reinstatement, associative identification, item memory, recollection and item familiarity to identify any group differences.

Associative reinstatement differed significantly across groups [$F(2, 33) = 7.64$, $p < 0.01$, *partial* $\eta^2 = 0.32$], with control participants performing significantly better than both patient groups [dominant TLE: $t(22) = 3.36$, $p < 0.01$, $d = 1.37$; non-dominant TLE: $t(22) = 2.82$, $p = 0.01$, $d = 1.20$]. The two patient groups did not differ significantly on this measure [$t(22) = 1.40$, $p = 0.18$, $d = 0.60$]. These results suggest that both MTLs contribute to associative reinstatement.

Other measures that rely on relational binding operations were also compromised in patients. Associative identification and recollection differed significantly across the three groups [associative identification: $F(2, 33) = 13.83$, $p < 0.001$, *partial* $\eta^2 = 0.46$; recollection: $F(2, 33) = 9.82$, $p < 0.001$, *partial* $\eta^2 = 0.37$]. Both patient groups showed deficits in associative identification [dominant TLE: $t(22) = 5.97$, $p < 0.001$, $d = 2.47$; non-dominant TLE patients $t(22) = 3.36$, $p < 0.01$, $d = 1.38$] and in recollection [dominant TLE: $t(22) = 3.03$, $p < 0.01$, $d = 1.27$; non-dominant TLE: $t(22) = 5.41$, $p < 0.001$, $d = 2.24$] relative to control participants. The two patient groups did not differ on these measures [associative identification: $t(22) = 1.28$, $p = 0.22$, $d = 0.54$; recollection: $t < 1$, $d = 0.28$].

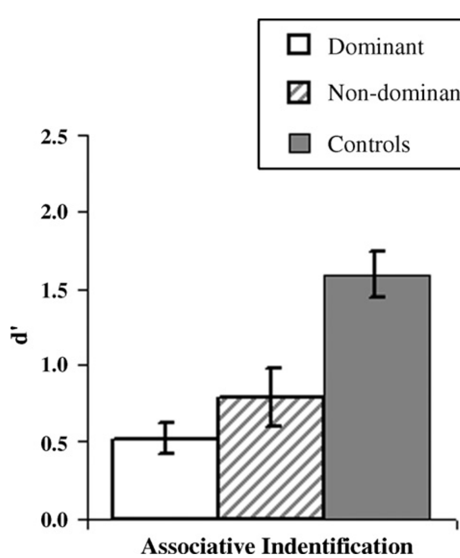

Fig. 2. Associative identification.

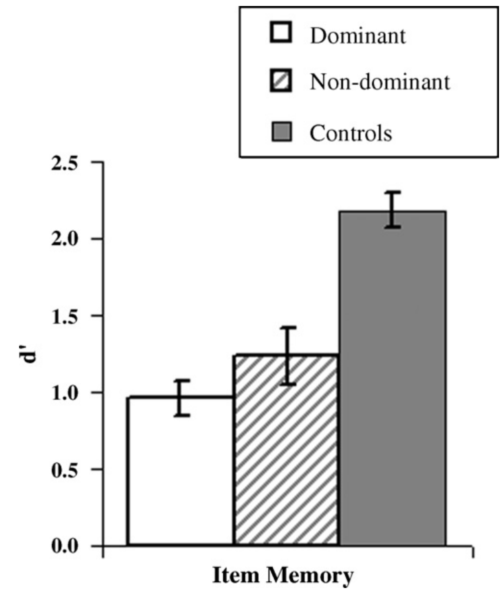

Fig. 3. Item memory.

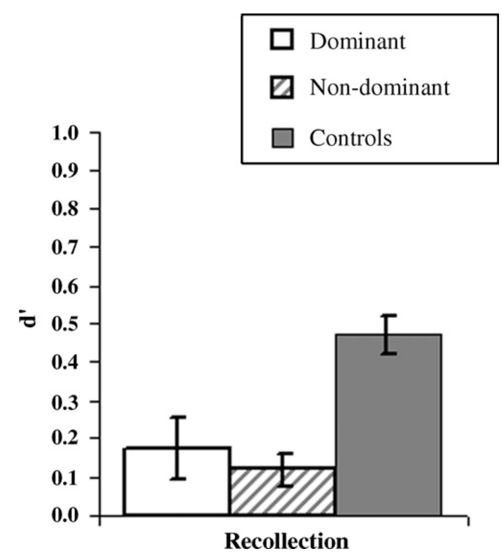

Fig. 4. Recollection.

Furthermore, item memory differed significantly across the three groups [$F(2, 33) = 19.58$, $p < 0.001$, *partial* $\eta^2 = 0.54$] with control participants performing significantly better than both patient groups [dominant TLE: $t(22) = 7.41$, $p < 0.001$, $d = 3.02$; non-dominant TLE: $t(22) = 4.27$, $p < 0.001$, $d = 1.79$] who did not differ significantly from one-another on this measure [$t(22) = 1.21$, $p = 0.24$, $d = 0.51$]. Though relational binding operations and recollection are not typically essential to support item memory, we believe that they are substantially involved in our pair recognition task. We discuss this point in more detail in Section 1.5.

A different pattern of results emerged on the item familiarity measure, which does not rely on relational binding operations. Item familiarity differed significantly across the three groups [$F(2, 33) = 3.22$, $p = 0.05$, *partial* $\eta^2 = 0.16$]. The dominant TLE group's item familiarity estimate was smaller than that of control participants [$t(22) = 2.50$, $p < 0.05$, $d = 1.02$]. However, the non-dominant TLE group's familiarity estimate was marginally greater than that of the dominant TLE group [$t(22) = 1.71$, $p = 0.10$, $d = 0.70$] and was not significantly different than that of the control group [$t < 1$, $d = 0.31$]. These results are consistent with the prediction that item familiarity is intact for material processed by the unaffected hemisphere, but impaired for material processed by the damaged hemisphere.

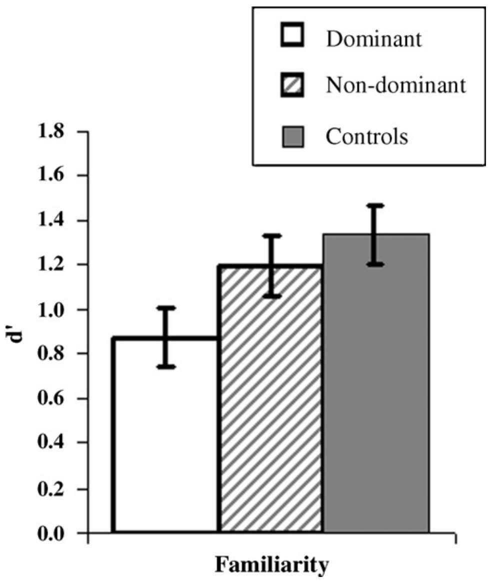

Fig. 5. Familiarity.

1.5. Discussion

Our main goal in this study was to investigate associative reinstatement in patients with unilateral TLE. We showed that associative reinstatement which relies on relational binding operations at encoding was compromised following TLE, regardless of the side of the lesion. Furthermore, we demonstrated similar deficits on other tests that also rely on relational binding operations were impaired, including associative identification and recollection, again, with no differential effect of the side of damage.

In contrast, we found that item familiarity was impaired solely in the dominant TLE group, but was intact in the non-dominant TLE group. A similar pattern of results regarding item familiarity in TLE patients was obtained on the Warrington Recognition Test (Warrington, 1984), a standardized forced-choice recognition test for single items. On this task, non-dominant TLE showed good recognition for single words and dominant TLE showed good recognition memory for faces. Of note, item memory was compromised in both groups, which appears at odds with the item familiarity findings. We address this point in more detail below. Together, findings on the item familiarity estimate and the Warrington Recognition Test are consistent with the material-specificity principle (Jones-Gotman, 1997; Milner, 1974; Morris et al., 1995) and with the idea that the contralesional MTL can support memory for material that is processed by this hemisphere as long as the memory task can be performed on the basis of single-item familiarity. However, this is not the case for measures such as associative reinstatement that rely on relational binding operations which are mediated by both MTL regions.

Our findings indicate that associative reinstatement indexes relational binding operations mediated by the MTL, and like other associative memory measures and recollection estimates, can be dissociated from item familiarity. This is concordant with previous findings that reinstatement is reduced in amnesic patients (Goshen-Gottstein et al., 2000; Kan et al., 2007) and in young adults under conditions that interfere with the creation of strong links at encoding (e.g., divided attention; Castel & Craik, 2003, and shallow relational encoding; Cohn & Moscovitch, 2007). We have also demonstrated in previous experiments that associative reinstatement is dissociable from associative identification and recollection as reinstatement does not require strategic retrieval operations, which likely rely on the prefrontal cortex and related structures. Notably, it is not affected by conditions that prevent participants from instantiating elaborate retrieval operations (e.g., speeded retrieval, short response deadline, overlapping pairing condition; Cohn & Moscovitch, 2007) and is similarly unaffected by normal aging (Cohn et al., 2008).

There are two current types of models of recognition memory. The Global Matching Models propose that recognition relies on a single process, with items and associations varying in memory 'strength' and different recognition tasks having different thresholds for response selection (see Clark & Gronlund, 1996, for a review of these models). The dual-process models stipulate that different independent processes support recognition memory (Mandler, 1980; see Eichenbaum et al., 2007; Yonelinas, 2002, for reviews). Familiarity is generally sufficient in supporting item recognition and recollection is required to support most types of associative memory. According to recently advanced proposals, there are exceptions wherein familiarity can support associations [e.g., unitized associations such as compound words or words integrated in a single lexical unit (Quamme, Yonelinas, & Norman, 2007); or intra-domain associations such as word–word pairs (Mayes, Montaldi, & Migo, 2007)]. Dual-process models also propose a functional dissociation within the MTL regions with the hippocampus and perirhinal cortex mediating recollection and familiarity, respectively. Part of the evidence supporting these models are findings showing recollection and associative identification deficits, but intact item familiarity and item memory, in patients with selective, bilateral hippocampal damage (Aggleton et al., 2005; Cipolotti et al., 2006; Holdstock et al., 2005; Mayes et al., 2002, 2004; Turriziani et al., 2004; Vargha-Khadem et al., 1997; Yonelinas et al., 2002, 2004) and intact recollection but impaired familiarity in one patient with a unilateral selective lesion to the perirhinal cortex (Bowles et al., 2007). Unfortunately, our results cannot speak to this dissociation because the resections in our patients included both the perirhinal cortex and the hippocampus. For the same reason, we cannot clarify what the contribution of familiarity (mediated by the perirhinal cortex) is to our associative reinstatement measure. However, we may speculate that the hippocampus, rather than the perirhinal cortex, is crucial to associative reinstatement in light of Kan et al.'s (2007) findings that impaired associative reinstatement in patients with bilateral lesions is restricted to the hippocampus, and given that our encoding task was more relational than unitized (i.e., sentence generation rather than single lexical unit formation), which is more hippocampally dependant according to Quamme et al. (2007). This remains to be verified in future studies.

The overall pattern of data are in keeping with a dual-process view of recognition memory, in that TLE patients were impaired on all associative memory measures but unimpaired on measures of single-item familiarity (in the experimental task and WRT). Although TLE patients were impaired in the item memory, our previous studies documented that this measure is influenced by recollection, in addition to item familiarity, and it is likely that the deficit arises from impaired recollection. From our previous experiments (Cohn et al., 2008; Cohn & Moscovitch, 2007), we have found that manipulations or conditions known to interfere with recollection (e.g., aging and short response deadline) had a significant impact on our item memory measure, but not on associative reinstatement and single-item familiarity estimate, suggesting that our pair recognition task engages recollective processes even when these are not required to comply with task demands. In our paradigm, test probes included two words (pair recognition task) rather than one (single-item recognition task) and included half-old items, which contain one familiar studied item. As a result, the increase in uncertainty in this task as compared to single-item tasks, which are more commonly used in the literature, may promote the use of recollection even for single items. The finding of proportional deficits in single item and pair recognition in a group of amnesic patients by Giovanello et al. (2003) appears to be inconsistent with our formulation. However, their methods were different from ours in many respects (i.e., they provided six presentation to patients, used a significantly shorter list), which may have increased the reliance on familiarity and reduced the uncertainty on the pair task. Based on our previous research with our task parameters, we propose that the deficit in item memory seen in our non-dominant TLE group is likely due to a substantial decline in recollection, especially in light of their patients' intact single-item familiarity as measured using the process-dissociation procedure and as shown by their intact performance on the verbal recognition task from the WRT.

Our second goal was to characterize the performance of TLE patients and test possible differences related to lesion laterality. The literature on this topic is sparse and mixed. As noted previously, we found that both TLE group were equally impaired on all measures that rely on relational binding. In contrast, item familiarity was impaired in the dominant TLE group, but intact in the non-dominant TLE group; this is similar to the pattern seen on the WRT. Together, these results suggest that the contralesional MTL can support single-item familiarity-based memory for material that is processed by this hemisphere. While item familiarity pertains to a single type of information, recollection encompasses both verbal and non-verbal aspects of the context in which the information was acquired. Thus, while the material used in our tasks was verbal, control participants likely bound different types of contextual information, both verbal and non-verbal, with the studied material. In contrast, damage to either hemisphere may have prevented binding of one type of lateralized information with the other, which explains the absence of an effect of lesion laterality on the relational measures and, specifically, the impairments seen in non-dominant TLE.

In sum, retrieval of associative information was impaired, irrespective of the side of lesion, and single-item familiarity was impaired solely for material processed by the damaged hemisphere. This pattern is consistent with some other studies investigating these memory types in TLE patients (Moran et al., 2005; Thaiss & Petrides, 2003), but conflicts with studies in which recollection was impaired solely for material processed by the damaged hemisphere (Bird et al., 2007; Moscovitch & McAndrews, 2002) or impaired solely in patients with dominant hemisphere lesions (Blaxton & Theodore, 1997). A number of reasons may account for the discrepancies pertaining to recollection. These include differences in the type of method used and encoding instructions. First, we used a process-dissociation method to derive purer estimates of recollection and item familiarity in TLE patients, while others have used introspective-based methods (e.g., remember-know: Blaxton & Theodore, 1997; Moscovitch & McAndrews, 2002; ROC: Bird et al., 2007). In these studies, patients may have understood and used remember judgments or confidence ratings in a different manner than did control participants. This concern is supported by the counter-intuitive findings obtained by Blaxton and Theodore (1997) using the remember-know procedure. These authors reported greater remember judgments for visual material in patients with non-dominant TLE relative to controls, suggesting that their recollection for material processed by the damaged hemisphere was enhanced. Second, differences in encoding tasks are noted across studies. The sentence generation task used here may engage non-verbal associative processing (e.g., imagery) in addition to verbal associative processing. In contrast, the antonym generation encoding task used by Moscovitch and McAndrews (2002) likely engaged only verbal associative strategies. The generation and retrieval of memory representations that consist of verbal and non-verbal elements likely depends on a bilateral network of structures that includes both MTLs. Disruption of the broader network may result in recollection deficits on tasks instantiating multiple types of processes, as in the case of two TLE groups in the present study.

2. Conclusions

Based on these results and on previous findings (Castel & Craik, 2003; Cohn et al., 2008; Cohn & Moscovitch, 2007; Kan et al., 2007), we propose that associative reinstatement provides a measure of relational binding operations and of MTL function that is not dependent on strategic retrieval operations which require the participation of prefrontal cortex and related structures. Although we found that measures that relied on relational binding operations were dependent on MTL regions bilaterally, it remains possible that these measures could be supported by unilateral MTL structures when only one type of process (verbal or non-verbal) is instantiated at encoding or retrieval. Recognition that does not rely on relational processing, however, is supported by unilateral MTL regions. Importantly, of all measures of associative memory, associative reinstatement may have the greatest specificity to MTL dysfunction in that unlike associative identification, it does not also implicate the prefrontal cortex.

Appendix A. Procedure

In Yonelinas et al.'s (1995) process-dissociation procedure, recollection is described as a threshold process and familiarity follows a signal detection process. We used a spreadsheet-based algorithm that computes recollection and familiarity estimates. The computations used controlled for response bias across tasks and participants by incorporating the false alarm rates to new pairs from each task.

Recollection is the difference between hits to rearranged pairs on the pair recognition task (familiarity + recollection) and the false alarm rate to rearranged pairs on the associative recognition task (familiarity only). Familiarity is expressed using a discriminability score (d') derived F with $\Phi(d'/2-c)$, where Φ represents the probability of an item's familiarity exceeding the criterion (c).

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