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Verbal memory in mesial temporal lobe epilepsy: beyond material specificity

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The idea that verbal and non-verbal forms of memory are segregated in their entirety, and localized to the left and right hippocampi, is arguably the most influential concept in the neuropsychology of temporal lobe epilepsy, forming a cornerstone of pre-surgical decision making, and a frame for interpreting postoperative outcome. This critical review begins by examining some of the unexpressed but inescapable assumptions of the material-specificity model: (i) verbal and non-verbal memory are unitary and internally homogenous constructs; and (ii) left and right memory systems are assumed to be independent, self-contained modules. The next section traces the origins of an alternative view, emanating largely from three challenges to these assumptions: (i) verbal memory is systematically fractionated by left mesial temporal foci; (ii) the resulting components are differentially localized within the left temporal lobe; and (iii) verbal and non-verbal memory functions are not entirely lateralized. It is argued here that the perirhinal cortex is a key node in a more extensive network mediating protosemantic associative memory. Impairment of this fundamental memory system is a proximal neurocognitive marker of mesial temporal epileptogenesis.

Keywords: verbal memory; temporal lobe epilepsy; associative memory; perirhinal cortex; material specificity

Introduction

Fifty years have elapsed since the publication of the first seminal papers on neuropsychological outcome after surgery for the alleviation of temporal lobe seizures (Scoville and Milner, 1957; Penfield and Milner, 1958). Since then the phenomenon of temporal lobe epilepsy (TLE) has been a source of knowledge about much, if not most, of what we know about the neurocognition of human memory. Surgical programmes have provided the impetus and rationale for the development of a major field of neuropsychological practice (Barr, 2007; Baxendale, 2008), charged with the responsibility of averting the cognitive disaster that befell the famous HM and others in a similar predicament (Baxendale, 2008).

Because neuropsychological practice in temporal lobe epileptology was born out of a series of postoperative disasters (Xia, 2006), it has understandably adopted a conservative stance, and an almost universal and persisting adherence to a single dominant model. The purpose of this article is to show that research and accumulated experience, particularly over the past 20 years, contains the seeds of a paradigmatic shift. This review will argue that it is now possible to synthesize the outlines of a revised...
neuropsychological model, with implications for pre-surgical decision making and our understanding of risks posed by surgery to memory function.

Material-specificity

Memory difficulties have long been regarded as the chief neuropsychological issue in TLE. Some degree of memory impairment can be documented in almost all cases (Fisher et al., 2000; Hermann and Seidenberg, 2008). Ongoing seizure activity deepens and extends memory impairments in the long term (Hermann et al., 2006), and despite the enormity of its success in the treatment of intractable TLE, surgical treatment also poses a risk to memory, particularly if seizure outcome is poor (Helmstaedter et al., 2003).

The most influential conceptualization of memory impairment in temporal lobe epileptology is, unquestionably, the notion of material-specificity. This parsimonious model owes much to the pioneering work of Brenda Milner and her colleagues at the Montreal Neurological Institute. At its most fundamental level it holds that the left and right temporal lobes process different types of material (Milner, 1970); i.e. ‘a complementary specialization of the two temporal lobes of man with respect to memory… the most significant variable is the verbal or non-verbal character of the material to be retained’ (p. 29–30). Milner (1970) wondered whether the prominence of the material specific effect, a predominantly postoperative phenomenon in her observations, was caused by the extent of anterior temporal damage, which involved mesial (amygdala, hippocampus, parahippocampal gyrus) as well as lateral structures. Nevertheless, it fell to the well-known ‘big H, little h’ correlational studies of Corsi to provide the empirical impetus for the notion that lateralized hippocampal damage is the cause of material-specific memory impairments. Corsi’s work was plagued by the impossibility of disentangling the effects of damage to the anterior temporal structures involved in en bloc resection, and dissecting out in particular the extent of hippocampal resection from the extent of epileptogenic pathology.

From a clinical perspective, memory impairments objectively restricted to one material type were mild and apparently devoid of the devastating loss of autonoetic consciousness seen in HM (Scoville, 1954; Scoville and Milner, 1957), who had undergone bilateral mesial temporal resections, or in cases PB and FC (Penfield and Milner, 1958), who had undergone left temporal resections in the presence of a putatively diseased contralateral temporal lobe (in the case of FC), or demonstrated right-sided pathology (in the case of PB) (Penfield and Mathieson, 1974). Objective study of these cases showed that new learning, irrespective of material type, was impaired, and the clinical syndrome of severe amnesia later came to be equated with the notion of a material non-specific (or general) learning deficit (Saykin et al., 1992).

The parsimony of the material specificity hypothesis, and its apparently straightforward mapping onto the factorially derived verbal/non-verbal distinction embodied in the major standardized neuropsychological instruments of the day, must have been appealing to an embryonic neuropsychological speciality. Once it had been accepted that material non-specific memory impairments point to a condition of bitemporal vulnerability, and are therefore the harbingers of a post-resection amnesia, the presence of a non-congruent memory disorder (i.e. a memory impairment implicating the contralateral hippocampus in cases with an apparently unilateral mesial temporal focus) was taken to contra-indicate a surgical approach to treatment. This logic, and indeed the material-specificity model, persists as a cornerstone of current pre-surgical decision making, and the principal paradigm for interpreting neurocognitive outcome (Baxendale, 2008).

The material-specificity model is not as straightforward as it might have appeared. It implicitly embodies a specific stance towards the structure of verbal and non-verbal memory, and their cerebral organization. In practice, its implementation depends on the following assumptions:

1) Verbal and non-verbal memory are unitary and internally homogenous constructs. This assumption arises from the common finding that a range of verbal memory tasks, from single word paradigms to linguistically complex discourse, intercorrelate in normal populations and its operation is reflected in the fact that widely different verbal memory paradigms have been used interchangeably, or in summation, to characterize putatively verbal-specific impairments. Correlations between any two verbal memory paradigms (such as verbal paired associates and prose passages, to cite a common example) are taken to mean that the correlated tasks are ‘really the same construct under two different labels’ (Schmidt and Hunter, 1999), and that either task is a valid measure of that construct. This approach to validity assigns no particular importance to the nature of the task (such as its cognitive architecture), or to the possibility that task-specific factors might be subserved by different causal mechanisms (Boorsboom et al., 2004). In particular, it does not accommodate the possibility that scores on two tasks, which correlate in a normal sample, might be differentially affected by a strategic cerebral lesion.

2) The left temporal-verbal memory system mediates all aspects of verbal memory, but does not deal with non-verbal memory, and vice versa for the right temporal memory system. In other words, the left and right temporal regions function as independent and self-contained material-specific modules, characterized by Dobbins et al. (1998) as the ‘Laterality/Independence assumption’ (p. 116). Although this assumption emanated from earlier interpretations of post-resection studies of memory, trends in the accumulating postoperative literature are poorly aligned with it. For example, postoperative decrements in verbal memory occur in a significant minority of patients after a right temporal resection (Baxendale et al., 1998a, 2007; Bell and Davies, 1998; Martin et al., 1998; Gleissner et al., 2002). In the non-verbal domain, evidence for an exclusive nexus between the right temporal lobe and spatial memory is considerably weaker, since many aspects of the domain are also impaired by left hippocampal sclerosis and anterior temporal resection (Glikmann-Johnston et al., 2008; McConley et al., 2008). Doubts about the foundations of the material-specificity
The emergence of task-specificity

An early inkling that the first assumption is unsustainable came in 1972 from a little known case with a left temporal focus on surface EEG. She was seen by Dr Kevin Walsh at the Austin Hospital, Melbourne, Australia, in response to the elegant referral question: 'does this lady have an amnesia to which she is not entitled?' The neuropsychological findings showed that verbal memory was normal, apart from some difficulty with 'novel' word pairs (the ‘hard’ paired associates of the Wechsler Memory Scale-Form I). Non-verbal memory was impaired. The patient re-presented 8 months later. Depth electroencephalography again implicated the left temporal lobe. In the interim the patient died of a pulmonary embolus. At post-mortem, the right temporal lobe, which had been electrically silent, was severely atrophic. Cases of unexpected amnesia are particularly informative (Kapur and Prevett, 2003), and a number of lessons can be drawn from this one. While she was unlikely to have been regarded as generally amnestic on the basis of conventional material-specificity criteria, because most aspects of her verbal memory were normal, a left temporal resection would have placed her at considerable risk of an HM-like syndrome. Important to the argument presented here, the simple separation of ‘hard’ (unrelated) from ‘easy’ (semantically) word pairs, rather than relying on the standard scoring procedure of summating hard and easy pairs, disclosed a dissociation of significant neurocognitive interest.

More than a decade later, Rausch and her colleagues at UCLA (Rausch, 1987–1988; Rausch and Babb, 1987, 1993) found that left hippocampal neuronal loss specifically predicted the ability to learn unrelated word pairs, but not immediate recall of prose. She suggested that the neuropsychological detection of left hippocampal sclerosis depended on a ‘specific verbal memory task’ (1987–8, p. 23), and characterized the cognitive demand as ‘simple, rote association’ (p. 21). In 1993, we showed that story recall did not differentiate between well characterized left and right mesial temporal foci, but was mildly impaired in both groups. Acquisition of unrelated word pairs, however, was prominently impaired in the left-sided group, but normal in the right-sided group, accounting for 36% of the between group variance (Saling et al., 1993). This finding was replicated in a second and larger group of well characterized patients with either left or right mesial temporal foci, producing a similar effect size (Saling et al., 2002). It seemed that the distinction between the groups of tasks could be drawn along a semantico-syntactic continuum. In hard paired associate learning tasks words are paired in a pseudo-random or arbitrary manner, minimizing any semantic or syntactic relationship between them. In neurocognitive terms, there is a very low probability that the conjunction was previously represented in semantic memory networks. At the opposite end of the continuum, prose such as that contained in the Logical Memory subtests is replete with semantic content and complex syntactical structure. I return to the implications of this conceptualization below.

A second line of work on epilepsy-induced dissociation of verbal learning was pioneered by Hermann and his colleagues at the University of Wisconsin. They showed in a number of studies that patients with left MTS were worse at word list learning. When language ability was partialled out, the side of focus (i.e. left versus right TLE) did not account for significant variance in list learning. Language adequacy has been found to be a powerful predictor of list learning (Hermann et al., 1988; Hermann et al., 1992). In contrast, language adequacy was unrelated to the magnitude of retroactive interference, leading Hermann et al. (1988) to suggest that the drop-off in recall across an interference condition might serve as ‘the best pure indicator of memory function in dominant temporal lobe patients’. We replicated Hermann’s finding (Saling et al., 2002), again showing that language adequacy accounted for the poorer performance of left TLE patients on list learning, but not on post-interference recall.

Since arbitrary associative memory and retroactive interference have played a crucial role in disclosing intratemporal specialization, cognitive mechanisms that unite them are of particular interest. When the interference condition has the same form as the material-to-be-learned (Dewar et al., 2007), semantic structure in memory tasks is protective, while arbitrariness increases susceptibility to the effects of retroactive interference (Bower et al., 1994; Burns and Gold, 1999; Blank, 2002; Musca et al., 2004; Sahakyan and Goodman, 2007). Arbitrariness and semantic structure are not absolutes, and the two coexist to varying extents in all meaningful verbal material. While semantic clustering is a common list learning strategy, an arbitrary component arises because specific items can be substituted (e.g. tambourine for drum) without affecting potential semantic linkages. The magnitude of the retroactive interference effect can be conceptualized, therefore, as a probe of arbitrariness across a variety of verbal learning tasks.

A strong case exists for the view that verbal learning tasks are differentially affected by left mesial temporal epileptogenic foci. For tasks where performance is supported by pre-established semantic associations, the effect of left mesial foci is minimal or absent. Related-paired associates, list learning or prose recall fall into this category. On the other hand, left mesial temporal foci exert a consistent effect on tasks that do not load on pre-established language abilities to any significant extent. This category includes ‘hard’ or arbitrary paired associates and indices of retention, such as post-interference recall. The material-specificity model, in its theoretical stance and in its clinical implementation, emphasizes the verbal versus non-verbal nature of material, to the exclusion of any other attribute of the task, and therefore cannot accommodate notions of dissociation (such as arbitrary versus semantic forms of learning) and intratemporal specialization.

The arbitrary-semantic distinction is represented in the temporal lobe as a medial versus lateral specialization, an idea that owes much to comparative work on verbal memory outcomes after
selective and en bloc temporal lobe resection. After standard anterior temporal lobectomy in patients with left MTS, memory tasks with a semantic component, such as related paired associate learning, and recall of passages (Saling et al., 2002), or which elicit the superimposition of semantic clustering, such as list learning (Helmstaedter et al., 1997; Saling et al., 2002), decline from preoperative levels. This change is not seen after selective amygdalolhippocampectomy (Helmstaedter et al., 1996, 1997), providing converging evidence of mediolateral specialization (Helmstaedter et al., 1997). Helmstaedter suggested that the lateral temporal cortex is involved in ‘short-term’ aspects of memory (Helmstaedter et al., 1996, p. 5), or in ‘data acquisition and working memory’ (Helmstaedter et al., 1997, p. 113), while the medial component is involved in consolidation processes. This conceptualization is based on putative paradigmatic differences between the acquisition and post-interference trials of the Rey Auditory Verbal Learning Test. The interpretation adopted here is that mediolateral specialization is more sharply drawn along semantic-protosemantic lines. The argument for this position is developed in later sections. It is worth pointing out at this stage, however, that tasks belonging to the same learning paradigm (paired associates), differing only in degree of semantic structure, are differentially associated with lateral and mesial structures (Weintrob et al., 2002).

Intratemporal and lateral specialization for verbal memory

Hippocampal sclerosis is the commonest epileptogenic pathology in refractory TLE. It is clearly detectable preoperatively by MRI, and hippocampal sparing is a key consideration in surgical planning. The animal literature (Gaffan, 2001) ‘makes an overwhelming case against the strong version of the hippocampal memory hypothesis’ (p. 9). In the present context three major lines of evidence are particularly important: (i) the addition of perirhinal lesions in monkeys with prior hippocampal damage exacerbates the memory impairment (Baxter and Murray, 2001); (ii) neurotoxic damage to the perirhinal cortex, with sparing of fibres of passage, impairs some aspects of learning, while neurotoxic damage to the hippocampus leaves the same aspects of learning intact (Malkova et al., 2001); (iii) Perirhinal lesions produce a more severe impairment of learning than entorhinal lesions, suggesting a role for the perirhinal cortex that transcends hippocampal deafferentation (Leonard et al., 1995).

In addition, there is a substantial recent literature that characterizes the perirhinal cortex as a conjunctival or associative processor (Bussey et al., 2005; Law et al., 2005; Jimenez-Diaz et al., 2006; Tendolkar et al., 2007), as well as an experimental lesion-based literature on primates implicating the entorhinal (Buckmaster et al., 2004) and perirhinal cortex (Murray et al., 1993; Higuchi and Miyashita, 1996; Buckley and Gaffan, 1998; Parker and Gaffan, 1998) in basic forms of associative memory. Given that impaired verbal paired associate learning is a hallmark of left MTS, an obvious question arises: to what extent is perirhinal cortex recruited in the face of associative memory demands in patients with mesial temporal lobe foci?

Alongside the issue of intramesial specialization, temporal lobe specialization for verbal memory on a broader scale needs to be considered: do arbitrary and verbal memory tasks map onto the medial and lateral components on the epileptogenic temporal lobe as definitively as the pre and postoperative lesion data suggest? Unrelated paired associate scores, obtained from 27 patients with left mesial TLE emanating from unilateral mesial temporal sclerosis (MTS), were regressed on resting glucose uptake in a whole brain $^{18}$F-fluorodeoxyglucose PET study (Weintrob et al., 2002). A peak correlation was observed in the ipsilateral perirhinal cortex. This contrasted with regressions involving related paired associate scores, which produced a peak correlation in the anterior aspect of the inferior temporal gyrus (Brodmann area 20).

These findings underline the relevance of the perirhinal cortex to associative learning in patients with left MTS. They also reveal the pattern of medial-lateral intratemporal specialization suggested by the postoperative memory data. Semantically loaded associates are clearly dependent on the anterior portion of the inferior temporal gyrus. This region is recruited in tasks based on pre-established semantic relations (Warburton et al., 1996; Dolan and Fletcher, 1997; Spitsyna et al., 2006), and has been implicated in early-stage semantic dementia (Hodges et al., 1992; Mummery et al., 1999, 2000; Chan et al., 2001). Performance on semantically loaded associates is also influenced, to a lesser extent, by perirhinal activity (Weintrob et al., 2002). The perirhinal region receives afferents from the primate area TE (van Hoesen and Pandya, 1975a), area 20/21 in humans (Gloor, 1997), forming a subsystem involved in the processing of item-to-item conjunctions, and the extraction of meaning from them. In our 1993 study related paired associates differed significantly between the left and right MTS groups, although the effect size was comparatively small. This is not a robust finding and we were unable to replicate it in a larger sample (Saling et al., 2002). Nevertheless, it raises that possibility that the disruptive effects of mesial temporal foci extend to semantically related material, albeit at a subtle level, possibly by compromising inferotemporal neocortex and/or its underlying white matter (Mitchell et al., 1999). Arbitrary paired associate learning also correlated with T2 signal in a left perirhinal region of interest, but not with hippocampal T2 relaxation time (Lillywhite et al., 2007), and so provides converging evidence for the hypothesis that the perirhinal region is a key substrate for arbitrary relational processing in temporal epilepsy. Post-interference recall on the Rey Auditory Verbal Learning Test, the other variable sensitive to left MTS, showed the opposite pattern, correlating better with hippocampal T2 relaxation time (Lillywhite et al., 2007). Measures of delayed recall in general are related to hippocampal integrity in previous work using T2 relaxometry in a single region of interest (Incisa della Rocchetta et al., 1995; Kalviainen et al., 1997; Baxendale et al., 1998).

Taken together with the studies reviewed above, activation evidence (Weintrob, 2004) suggests that the perirhinal cortex represents a node in a more extensive network mediating arbitrary paired associate learning. Regional cerebral blood flow, using PET and $[^{18}]$OHI$_2$O, with a paradigm involving the acquisition of arbitrary verbal paired associates, was pre-dominantly left sided,
involving dorsolateral pre-frontal, fusiform, parahippocampal and perirhinal cortices, and extensive posterior cingulate deactivation. Patients with left MTS, in contrast, showed right-sided activation involving dorsolateral pre-frontal cortex, and bilateral recruitment of the anterior cingulate region. While a right dorsolateral pre-frontal region of interest correlated with paired associate performance in the patient group, it does not represent an effective compensatory shift since task performance was markedly worse in patients than controls. A similar conclusion has been reached on the basis of fMRI evidence (Powell et al., 2007). Contralateral activation is more appropriately regarded as a marker of network disruption in the presence of mesial temporal pathology (Weintrob, 2004; Powell et al., 2007).

Déjà vu, familiarity and recollection

The perirhinal cortex has long been thought to be the source of a sense of familiarity, or knowing that an event has been encountered previously (Brown and Aggleton, 2001). Recollection, a veridical memory of the detailed context surrounding a familiar event, is thought to be a hippocampal function (Aggleton et al., 2005). This putative dissociation is controversial, but a recent case study (Bowles et al., 2007) offers strong support. The patient, NB, a 21-year-old female with intractable temporal lobe seizures, underwent an anterior hippocampal-sparing resection for removal of a ganglioglioma. The resection involved amygdala, entorhinal cortex, and perirhinal cortex, but spared the hippocampus and parahippocampal cortex. Four different experimental paradigms provided converging evidence for the finding that familiarity was impaired but recollection was entirely spared. Findings such as this provide a neurocognitive framework for understanding transient seizure-induced disorders of familiarity. Déjà vu and jamais vu involve an inappropriate attachment of familiarity or unfamiliarity to encountered events. Direct stimulation of perirhinal cortex induces the phenomenology of déjà vu more frequently than stimulation of hippocampus or amygdala (Bartolomei et al., 2004).

The case of Dr Z, whose descriptions of his own episodes of déjà vu (which he characterized as the ‘dreamy state’) contributed to the Jacksonian concept of TLE. At post-mortem Dr Z had a ‘small cavity, collapsed and almost empty, with indefinite walls’ in the left uncinate gyrus. The rest of the brain was thought to be normal. As Weintrob (2004) has pointed out, the coronal section provided by Jackson (Hughlings-Jackson and Coleman, 1898, p. 588) shows that the lesion lies just lateral to the fundus of the collateral sulcus, a zone of transition between the ento and perirhinal cortices (Insauti et al., 1998). The case of Dr Z is also well known for his amnesic episodes which fit well with recent descriptions of transient epileptic amnesia (Butler et al., 2007; Butler and Zeman, 2008). In the most extensive account produced to date Butler et al. (2007) note that the anterograde amnesia was ‘incomplete’ in more than half of their sample, and some patients felt that they could ‘remember not being able to remember’. One might speculate that the incompleteness of the amnesic episode in the small majority of cases reflects partial preservation of recollection of broad contextual information, but a loss of familiarity with specific events.

Rhinal cortex, memory and epileptogenesis: arbitrary association as an ‘endophenotype’

Measures in epilepsy neuropsychology have tended to be global in nature, essentially summarizing a variety of tasks to form a factually derived scale, in line with the idea that comprehensiveness is the goal of the ideal neuropsychological examination. The cost of this approach is loss of neurocognitive specificity. Little attention has been devoted to the notion of neurocognitive markers, i.e. components of the cognitive domain that might have a more proximal relationship to the neurobiological aspects of the disease, and therefore greater diagnostic sensitivity at a pre-surgical level.

The evidence reviewed thus far indicates that left mesial temporal foci exert a primary influence on a neurocognitive system responsible for the rapid uptake of links or relations that have yet to be established in personal episodic or semantic memory, or which might conflict with pre-established knowledge (Saling, 2005). The role of this system is to acquire the myriads of co-occurrences that signpost behavioural trajectories over time, providing a temporary and consciously accessible record (Byrne et al., 2007; Bird and Burgess, 2008; Moscovitch, 2008), irrespective of the meaningfulness or ultimate significance of its contents (Eichenbaum et al., 1994; McClelland and Goddard, 1996; Moscovitch, 2008). The wider hippocampal system, including rhinal cortices, has been characterized as domain-specific in that it deals with ‘consciously apprehended information and none other’ (Moscovitch, 2008). It behaves in a modular fashion in that it picks up information obligatorily, and ‘delivers the stored information as output in response to a cue’ (p. 66, emphasis added), disclosing the fundamentally associative nature of the system. Further, and of particular interest in the present context, ‘the output [is] shallow…the memory is not interpreted as to its significance or veridicality’ (p. 66). The shallowness of hippocampal system processing allows for the retention of contingencies that are initially devoid of previously represented meaning or significance. This property is phylogenetically ancient, providing a buffer (McClelland and Goddard, 1996) against the speed and unpredictability of environmental events (McClelland and Goddard, 1996; Moscovitch, 2008). The rhinal cortices are well placed to mediate this aspect of the system’s function.

The nature of perirhinal involvement in cognition is controversial, but the themes of conjunction and association are consistently raised (Weintrob et al., 2002, 2007; de Curtis and Pare, 2004; Weintrob, 2004; Bussey et al., 2005; Fernandez and Tendolkar, 2006; Jimenez-Diaz et al., 2006; Lillywhite et al., 2007; Tendolkar et al., 2007). A model advanced by Fernandez and Tendolkar (2006), e.g. imbues the ento and perirhinal cortices with a ‘gatekeeper’ role in declarative memory, and postulates that this gating function is modulated by the semantic-conceptual
status of incoming information. Items with no prior representation in semantic memory elicit widespread rhinal activity, increasing the probability of transfer to the hippocampus for encoding. The subjective counterpart is unfamiliarity. Rhinal activity is sparse in the face of items with a pre-established semantic representation, reducing the probability of transfer to the hippocampus and inducing a subjective sense of familiarity. This mechanism directs limited encoding resources away from familiar towards novel information (p. 358), thereby optimizing the operation of the declarative memory system. On the other hand, electrophysiological evidence derived from patients with TLE suggests the rhinal-hippocampal coupling is potentiated by greater semantic content of verbal material, increasing the probability of transfer between rhinal cortex and hippocampus (Fell et al., 2006). While these differing views are yet to be resolved, it is becoming clearer that activity at this critical interface is modulated by a semantic dimension.

Entorhinal (Bernasconi et al., 2003) and perirhinal volumes (Boniha et al., 2003) are frequently reduced in TLE. These structures are considered to be highly significant in the initiation of epileptiform activity (Schwarz and Witter, 2002; Bartolomei et al., 2005). Electrophysiological evidence suggests that the rhinal cortices regulate the interaction between association neocortex and the hippocampus (Schwarz and Witter, 2002; de Curtis and Pare, 2004; Fell et al., 2006; Fernandez and Tendolkar, 2006), and it could be argued that epileptogenesis and the origins of declarative memory dysfunction are inextricably united at the rhinal-hippocampal interface (de Curtis and Pare, 2004).

It follows, then, that fundamental forms of associative memory, uncomplicated by semantic loadings, can be regarded as proximal to the neurobiological mechanisms of mesial TLE, and therefore potentially endophenotypic. On the other hand, the memory phenotype of mesial TLE as it manifests on semantically-loaded and linguistically complex tasks (Giovagnoli et al., 2005), is likely to be more distal. It is suggested here that the acquisition of arbitrarily contiguous items is usefully conceptualized as an internal neurocognitive marker of dysfunction in rhinal cortex and rhinal-hippocampal interface. The immediate impact of this conceptualization lies in pre-surgical diagnosis, leaving open the possibility that it might turn out to be a candidate endophenotype in familial temporal lobe epilepsies.

**Arbitrary association in non-verbal memory: is there a neurocognitive marker for right mesial temporal foci?**

Defining cognition in terms of what is thought to be absent (‘non-verbal’) opens up a large and heterogeneous category containing a multiplicity of memory functions relating to perceptual, spatial, facial, musical or social and emotional domains. It is commonly observed that the nexus between right temporal foci or resections and non-verbal memory is not as consistent as that between left temporal damage and verbal memory (Bell and Davies, 1998). This comment is usually made in relation to visuospatial forms of non-verbal memory, the domain most frequently studied in patients with TLE. The material-specificity perspective makes a series of implicit assumptions about spatial memory which mirror those relating to verbal memory. The most obvious of these is that the domain is unitary, leading to the expectation that almost any test of spatial memory will be sensitive to right temporal lobe damage. This, however, is clearly not the case, and a number of standard tests of visuospatial memory, commonly used in evaluation of TLE, do not reliably distinguish between left or right TLE (Lee et al., 2002; McConley et al., 2008).

Since the formulation of the material-specificity model, a substantial neuroscience of spatial memory has emerged, pointing to a multiplicity of dissociable components (Schacter and Nadel, 1991; Hartley et al., 2003; Bird and Burgess, 2008; Burgess, 2008; Doeller et al., 2008). At a neuronal level, hippocampal ‘place’ cells respond to the subject’s location, while parahippocampal cells respond to the landmark being viewed. Of particular importance, the hippocampus contains ‘place-goal conjunctive’ cells, which appear to play a role in ‘associating goal-related contextual inputs with place’ (Ekstrom et al., 2003). Place cells are thought to drive spatial recall by re-activating a widespread network representing geometric and featural aspects of environments, the position of objects within them, and self-motion or path integration signals (Byrne et al., 2007). At an interhemispheric level, regional activity during way-finding through virtual environments is not restricted to the right mesial temporal region: in all likelihood, there is a dynamic interaction between left and right temporal lobes, depending on task demands (Burgess et al., 2002; Sommer et al., 2005; Treyer et al., 2005), and individual levels of navigational ability (Hartley et al., 2003). The uptake and recall of object location, however, is one component of spatial learning and memory most consistently lateralized to the right mesial temporal region (Burgess et al., 2002; Sommer et al., 2005; Treyer et al., 2005; Doeller et al., 2008).

Despite some bilateral findings (Glikmann-Johnston et al., 2008), performance on object-location tasks tend to be selectively impaired in patients with right mesial temporal foci (Abrahams et al., 1997, 1999; Bohbot et al., 1998), with circumscribed thalamohippocampal lesions to the hippocampus or parahippocampal cortex for the relief of mesial temporal seizures (Bohbot et al., 1998; Stepankova et al., 2004), or after temporal lobe resection (Smith and Milner, 1981, 1989; Pigott and Milner, 1993; Nunn et al., 1998, 1999; Crane and Milner, 2005; Parslow et al., 2005; Diaz-Asper et al., 2006). Interestingly, Diaz-Asper’s study showed that right lateralization applied only to object location in 3D, but not 2D displays, the latter task being impaired irrespective of side of resection. Similarly, in a post-amygdalohippocampectomy study object-location memory, assessed within a two-dimensional frame, was found to be worse after left-, rather than right-sided surgery (Kessels et al., 2004). This pattern of findings suggests the existence of task-specificity within the object-location paradigm. Further evidence of fractionation in object-location learning comes from the finding that lateralization at a mesial temporal level might depend on whether location or identity of the object is the more salient component: detection of changes in location causes right mesial temporal activation in normals, while detection of changes...
in the nature of the object activates the left mesial temporal region (Treyer et al., 2005).

The question of specialization within the right mesial temporal region is raised by the finding that performance on a human analogue of the Morris water maze is selectively impaired in patients with right posterior parahippocampal lesions (Bohbot et al., 1998), but is preserved in HM, whose resection did not include this region (Bohbot and Corkin, 2007). It is possible that parahippocampal cortex represents the geometric properties of the environment (Epstein and Kanwisher, 1998; Burgess et al., 2002; Bird and Burgess, 2008). Interestingly, thermocoagulatory damage to right parahippocampal or right perirhinal cortex does not increase object-place association deficits induced by ipsilateral hippocampal damage (Stepankova et al., 2004). Object-object, and face-face associative learning, however, was heavily influenced by the extent of anterior parahippocampal lesions in left and right temporal lobe resections for the treatment of TLE (Weniger et al., 2004).

The discovery of ‘grid cells’ in the entorhinal cortex (Hafting et al., 2005) is a potentially important step in appreciating mesial temporal specialization for spatial memory in patients (Philbeck et al., 2004). These cells compute positional information independent of external spatial context, and are responsive to self-motion or ‘path integration’ cues (proprioceptive, vestibular, movement generated re-afference). Philbeck et al. (2004) demonstrated path integration deficits in patients who had undergone right anterior temporal lobotomies. The deficit was manifested as a tendency to overshoot during locomotion towards a previously seen target with vision excluded. The overshoot errors were not explained by a misperception of the target’s position.

In summary, the complexity of spatial memory and its cerebral representation poses another difficulty for the material-specific hypothesis in its strong form. While some components of the domain are more sensitive to right than left temporal lobe damage (Kessels et al., 2001), the underlying neurocognitive architecture remains elusive, and the left temporal lobe also appears to play a significant role in many spatial memory tasks.

With the aim of developing an associative marker of right mesial temporal pathology, Wilson and Saling (2007) studied the ability of patients with right or left mesial temporal epilepsy to learn musical paired associates, constructed to mimic the arbitrary (‘hard’) and semantically related (‘easy’) paradigm in verbal paired associates. Each member of an easy pair consisted of a three note tonal motif constructed around the tonic and dominant chords of C major. Motifs comprising the hard pairs did not conform to a conventional scale, resulting in an unfamiliar novel and non-tonal pattern. While the relationship between paired tonal items is not directly analogous to the predicative, categorical or antonymous relations in easy word pairs, they nevertheless occur within a common tonal framework, which is available as a pre-existing support for learning. The acquisition of the hard pairs, on the other hand, is unsupported by a conventional musical framework. Learning was assessed by means of a recognition paradigm. The right mesial TLE group was impaired on easy musical pairs, while the left mesial TLE group did not differ from patient controls. Both groups, however, were impaired on the hard musical pairs, the left mesial TLE patients faring somewhat worse. The right lateralized component is an inability to make use of a tonal framework to support learning, and might constitute a promising marker of right mesial temporal pathology. Like the verbal and spatial domains, lateralization is task- rather than material-specific (Wilson and Saling, 2007). Crucially from a diagnostic point of view, the occurrence of verbal and non-verbal memory impairments in left TLE should not be surprising, and should not in itself raise the question of amnesia.

The verbal memory syndrome of left TLE

Figure 1 summarizes the model proposed here. For practical clinical purposes, a two component left temporal model of verbal memory can be defined: a mesial protosemantic component, operationalized as arbitrary paired associate learning and a lateral semantic component, operationalized as performance on tasks that are meaningfully structured, or on which semantic structure can readily be imposed (related paired associates, word lists, passages). These components are dissociable. The pattern of verbal memory impairment in patients with left mesial temporal foci consists of impaired acquisition of semantically unrelated word pairs, with relative preservation of semantically structured forms of verbal learning.

Preserved verbal memory function on preoperative assessment is a well-established risk factor for decline after left temporal lobectomy. This principle has been built around a conventional neuropsychological armamentarium, consisting of tasks with varying degrees of semantic loading, many of which are explicitly related to measures of verbal intelligence. The postoperative decline in patients with mesial temporal atrophy is, not surprisingly, a change in semantically based function imposed by resection of relatively normal neocortex in anterior temporal lobectomy. To the extent that mesial temporal epileptogenic pathology is present, however, arbitrary relational learning is highly likely to be impaired. Cases with the best psychometrically defined memory outcome are those with impaired preoperative memory across both components. Neurologically, these are most likely to have mesial temporal pathology, and secondary damage to neocortical tissue or subjacent white matter. It is, therefore, not so much a matter of reduced hippocampal adequacy, as reduced temporal lobe adequacy. Conversely, cases at greatest risk for memory change are those with late onset seizures, no evidence of structural pathology, and who are normal across arbitrary and semantic components of memory function.

Memory after temporal lobe resection

Amnesia is a rare postoperative memory complication. The number of patients known to have become amnesic after a unilateral temporal lobectomy is small (Baxendale, 1998; Kapur and Prevette, 2003), and all are likely to have had undetected bilateral mesial temporal damage prior to surgery. A recent survey showed...
that there are no reports of cases of postoperative amnesia with presurgical neuroimaging evidence of a normal contralateral temporal lobe (Baxendale et al., 2008b). The bi-temporal model of amnesia therefore remains an important concept in pre-surgical decision-making, and patients with pre-surgical neuroimaging evidence of bilateral damage should always be considered to be at an elevated risk of an amnestic syndrome (Baxendale et al., 2008b). Recent findings (Bohbot and Corkin, 2007) suggest that conceptulizing amnesia within the framework of material-specificity theory, by defining it as a material non-specific phenomenon, could lead to the counter-clinical conclusion that not even HM is amnestic. Bohbot and Corkin found that HM is capable of rapid place learning on a human analogue of the Morris water maze despite his well-documented bilateral mesial temporal resection. The neuroanatomical basis of HM’s preserved place learning lies in the preservation of his right posterior parahippocampal cortex, on which this task depends (Bohbot et al., 1998).

This example makes it clear that while a ‘general’ or ‘material non-specific’ memory impairment might be seen in patients with severe amnesia, this is not invariable. More importantly, material non-specific impairments do not constitute a sufficient condition for the diagnosis of amnesia.

Cases with left mesial temporal seizures, congruent MTS, but apparently normal verbal memory (Loring et al., 2004), reveal a pivotal distinction between the material-specificity approach and the view presented here. In conventional approaches to neuropsychological assessment semantic aspects of verbal memory are over-represented, or conflated with arbitrary forms. The net result is reduced sensitivity to mesial damage. When arbitrary and semantic forms are considered separately, however, patients with well circumscribed left MTS exhibit a differential pattern, characterized above as the verbal memory syndrome of left mesial TLE. The clinical relevance of this formulation is illustrated by a less frequent, but no less important presentation characterized by well defined left hippocampal sclerosis, but normal arbitrary and semantic forms of verbal memory. Contrary to the principle that high (putatively left) hippocampal adequacy leads to postoperative verbal memory decline, these patients are more likely to retain their memory function at preoperative levels. We have recently assembled a cohort representing ~3% of patients seen in the Comprehensive Epilepsy Program at Austin Health, Melbourne. Since the arbitrary associative marker is normal, early re-organization of verbal memory at a fundamental level is implied.

The verbal memory syndrome of left mesial TLE also provides a clearer understanding of the memory effects of anterior temporal lobe resections intended to spare hippocampus. We studied two cases who underwent anterior temporal resections, one for an anteromesial dysembryoplastic neuroepithelial tumour involving the left amygdala (Case #1), and the other for a ganglioglioma in a similar location (Weintrob et al., 2007). Verbal memory was entirely normal preoperatively. Both resections involved the ento and perirhinal cortices, impinging as well on the anterior 2–3 cm of the temporal neocortex, but sparing the hippocampus. At a 1 month postoperative review acquisition of unrelated paired associates was severely impaired, with an accompanying impairment of list learning. Related verbal paired associates

![Diagram](https://example.com/diagram.png)

**Fig. 1** Diagrammatic representation of the left inferior temporal region extending from inferior temporal cortex (ITC) laterally to the hippocampal complex (HC) medially. (A) Summary of mediolateral specialization underlying verbal memory. Rhinal-hippocampal cortices are involved in the uptake, temporary retention and processing of protosemantic conjunctions (blue shading). Incoming associations are represented in perirhinal cortex, and compared with pre-established semantic representations in ITC (red lines). Unfamiliarity, mediated by rhinal gating mechanisms, determines the likelihood of hippocampal involvement (broken blue line). (B) Mesial temporal sclerosis (dark green speckled shading) and epileptogenesis impairs rhinal memory mechanisms, resulting in degraded representation of arbitrary linkages, inefficient attribution of familiarity (broken green line) and impaired rhinal-hippocampal transaction (black broken line). Learning and memory are heavily dependent on top-down semantic input from ITC and other neocortical systems (thick green line). CS = collateral sulcus; ERC = entorhinal cortex; HC = hippocampus; ITC = inferior temporal cortex; AM = association module.
were unaffected. At the 12-month review, performance on unrelated pairs showed no recovery, despite a return of list learning to normal levels. Two control cases whose resections did not involve ento or perirhinal cortex retained their ability to learn unrelated paired associates. Since publication of these findings, Case #1 has been re-assessed, 7-years post-resection and continues to show a selective impairment of arbitrary word pairs, able to learn only 17% of unrelated paired associates, compared with a control value of 61%. This finding provides converging evidence for the model proposed here by showing that the mesial temporal memory syndrome can be replicated by anterior temporal resections that do not involve hippocampus.

Predicting post-surgical memory outcome

Until recently, the Wada technique was regarded as the ‘gold standard’ for estimating the risk of postoperative amnesia. Since 1999, when the first international survey was conducted, routine use of the Wada has declined dramatically (Baxendale et al., 2008a). The Wada also gained ‘gold standard’ status for evaluating lateralized material-specific memory outcomes. Recent predictive studies, however, show that baseline neuropsychological evaluation, structural imaging and neuropathology are effective predictors of quantitative postoperative memory status (Baxendale et al., 2006), with the Wada making little or no independent contribution (Chelune and Najm, 2000; Stroup et al., 2003; Lineweaver et al., 2006).

Predictive models such as these have come to play a role in pre-surgical counselling providing an empirical base for informed consent. While actuarial models might be helpful in meeting an immediate management issue, they yield a short term quantitative end-point with an unknown relationship to subjective and adaptive aspects of postoperative memory function (Ferguson et al., 2006), or to neurocognitive changes that evolve over the long term.

Even in cases with good seizure outcomes, adjustment difficulties have the potential to bring increased salience to stable postoperative memory dysfunctions. Contrary to the expectation that postoperative seizure freedom should result in optimal quality of life, it can provoke a burden of normality, manifesting as a complex trajectory of now well documented adjustment difficulties (Wilson et al., 2001, 2004). Psychometric memory findings account for little of the inter-individual variation in subjectively perceived or ecologically significant memory outcomes (Sawrie et al., 1999; Lineweaver et al., 2004; Baxendale and Thompson, 2005). Minor psychometrically defined memory dysfunction might be amplified over time by adverse seizure outcome or ageing, pre-existing psychological vulnerabilities, distorted metamemory perspectives, newly emerging anxiety and depression, memory demands of individual ecological niches, adjustment difficulties or the absence of neuropsychological support. Conversely, a more significant psychometric impairment might not manifest as a significant disability if these settings are optimized. A definitive long-term study of the functional significance of postoperative psychometrically defined memory status has yet to be done.

There is also a growing awareness that treatment resistant TLE is associated with progressive memory change (Helmstaedter and Elger, 1999; Jokeit and Ebner, 1999; Pitkanen and Sutula, 2002; Helmstaedter et al., 2003; Dodrill, 2004; Hendriks et al., 2004; Hoppe et al., 2006; Seidenberg et al., 2007; Hermann et al., 2008). Seizure load appears to be the major risk factor (Thompson and Duncan, 2005). Poor seizure outcome after unilateral temporal lobe resection might therefore set up a double jeopardy (Helmstaedter et al., 2003), and Baxendale has suggested that poor seizure control in cases with bitemporal pathology poses a lifetime risk of amnesia (Baxendale, 2007; Baxendale et al., 2008b).

Conclusion

Despite its simplicity, the idea of material-specificity came to dominate neuropsychological practice in temporal lobe epileptology, offering a monolithic diagnostic strategy, an operational definition of amnesia, a framework for assessing the cognitive risks associated with epilepsy surgery and understanding postoperative outcomes, and a rationale for deploying the dominant psychometric paradigm of the day. With advances in the cognitive neuroscience of memory, the application of theoretically driven paradigms to the problem of memory function in focal epilepsies, and a broader understanding of the course of postoperative recovery, the notion of material-specificity has become too restrictive on a number of levels.

Material-specificity achieves parsimony by assuming two ‘mirror-image’ categories of memory distinguished on the basis of (i) presence or absence of words; (ii) fully lateralized to the left or to the right; and (iii) associated more closely with auditory than verbal memory and vision in the case of non-verbal memory. Reviews within the field have drawn attention to the tighter verbal-left temporal nexus, encouraging a continued search for a form of non-verbal memory that exhibits equal but opposite properties of lateral representation. Studies reviewed here strongly suggest that verbal and non-verbal memory are not opposites in terms of their respective patterns of cerebral organization, and at complex levels of expression neither are fully lateralized. This has obvious implications for neuropsychological approaches to a mesial temporal disorder that commonly manifests as a lateralized phenomenon. For instance, the definition of amnesia as a material non-specific impairment loses meaning, because a left mesial temporal focus is capable of affecting aspects of non-verbal, as well verbal memory. Similarly, with the use of discourse-based tasks, a right mesial temporal focus might also exert a material non-specific, or even a purely verbal effect on the assessment instrument.

I argue that neuropsychological practice in epileptology needs to incorporate an approach that recognizes the relationship between lateral and intratemporal specialization, on one hand, and the neurocognitive structure of its assessment techniques. This is particularly important at a preoperative level, where questions of congruity, anomalous organization or re-organization of memory...
functions arise. Butler and Zeman (2008) point out that the insensitivity of standard memory tests poses a challenge to current theoretical models. In terms of the view presented here, insensitivity of standard memory tasks to mesial temporal foci arises from the conflation of differentially represented components. Effective neuropsychological markers of lateralized mesial temporal dysfunction are likely to be elemental and fundamental aspects of the function, ideally stripped of associations with general intellectual function, or complex expressions that are now known to be bilaterally represented. The rapid uptake of co-occurrences, devoid of a previously represented connection, are fundamental to the construction of episodic and semantic memories, and associative paradigms based on this principle are promising candidate markers of lateralized mesial temporal dysfunction, as are paradigms based on retro-active interference, path integration or music tonality. With the advent of sophisticated neuroimaging, the anatomical distribution of epileptogenic pathology can be characterized in vivo, as can the boundaries of surgical resection. Correspondingly, concepts of intratemporal specialization should assume a prominent position in neuropsychological practice.

While the principle of material-specificity receives its strongest support at a postoperative level, the broader issues of distress associated with subjective memory symptomatology and the functional impact of memory disability assume greater prominence. The medium and long-term implications of psychometrically defined changes in memory for real world functional capacities are not known. Current evidence does suggest that optimal memory outcomes are intimately dependent on seizure relief, and in all likelihood, successful management of the psychosocial vicissitudes that often follow surgical treatment.

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