Memory impairment in humans after bilateral damage to lateral temporal neocortex

Mei-Chun Cheung and Agnes S. Chan[CA]

Department of Psychology, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong, China

[CA]Corresponding Author: aschan@psy.cuhk.edu.hk

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The hippocampus and its adjacent medial temporal regions are crucial for episodic memory. However, it is far less obvious whether other temporal regions beyond the medial part are important for memory processing. The memory performance of a group of patients with bilateral lesions over the lateral temporal lobe sparing the hippocampus was assessed and compared with that of patients with relatively spared cortex and patients with bilateral damage to the lateral temporal lobe and the hippocampus. The results demonstrate that bilateral damage to the lateral temporal lobe results in memory impairment across verbal and visual modalities. *NeuroReport* 14:371–374 © 2003 Lippincott Williams & Wilkins.

Key words: Episodic memory; Hippocampus; Lateral temporal cortex

INTRODUCTION

The involvement of the temporal lobe in learning and memory has been extensively explored for over a century. A breakthrough was made in the 1950s by the report of patient H.M. [1] who manifested dense amnesia after bilateral resections of the medial temporal pole, including most of amygdaloid complex, entorhinal cortex, dentrate gyrus, hippocampus and subicular complex. This report became a landmark in understanding the medial temporal lobe in memory and provided strong evidence that damage limited to the medial part of the temporal lobe is sufficient to produce memory impairment. After this publication, studying the neuroanatomic correlates and function of the medial temporal lobe in humans [2] and animals [3,4] became a major topic of investigation for neuroscientists who are interested in memory. Follow-up studies on patients with more focal lesion further narrowed the critical region for memory to hippocampal formation [5] and then to the CA1 field of the hippocampus [6]. To confine the region within the medial temporal lobe, an animal model of amnesia has been built based on the lesion studies of monkeys with bilateral damage limited to the hippocampus (H lesion) and combined damage to the hippocampus and its adjacent regions, including the parahippocampal, perirhinal and entorhinal cortices [7]. These findings strongly suggest that the hippocampus and its adjacent cortical regions are involved in memory processing.

While it is unlikely there is any doubt that the hippocampus and its adjacent cortical regions are significant for memory, whether its role is specific is far less well understood. That is, whether the temporal lobe regions beyond the hippocampal formation, including the lateral temporal neocortex, are also important for memory. Although existing animal studies on this topic are relatively limited, their findings seem to suggest that memory processing may not be limited to the medial portion. A couple of studies report that monkeys with bilateral lesions over the anterior temporal neocortex (i.e. temporal pole and portions of the inferotemporal cortex) demonstrate impaired learning and memory [8,9]. While patients with bilateral lesions over the lateral temporal lobe have not been reported, studies on patients with unilateral damage of the anterior temporal region sparing the hippocampus are consistent with the findings from animal studies [10,11].

As there are some hints that other areas within the temporal lobe beyond the medial region are important for memory, further studies on patients with bilateral lesions over the lateral temporal lobe with spared hippocampus will be significant to further our understanding of the neuroanatomic correlates of temporal lobe with memory. If the anterior lateral temporal cortex is important for learning and memory, patients with lesions over this region, but spared medial portion, should demonstrate the same memory impairment as those with medial temporal lobe lesions. Findings of such comparison will stimulate a new perspective on the concept of temporal lobe and memory.

MATERIALS AND METHODS

Subjects: Fifteen subjects were selected from a database of 100 nasopharyngeal carcinoma patients who had undergone radiotherapy at the Queen Elizabeth Hospital in Hong Kong on a voluntary basis. Radiation-induced brain lesions developed in some patients as a late complication and their locations were identified using the templates developed by Talairach and Tournoux [12]. Specifically, the T2 weighted MRI horizontal scans of each subject were overlapped by the templates with the horizontal degree close to the images, and the exact location of each lesion was read from the

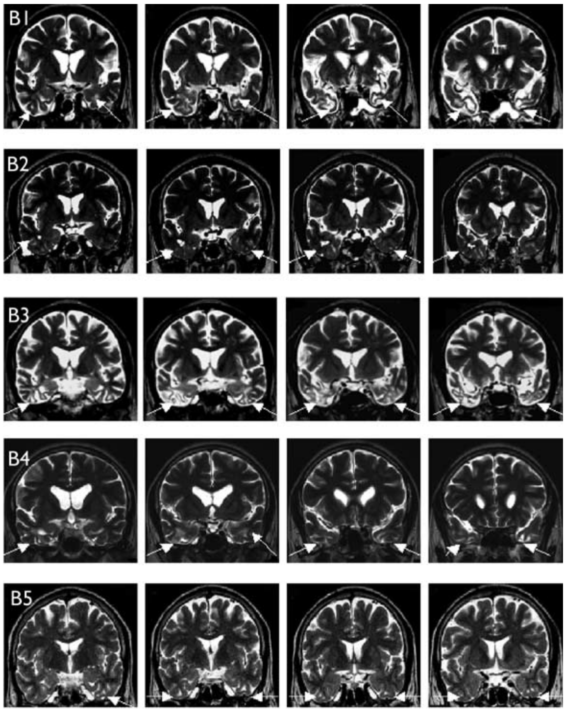

Fig. 1. Coronal T-2 weighted images from the temporal pole to the hippocampus for five patients (B1–B5) in the BLT group. The damage (white arrows) was mainly found in the lateral temporal lobe starting from the temporal pole, relatively sparing the hippocampus.

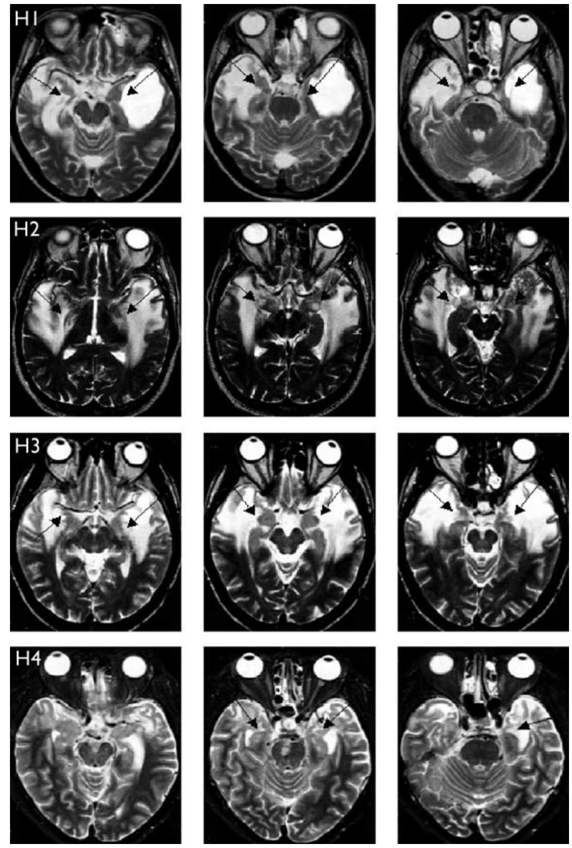

Fig. 2. Axial T-2 weighted images through the temporal lobes of four patients (H1–H4) in the BLT+H group. The extent of the damage to the lateral and medial temporal lobes can be seen; it extends caudally from the temporal pole, laterally includes inferior, middle and superior temporal gyri and medially includes the hippocampus (black arrows) bilaterally.

corresponding landmarks on the templates. According to the location and the presence or absence of lesions, the subjects were divided into three groups. Five subjects (three male and two female, age 56.80 ± 9.65, years of education 5.40 ± 3.78) developed bilateral temporal lobe lesions sparing the hippocampus (BTL). Using the MRI evidence as shown in Fig. 1, their lesions were localized bilaterally to the lateral aspect of the temporal lobe, mainly over the inferior temporal gyrus. The extent of the lesion starting from the temporal pole continued caudally and ended in the level of amygdala ($\sim$3–4 cm from the temporal pole). The amygdala and medial portion of the temporal lobe, including the hippocampus, parahippocampal, perirhinal and entorhinal cortex were spared in these patients.

Four subjects (all male, age 49.50 ± 11.82, years of education 10.50 ± 7.59) had extensive bilateral lesions over the temporal lobes and anterior portion of the hippocampus (BTL+H). As showed in Fig. 2, the damage started bilaterally from the temporal pole, extending caudally to cover the inferior, middle and superior temporal gyri on the lateral side. At the level of the amygdala, the damage extended medially to the amygdala, further caudally to the rostral portion of the head of the hippocampal formation. Posterior parts of the hippocampal formation, however, were spared.

The remaining six subjects (three male and three female, age 47.00 ± 7.48, years of education 8.83 ± 4.92) having negative MRI scans were served as control (NEG), and showed intact temporal cortex and hippocampus. Three groups were matched in terms of age ($F = 1.53$, $p > 0.05$) and education ($F = 1.07$, $p > 0.05$). All reported a negative history of head injuries, neurological diseases and alcoholism.

Neuropsychological assessment: A battery of standardized neuropsychological tests was administered to the subjects individually by an examiner who was blind to their pathological involvement. The assessment was performed at least one year after radiotherapy to ensure that the lesions were permanent damage. In order to test whether the impairment was modality specific, both verbal and visual memory performance was assessed. Furthermore, to rule out the possibility of other cognitive functions affecting memory performance, the assessment also included global cognitive function, attention, language, and visual ability. Written, informed consent was obtained from all subjects.

Tests of mental function: In order to screen out the possibility of dementia, the Cantonese version of the Mini-Mental Status Examination [13] was used. The Digit Span of the Wechsler Adult Intelligence Scale-Revised [14] was used to test attention. Verbal memory was assessed by the Hong Kong List Learning Test (HKLLT) [15] and a story recall test, respectively. The story recall test included two Chinese stories comprising a total of 50 ideas orally presented to the subjects who recalled the ideas immediately and after 30 min. The maximum score for the test was 50 points. The Visual Reproduction subtest of the WMS-R (WMS-R VR) [16] and the Brief Visuospatial Memory Test-Revised (BVMT-R) [17] were used to assess the visual memory respectively. Expressive language ability was assessed by a short form of the Boston Naming Test (BNT) [18] in which subjects were required to name 30 line drawings selected from the full version. To test visual ability, subjects were required to copy four figures from the WMS-R VR [16] and the complex figure from the Rey–Osterrieth Complex Figure Test [19].

Statistical analysis: Since the sample size was relatively small, the summary scores for verbal and visual memory were computed. The raw scores for the immediate and 30 min delayed recall trials of the HKLLT and the story recall test were first transformed into z-scores by subtracting their raw scores from the mean score of the corresponding tests for NEG group with an adjustment for the standard deviation of the latter group. The z-scores were then summed and averaged to become the summary score for verbal memory. Similar computation was done for the raw scores of the immediate and 30 min delayed recall trials of WMS VR and BVMT-R to form the summary score for visual memory. For the other cognitive tests, the raw scores for three groups of patients were used for comparison and analysed by both parametric (one-way factorial ANOVA) and non-parametric analyses (Kruskal-Wallis H). *Post-hoc* pair-wise comparisons were submitted to Tukey's honestly significant difference (HDS) to determine group difference.

RESULTS

The performance in tests of global cognitive functioning, attention, language and visual abilities was compared for three groups of patients and the results demonstrated no significant difference, except in the language ability (BNT) which revealed a significant group difference ($p < 0.002$; Table 1). Further statistical analysis by pair-wise comparisons showed that the BLT+H group (raw score 13.75 ± 5.74) significantly named fewer items than both the BLT (raw score 22.80 ± 2.86) and NEG (raw score 24.83 ± 2.79) groups but there was no significant difference between the BLT and NEG groups. Non-parametric analysis showed a similar pattern of group difference on language ability ($p < 0.05$). These results suggested that the three groups were in general matched in terms of their global cognitive functioning, attention and visual ability while the BLT and NEG groups were further matched in terms of their language ability.

To avoid committing family-wise statistical errors and biases in the parameter estimates, z-scores from two verbal memory tests were added to form the summary score for verbal memory while z-scores for two visual memory tests were summed to form the summary score for visual memory. It should be noted that statistical analyses performed on their raw scores yielded consistent results.

Comparison between groups showed significant difference on both verbal ($p < 0.0004$) and visual memory ($p < 0.003$; Fig. 3). *Post hoc* analysis showed that, consistent with previous findings for patients with damage to the hippocampus, the BLT+H group was significantly poorer than the NEG group on both verbal ($p < 0.0004$) and visual memory ($p < 0.004$), demonstrating memory impairment in the verbal and visual domains. At the same time, significant group differences also existed between the BLT and NEG groups on both verbal ($p < 0.006$) and visual memory ($p < 0.02$), suggesting that the BLT group in general recalled fewer items than the NEG groups across the memory tests. This memory impairment was non-material specific and both verbal and visual modalities were affected. However, no group difference was found between the BLT and BLT+H groups and their memory deficits were comparable to each other.

Table 1. Neuropsychological test results.

	NEG (n=6)		BLT (n=5)		BLT+H (n=4)		ANOVA	
Test	Mean	s.d.	Mean	s.d.	Mean	s.d.	F	p
CMMSE	28.00	2.68	27.40	1.82	26.25	3.77	0.48	0.63
Digit Span	18.67	3.78	14.60	2.51	14.25	4.19	2.59	0.12
BNT[a]	24.83	2.79	22.80	2.86	13.75	5.74	11.06	0.00
Rey-O Copy	28.30	3.51	24.20	2.66	23.63	6.06	1.81	0.21
VR Copy	36.60	1.52	32.60	4.39	30.33	7.23	2.15	0.17

[a]Only the BLT+H group is significantly poorer than the BLT ($p < 0.01$) and NEG ($p < 0.002$) groups. No difference was found between the BLT and NEG groups. NEG, patients with relatively spared hippocampus and temporal cortex; BLT, patients with temporal lobe lesion sparing the hippocampus; BLT+H, patients with lesions over the hippocampus and temporal lobe; ANOVA, analysis of variance; CMMSE, Cantonese version of Mini-Mental Status Examination; Digit Span, Wechsler Adult Intelligence Scale-Revised Digit Span subtest; BNT, Boston Naming Test; Rey-O Copy, Copy trial of Rey-Osterrieth Complex Figure Test; VR Copy, Copy trial of Wechsler Memory Scale – Revised Visual Reproduction subtest.

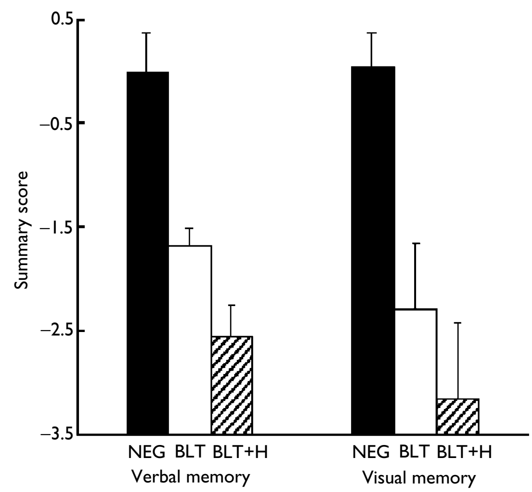

Fig. 3. Summary scores for verbal and visual memory. More negative scores indicate poorer memory performance.

DISCUSSION

This study yielded some interesting findings that may merit further consideration. Our understanding on memory system in humans is mainly based on the animal model in which the medial temporal lobe, including the hippocampus and its adjacent temporal lobe, is the critical region for memory processing [7]. Although the animal model on human memory system is well established, it is still under investigation whether other temporal lobe regions beyond these areas, such as the lateral temporal neocortex, are important for memory processing. The main reason for our lack of understanding of this question is that while only one study examining the memory impairment of a patient with bilateral temporal lesions has been described [20], empirical data on humans with bilateral damage to the temporal lobe, sparing the hippocampal formation have not yet been reported. In addition, animal studies on this topic are relatively limited. Therefore, the present study provided initial empirical evidence on a group of patients who manifested memory impairment after bilateral damage to lateral temporal cortex sparing the hippocampus. Their memory impairment was comparable to that of patients having lesions including the hippocampus. In addition, the impairment was non-material specific, in that both their verbal and non-verbal memory was adversely affected. Therefore, consistent with previous animal studies with bilateral damage [8,9] and human studies [10,11] with unilateral damage to the lateral temporal lobe, our study further supported that the temporal lobe beyond the medial portion seems to be involved in mediating memory performance.

Change in neuronal activity of the lateral temporal neocortex during memory processing has been reported in patients with left or right temporal lobe epilepsy. Extracellular microelectrode recordings were used to record the neuronal activity of the patients undergoing temporal craniotomy in which the patients were awake to perform the behavioural tasks. The results indicated that significant excitation in the neurons of the left lateral temporal lobe neocortex was recorded during verbal associative learning [21] and memory of names and words [22] while inhibitory neuronal activity was found in the right lateral temporal cortex during short-term visuospatial memory [23]. Apart from the findings on neuronal activity, a recent functional magnetic resonance imaging study on normal subjects examined the activation pattern for word and picture encoding using event-related paradigms. Greater activation over the left lateral temporal cortex, particularly areas BA21/22 during word encoding, as compared with that of picture encoding, was observed. A novelty effect selective for words in the left lateral temporal neocortex was also observed [24]. Therefore, it seems that based on the findings from lesion analysis as well as studies on cortical neuronal activity and functional imaging, there is more and more converging evidence showing that the lateral temporal neocortex is also part of the neural substrate for memory processing.

Although the present study may be considered as an initial set of empirical data, suggesting the involvement of lateral temporal lobe in memory processing, there are several limitations that need to be addressed before conclusive evidence can be reached. The number of patients in each group (five in average) is still relatively small. Though the findings may provoke some insights to reconsider the model of memory and the involvement of the temporal lobe, further studies with larger sample size are needed to verify the results. However, while it is easy to identify patients with unilateral damage to the lateral temporal lobe, patients with bilateral pathological change are relatively scarce. Therefore, it may be difficult to investigate the role of the temporal lobes bilaterally within same subjects and animal studies can be considered to utilise for further investigation.

Although it was MRI evidence that the five patients with damage to the lateral temporal lobe had relatively spared hippocampus, one can question its intactness by arguing that the abnormality of the hippocampus may not be detectable by MRI technique. Given that the lesions of our patients were the sequels of radiotherapy, it is conceivable that their hippocampus may be abnormal in terms of metabolism. Though the MRI scans did not reveal the structural involvement of the entorhinal cortex, the possibility of abnormality in this critical region cannot be definitely ruled out solely based on the MRI findings. Therefore, further studies to detect any abnormality within the medial temporal lobe by other sensitive methods, such as magnetic resonance spectroscopy, perfusion or diffusion imaging, are highly recommended to help resolve this issue. However, previous study has demonstrated that radiotherapy *per se* was not associated with cognitive impairment [25]. That is, cognitive impairment was only observed in patients with lesions evidenced by MRI scans but not in those with negative MRI scans. Therefore, it is still reasonable to suggest that the MRI evidenced lesions reveal a significant neuroanatomical involvement in the lateral temporal lobe associated with memory processing and damage to the lateral temporal cortex may disrupt the flow of information into the medial temporal lobe memory system.

CONCLUSION

The current study demonstrates that apart from the medial temporal lobe, the lateral temporal region is also responsible for memory processing in humans. Bilateral damage to the lateral temporal lobe can lead to verbal and visual memory impairment. Further investigation to specify the exact region(s) in the lateral temporal lobe for memory will provide valuable information to our understanding of the neural substrates involved in memory processing.

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