Impairment of paired associate learning following the perirhinal cortex damage

Mie Matsui (mmatsui@ms.toyama-mpu.ac.jp)
〔Toyama Medical & Pharmaceutical University〕

嗅周皮質に限局された脳硬塞後の対連合記憶学習障害

松井 三枝
富山医科薬科大学 医学部

要約

従来、健忘症患者の報告から、海馬体が記憶機能に重要な役割を果たすとされてきた。さらに、人間以外の霊長類やラットによる多くの実験研究から、海馬体のみならず、その周辺の皮質構造も記憶機能に関与してきていることが指摘されてきた。すなわち、記憶障害の原因として海馬体だけでなく、嗅周皮質、内嗅皮質および海馬傍回等の役割も重視されてきた。本研究では、嗅周皮質に限局された脳硬塞のある患者に、種々の神経心理学的精査を行ない、その病変がもたらした神経心理学的機能障害を検討し、嗅周皮質の役割について考察することを目的とした。当該患者が臨床的に安定した病態を示してから、脳磁気共鳴画像により、病巣の同定を行なったところ、左の嗅周皮質に病巣が認められた。標準化された神経心理学的検査を行なったところ、簡易精神機能スケール（MMSE）では問題を認めず、知能（WAIS-R）は平均水準であった。失語、失行、失認に関する検討でも問題は認められなかった。ウエクスラー記憶尺度（WMS-R）では、全体としての記憶指数は平均的であった。しかし、その下位検査のプロセス分析を行なったところ、有関連単語ではなく、無関連単語の対連合記憶学習のみ、困難であることが示された。さらに、さまざまな対連合記憶学習課題（図形と図形の対、色と色の対、図形と色の対、単語と色の対、単語と単語の対）を施行して、精査を行なったところ、言語性および非言語性課題においてともに、無関連の対連合記憶学習が困難であることが示された。また、言語課題においては、提示によるモダリテイの差異について検討したところ、聴覚的な提示と視覚的な提示で異ならず、いずれも、無関連の対連合記憶学習のみが困難であることが示された。これらの結果から、本症例は選択的に無関連対連合記憶学習の障害をきたしていることが明らかとなった。このことは、嗅周皮質が、新しい刺激と刺激との関連の記憶の形成に関わることを示唆している。嗅周皮質はモダリテイにかかわらず、記憶過程で、新しい連合形成と検索に重要な役割を果たしているのかもしれない。

Key words

perirhinal cortex, paired associates, memory, neuropsychology, MRI

1. Introduction

In 1957, Scoville and Milner first reported in the case study of H.M. that bilateral medial temporal lobe resection might be responsible for amnesia. Thirty years later, Zola-Morgan et al. (1986) demonstrated in the case of R.B. that neuronal loss of bilateral cornu Ammonus (CA) 1 might be related to amnesia. Thereafter, the importance of the hippocampal formation in human memory has been claimed in consecutive patients with bilateral medial temporal cortex damage. Recently, Corkin et al. (1997) studied H.M. again this time using the Magnetic resonance imaging (MRI), and confirmed that the causative lesions are not only the hippocampal formation but also the adjacent cortical structures. Many experiments have been simultaneously done using laboratory animals (Mishkin, 1978; Zola-Mogan and Squire, 1986) to demonstrate that the hippocampus is important in consolidating memories. In these experiments, however, the lesions involved not only hippocampus but also the adjacent cortical structures. Monkey studies have also shown that memory impairment is related not only to the hippocampal formation but also to the adjacent cortical structures including the perirhinal cortex, the entorhinal cortex, and the parahippocampal gyrus. Among monkey studies, the perirhinal cortex has received attention, since there is growing evidence that it contributes to visual recognition memory and paired associate memory (Meunier et al., 1993; Suzuki, 1996a; Murray and Bussey, 1999).

In recent studies on monkeys undergoing a small brain lesion by microsurgical procedures, the perirhinal cortex has been shown to play an important role in paired associate learning. Murray et al. (1993) reported that visual-visual associative memory was impaired by the combined lesions of the perirhinal cortex and entorhinal cortex. Higuchi and Miyashita (1996) also demonstrated that the formation of mnemonic neuronal responses to visual paired associates was impaired by the combined perirhinal and entorhinal lesions. Recently, Buckey and Gaffan (1998) reported that the perirhinal cortex ablation shows an impairment in paired associate learning task. In these animal studies, unfortunately, it was impossible to explore verbal paired associate learning. In this sense, the present case is extremely unique because the role of the perirhinal cortex in verbal paired associate learning could be studied.

Buffalo et al. (1998) recently showed in two human cases that the perirhinal cortex is important for visual recognition memory. However, in these cases, the lesion was seen bilaterally and included the amygdaloid complex, the entorhinal cortex, the hippocampus, and the parahippocampal cortex as well as the perirhinal cortex. In addition, their performances of paired associates were poor. To date, there has been no report of a human case with lesion confined only to the perirhinal cortex. The current paper is aimed to report a case who showed damage confined to the left perirhinal cortex on MRI and association memory dysfunction on neuropsychological tests. Here, we would like to propose that the perirhinal cortex may be related to association memory in humans.

2. Material and Methods

2.1 Case history

The patient, a 71-year-old right-handed man, suddenly lost consciousness and was admitted to the hospital. Prior to this, he had a past history of ossification of posterior longitudinal ligament (OPLL), arterial fibrillation, and two episodes of transient ischemic attack (TIA). Neurological examination upon admission showed a mild right motor weakness which soon improved. Aphasia, apraxia and agnosia were not seen. Computed tomography (CT) on the following day showed a small low density area in the left temporal lobe, and he was diagnosed as having cerebral infarction. Regional cerebral blood flow (rCBF) was measured using single photon emission computed tomography with N-isopropyl-p-[I-123] iodoamphetamine (I-123 IMP) 2 weeks after admission. A decrease of rCBF was seen in the left medial temporal area. Thereafter, there had been no description of motor paralysis on his medical records as neurological findings, although he might have given a sign of subtle motor weakness. Generally speaking, the mild right motor weakness indicates additional lesion. In this case, there was no additional lesion except the temporal region on the CT, but subtle decreased rCBF of the left thalamus as well as the left medial temporal area were seen. As he complained of memory impairment, neuropsychological tests were repeatedly done with follow-up studies of Magnetic Resonance Imaging (MRI) scans. A detailed account of the MRI results is given below.

The Mini-Mental State Examination (MMS; Folstein et al., 1975) was given five times: 4 days, 3 weeks, and 1, 2 and 5 months after onset. Four days after onset, MMS score was 24 out of 30. Three weeks after onset, MMS (score=29 of 30) was improved and maintained thereafter.

2.2 MRI study

MRI scans were done, using a 1.5-tesla superconducting magnet (Toshiba, Tokyo, Japan). With special attention to the medial temporal lesion, the axial images were sliced parallel to the long axis of the temporal horn, while coronal images were sliced perpendicular to the axial images. Both T1-weighted sequence (TR=4500ms, TE=100ms, NEX=2, FOV=20cm, matrix=192X256) and T2-weighted sequence (TR=400ms, TE=15ms, NEX=2, FOV=20cm, matrix=192X256) were used. In the axial images, 11 intersliced, 3mm-thick sections in the area overlapping the temporal lobe with 0.8mm interslice gap were obtained. In the coronal images, 11 intersliced, 3mm-thick sections in the area overlapping the brain stem with 0.6mm interslice gap were obtained. Furthermore, to study whole brain images at 3 months after onset, an axially-acquired 3D T1-weighted Field Echo (FE) sequence (TR=35ms, TE=7ms, NEX=1, FOV=20cm, matrix=192X192) was used. This sequence produced 190 contiguous slices of 1.0mm thickness which covered the whole brain.

2.3 Neuropsychological assessments

The following three types of tests, including the standard neuropsychological test, memory tests and paired-associate learning task, were administered after MRI lesion was confined to the perirhinal cortex.

2.3.1 The standard neuropsychological tests

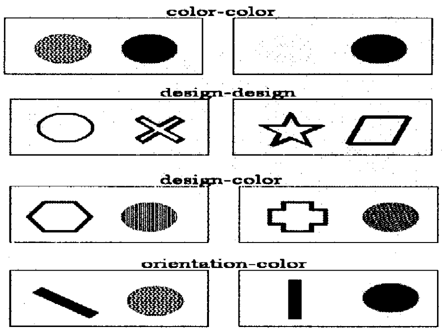
The standard clinical neuropsychological tests comprised of Wechsler Adult Intelligence Scale-Revised (WAIS-R; Wechsler, 1981), Visual Perception Test for Agnosia (VPTA; Japanese Brain Function Test Committee, 1997), and Judgement of Line Orientation Test (JLOT; Benton et al., 1983).

2.3.2 Memory tests

Wechsler Memory Scale-Revised (WMS-R; Wechsler, 1987; the Japanese version of the WMS-R, Sugishita, 2001) and Rey-Osterrieth complex figure test (Osterrieth, 1944) were administered to test memory function in detail. In the Rey-Osterrieth complex figure test, he was asked to copy the figure and to reproduce a figure 5 and 30 minutes after completion of the task. In addition, the Face Test in WMS-III (Wechsler, 1997) was performed to check face recognition memory.

2.3.3 Paired-associate learning tasks

During the above follow-up of neuropsychological tests, detailed analysis of paired association memory was examined using a variety of paired associates including design-design, color-color, orientation-color, design-color, word-color and word-word associations. Among these, design-design, color-color, orientation-color and word-color pairs were unrelated associate learning tasks. Design-color and word-word pairs were both unrelated and related associate learning tasks. Their frame were all based on paired associate subtests in WMS-R. Namely, the standard method of presentation and testing of the material was adopted because of the widespread use of WMS-R in this format. Most materials were newly devised to examine paired associate learning in detail. Examples of materials used for these tests are shown in Figure 1. The six pairs each were created for design-design, color-color, orientation-color, design-color and word-color associations. Each pair was drawn on a card (9 x 5.5 cm). The six pairs were presented in succession, each pair for 3 sec., then only the left side of each pair, design, color, line of orientation or word was given. He was then required to look for the associate on a multiple choice sheet bearing 6 colors or 6 designs corresponding to the second member of the pairs. Order of presenting and testing the pairs was varied randomly on successive trials, and errors were corrected on each trial. Three trials were given.



Each pattern in circles means different color such as red, green, yellow, blue, pink etc.

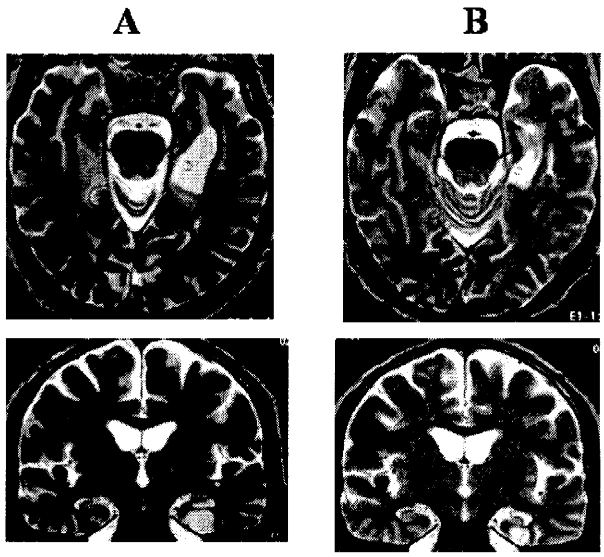
Figure 1: Examples of the paired associates (color-color, design-design, design-color, and orientation-color) tests

There were 4 kinds of word-word associates tasks which were auditory or visually presented unrelated (difficult) or related (easy) pairs. Each word-word associate tasks had 8 pairs. Eight highly related word pairs were compiled using the Japanese word association norms of Umemoto (1969). Response words were either the first or second highest associate. The unrelated word pairs were 8 pairs of high frequency words chosen to exclude obvious associations. There were also 2 kinds of design-color associate tasks which were presented unrelated (difficult) or related (easy) pairs. Six related design-color pairs were guided from high association norms (referred Umemoto, 1969) such as pairs of design like apple and red color, while unrelated pairs had no such a high association. The pairs were presented at a rate of one pair every 3 sec. Immediately after presentation of the complete list, the first word of each pair was presented for 5 sec or until he responded, and he attempted to give the appropriate response. Three trials were given and the order of presentation and testing items were different for each trial. Each task was administered on different days to avoid interference among tasks.

3. Results

3.1 MRI

MRI four days after admission showed infarction of the left medial temporal lobe involving cornu Ammonus (CA) 1-4, dentate gyrus, subiculum, and perirhinal cortex (Figure 2, A). One month later, the MRI lesion was confined to the left perirhinal cortex (areas 35 and 36 of Broadman, 1909). The extent and locus of lesion were not changed on the subsequent MRI examination (Figure 2, B). The whole brain analysis 3 months later showed no abnormality except for the perirhinal cortex described above. On the coronal planes by reconstruction of 3D-MRI, the length of the lesion was about 1.8 cm from anterior to posterior. According to Amaral and Insausti (1990), the perirhinal cortex as well as the entorhinal cortex extends caudally to the level of the anterior limit of the lateral geniculate nucleus or about midway back through the hippocampal formation. Then, the perirhinal cortex is continuous caudally with parahippocampal gyrus. Based on this definition, the lesion extended in anterior and posterior at the level of the lateral geniculate nucleus, and included the perirhinal cortex and the anterior part of parahippocampal gyrus, which were consistent with this is area 35 and the latter half of area 36 according to the definition by Broadman (1909).



Axial slices are shown in the upper, while coronal slices in the lower row. In each MRI image, right and left hemispheres are shown in the left and right sides, respectively.

A: Four days after admission, MRI shows infarction of the left medial temporal lobe involving CA1, subiculum and perirhinal cortex.

B: Four month after onset, MRI lesion is confined to the left perirhinal cortex.

Figure 2: Magnetic resonance images (MRIs)

3.2 Neuropsychological assessments

3.2.1 The standard neuropsychological tests

The results of standard clinical neuropsychological testing are shown in Table 1. WAIS-R showed full IQ of 96 (verbal IQ=91, performance IQ=103). His profile was well-balanced without any poor score. From VPTA, his basic visual perception, cognition of objects, picture, faces, color, symbol, visuo-space, and topography were all found to be normal. From the JLOT, his spatial perception was found to be normal.

Table 1: The results of standard clinical neuropsychological tests

Test	Score	Comment
WAIS-R		
Verbal tests		
information	9	
digit span	8	
vocabulary	7	
arithmetic	11	
comprehension	9	
similarities	7	
Performance tests		
picture completion	12	
picture arrangement	9	
block design	12	
object assembly	10	
coding	9	
Verbal IQ	91	average
Performance IQ	103	average
Full scale IQ	96	average
Visual Perception for Agnosia		
basic function for visual perception		normal
objects/picture recognition		normal
face recognition		normal
color perception		normal
symbol recognition		normal
visuo-spatial recognition		normal
topographical orientation		normal
Judgement of Line Orientation Test		Normative data
	27/30	22.7

Note: WAIS-R=Wechsler Adult Intelligence Scale revised. The IQ in the WAIS-R yields mean scores of 100 in the normal population with standard deviation of 15. The normative data of the Judgement of Line Orientation Test is for 65-74 age group in men (Benton et al.,1983).

Table 2: The results of memory tests

Test	Score	
WMS-R	Memory index	
Attention index	91	
Verbal memory index	103	
Visual memory index	97	
General memory index	101	
Delayed memory index	97	
WMS-R	score	Mean±SD in Age 70-74
Information/Orientation	14	13.2±0.8
Mental Control	4	4.4±1.5
Figural Memory	5	6.1±1.4
Logical Memory I	22	18.5±7.5
Visual Paired Associate I	3	9.0±4.1
Verbal Paired Associate I	16	15.0±4.4
Visual Reproduction I	30	34.2±5.9
Digit Span	9	12.1±3.6
Visual Memory Span	15	15.1±2.6
Logical Memory II	12	13.2±6.8
Visual Paired Associate II	1	4.0±1.9
Verbal Paired Associate II	4	6.3±1.6
Visual Reproduction II	28	28.0±8.6
Face Recognition (WMS-III)	score	
	10	
Rey-Osterrieth Complex Figure Test		Mean±SD in Age 70-74
Copy	35	32.0±3.3
5-min. delay	20.5	
30-min. delay	18.5	15.4±6.4

Note: WMS-R=Wechsler Memory Scale revised. The Memory index in the WMS-R yield mean scores of 100 in the normal population with standard deviation of 15. The mean scores for normal controls in the WMS-R are from Sugishita (2001). The scaled score in the face recognion test (WMS-III) yields a mean score of 10 and a standard deviation of 3 in the normal population (Wechsler, 1997). The normative scores of the Rey-Osterrieth Figure Test are from Spreen and Strauss (1988). The maximum score is 36.

3.2.2 Memory tests

The results of memory tests were summarized in Table 2. General Memory Quotient (general MQ) in WMS-R showed an average score of 101 two months after onset. Moreover, all indexes (Attention/Concetration=91, Verbal Memory=103, Visual Memory=97, Delayed Recall=97) were average. The Visual Paired Associates scores in WMS-R, however was very poor (Table 2). There was difference of scores between Verbal- and Visual- Paired Associates in WMS-R. Verbal Paired Associates in WMS-R include both related- and unrelated- paired associate learning task, while Visual Paired Associates include only unrelated paired associate learning task. The score of Verbal Paired Associates was normal: total score in I (immediate recall) and II (delayed recall) were 16 and 4, respectively. But, actually the scores of related paired associates were 12 of 12 in Verbal Paired Associates I and 4 of 4 in Verbal Paired Associates II, while the scores of unrelated paired associates were 4 of 12 in I and 0 of 4 in II. The Rey-Osterrieth complex figure test showed that his figure recall was normal compared to the standardized data for the 70-74 age group (Spreen and Strauss, 1998). Face recognition was average.

3.3.3 Paired-associate learning tests

The results with a variety of the paired associates are presented in Table 3. His performance was poor in color-color, design-design, orientation-color, unrelated (difficult) design-color, word-color and unrelated (difficult) auditory word-word and visual word-word associate learning. On the other hand, his score was within normal limits in the related (easy) design-color, related (easy) auditory word-word and visual word-word associate learning tasks.

Table 3: The results of paired association learning tests

paired associate	Trial 1	Trial 2	Trial 3	all
design-design	1	0	1	2
color-color	1	0	0	1
space-color	1	0	1	2
design-color (hard)	2	0	1	3
design-color (easy)	4	6	6	16
word-color	0	1	0	1
word-word (hard, auditory)	0	0	1	1
word-word (easy, auditory)	7	8	8	23
word-word (hard, visual)	0	0	1	1
word-word (easy, visual)	5	6	7	18

Note: The paired associate scores are the number of pairs (design or color or word) recalled on three successive trials. The maximum score is 6/trial in design-design, space-color, design-color and word-color paired associate learning tasks. The mean total score of three trials in the normal population for the same age is 9.0 (SD=4.1). The maximum score is 5/trial in color-color paired associate learning task and 8/trial in word-word paired associate learning tasks.

4. Discussion

In the present study, the effects of damage to the left perirhinal cortex were studied in detailed and consecutive neuropsychological tests done on the patient. On MRI, he showed an infarction confined to the left perirhinal cortex and no other brain lesions were detected on the whole brain analysis. He showed severe impairment in paired-associate learning, while he showed no impairment in other memory tasks including word memory, digit span, logical memory, visual reproduction, Rey-Osterrieth complex figure recall, and face recognition. In addition, his intelligence and visual perception including object recognition, picture recognition, face recognition, color perception, symbol recognition, visuospatial perception, topographical orientation, and judgement of Benton line orientation were all normal for his age. It is widely accepted that amnesic patients with extensive damages of the medial temporal lobe or with Korsakoff syndrome have shown impairments in many memory tasks including paired associate memory (Meyer and Yates, 1955; de Renzi, 1968; Brooks and Baddeley, 1976; Winocur and Weiskrantz, 1976; Cutting, 1978; Goldstein et al., 1988). In this sense, a case like this patient with selective impairment of paired associate memory caused by left perirhinal lesion is extremely rare because he did not appear to have memory task impairment.

The relation of the perirhinal cortex to paired association memory has been suggested in monkey studies. Murray et al. (1993) reported that visual-visual associative memory was severely impaired by lesions of the perirhinal cortex. Higuchi and Miyashita (1996) also demonstrated that mnemonic neuronal responses of inferotemporal neurons to visual paired associates were lost due to lesions of the perirhinal and entorhinal cortices. In addition to visual paired associate, it is claimed that the perirhinal cortex is critically important in tactual-visual association and retention and relearning of auditory-visual conditional problems (Murray and Bussey, 1999). In monkey studies, bilateral lesions to the perirhinal cortex showed impairments not only in the paired associates but also in visual recognition memory (Meunier et al., 1993). In contrast, visual recognition memory was not seen in the patient. This might be because his perirhinal damage was limited to the left hemisphere.

Previous neuropsychological studies in human amnestic patients have shown impairments in declarative memory including paired associate memory. He was impaired only in the unrelated paired associates regardless of verbal or non-verbal, and visual or auditory, but was not impaired in related paired associates. As for the paired-associate tests in the monkey studies, only visual stimuli such as design-design (Higuchi and Miyashita, 1996), alphanumeric character (Murray et al., 1993; Buckley and Gaffan, 1998) and digit (Buckley and Gaffan, 1998) have been used. In human studies, one can administer word-word paired-associates (Buffalo et al., 1998). The present tasks were to study impairment of paired associate learning including design-design, color-color, orientation-color, design-color, word-color and word-word associations. He showed impairment of both verbal and non-verbal paired associate learning, thereby indicating that the perirhinal cortex lesion cause impairment of both verbal and non-verbal paired associate learning. Furthermore, whatever the non-verbal stimulus, be it, color, design, or orientation, impairment of paired associate learning was specifically seen only in unrelated pairs. When he was asked to perform both visual (design-design, color-color, orientation-color, design-color, word-color and word-word) and auditory (word-word) tasks, he showed impairment regardless of modality. As for modality, visual-visual association tasks (Murray et al., 1993; Higuchi and Miyashita, 1996; Buckley and Gaffan, 1998) and odor-odor association tasks (Bunsey and Eichenbaum, 1993; Eichenbaum and Bunsey, 1995) were presented in monkeys and rats, respectively. Using functional MRI (fMRI), Reber et al. (2002) reported laterality effects reflecting increased right hemisphere activity during picture encoding in parahippocampal cortex and increased left hemisphere activity during word encoding in the posterior hippocampus and parahippocampal cortex in healthy human. Our case with lesion of the left perirhinal cortex showed impairment of both word and non-word tasks. However, we used the paired associative learning tasks, but not encoding single items tasks in Reber et al. (2002). Because his visual reproduction (in both WMS-R and Rey-Osterrieth complex figure test) was intact (see Table 2), these results suggest effect of task, namely, paired associative learning task but not encoding simple items task, is larger than effect of hemisphere in the perirhinal cortex.

Although he showed impairment of unrelated paired associates, his ability to recall or recognize related pairs was normal. This may be explained by the phenomenon of "priming" (Poulos and Wilkinson, 1984), since priming is an automatic process based on previously encountered stimuli and essentially depends on activation of preexisting memory representations. Accordingly, related paired associates are linked to priming, while unrelated paired associates have no preactivated memory representation. A new association would therefore have to be formed between the unrelated A and B pairs. Although he could activate preexisting associations, he could not establish new associations. Eichenbaum and Bunsey (1995) stated that representation (imaging) of stimulus in paired associates was encoded by two different ways: one is the encoding of paired associates as fused, unitized, or configural representations. The parahippocampal regions including the perirhinal cortex mediate this type of encoding. Another is relational representations, in which stimulus items in paired associates are encoded separately and stored in memory. Then, the individual items in memory bring the representations associated. The hippocampus is important for such representations. From this standpoint, the perirhinal cortex, which is part of the parahippocampal regions, may be related to formation of new configural representations based on unrelated paired associates. From another point of view, unrelated pairs are considered as novel associative pairs. Duzel et al. (2003) measured the activity of both hippocampal and parahippocampal areas in healthy young adults during an associative recognition memory task using fMRI. As a result, the hippocampus was activated for recognition of new associations. They suggested that the associative novelty response might be special to the hippocampus, whereas item novelty effects might be common to other medial temporal lobe structures. Further research on this idea would clarify function of the perirhinal cortex. It has also been demonstrated that membrane potentials of neurons in the perirhinal cortex are activated by judging the relative familiarity or novelty of stimuli using electrophysiological recordings from single neurons in monkeys (Fahy et al., 1993; Xiang and Brown, 1998). Recently, Zhu et al. (1997) and Wan et al. (1999) reported the neurons in the perirhinal cortex were activated by novel stimuli, employing the counts of nuclei stained for products of the immediate early gene *c-fos*. These data together suggest that the perirhinal cortex plays a pivotal role in the formation and retrieval of new association between stimulus and stimulus irrespective of modality.

According to neuroanatomical studies of monkeys (Suzuki and Amaral, 1994a; Suzuki and Amaral, 1994b; Suzuki, 1996a; Suzuki, 1996b), the perirhinal cortex was interconnected with unimodal and polymodal cortical association areas. The perirhinal cortex is the first cortical area of the ventral visual stream within the medial temporal lobe and the major source of cortical input to the hippocampus via the entorhinal cortex. According to recent monkey studies, the perirhinal cortex is also connected reciprocally with the hippocampus CA1 (Suzuki and Amaral, 1990; Yukie, 1993; Blatt and Rosene, 1998; Saleem and Hashikawa, 1998). Such a neuroanatomical relationship may be related to the information processing in the perirhinal cortex. The perirhinal cortex seems to be important evolutionally because the relative size of the perirhinal cortex is larger in humans compared to monkeys and rats (Burwell et al., 1996). Since the perirhinal cortex has interconnections with sensory cortical fields serving non-visual modalities as well as visual areas (Murray and Bussey, 1999), our consistent results over modality can be explained. It is likely that the perirhinal cortex of humans composes the relationship between stimulus and stimulus of words and objects by connecting the hippocampal formation and the temporal auditory and occipital visual cortices. Furthermore, exchanging information between the neocortex and the hippocampal formation may be indispensable for mnemonic processing. This study suggests the perirhinal cortex may play an important role not only in mediation for information flow between hippocampus and neocortex but also in memory process itself. This implies there is memory functional specialization within the medial temporal lobe.

The present findings should be considered in light of the limitations of the study. In the paired association learning tests, unrelated pairs of stimuli versus related pairs of stimuli were used and the patient showed memory impairment on only unrelated pairs of stimuli. However, difference of relationship between stimuli might be interpreted as difference of level on difficulty of the task. In the present study, related pairs tasks were almost equal to easy tasks, and unrelated pairs tasks were similar to difficult tasks. Strictly speaking, therefore, we couldn't discriminate those. For example, related and difficulty pairs (such as abstract and related words pair) should be examined. For this, we need to take a consideration of concreteness, familiarity, and/or imaginability on stimulus. Second, we found his characteristics of memory impairment using neuropsychological behavioral tasks. The clinical neuropsychological data, however, did not allow us to distinguish between his memory impairment at encoding process and at retrieval process. Further research using functional MRI could elucidate memory process in such a case and the role of the perirhinal cortex much more.

In summary, this study has presented the case with the perirhinal cortex infarction, showing selective impairment of the paired associate learning. He showed only impairment of the verbal and non-verbal paired associate learning, especially of the unrelated associations. It was suggested from the neuropsychological examination that the perirhinal cortex is closely related to the formation of stimulus-stimulus association memory. The perirhinal cortex may play a pivotal role in the formation and retrieval of new association between stimulus and stimulus irrespective of modality.

Acknowledgements

The author thanks Dr. Masao Yukie, Tokyo Metroporitan Organization for Medical Research and Prof. Morihiro Sugishita, Tokyo University for critical reading of the manuscript and for valuable suggestions.

References

Amaral, D.G., & Insausti, R. 1990 Hippocampal formation. In: G. Parxinos, (Ed.) *The human nervous system*. Academic Press, 711-755.

Benton, A.L., Hamsher, K.S., Varney, N.R., & Spreen, O. 1983 *Contributions to neuropsychological assessment*. Oxford UP.

Blatt, G.J., & Rosene, D.L. 1998 Organization of direct hippocampal efferent projections to the cerebral cortex of the rhesus monkey: projections from CA1, prosubiculum, and subiculum to the temporal lobe. *Journal of Comparative Neurology*, 392, 92-114.

Broadman, K. 1909 *Vergleihende Lokalisationslehre der Groshirinrinde*. Barth.

Brooks, D.N., & Baddeley, A.D. 1976 What can amnesic patients learn? *Neuropsychologia*, 14, 111-122.

Buckley, M.J, & Gaffan, D. 1998 Perirhinal cortex ablation impairs configural learning and paired-associate learning equally. *Journal of Neuroscience*, 36, 535-546.

Buffalo, E.A., Reber, P.J., & Squire, L.R. 1998 The human perirhinal cortex and recognition memory. *Hippocampus*, 8, 330-339.

Bunsey, M., & Eichenbaum, H. 1993 Critical role of the parahippocampal region for paired-associate learning in rats. *Behavioral Neuroscience*, 107, 740-747.

Burwell, R.D., Suzuki, W.A., Insausti, R., & Amaral, D.G. 1996 Some observations on the perirhinal and parahippocampal cortices in the rat, monkey, and human brains. In: T. Ono, B.L.McNaughton, S.Molotchnikoff, E.T.Rolls, & H.Nishijo (Eds.) *Perception, memory and emotion: frontiers in neuroscience*, Pergamon, 95-110.

Burwell, R.D., Witter, M.P., & Amaral, D.G. 1995 Perirhinal and postrhinal cortices of the rat: a review of the neuroanatomical literature and comparison with findings from the monkey brain. *Hippocampus*; 5, 390-408.

Corkin, S., Amaral, D.G., Gonzalez, R.G., Johnson, K.A., & Hyman, B.T. 1997 H.M.'s medial temporal lobe lesion: Findings from magnetic resonance imaging. *Journal of Neuroscience*; 17, 3964-3979.

Cutting, J. 1978 A cognitive approach to Korsakoff's syndrome. *Cortex*; 14, 485-495.

De Renzi, E. 1968 Nonverbal memory and hemispheric side of lesion. *Neuropsychologia*, 6, 181-189.

Duzel, E., Habib, R., Rotte, M., Guderian, S., Tulving, E., & Heinze, H.J. 2003 Human hippocampal and parahippocampal activity during visual associative recognition memory for spatial and nonspatial stimulus configurations. *Journal of Neuroscience*, 23, 9439-9444.

Eichenbaum, H., & Bunsey, M. 1995 On the binding of associations in memory: clues from studies on the role of the hippocampal region in paired-associate learning. *Current Directions in Psychological Science*, 4, 19-23.

Fahy, F.L., Riches, L.P., & Brown, M.W. 1993 Neuronal activity related to visual recognition memory: long-term memory and encoding of recency and familiarity information in the primate anterior and medial inferior temporal and rhinal cortex. *Experimental Brain Research*, 96, 457-472.

Folstein, M.F., Folstein, S.E., & McHugh, P.R. 1975 'Mini-mental State'. A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatry Research,* 12, 189-198.

Goldstein, L.H., Canava, A.G.M., & Polkey, C.E. 1988 Verbal and abstract designs paired associate learning after unilateral temporal lobectomy. *Cortex*, 24, 41-52.

Higuchi, S., & Miyashita, Y. 1996 Formation of mnemonic neuronal responses to visual paired associates in inferotemporal cortex is impaired by perirhinal and entorhinal lesions. *Proceedings of the National Academy of Sciences of the United State of America*, 93, 739-743.

Japanese Brain Function Test Committee. 1997 *Visual perception test for agnosia*. Sinkou igaku Syuppan.

Meunier, M., Bachevalier, J., Mishkin, M., & Murray, M. 1993 Effects on visual recognition of combined and separate ablations of the entorhinal and perirhinal cortex in rhesus monkeys. *Journal of Neuroscience*, 13, 5418-5432.

Meyer, V., & Yates, A.J. 1955 Intellectual changes following temporal lobectomy for psychomotor epilepsy. *Journal of Neurology, Neurosurgery and Psychiatry*, 18, 44-52.

Mishkin, M. 1978 Memory in monkeys severely impaired by combined but not by separate removal of amygdala and hippocampus. *Nature*, 273, 297-298.

Murray, E.A., & Bussey, T.J. 1999 Perceptual-mnemonic functions of the perirhinal cortex. *Trends in Cognitive Sciences*, 3, 142-151.

Murray, E.A., Gaffan, D., & Mishkin, M. 1993 Neural substrates of visual stimulus-stimulus association in rhesus monkeys. *Journal of Neuroscience*, 13,: 4549-4561.

Osterrieth, P.A. 1944 Le test de copie d'une figure cmplexe. *Archives de psychologie*, 30, 206-356; translated by Corwin, J. and Bylsma, F.W., 1993, *The Clinical Neuropsychologist* 7, 9-15.

Poulos, C.X., & Wilkinson, D.A. 1984 A process theory of remembering: its application to Korsakoff amnesia and a critique of context and episodic-semantic theories. In: L.R. Squire, & N. Butters, (Eds.) *Neuropsychology of memory.* Guilford Press, 67-82.

Reber, P.J., Wong, E.C., & Buxton, R.B. 2002 Encoding activity in the medial temporal lobe examined with anatomically constrained fMRI analysis. *Hippocampus*, 12, 363-376.

Saleem, K.S., & Hashikawa, T. 1998 Connections of anterior inferotemporal area TE and perirhinal cortex with the hippocampal formation in the macaque monkey. *Society of Neuroscience Abstract*, 24, 898.

Scoville, W.B., & Milner, B. 1957 Loss of recent memory after bilateral hippocampal lesions. *Journal of Neurology, Neurosurgery and Psychiatry*, 20, 11-21.

Spreen, O., & Strauss, E. 1998 *A compendium of neuropsychological tests, second edition.* Oxford UP.

Sugishita, M. 2001 *The Japanese version of the Wechsler memory scale-revised.* Nihon Bunka Kagakusha.

Suzuki, W.A. 1996a The anatomy, physiology and functions of the perirhinal cortex. *Current Opinion in Neurobiology*, 6, 179-186.

Suzuki, W.A. 1996b Neuroanatomy of the monkey entorhinal, perirhinal and parahippocampal cortices: Organization of cortical inputs and interconnections with amygdala and striatum. *Seminars in the Neuroscience*, 8, 3-12.

Suzuki, W.A., & Amaral, D.G. 1990 Cortical inputs to the CA1 field of the monkey hippocampus originate from the perirhinal and parahippocampal cortex but not from area TE. *Neuroscience Letters*, 115, 43-48.

Suzuki, W.A., & Amaral, D.G. 1994a Topographic organization of the reciprocal connections between the monkey entorhinal cortex and the perirhinal and parahippocampal cortices. *Journal of Neuroscience*, 14, 1856-1877.

Suzuki, W.A., & Amaral, D.G. 1994b Perirhinal and parahippocampal cortices of the macaque mankey: cortical afferents. *Journal of Comparative Neurology*, 350, 497-533.

Umemoto, T. 1969 *Norm of association*. Tokyo Univ. Press.

Wan, H., Aggleton, J.P., & Brown, M.W. 1999 Different contributions of the hippocampus and perirhinal cortex to recognition memory. *Journal of Neuroscience*, 19, 1142-1148.

Wechsler, D. 1981 *Wechsler adult intelligence scale-revised manual.* Psychological Corporation.

Wechsler, D. 1987 *Wechsler memory scale-revised manual.* Psychological Corporation.

Wechsler, D. 1997 *Wechsler memory scale-third edition.* Psychological Corporation.

Winocur, G., & Weiskrantz, L. 1976 An investigation of paired-associate learning in amnesic patients. *Neuropsychologia,* 14, 97-110.

Xiang, J.Z., & Brown, M.W. 1998 Differential neuronal encoding of novelty, familiarity and recency in regions of the anterior temporal lobe. *Neuropharmacology*, 37, 657-676.

Yukie, M. 1993 Organization of the hippocampal projections to the parahippocampal and inferotemporal cortices in the macaque monkey. *Society of Neuroscience Abstract,* 19, 357.

Zhu, X.O., McCabe, B.J., Aggleton, J.P., & Brown, M.W. 1997 Differential activation of the rat hippocampus and perirhinal cortex by novel stimuli and a novel environment. *Neuroscience Letters*, 229,141-143.

Zora-Morgan, S., Squire, L.R., & Amaral, D.G. 1986 Human amnesia and medial temporal region: Enduring memory impairment following a bilateral lesion limited to field CA1 of the hippocampus. *Journal of Neuroscience*, 6, 2950-2967.

Zora-Morgan, S., & Squire, L.R. 1986 Memory impairment in monkeys following lesions limited to the hippocampus. *Behavioral Neuroscience*, 100, 155-160.

(Received December 16, 2003; revision accepted March 5, 2004)