“Verbal And Visual Memory Binding In Patients With Unilateral Temporal Lobectomy”

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Abstract

The role of the medial temporal lobes in long-term declarative memory is well established, but their role in short-term relational memory and learning, however, is still under investigation. Research suggests there are dissociations between items that form unified representations (e.g. shapes with colours) and inter-item bound representations that do not form single entities (e.g. word pairs). Evidence from brain damaged patients also suggests a functional dichotomy between left and right hemisphere for language and visuo-spatial memory respectively. This study investigates the role of the left and right medial temporal lobes in verbal and visual memory in patients after unilateral anterior temporal lobectomy for temporal lobe epilepsy (left = 9, right = 12, controls = 53). Subjects underwent a binding paradigm to assess short-term memory (STM), learning, and long-term memory (LTM) for unitized visual representations (shapes and patterns versus shape-pattern combinations) and inter-item verbal associations (single words versus word-pairs), as well as a battery of neuropsychological tests to assess verbal and visual memory, executive function, attention, and visual perception. Binding in STM reduced performance for all groups. Both patient groups performed worse than controls in all conditions of STM, learning, and LTM. Patient groups displayed an additional binding deficit in the verbal STM condition. Only left-sided patients had LTM verbal binding deficit. There were no binding deficits in the visual tasks. Findings suggest that binding in STM is resource demanding but does not additionally impact learning. MTL damage in either hemisphere affects both verbal and visual memory and learning. While MTL damage does not affect intra-item visual binding it does affect STM binding of within-domain verbal material. The LTM deficit in bound verbal material seen in left patients is explained via a laterality affect. Results are discussed in relation to working memory theory.

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Introduction

Structures within the medial temporal lobes (MTL) are crucially involved in processing information related to long-term declarative memory (Cohen & Squire, 1980; Schacter & Tulving, 1994; Squire, 1992). The MTL is a hierarchical system composed of the hippocampus, amygdala, and parahippocampal region (entorhinal cortex, perirhinal cortex, and parahippocampal cortex). Selective bilateral damage to the hippocampus causes long-term anterograde amnesia (Zola-Morgan, Squire, & Amaral, 1986) while more extensive MTL damage extenuates impairment such as the famous case of H.M. (Milner, 1972; Scoville & Milner, 1957). Amnesics have an impaired ability to form new relational memories in long-term memory (LTM) (Giovanello, Verfaellie, & Keane, 2003; Holdstock, Mayes, Gong, & Kapur, 2005; Mayes et al., 2004). While there is no clear functional dichotomy between the regions of the MTL (Squire, Stark, & Clark, 2004) the hippocampus is primarily responsible for forming relations among associated items that rely on recollection whilst the surrounding cortices are thought to involve the processing of individual items that rely more on familiarity (Brown & Aggleton, 2001), although both the hippocampus and parahippocampal region interact to form relational memories (Eichenbaum, 2000, 2006).

A potential explanation for the relationship between the hippocampus and surrounding cortices in relational memory is the nature of the associative relationship. One view is the domain dichotomy (DD) view posited by Mayes et al. (2004) and Mayes, Montaldi, and Migo (2007). In this model the perirhinal cortex is responsible for intra-item associations and within-domain associations. An intra-item association occurs when features within an object form a single unified representation. Within-domain associations occur when separate items within the same domain are linked together but do not form a unified representation (e.g. word pairs or image-image combinations). Associations between items from different domains, known as between domain associations, are mediated by the hippocampus presumably because the domain information is not cortically close by. The former associations are purported to rely on familiarity based mechanisms whilst hippocampal related between-domain associations rely more on recollection. Interaction occurs between the perirhinal cortex and hippocampus because tests of memory rarely rely on strictly familiar or recollective mechanisms. Additionally the hippocampus is thought to be directly involved in the learning of relations between items that can make up objects.

Such that the perirhinal cortex mediates the memory of a face-face pairs and the hippocampus mediates the memory of the relationships between individual features of the face. Strong evidence for this point of view comes from a bilaterally damaged hippocampal patient Y.R. (Mayes, Holdstock, Isaac, Hunkin, & Roberts, 2002; Mayes et al., 2004) who was impaired on relational memory for items from different domains (e.g. object and spatial location or names and faces) while memory for intra-item associations remained intact. Recently there has been several studies that strongly support a dichotomy between recollective and familiarity based processes (Bowles et al., 2007, 2010; Martin, Bowles, Mirsattari, & Köhler, 2011). The studies reported on patient N.B. who presented with a clear impairment in familiarity memory but normal recollection. Patient N.B. had resection of the perirhinal and entorhinal cortices but an intact hippocampal formation. Furthermore the impairment appeared to be confined to verbal information only (Martin et al., 2011) suggesting a lateralisation of familiarity processing. It remains to be seen if the sparing of intra-item and within-domain associations in this patient hold up according to the DD point of view. Preservation on tasks of short-term memory (STM) in amnesics with bilateral MTL damage (Cave & Squire, 1992; Scoville & Milner, 1957) and dissociations between verbal STM and LTM in perisylvian cortex lesion patients (Shallice & Warrington, 1970) have contributed to the assertion that STM and LTM are composed of neurally distinct networks. However, converging evidence indicates that this distinction is not so clear (Ranganath & Blumenfeld, 2005) which suggests that associative learning and holding associations in STM may also involve structures within the MTL.

The processes that combine separate elements and relate them together can be collectively known as 'binding'. This occurs at a number of different levels (Zimmer, Mecklinger, & Lindenberger, 2006). At the perceptual level items within visual attention, such as shape, colour, or location, are processed through separate channels (Denys et al., 2004; Kandel & Wunitz, 2000; van Essen & Dury, 1997), and according to Feature Integration Theory (Treisman & Gelade, 1980), they are bound together when they fall within locally attended space. STM binding is distinct from perceptual and LTM binding. Holding short-term representations of related items in memory is essential for accurately understanding and manipulating information in a dynamic environment. Studies of hippocampally damaged patients and neuroimaging of healthy subjects have implicated the hippocampus in STM binding of object-location representations (Hannula, Tranel, & Cohen, 2006; Hannula & Ranganath, 2008; Mitchell, Johnson, Raye, & D'Esposito, 2000; Olson, Page, Sledge Moore, Chatterjee, & Verfaellie, 2006). Contrastingly, in two fMRI studies (Piekema, Kessels, Mars, Petersson, & Fernàndez, 2006; Piekema, Rijpkema, Fernàndez, & Kessels, 2010), there was no hippocampal activation during item-colour associations in neurologically healthy participants. These studies may reflect the dissociation between hippocampally mediated between-domain associations represented by the former studies while the latter may reflect intra-item associations mediated by the parahippocampal region. Strong support for extra-hippocampal MTL involvement in intra-item visual STM binding comes from patient E.S. reported by Parra, Della Sala, Logie, & Abrahams (2009a). Despite no self-reports of memory difficulties E.S. was clearly impaired on visual STM for intra-item associations. Patient E.S. had anterior temporal lobe damage external to the hippocampus following surgery to remove a left sphenoid wing meningioma. In a series of experiments (Parra et al., 2009a) E.S. was found to have normal perceptual abilities, normal single-item visual and verbal memory, and normal bound verbal memory, but impaired intra-item visual memory for shape-colour and object-colour bindings. Interestingly her performance equated that of controls when she had to verbally name the objects during the object-colour condition. This suggests that while material specific visual and verbal binding are mediated by separate processes they can readily interact to support STM relational encoding. Binding deficits were also found for both verbal STM (Parra et al., 2009b) and visual STM (Parra et al., 2010) in early Alzheimer's disease where the MTL is one of the first affected regions.

Despite the evidence for MTL involvement in STM binding there are discrepancies. Piekema et al. (2010) found significant MTL activation in a task pairing house-face associations but not object-location and object-colour associations in healthy adults. In another study Piekema et al. (2007) found a binding deficit in patients with amygdalohippocampectomy and Korsakoff's Syndrome but this was no greater than the patients' deficit for single item memory suggesting that binding in STM was not a separate mechanism. However the authors employed an 8 second delay for all conditions of the experiment suggesting that the results observed applied to working memory maintenance which may have masked a specific binding deficit. Baddeley, Allen, and Vargha-Khadem (2010) reported normal performance in a patient with selective bilateral hippocampal damage on tasks of binding colours and shapes, words into sentences, and of binding features with spatial and temporal elements. This type of inter-item binding should have been disrupted with damage to both hippocampi. They concluded that the hippocampus was not required for short-term visual or verbal binding. However it should be noted that their patient had selective hippocampal atrophy from a very early age and may have developed compensatory mechanisms. These discrepancies across studies suggest that the process of binding short-term information in memory of patients with MTL lesion still requires investigation.

Working memory (Baddeley & Hitch, 1974; Baddeley, 1986) is the most popular theoretical concept for explaining the processes underlying STM. The model consists of a system of separate stores and components. The episodic buffer (Baddeley, 2000, 2001, 2003) was introduced to account for the temporary storage of integrated information from the working memory sub-systems and LTM, although the buffer may not be directly responsible for binding operations (see Baddeley, Hitch, & Allen, 2009). Alternatively Cowan's embedded processes model (1988, 1995, 1999, 2005) views working memory as a process within LTM where activated portions of LTM interact with attention to hold items in working memory. Binding occurs when portions of LTM are activated and new links are formed. The new associative item would then be formed in LTM. Accordingly structures within the MTL may be responsible for binding operations in working memory.

Research indicates that visual STM can hold about 3 or 4 objects that are composed of a number of individual features (Cowan, 2001, 2011; Luck & Vogel, 1997; Vogel, Woodman & Luck, 2001). Some authors suggest that visual STM is object based where the binding of features into integrated objects is automatic requiring no additional attentional resources (Luck & Vogel, 1997; Vogel et al., 2001). There does appear to be an advantage to binding visual features into integrated objects (Xu, 2002a). However this advantage is diminished when features composing the object are from the same dimension (Xu, 2002b). Indeed this has been shown for colour-colour object combinations (Parra et al., 2009b, Parra, Cubelli, & Della Sala, 2011; Xu, 2002b). Thus in opposition to the object based view Wheeler and Treisman (2002) contend that object memory is feature based and that this requires additional cognitive resources. In STM the cognitive demand of binding is not clear. Studies investigating object or shape-colour conjunctions have presented mixed results in healthy subjects with improvements (Parra et al., 2009a, b; Piekema et al., 2007) and declines (Brockmole, Parra, Della Sala, & Logie, 2008; Parra et al., 2009a; Piekema et al., 2010) in bound memory performance versus single item conditions. Crucially performance in binding conditions are usually compared to memory for single items separately (i.e. object-colour memory versus colour memory *or* object memory) and the total number of features in the binding condition and single feature condition do not match. This distorts the assessment of cognitive demand. For example Allen, Baddeley, and Hitch (2006) compared memory for either four colours, four shapes, or a mix of four colours and shapes with 4 bound items which were made up of 8 separate features. Performance was significantly better for colour only whilst there was no difference in remembering shape only or colour-shape binding. However there may have been a different outcome if memory in the single item condition was matched for the total number and type of features in the bound condition. Only one study (Parra et al., 2010) matched the number of features across conditions which resulted in equal performance. It is not clear if there is a cognitive cost to binding visual information in STM due to the methodological considerations of these previous studies. Memory for words or non-visual information is better remembered when they can be integrated in to chunks or sentences (Baddeley et al., 2010; Cowan, 2001; Miller, 1956). Currently there is very little data on resource demands when binding within-domain verbal STM outside of linguistics. Most verbal STM binding studies have tested verbal-location conjunctions or have not tested demand directly. In a verbal STM binding study Parra et al. (2010) found no additional cost to binding object-colour conjunctions compared to individual features in healthy subjects. However, the stimuli were presented visually leading to the increased likelihood of using visual coding. Binding for aurally presented word pairs was tested in experiment five of Parra et al. (2009a). Healthy subjects showed better performance for the bound condition compared to memory for individual features. However there were no statistical results published to verify this. This study will directly compare memory performance for words and unrelated pairs of words which will reduce semantic aid.

Anterior temporal lobectomy (ATL) is a common treatment for medically intractable temporal lobe epilepsy (TLE) and involves the removal of the mesial temporal lobe structures. As such ATL patients provide a useful sample to investigate MTL involvement in memory binding. Evidence from patients with TLE or damage to the temporal lobe suggests that laterality of damage impacts on material specific memory (Deweer, Pillon, Pochon, & Dubois, 2001). Patients with left TLE, mesial temporal sclerosis or ATL are associated with a decline in verbal semantic memory (Giovagnoli, Erbetta, Villani & Avanzini, 2005) and verbal episodic memory (Lee, Yip, & Jones-Gotman, 2002; Martin et al., 2001; Naugle, Chelune, Cheek, Luders, & Awad, 1993; Pillon et al., 1999; Rausch et al., 2003) even in patients with normal pre-operative verbal memory (LoGalbo et al., 2005). Verbal memory decline after surgery however is not exclusive to patients with left sided epileptogenic origin. A recent review suggested the risk of verbal memory decline after left temporal lobectomy or right temporal lobectomy was 44% and 20% respectively (Sherman et al., 2011). Additionally Gleissner, Helmstaedter, Schamm, and Elger (2002) reported declines in verbal memory of 51% and 32% after surgery in patients undergoing amygdalohippocampectomy in the left and right hemisphere respectively. These findings suggest that while the left side, particularly the hippocampus, is predominantly involved in verbal memory the right temporal lobe plays a significant role. Indeed it has been noted that material specificity is unlikely to be fully lateralized (Dobbins, Tulving, Knight, & Gazzaniga, 1998; Saling, 2009).

Data on non-verbal memory deficits in right sided temporal damage is not as clear or as strong as left-sided verbal impairment. Spatial deficits have been reported in right-sided patients (Abrahams et al., 1999; Dulay et al., 2009; Nunn, Graydon, Polkey, & Morris, 1999; Pillon et al., 1999) with one report suggesting patients were six times more likely to have spatial difficulties after right ATL even when no group differences existed before surgery (Dulay et al., 2009). Contrastingly spatial deficits have been reported regardless of hemisphere involved (Glikmann-Johnston et al., 2008). Differences in findings may result from sub-sets of spatial skills that are mediated by different areas of the brain including both hippocampi (Bohbot, Iaria, & Petrides, 2004; Glikmann-Johnston et al., 2008; Kessels, Hendriks, Schouten, Van Asselen, & Postma, 2004; see also Postma, Kessels, & van Asselen, 2008). It may be that most spatial tests tap functions of the right hippocampus or that the right hippocampus orchestrates a super ordinate spatial function and further testing in the area will elaborate upon this. Evidence on deficits to visual memory tend to find no laterality effect (e.g. Naugle et al., 1993) or with a trend toward right laterality (Lee et al., 2002). One study found that only patients with right TLE with hippocampal sclerosis were impaired on a visual memory test (Gleissner, Helmstaedter, & Elger, 1998). Recent evidence suggests that the type of test used to measure visual memory plays a role (Dulay et al., 2009). Dulay et al. note that in their own study and in a review of seven other studies of TLE patients after ATL that the majority of patients show no change or improvement in visual memory ability. However it was clear that a risk to visual memory does exist with approximately 22% of their sample inheriting some form of decline post ATL.

The reasons behind variable performance on material specific domain tests pre and post surgery and why some patients decline and others improve are not fully understood. One partial explanation may be functional reorganisation which is the capacity of the brain to compensate for neuronal or functional loss. Language functions, for instance, can shift hemisphere following removal of the left hemisphere (Hertz-Pannier et al., 2002). Functional magnetic resonance imaging (fMRI) of TLE patients has shown greater activation in the contralateral MTL during encoding of information normally processed in the material specific hemisphere such as verbal encoding in left TLE patients activating the right hippocampus as opposed to the left hippocampus in healthy subjects (Richardson, Strange, Duncan, & Dolan, 2003). Similarly Powell et al. (2007) found that left TLE patients had greater activation in the right parahippocampal gyrus for word encoding. Right TLE patients had greater activation in the left hippocampus for picture encoding. Crucially increased activation in the contralateral MTL and decreased ipsilateral activation correlated with worse performance suggesting that these patients had poor compensatory mechanisms or dedifferentiation. Hemispheric dominance of language also decreases in epilepsy patients with atypical lateralization especially in those with early epilepsy onset (Pataraia et al., 2004; Springer et al., 1999). Korsnes, Hugdahl, and Bjørnaes (2009) reported a patient with right sided epileptogenic focus who underwent neuroimaging assessment two years pre and post hippocampal removal. Although they found significant activation in the left hippocampus when viewing familiar and novel pictures before surgery they found no subsequent left activation post-surgery despite similar performance. This pattern of results suggests pathological tissue disrupts ipsilateral neural efficiency with the adoption of compensatory strategies in the contralateral hemisphere post epilepsy onset. Improvements in memory after resection have been noted (Baxendale, Thompson, & Duncan, 2008) with outcome more favourable in patients who are seizure free post operatively and have early onset epilepsy (Griffin & Tranel, 2007; Seidenberg et al., 1997) or shorter epilepsy duration (Baxendale et al., 2008), and improvements in memory may also occur with time since resection particularly after right ATL (Andersson-Roswall, Engman, Samuelsson, & Malmgren, 2010; Grammaldo et al., 2009) suggesting more adequate compensation after the removal of pathological tissue in some patients. This is related to the 'functional adequacy' theory (Chelune, 1995) where the remaining non-pathological ipsilateral tissue is more efficient than the contralateral structures compensating for it. Recent fMRI evidence supports this claim (Bonelli et al., 2008) where the ipsilateral hippocampus was the best predictor of verbal and visual memory outcome after ATL. Furthermore post-operative improvements in domain specific memory are associated with resection of the contralateral temporal lobe (Baxendale et al., 2008): verbal improvements after right ATL and visual improvements after left ATL, suggesting improvements can stem from reduced electrical interference. In addition one study found that those who have had hippocampal insult for longer had better associative memory for colours and locations (Braun et al., 2008) suggesting more time to form adequate strategies related to hippocampal function. Although unresolved the evidence here may suggest a combination of factors for differences in memory outcome including individual differences. This leads to the question of compensation of memory binding function in TLE patients after ATL. Although it is beyond the scope of this paper to assess pre and post binding performance it may be possible to infer compensation from the data. As such if compensation does occur one would expect intact performance in some patients albeit with reduced efficiency compared to controls. These patients may include those who have had an earlier onset of epilepsy or shorter duration of epilepsy.

Word pair learning and visual pair learning can be impaired after ATL (Savage, Saling, Davis, & Berkovic, 2002; Owen, Sahakian, Semple, Polkey, & Robbins, 1995). The processes involved in learning intra-item visual bound representations have received little attention. Dishon-Berkovits and Treisman (unpublished but described in Treisman, 2006) and Colzato, Raffone, and Hommel (2006) reported that bound visual objects can be incidentally learned but that learning does not influence short-term visual memory in the healthy brain. Recently Logie, Brockmole, and Vandenbroucke (2009) measured how repeated exposure to elements of bound stimuli affect the ability to remember short-term visual representations and to implicitly learn these representations while controlling for some of the methodological limitations of those previous studies. The authors found that repeated exposure to the same stimulus did not affect the ability to remember new representations. Moreover only some learning actually occurred despite repeatedly displaying the same items across every display. Logie et al. concluded that bindings are fragile and new displays readily displace previously studied arrays and that *if* learning occurs it is more likely with bound objects than single features. Although this suggests binding in STM and LTM representations might involve different processes the two must interact to some degree, particularly as memory improves when the stimuli involve familiar items from LTM (Colzato et al., 2006). Moses and Ryan (2006) outline relational and conjunctive theory in regard to MTL involvement in learning. Whilst relational theory predicts that the hippocampus is involved in the formation of explicit associations between distinct items conjunctive theory predicts that the hippocampus forms unique representations. In conjunctive theory damage to the hippocampus should impair the rapid formation of intra-item bindings but these formations will still occur over multiple trials due to the role of the surrounding cortex. The theories differ in how items are processed and retrieved from storage and tasks employing a learning phase on temporally damaged patients may shed light on these theories.

This study explores the role of the MTL in short-term memory, learning, and long-term memory for within-domain verbal binding and visual intra-item binding using unilateral ATL patients and healthy controls. Subjects will be assessed with a binding paradigm used to explore the effects of laterality on binding information from the verbal and visual domains. Subjects will undergo a battery of neuropsychological tests to ensure any difficulties are not due to cognitive impairments other than those involved in binding (see methodology for assessment list). As other brain areas involved in perception (e.g. parietal lobes) and executive function (e.g. frontal lobes) are typically undamaged after TLE and ATL I predict that patients will replicate previous studies evidencing normal working memory (Tudesco et al., 2010), and executive function and attention (Sherman et al., 2011). Verbal memory will decline in both left and right ATL patients with worse performance in the left group (Tudesco et al., 2010; Sherman et al., 2011) and verbal fluency will also be impaired especially in the left group (Martin et al., 2000; Tudesco et al., 2010). Visual memory will be impaired at the group level (Dulay et al., 2009; McConley et al., 2008).

In STM I attempt to ascertain whether structures within the MTL are crucially involved in binding and if there is a lateralised effect to binding. To directly test binding of features in STM memory for individual features will be compared to memory for those features bound together.

The binding tasks involve participants remembering word pairs and integrated visual objects. Given that patients with TLE or ATL may present with verbal and visual deficits I hypothesise that the patients will show a deficit in verbal and visual STM. Left ATL patients may show an additional deficit in verbal STM binding and right ATL patients may show a greater incidence of visual STM binding deficit. Alternatively there will be no difference between patient groups on the visual binding task where laterality is not a strong function in non-verbal material. Given that the visual STM binding task uses abstract shapes and patterns if visual STM is object based I would expect healthy subjects to perform better in the binding condition than the individual features condition. Accordingly if binding is feature based performance should be the worse in the binding condition versus individual feature condition.

The present study employs a learning phase to explore associative learning. After the learning criteria has been met subjects will be administered a LTM task in which subjects will be asked to recall (verbal condition) or recognise (visual condition) the previously learned stimuli. If associative learning in LTM is a separate process than STM binding then ATL patients should show relatively normal performance on the LTM test while STM for bound objects should be disrupted. However if learning associations over presentations is relevant to transferring bound items into LTM then disrupted STM performance will impair learning and LTM. The task employs unfamiliar shapes and patterns and semantically unfamiliar word pairs rendering input from LTM more difficult. Thus I would expect ATL patients to have difficulty in learning associations and poorer performance on the LTM component than controls.

Methodology

Participants

Patients who underwent unilateral anterior temporal lobectomy (ATL) following medically intractable temporal lobe epilepsy were selected (n=23, left ATL=9, right ATL=13). Patients were recruited from the Southern General Hospital in Glasgow, UK. All patients had a unilateral epileptogenic focus originating in the mesial temporal lobe. This was confirmed by EEG video telemetry, SPECT, and /or depth electrodes. All patients had left hemisphere dominance as confirmed by the intracartoid sodium barbiturate amytal test (WADA) apart from one right-handed patient where dominance was unequivocal via EEG and SPECT and did not undergo a WADA test. Patients had no other neurological or psychotic conditions and had a verbal IQ ≥ 75 as predicted by the WTAR (Wechsler, 2002). One right ATL patient with a predicted verbal IQ of 73 was dropped from the analysis.

The ATL typically consisted of the entire removal of the anterior temporal lobe approximately 4-5cms from the temporal pole sparing around 2cms of the superior temporal gyrus of the dominant side (left in these patients). Resection continues medially until the mesial structures are removed and the hippocampus is exposed. The hippocampus is typically resected 2-3cms.

Healthy controls (n=53) were recruited from the University of Edinburgh's volunteer panel. Controls were paid £6 per hour as incentive for taking part. One control had schizophrenia but was included due to the absence of STM binding deficit in that population (Gold, Wilk, McMahon, Buchanan, & Luck, 2003; Luck, Foucher, Offerlin-Meyer, Lepage, & Danion, 2008; Luck, Buchy, Lepage, & Danion, 2009; Luck, Danion, Marrer, Pham, Gounot, & Foucher, 2010).

All participants had normal to corrected-to-normal vision, spoke English as their first language, and had normal hearing. All participants gave written consent prior to testing. One patient deviated more than three standard deviations from the group mean for age (age=65, group mean=35.79, z=3.39). Visual STM binding is unaffected by age (Brockmole, Parra, Della Sala, & Logie, 2008; Parra, Abrahams, Logie, & Della Sala, 2009c) but binding information in LTM is affected (Chalfonte & Johnson, 1996) as is binding for word pairs (Castle & Craik, 2003) including immediate recall (Naveh-Benjamin, Cowan, Kilb, & Chen, 2007). For this reason this case was excluded from analysis. Subsequently the patient sample was updated (n=22, left ATL=9, right ATL=12). Patients and controls were matched for age (t=-1.70, df=72, p=.094) but not for education (t=3.39, df=72, p=.001). Demographic details and results from the one-way between groups ANOVA can be seen in table 1. On average controls had more formal years of education than left ATL (mean difference (MD) = 3.34, standard error (SE) = 1.32, p=.035) and right ATL (MD=3.05, SE=1.17, p=.029) while there was no significant difference between patient groups.

Table 1. Demographic details for controls, right ATL patients, and left ATL patients.

	Controls (n=53)	**Right ATL** (n=12)	**Left ATL** (n=9)	**ANOVA (F)** df=2
Age				
Mean (S.D.)	34.42 (7.072)	36.67 (10.456)	39.44 (8.819)	1.748 (.182)
Range (min-max)	29 (25-54)	30 (20-50)	31 (26-57)	
Education				
Mean (S.D.)	17.34 (3.552)	14.29 (3.570)	14.00 (4.330)	5.698 (.003)
Range (min-max)	17 (6-23)	13 (9-22)	10 (11-21)	
Gender‡ male/female	16/37	3/10	5/4	

‡chi-squared could not be calculated because the expected cell frequencies were too low

Neuropsychological Assessment

The neuropsychological battery comprised tests of memory, perception, and executive function. Controls underwent the same testing protocol and were used as the normative sample.

Short-term Memory capacity (Digit Span): - Digit Span (Wechsler Memory Scale - third edition, Wechsler, 1997) is a general measure of verbal working memory capacity. Participants had to correctly repeat five digit sequences out of six before moving to the next string length. Digit span was taken as the maximum list length correctly attained.

Verbal episodic memory recall (Logical memory WMS-III):- Recall was assessed by the immediate and delayed logical memory subtests of Wechsler Memory Scale III. This examines the immediate recall of episodic verbal information and retention of that information in LTM over 25-30minutes.

Verbal fluency (Controlled Oral Word Association test):- Phonemic fluency was assessed by the letter fluency test (letters F.A.S.) and semantic fluency test (Animals). Participants were given one minute to generate in each task as many exemplars as they could for each given cue. This test taps access to verbal memory and executive skills (search strategies, cue generation, and self-monitoring, Rosen & Engle, 1997).

Visual Memory (Rey-Osterrieth Complex Figure, ROCF):- The ROCF (Osterrieth, 1944; Rey, 1941) is a test of visuo-spatial reconstruction and visual memory. Copy and immediate recall trials were used to test perceptual ability (copy condition) and episodic visual short-term memory (immediate recall).

Attention (Trail Making Test):- Part A of the Trail Making Test measures perceptuo-motor ability and attention while Part B places more demand on working memory and executive function for dividing attention and task switching. Critically (B)-(A) provides a more isolated measure of executive ability (Sánchez-Cubillo et al, 2009).

Verbal IQ (WTAR):- Wechsler Test of Adult Reading (WTAR, Wechsler, 2002) requires the pronunciation of irregularly spelled words. It was used as a test of pre-morbid verbal ability and to predict WAIS-III (Wechsler Adult Intelligence Scale third edition) verbal IQ (VIQ). Standardised norms were obtained from the United Kingdom standardized sample of the test.

Visual perception (VOSP):- The Object Decision and Dot Counting sub-tests of the Visual Object and Space Perception (VOSP, Warrington & James, 1991) battery were used to assess object perception and space perception respectively and to give a general indication of visual perception.

Materials and Design

Memory binding tasks

Participants were assessed using a personal computer at the Psychology Department of The University of Edinburgh or on a Dell Latitude E6510 laptop if testing took place at the home of the participant. This did not affect the presentation or properties of the tasks. The PC was fixed at eye level whereas the laptop was set to the personal preference of the participant. The binding paradigms were run on the computers using an E-prime script (Psychological Software Tools, Pittsburgh, PA).

There were two binding paradigms to test material specific memory; the verbal task and the visual task. Each task had two conditions; an unbound condition where memory was tested for single features and a bound condition where features were combined. The verbal bound condition tested memory for relational or within-domain binding. The visual bound condition tested memory for conjunctive or intra-item binding.

Verbal Memory Binding

In the verbal task lists for single (unbound condition) and paired words (bound condition) were presented aurally through the PC or laptop's speaker system. Stimuli consisted of common nouns/objects (i.e. mountain, necklace, sailboat, bottle, cannon, football, pencil, guitar, toaster, anchor, and hammer) and adjectives (i.e. upright, ebony, knitted, stamped, pearly, stainless, happy, burnt, locked, folded, and carved) that had frequencies above 80%. Word lists in each trial were taken from this limited set to reduce memory for gist and increase the reliance on working memory within each trial. Word pairs were made of adjective-noun combinations. The unbound condition consisted of 8 words in each trial, four adjectives and four nouns. All four adjectives or nouns were presented at the beginning or end of each list, counterbalanced across trials, to avoid the use of semantically linking the adjectives and nouns together. Word-pairs in the bound condition were always presented in adjective-noun order. Words were combined in a way that made semantically relating them difficult (e.g. burnt-necklace). There were 4 word pairs in each condition consisting of eight total words thereby equating features across both conditions allowing for direct comparison. Eight total features were selected to effectively tax working memory capacity and avoid ceiling and floor effects. There were 5 trials in each condition. Word list trials were randomized between participants and the order of condition presentation was counterbalanced across participants. On each trial stimulus presentation was accompanied by a green border on the screen which signified it as the study material. The response screen would be donated with a red border.

Visual Memory Binding

The visual binding paradigm (see figure 1A) was adapted from that reported in Brockmole et al. (2008). Stimuli consisted of 10 six-sided abstract polygons and 10 abstract patterns

(Appendix A). As in the verbal task stimuli were always taken from this limited set to avoid memory for gist and increase reliance on working memory between presentations and trials. Shapes and patterns were unfamiliar and were constructed so as to be difficult to code verbally. Shapes were previously piloted for their discriminability. The visual stimuli were presented on the computer screen approximately 70cms from the participant allowing a visual angle of around 20°. Arrays of stimuli were presented using an unseen 5x5 grid on a white backdrop which sustained 10° at the aforementioned distance. Each cell of the grid sustains 2° of visual angle and each object within these cells was 1.45° separated by 2°. The binding paradigm had two conditions: bound and unbound. In the unbound condition 4 shapes were presented above the set of 4 patterns in the array, totalling 8 features. Shapes were presented in black outline which were unfilled. Patterns were presented in individual square grids of equal size. In the bound condition 4 shapes were displayed each filled with a different pattern. The shapes and patterns combinations displayed 8 features in total equating the number of features in the unbound condition. Bound and unbound condition order was counterbalanced across participants. There were six trials per condition. On each trial the stimulus was presented on screen within a green border which signified it as the study material. The screen would automatically change to the test array which was displayed with a red border. The stimulus array consisted of 8 features (4 shapes and 4 patterns). These would be presented separately in the unbound condition or combined in the bound condition so there would be 8 objects in the unbound condition and 4 in the bound condition. Participants used the mouse to click on 4 items (unbound condition) or 2 items (bound condition), thus it was a recognition test. Each response screen consisted of half the same items as the study screen. The other half were lures from the sample set or recombination foils in the bound condition. Participants were not told if they had selected correctly or not. Items within the response screen varied on each presentation so that the whole stimulus array was learnt. Once the learning criteria had been met participants would count backwards as indicated by on screen instructions. After 15 seconds a test array would appear for the LTM phase. Once participants had responded a new trial would begin. A new trial was indicated by a yellow screen with the words "new trial" to avoid any confusion.

Both the verbal and the visual task consisted of three phases. A STM phase, a learning loop, and a LTM phase. STM performance was taken as the total amount of items recalled/recognized in the first presentation of each trial. In the learning phase participants were presented with the same stimuli in each attempt (within a trial) until a minimum number of presentations and responses were given; three in the verbal task and four in the visual task. As the visual task was recognition based, the additional attempt was given to ensure all stimuli had been presented more than once and to increase the possibility of learning taking place. If the participant had successfully recalled/recognized all items they moved on to the LTM phase. If an incorrect answer was given the participant would be presented with the stimulus array again until they correctly remembered all the items in the verbal task or completed two consecutive attempts correctly in the visual task, or until a maximum number of presentations had been reached (10 in the verbal and 12 in the visual). The trial would then move on to the LTM phase. In this phase subjects were required to count backwards in steps of 3. This concurrent task was employed to disrupt working memory rehearsal and has previously been demonstrated to be effective in disrupting visual memory and to be equally disruptive for single or combined features (Allen et al., 2006). Score on the LTM phase was the total number of correctly recalled/recognized items. Thus for STM and LTM phases the dependent variable was the total number of correctly identified items. The dependent variable for the learning phase was the number of attempts taken until criterion (100% correct or maximum attempts reached). In the bound condition item memory was scored correct only for accurately recalled/recognized combinations. For each presentation stimuli were presented for 1 second per feature, thus, total study time was equal across conditions. There was a 2 second gap between stimulus presentation and response. Once criteria had been met subjects counted backward for 15 seconds then recalled the stimulus from LTM. There was no time limit on responses in each phase or in each presentation (see figure 1 parts A and B for a diagrammatic overview).

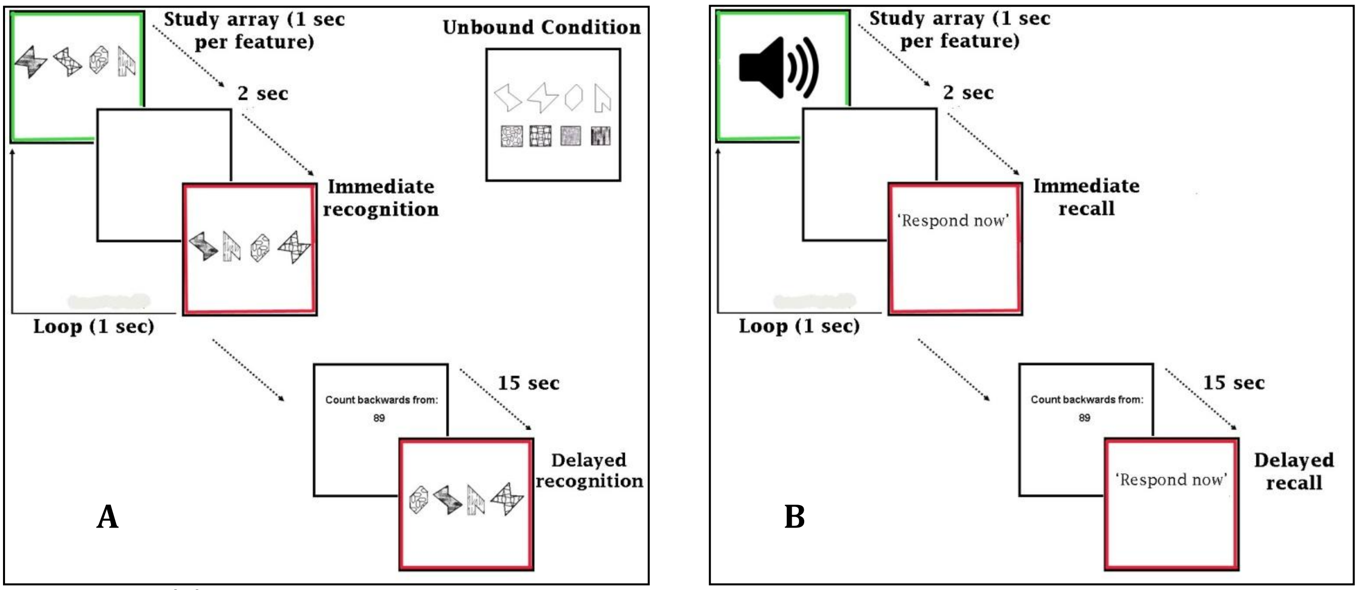

Figure 1(A) Schematic diagram of the visual bound condition. An example of an unbound visual array is the upper right corner. **(B)** Schematic diagram of verbal task.

Procedure

Subjects were told this would be a test of memory. For each task instructions were presented on the screen. In the verbal task subjects listened to the entire list of words and repeated them to verify they had understood all the words. Instructions would appear on the screen to inform participants of the task demands and which condition (bound or unbound) was impending. Lists of words were aurally presented through the computer speakers. After each list the words 'respond now' appeared on the screen and participants recalled the words. Order of items recalled was irrelevant. In the LTM phase participants counted backwards aloud as indicated by on screen instructions. After 15 seconds the words 'respond now' would appear again. Participants then recalled the same list of words. The experimenter recorded spoken responses on a scoring sheet. The visual task followed a similar procedure. Instructions appeared on the screen to inform the participant of the condition and how to perform the task. Participants also viewed an example trial for each of the conditions along with a side-by-side comparison of the study array and test array. Responses were recorded by the E-prime software.

Participants underwent either neuropsychological assessment then the binding paradigms or in the opposite order. This was counterbalanced across participants. Subjects were asked to give feedback on the strategies used to code unbound and bound features and these were recorded by the experimenter on paper (Appendix B). All participants were briefed before testing and debriefed afterward with the opportunity to ask any questions.

Analysis

Statistical analysis was conducted using PASW Statistics 18, Release Version 18.0.0 (Ó SPSS, Inc., 2009, Chicago, IL, www.spss.com). Characteristics of sub group differences in ATL patients were collected: handedness, presence of hippocampal sclerosis, epilepsy onset age, epilepsy duration, time since surgery, presence of post surgical seizures, and presence of anti-convulsant medication. However, correlations could not be carried out with any power due to the small sample size.

A binding paradigm to assess memory for visuo-spatial material was created but was later omitted due to problems in the length of time required to test patients.

Not all data could be used in the analysis. One control and three patients used an older version of the visual task. The STM component of the task was the same and could be used but data for the learning phase and LTM component were dropped because the older version of the task did not require the learning of all the material to reach criterion and thus the LTM component measured memory only for the limited information learned.

Furthermore one patient completed only the verbal task and half of the neuropsychological assessment. Cases were excluded pairwise in the analysis with the limitation of a reduction is sample size for repeated samples calculations.

Results

Neuropsychological Assessment

The scores on the neuropsychological battery were compared across groups using a one-way ANOVA followed by Tukey-HSD *post hoc* tests (table 2). One left ATL patient did not complete all the assessment battery. The missing case was excluded in a case-by-case analysis. Levene's test of homogeneity of variance was violated for several of the neuropsychological tests. The Brown-Forsythe *F* statistic was used to compare means in these cases (see table 2).

Table 2. Group comparisons and *post-hoc* tests for neuropsychological battery

Cognitive Test	Controls		LATL		RATL		ANOVA		Tukey-HSD (p)		
	(n)	mean (SD)	(n)	mean (SD)	(n)	mean (SD)	F	p	controls vs LATL	controls vs RATL	LATL vs RATL
Logical Memory (WMS-III)											
Immediate recall	53	45.36 (8.04)	8	26.63 (10.30)	12	40.5 (10.48)	16.47	<.001***	<.001***	.196 ns	.002**
Immediate recall thematic	53	8.34 (7.12)	8	10.50 (5.93)	12	8.33 (8.82)	.312	.733 ns			
Delayed recall	53	25.70 (6.77)	8	13.00 (7.62)	12	24.92 (7.91)	11.35	<.001***	<.001***	.936 ns	.001***
Delayed recall thematic	53	8.89 (4.34)	8	6.50 (2.67)	12	6.50 (6.17)	BF 19.11	.176 ns			
Verbal Fluency											
Phonemic (FAS)	53	49.17 (12.72)	9	30.89 (9.12)	12	40.17 (18.17)	8.32	.001***	.001***	.096 ns	.264 ns
Semantic (Animal)	53	23.60 (4.13)	9	14.56 (4.30)	12	19.42 (5.35)	18.75	<.001***	<.001***	.010**	.036*
Trail Making Test											
A	53	32.23 (11.97)	9	43.11 (18.34)	12	34.75 (21.42)	BF 21.30	.299 ns			
B	53	57.38 (22.48)	9	85.78 (40.02)	12	76.33 (59.73)	BF 19.44	.183 ns			
B-A	53	25.15 (16.42)	9	42.67 (26.79)	12	41.58 (44.00)	BF 18.77	.185 ns			
VIQ	53	109.81 (4.68)	9	105.33 (4.98)	12	100.08 (12.03)	BF 15.95	.008**	.137 ns	<.001***	.160 ns
ROCF											
copy	53	35.11 (1.10)	9	33.78 (2.54)	12	32.83 (6.30)	BF 14.74	.263 ns			
Immediate recall	53	22.73 (6.82)	9	14.50 (7.45)	12	15.79 (10.12)	7.58	.001**	.009**	.014*	.919 ns
Object decision	53	16.79 (2.46)	8	15.50 (2.45)	12	16.83 (3.24)	.893	.414 ns			
Dot counting	53	9.83 (.55)	8	9.88 (.35)	12	9.83 (.39)	.027	.973 ns			
Digit span	53	6.58 (1.31)	9	5.67 (1.12)	12	5.67 (1.37)	3.77	.028*	.129 ns	.076 ns	1.00 ns

BF = Brown-Forsythe analysis
*p<.05 **p≤.01 ***p≤.001 ns = not-significant

Verbal memory: As assessed by the logical memory subtest of WMS-III left ATL patients (LATL) were impaired on immediate and delayed recall compared to controls and right ATL patients (RATL). There were no statistically significant differences between groups on the thematic scores for either immediate or delayed recall. In the digit span task one-way ANOVA reported a significant difference between groups, however alpha corrected *post hoc* analysis revealed no significant differences between groups. *Verbal fluency:* LATL were impaired on the FAS whereas both LATL and RATL performed significantly worse than controls on the animal fluency test. Furthermore LATL performed significantly worse than RATL. *VIQ:* RATL showed a lower verbal IQ than both LATL and controls. *Visual perception and memory:* There were no differences in visual perceptive abilities between groups as assessed by TMT (trail making test) A (visual tracking), objects decision task, dot counting task, or ROCF copy. Visual memory, however, was equally impaired in both patient groups compared to controls as assessed by ROCF immediate recall. *Executive ability:* There were no group differences in executive ability as measured by the TMT A, TMT B, or TMT B-A.

Verbal Binding

Short-Term Memory Phase

Performance (% correct) on the verbal STM task was analyzed with a 3 (Group = Controls, LATL, and RATL) x 2 (Condition = unbound, bound) mixed analysis of variance (ANOVA). Performance of the groups across conditions is presented in Figure 2. There was a significant main effect of condition [Wilk's Lambda=.448, $F(1,71)=87.55$, $p<.001$, partial eta squared=.55] with all groups showing a reduction in performance from the unbound to bound condition. There was also a significant main effect of group [$F(1,71)=24.26$, $p<.001$, partial eta squared=.41] with controls showing the best performance followed by RATL then LATL. The interaction between group and condition was significant [Wilk's Lambda=.834, $F(1,73)=14.567$, $p<.001$, partial eta squared=.18] indicating that there was an unequal change in performance across conditions.

A one-way between groups ANOVA with compared group differences within each condition. A Bonferroni adjustment of alpha level was set at .017. There were statistically significant differences between groups in both unbound and bound conditions; verbal STM unbound [$F(2,71)=14.14$, $p<.001$] and verbal STM bound [$F(2,71)=21.99$, $p<.001$]. *Post hoc* comparisons using the Tukey-HSD test revealed differences across conditions where both patient groups performed significantly worse than controls with no significant difference between those groups of patients (see table 3 for means and standard deviations). Paired sample t-tests (table 3) compared differences within each group across unbound and bound conditions. In the verbal STM task all groups performed significantly worse in the bound condition. Effect sizes suggest patients performed disproportionately more poorly across conditions than did controls.

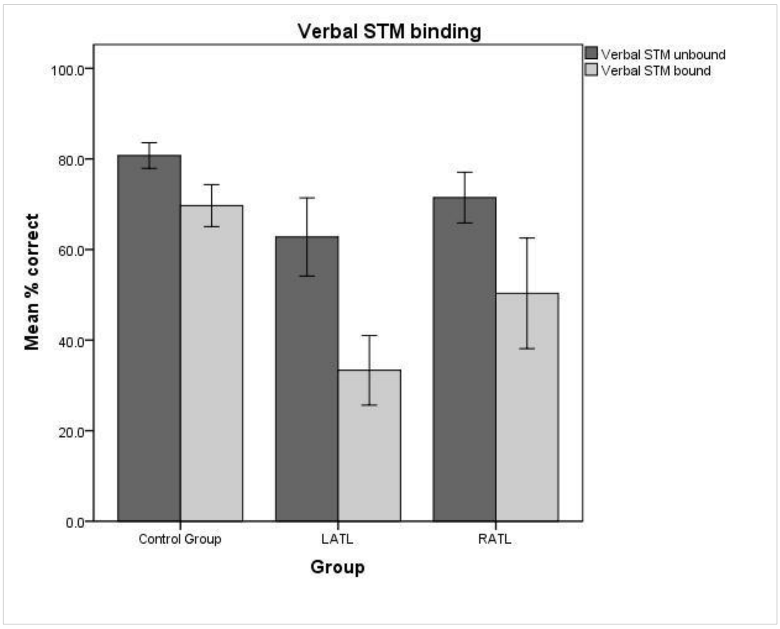

Figure 2. Verbal STM binding: mean group and condition differences

Results indicate that binding in verbal STM causes a drop in memory performance regardless of MTL state and that MTL damage results in a greater drop in memory performance when binding is required, particularly with left MTL damage.

Table 3. Paired t-tests across verbal binding conditions

	Verbal STM			
	Means (S.D.)		t (p)	Effect size eta squared
	Unbound	Bound		
Control (n=53)	80.74 (10.27)	69.70 (16.86)	5.657 (<.001)	.381
LATL (n=9)	62.78 (11.21)	33.33 (10.0)	12.95 (<.001)	.954
RATL (n=12)	71.47 (8.82)	50.33 (19.22)	4.07 (.002)	.600

Learning phase

The verbal (and visual) learning and LTM phases were assessed using non-parametric tests. This was due to small sample sizes and because the variables violated parametric assumptions due to non-normality of distribution. Bonferroni adjustments were made to control for type I error in *post hoc* multiple comparisons. The revised alpha level was .017. Performance across groups and conditions is presented in figure 3. A Kruskal-Wallis Test was used to explore verbal performance (number of attempts to criteria) between the three groups. There was a statistically significant difference in performance levels between the groups in the unbound verbal condition, X^2 (2, n=73)=28.16, p<.001. Controls took the least amount of attempts (median (md) = 3.20) followed by RATL (md=3.80) then LATL (md=5.70). Mann-Whitney U tests were carried out to establish explore group differences. The Mann-Whitney U tests revealed significant differences in the number of attempts to criterion between controls and both LATL (U=25, z=-4.20, p<.001, r=.54) and RATL (U=101, z=-3.84, p=.001, r=.48) but not between patient groups.

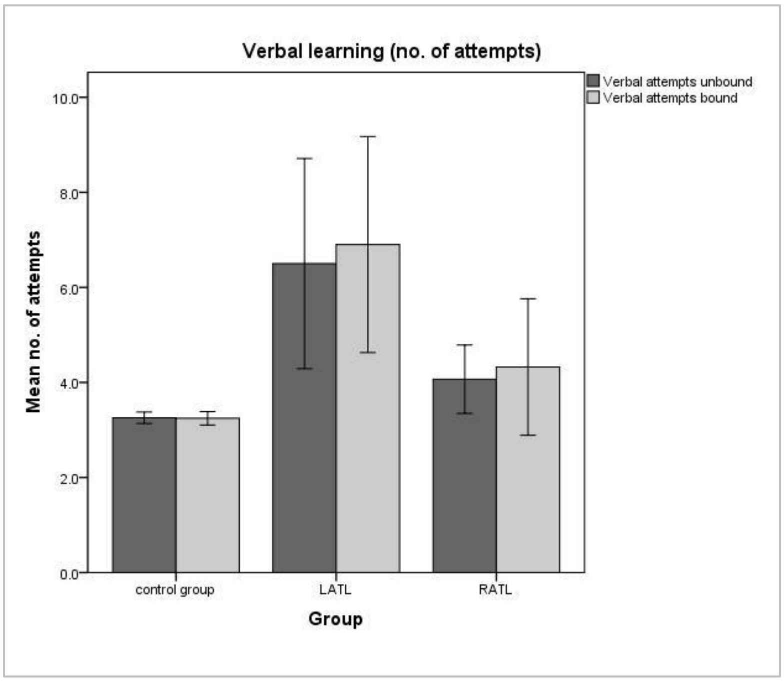

Figure 3. Verbal learning: mean group and condition differences

In the verbal bound condition the Kruskal-Wallis Test revealed a significant group difference, $X^2(2, n=74)=29.94$, p<.001. Like the unbound condition controls took the least amount of attempts (md=3.00) followed by RATL (md=3.40) and LATL (md=7.40). Mann-Whitney U tests revealed significant differences between controls and both LATL (U=19, z=-4.85, p<.001, r=.62) and RATL (U=131, z=-3.48, p=.001, r=.43). There was a significant difference between LATL and RATL (U=20, z=-2.43, p=.015, r=.53).

The Wilcoxon Signed Rank Test was used to compare each group across unbound and bound conditions. There was no statistically significant difference across conditions for controls (z=-.98, p=.325), LATL (z=-1.02, p=.309), or RATL (z=-.94, p=.348).

Results indicated that patients took significantly more attempts to learn verbal material regardless of whether items were presented individually or in pairs.

Long-Term Memory Phase

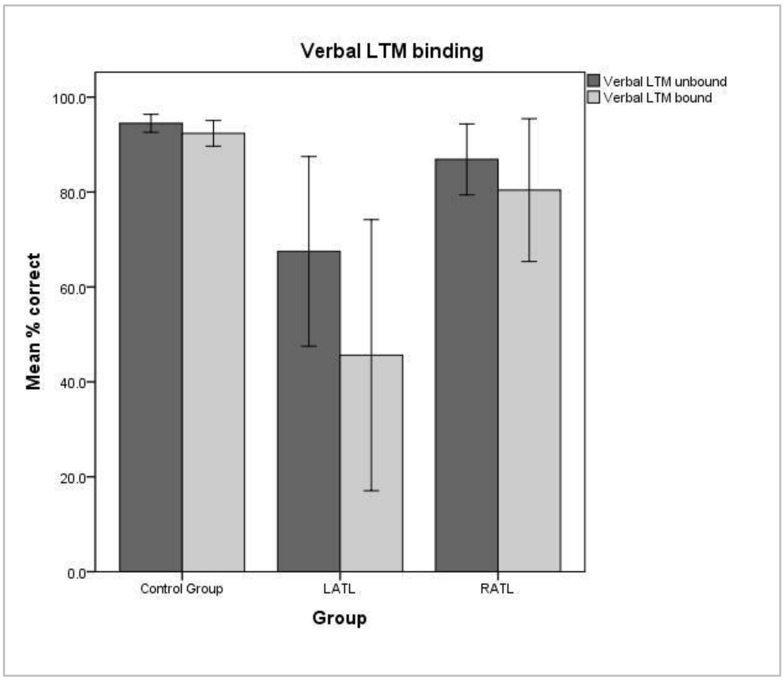

Figure 4. Verbal LTM binding: mean group and condition performance

Performance across groups and conditions is presented in figure 4. A Kruskal-Wallis Test was used to explore verbal performance (% correct) between the three groups. There was a statistically significant difference in performance levels between the groups in the unbound verbal condition, X^2 (2, n=73)=20.97, p<.001. Controls recalled the most (md=97.50) followed by RATL (md=90.00) then LATL (md=71.25). The Mann-Whitney U tests revealed significant differences in performance between controls and both LATL (U=20.5, z=-4.169, p<.001, r=.53) and RATL (U=178, z=-2.41, p=.016, r=.30) but not between patient groups.

In the verbal bound condition the Kruskal-Wallis Test revealed a significant group difference, X^2(2, n=74)=22.14, p<.001. Like the unbound condition controls correctly recalled the most in LTM (md=95.00) followed by RATL (md=87.50) and LATL (md=37.50). Mann-Whitney U tests revealed significant differences between controls and LATL (U=21, z=-4.47, p<.001, r=.57) but not RATL (U=205, z=-1.98, p=.048). There was a significant difference between LATL and RATL (U=16, z=-2.72, p=.007, r=.59).

The Wilcoxon Signed Rank Test was used to compare each group across unbound and bound verbal conditions. There was a statistically significant difference across conditions for controls (z=-2.01, p=.045) and LATL (z=-2.52, p=.012), but not RATL (z=-.98, p=.325).

Results showed that patients perform more poorly than controls in unbound verbal LTM but only LATL in the bound condition. Controls and LATL significantly dropped performance across conditions suggesting that retaining bound verbal information is more difficult than retaining unbound information and that this LTM binding difficulty is additionally impaired after left MTL damage.

Visual binding

Short-Term Memory Phase

Performance (% correct) on the visual STM task was analyzed with a 3 (Group = Controls, LATL, and RATL) x 2 (Condition = unbound, bound) mixed ANOVA. Performance of the groups across conditions is presented in Figure 5. There was a significant main effect of condition [Wilk's Lambda=.812, $F(1,70)=16.23$, $p<.001$, partial eta squared=.188] with a drop in performance in all groups in the bound condition. There was a significant main effect of group [$F(2,70)=23.19$, $p<.001$, partial eta squared=.399] with controls showing the best performance followed by RATL then LATL. There was no significant interaction between group and condition [Wilk's Lambda=.967, $F(2,70)=1.19$, $p=.312$, partial eta squared=.03] indicating that there was equal change in performance across conditions for the three groups.

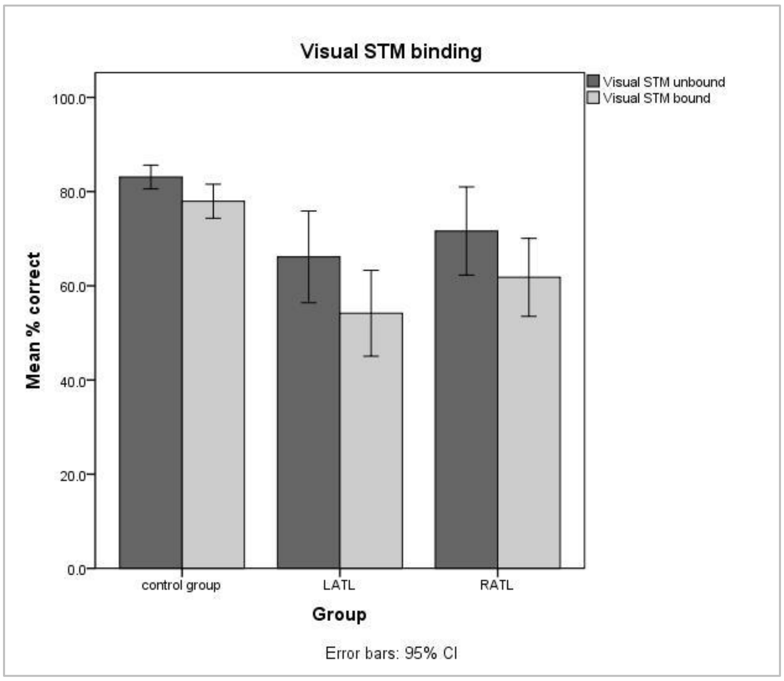

Figure 5. Visual STM binding: mean group and condition differences

Bonferroni adjusted Tukey-HSD *post hoc* analysis of the main effect of group revealed that patients performed significantly worse than controls with no significant difference between those patient groups (see table 4 for means and standard deviations).

Paired sample t-tests (table 4) revealed that controls and LATL significantly dropped performance in the bound condition.

Table 4. Paired t-tests across visual binding conditions

	Visual STM			
	Means (S.D.)		t (p)	Effect size
	Unbound	Bound		
Control (n=53)	83.1 (9.15)	77.94 (13.13)	2.84 (.006)	.134
LATL (n=8)	66.15 (11.65)	54.16 (10.89)	2.76(.028)	.522
RATL (n=12)	70.29 (14.92)	60.25 (13.67)	2.07 (.061 ^{ns})	

Results indicate that visual STM is worse in patients with MTL damage and a drop in performance in the bound condition does not depend on structural state of the MTL.

Learning Phase

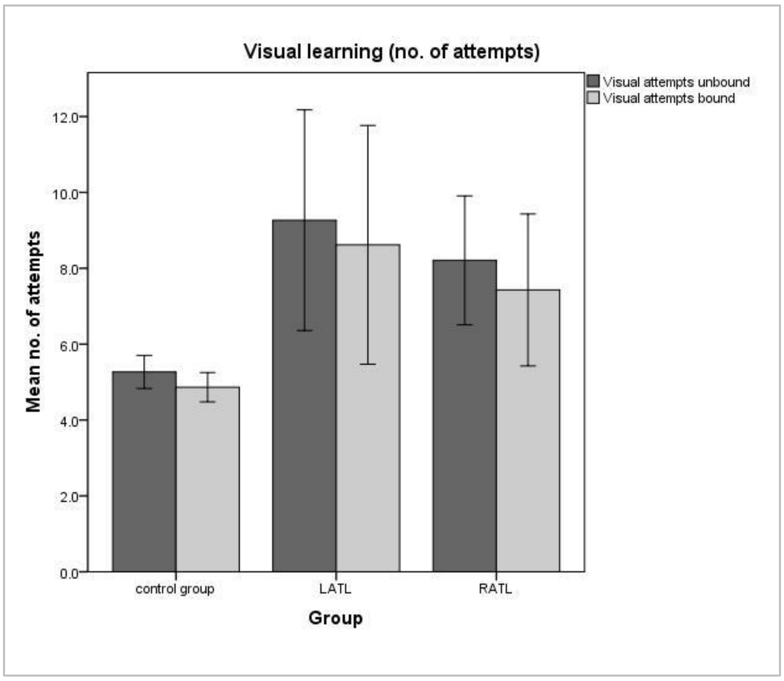

Figure 6. Visual learning: mean group and condition differences

Performance across groups and conditions is presented in figure 6. A Kruskal-Wallis Test was used to explore visual learning performance (number of attempts to criterion) between the three groups. There was a statistically significant difference in performance levels between the groups in the unbound visual condition, X^2 (2, n=68)=20.81, p<.001. Controls took the least amount of attempts (median (md) = 4.55) followed by RATL (md=8.05) then LATL (md=9.60). Mann-Whitney U tests were carried out which revealed significant group differences in the number of attempts to criterion between controls and both LATL (U=30, z=-3.23, p=.001, r=.42) and RATL (U=73, z=-3.59, p<.001, r=.46) but not between patient groups.

In the visual bound condition the Kruskal-Wallis Test revealed a significant group difference, X^2(2, n=68)=18.50, p<.001. Like the unbound condition controls took the least amount of attempts (md=4.50) followed by RATL (md=7.25) and LATL (md=9.50). Mann-Whitney U tests revealed significant differences between controls and both LATL (U=30, z=-3.24, p=.001, r=.43) and RATL (U=93.5, z=-3.21, p=.001, r=.41) but not between patient groups. The Wilcoxon Signed Rank Test was used to compare each group across unbound and bound conditions. There was a significant reduction in the number of attempts in the bound condition compared to the unbound condition in controls only (z=-2.39, p=.017, r=.23). Patient groups also saw a reduction in the number of attempts to criterion, however, the differences were not statistically significant for either LATL (z=-.73, p=.465) or RATL (z=-1.12, p=.262).

As with verbal learning results indicated that patients took significantly more attempts to learn visual material regardless of whether items were presented individually or combined. Binding visual material aided learning in the healthy brain but not significantly after MTL damage.

Long-Term Memory Phase

Performance across groups and conditions is presented in figure 7. A Kruskal-Wallis Test was used to explore visual memory performance (% correct) between the three groups. There was a statistically significant difference in performance levels between the groups in the unbound visual condition, X^2 (2, n=68)=18.33, p<.001. Controls recalled the most (md=95.80) followed by RATL (md=81.25) then LATL (md=75.00). Mann-Whitney U tests were carried out *post hoc* to establish significant group differences. The Mann-Whitney U tests revealed significant differences in performance between controls and both LATL (U=35.5, z=-3.15, p=.002, r=.41) and RATL (U=90, z=-3.33, p=.001, r=.42) but not between patient groups.

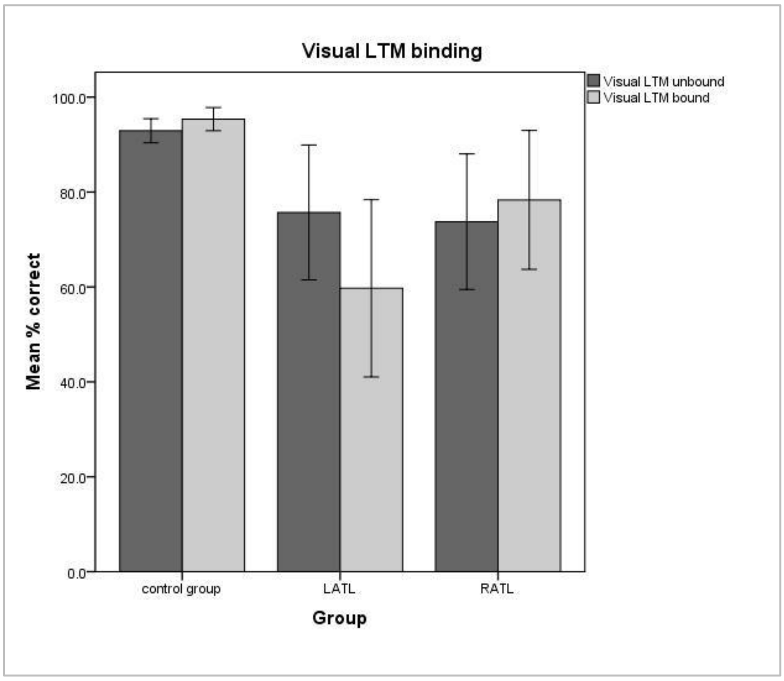

Figure 7. Visual LTM binding: mean group and condition performance

In the visual bound condition the Kruskal-Wallis Test revealed a significant group difference, $X^2(2, n=68)=21.23$, $p<.001$. Like the unbound condition controls correctly recalled the most in LTM (md=100.00) followed by RATL (md=75.00) and LATL (md=58.35). Mann-Whitney U tests revealed significant differences between controls and LATL (U=8.50, z=-4.28, p<.001, r=.56) and RATL (U=146, z=-2.53, p=.011, r=.32). There was no significant difference between LATL and RATL.

The Wilcoxon Signed Rank Test was used to compare each group across unbound and bound visual conditions. There were no statistically significant differences across conditions for any of the groups, although LATL were the only group to show a drop in performance across conditions while controls and RATL showed a slight increase in performance. Results showed that patients retained less visual information than controls in unbound and bound verbal LTM suggesting a general LTM impairment.

Discussion

This study was designed to explore memory for individual and bound features in the healthy brain and in patients with either left or right ATL after refractory temporal lobe epilepsy. This was assessed in STM, learning, and LTM using both verbal within-domain (adjectives and nouns versus word pairs) and intra-item visual (shapes and patterns versus unitized shape-pattern combinations) information.

Memory for verbal information was generally impaired in both right and left ATL with an additional impairment in binding verbal information in STM, which was poorest in left sided patients. ATL patients took longer to learn verbal information regardless of whether it was unbound or bound and accordingly LTM was impaired in both groups. However, only left sided patients showed an additional impairment in retaining bound information in LTM. STM for visual information was worse in both patient groups in both conditions but unlike verbal information there was no additional impairment in remembering bound information. Patients took longer to learn visual material regardless of binding status and accordingly both sets of patients retained less in LTM across unbound and bound material. There were no additional deficits in retaining bound information for either patient group.

Short-term memory binding

A number of conclusions can be drawn;

1. MTL damage in either hemisphere results in impaired STM for single features. Normal digit span performance suggests it was not a working memory capacity difficulty. However, numbers can be coded both visually and verbally which may have masked difficulty in material specific working memory rehearsal. The deficit in visual memory cannot be explained by any dysfunction in visual perception or attention as patients performed normally on measures of these tests in the neuropsychological battery. Additionally visual discrimination for shape and pattern span memory has previously been demonstrated to be unaffected in left and right ATL patients (Mendola et al., 1999; Pigott & Milner, 1994). Likewise the verbal adjectives and nouns were presented before testing and no patients showed difficulty in perceiving or understanding the words. Therefore damage to mesiotemporal structures impairs memory for single features even at short delays.

2. Unilateral MTL damage results in a verbal binding deficit but not a visual binding deficit suggesting intra-item binding and within-domain binding are separate processes. Both patient groups were impaired in binding verbal information suggesting the mechanisms responsible for holding within-domain verbal information in STM require the function of both MTLs rather than the function of one over the other. The more prominent

deficit seen in left sided patients may be due to the breakdown in more global verbal functions associated with left temporal damage. The deficit in verbal STM binding cannot be explained by executive impairment with patients performing as well as controls on the TMT-A, B, and B-A. Verbal fluency, which can be used as an executive ability test, was impaired in both sets of patients replicating findings from previous reports (Luckhurst & Lloyd-Jones, 2001; Martin et al., 2000; Tudesco et al., 2010). However, semantic fluency was impaired in both sets of patients while phonemic fluency was impaired only in left ATL patients. As no other executive deficits were found the impairment in verbal fluency is more consistent with temporal damage than impairment in executive ability (Henry & Crawford, 2004). VIQ was significantly lower in right ATL patients but remained within normal limits (i.e. mean of 100.08). Lower VIQ scores after right sided ATL has been reported elsewhere (Engman, Andersson-Roswall, Samuelsson, & Malmgren, 2006).

The results suggest that the left or right hippocampus and parahippocampal region are not responsible for any mechanism involved in short-term intra-item visual binding. This is consistent with previous studies reporting a lack of hippocampal involvement during intra-item associations in imaging studies (Piekema et al., 2006, 2010) and extends this dissociation to the MTL of both hemispheres. Subject E.S. (Parra et al., 2009a) had a specific visual STM binding deficit whose damage was confined to the left anterior temporal lobe and it is possible that the mechanism responsible for intra-item binding in STM is located outside the region typically resected during ATL. This study did not analyse individual differences and alternatively a deficit may present in some individuals that is masked in group analysis.

3. There is no clear division in material specific laterality of function. Visual memory was impaired in patients regardless of laterality. This complies broadly with previous studies where visual memory deficits for patterns and simple and abstract designs have been found in ATL patients regardless of laterality (Gleissner et al., 2002; Owen et al., 1995; Sivan, 1992; Weidlich & Lamberti, 1980). Instead there were general memory deficits in both visual and verbal memory regardless of side of surgery with only verbal memory being worse after left ATL which supports the view that material functions are not fully lateralized (Saling, 2009). Only left ATL patients were impaired on the immediate test of logical memory highlighting the left hemisphere's more prominent role in verbal function. As there

was a verbal STM binding deficit after both right and left ATL it can also be claimed that binding is not a lateralized function.

4. Binding in STM appears to be resource demanding in the healthy brain. This held for both visual intra-item binding and within-domain verbal binding. While the use of additional resources might be expected in creating explicit links between features such as in the verbal binding task, binding unitized representations into visual STM has been considered to be automatic (Luck & Vogel, 1997; Vogel et al., 2001). This study tested memory for bound representations and for memory of an equal number and type of features in the unbound condition. In visual memory the only other study to do so was in the healthy elderly (Parra et al., 2010). In that study memory for object-colour binding was the same as that for objects and colours unbound but both objects and colours were highly nameable (e.g. orange, car, or green-chair). The present study used abstract shapes and patterns which are more difficult to verbally code and use representations from LTM. Thus it was arguably more a test of raw short-term visual memory and capacity. Therefore it can be suggested that binding in visual STM places additional demand on working memory to form links between features and supports the feature based view of visual STM capacity (Wheeler & Treisman, 2002).

Learning and long-term memory

Both patient groups took longer to learn the stimuli than controls suggesting a general impairment in the ability to transfer information into LTM or retrieve it. In some cases patients never correctly learned all the study stimuli taking all the allowed presentations before moving on to the LTM phase. This highlights a practical concern in assigning LTM performance purely to retention over a measure of learning ability. Deficits in word pair learning was disrupted in left ATL patients in line with previous findings from patients with damage to the left hippocampus (Savage et al., 2002) or left rhinal cortices (Weintrob, Saling, Berkovic, & Reutens, 2007). Nevertheless left ATL patients, as a group, took the same number of attempts to reach criterion in both unbound and bound conditions yet performance in the LTM task was poorer in the bound condition suggesting a binding deficit in verbal retention or retrieval. Poor performance on the short-term condition, learning, and LTM condition suggests that working memory is in part related to the process of

transferring information into LTM, particularly for bound information after left ATL.
Indeed the MTL is involved to some extent in subsequent memory effects from STM to LTM (Axmacher et al, 2008; Axmacher, Elger, & Fell, 2009; Ranganath, Cohen, & Brozinsky, 2005). Interestingly left sided patients showed a drop in retaining visually bound compared to unbound information in LTM whereas right sided patients and controls showed a slight improvement in retaining bound visual information. The differences were not significant however but testing with larger samples may expand on this. The slight improvement in retaining bound visual information after learning would be consistent with Logie et al.'s (2009) idea that learning in visual STM is more likely with objects than individual features in the healthy brain and would extend that assertion to intentional learning.

The fact that within-domain binding was impaired in LTM whereas intra-item binding was not loosely supports the idea of relational theory, as explained by Moses & Ryan (2006), where the hippocampus mediates relations of distinct elements and the cortex mediates unitized representations. In this case the cortex must refer to an area outside of the surgical region. This would also suggest the left hippocampus mediates within-domain learning whereas the right does not. In relation to the Domain Dichotomy (DD) model within-domain verbal STM binding may have been impaired in the patients because of damage to either perirhinal cortex. The long term memory binding retention deficit in the left ATL patients suggests a role of the left MTL in binding long-term verbal material. Similarly Smith, Bigel, and Miller (2011) found that learning paired designs was impaired in both left and right temporal lobectomy, also supporting the view that either hemisphere supports within-domain binding. In that study the right temporal lobectomy group had an additional impairment in LTM visual binding. These convergent findings suggest that learning within-domain bindings occurs in both MTLs regardless of material but, crucially, LTM for bound within-domain information depends on left MTL function while LTM for bound visual within-domain information depends on right MTL function. In other words left temporal damage impairs long-term verbally bound memory whilst right temporal damage impairs long-term visually bound memory. This is also in line with Helmstaedter, Grunwald, Lehnertz, Gleissner, and Elger's (1997) assertion that temporomesial structures mediate long-term material specific memory. Interestingly the findings of Smith et al. (2011) held for four patients with intact hippocampi supporting the DD view that within-domain associations are mediated by the perirhinal cortex and not the hippocampus.

Working memory and binding

Verbal and visual feature memory was disrupted in STM and LTM in both sets of patients. Part of the impairment may be explained by a breakdown in coding incoming information. Although subject feedback was unquantified patients appeared less likely to report the use of visual coding to verbal material or of giving verbal codes to visual features. The study of E.S. (Parra et al., 2009a) provided evidence for a specific mechanism for binding visual information that disappeared when she was asked to assign verbal code to the images. Contrastingly patient M.J.K. (Best & Howard, 2005), who had a phonological impairment, used visual coding to remember verbal material. Indeed automatically assigning verbal codes to visual information is an automatic process (Postle, D'Esposito, & Corkin, 2005) and Postle (2007) notes that "the ability to represent an item (or piece of information) in multiple codes, despite the unimodal channel by which it may have been perceived, should facilitate one's ability to manipulate or transform the representation of this information" (p.342). The poor performance in both unbound and bound conditions may have been in part due to the breakdown in this process in working memory and of accessing coding information from LTM. In healthy subjects binding performance seems to increase with the ease at which verbal codes can be assigned to visual stimulus. For instance STM for highly nameable objects (e.g. guitar) and colours improved performance versus memory for individual features (Parra et al., 2009a, b) whereas performance for individual features was superior when object-colour combinations were made with abstract shapes (Parra et al., 2009a; Brockmole et al., 2008). Thus in the patients here it can be argued that a deficit in STM binding of verbal information was due to a breakdown in multicoding information but also a loss in the function which binds items in STM. Presumably this binding deficit did not occur in visual memory because the supporting intra-item binding mechanism lay outside the surgical lesion site but the reduced ability to multicode impaired unbound performance. Thus one could argue that multiple coding of unimodal information is a function that is separate from the function of holding bound information in working memory.

Performance from both healthy and patient groups indicated that binding was not an automatic process but used additional cognitive resources. It is possible that the episodic buffer of working memory mediates the multiple coding of items, but not the binding process. However, Baddeley (2007) has suggested that the buffer might be used for higher order processing and evidence suggests coding may help bind information so it enters the buffer from a different route (Parra et al., 2009). Thus the findings here may suggest a separate function for accessing cross-modal information, one that may be compatible with the idea of a shared central resource (Ricker, Cowan, and Morey, 2010). Cowan's model (1988, 1995, 1999) may explain why the unbound features were easier to remember in STM than the bound features in that more resources would be needed to rapidly form links between combinations of features rather than independent features. But poorer bound performance could also have resulted from bindings being unavailable in the episodic buffer due to the demand on creating or holding them.

Conclusion

The findings here suggest that MTL damage impairs short-term memory, learning, and LTM for single features as well as bound representations but damage to this region specifically impairs within-domain verbal binding regardless of laterality. Left ATL results in dysfunction of binding in within-domain verbal LTM and further investigation is required to explore the suggestion that right ATL damage impairs LTM for bound within-domain visual memory. The results here are complicated by the small sample sizes and as such the variance within patient group performance could not be explored for evidence of any trans-hemispheric reorganization. Future studies could explore multiple encoding in binding information whilst employing tests assessing both intra-item and within-domain information across verbal and visual domains. Finally, it is concluded that binding in STM is cognitively demanding, even during intentional binding conditions, and that binding is due to specific binding mechanisms.

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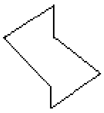
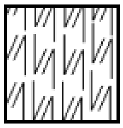
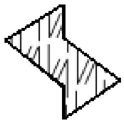
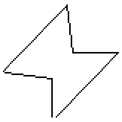
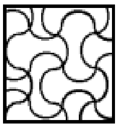
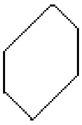
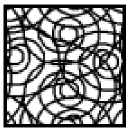
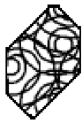
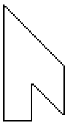
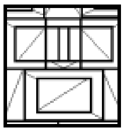
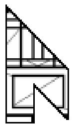
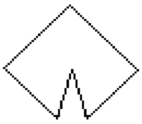
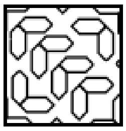
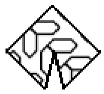
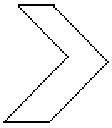
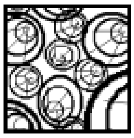
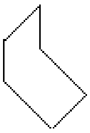
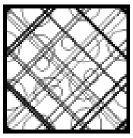
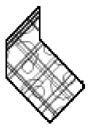
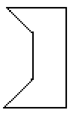
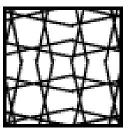
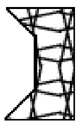
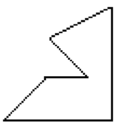
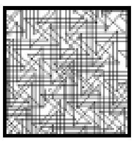
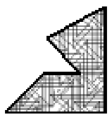
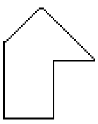
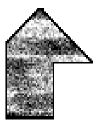
Appendix A

Images for visual binding paradigm. Items are not to scale.

Abstract shapes for visual task	Abstract patterns for visual task	Examples of shape and pattern recombinations
		
		
		
		
		
		
		
		
		
		

Appendix B

Participant self-report feedback form. Experimenter recorded answers.

Participant feedback form

Verbal Task

Which one was easier?

Strategies to remember (adjective & noun binding)?

Strategies to remember (adjective and noun unbound)?

Visual Task

Which one was easier?

Strategies to remember (shape & pattern binding)?

Strategies to remember (shape and pattern unbound)?

ID: ______________________ **Date:** ______________________