Isolated and Focal Retrograde Amnesia: A Hiatus in the Past

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Yamadori, A., Suzuki, K., Shimada, M., Tsukiura, T., Morishima, T. and Fujii, T. Isolated and Focal Retrograde Amnesia: A Hiatus in the Past. Tohoku J. Exp. Med., 2001, 193 (1), 57-65 —— Two cases of isolated retrograde amnesia were reported. Both showed the same clinical pattern in development and resolution of amnesia despite of different etiologies. Sudden insult to the brain (trauma in Case 1 and viral encephalitis in Case 2) caused concurrent anterograde and retrograde amnesia. Fortunately both recovered from the anterograde amnesia completely. However, both were left with a period of postictal amnesia of a few months and retrograde amnesia of up to 14 months’ duration. The analysis of their pattern of temporal evolution and dissolution of amnesia support the hypothesis that recently acquired episodic information requires a certain amount of constant activation for a certain period of time in order to be organized into a durable memory. The nature of this activation as well as its origin remains to be solved. —— isolated retrograde amnesia; anterograde amnesia; postictal amnesia; memory trace; memory activation

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Retrograde amnesia refers to a difficulty of retrieval of episodic memory that extends backward from the time of the onset of a brain damage, while anterograde amnesia refers to a failure to retain information about ongoing events. In most amnesic cases retrograde amnesia is observed coupled with anterograde amnesia (Squire 1992). In this paper this type of amnesia will be called global amnesia. But in rare instances, retrograde amnesia is observed without concomitant anterograde amnesia. This "isolated" retrograde amnesia is often temporally graded like the global type (Roman-Campos et al. 1980). In 1992 we reported a unique case of isolated retrograde amnesia that was a result of the recovery from a viral encephalitis and status of complex partial seizures (Yoneda et al. 1992).

Over the past years we have encountered two additional cases of such isolated cases of retrograde amnesia. The cases provided us a rare chance to look into the problem of retrieval

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and store of an episodic memory in the purest form, since they affected only the memory of premorbid events when encoding and storing systems must have been functioning normally. Analysis of the present cases and review of the literature led us to a hypothesis that a certain amount of memory-specific activation for a certain period of time is required before an episodic memory becomes stable.

**Patients**

**Case 1**

In May 18, 1997, a 20-year-old right-handed female student of a nursing college had a collision accident with a truck while riding a motor bicycle and sustained a brain contusion. She was brought to a nearby hospital in a comatose state with a left hemiparesis. After regaining consciousness she was found unable to vocalize and communicated through writing. A month later she started talking, and 2 months later started walking with assistance. On August 23, she was transferred to the Department of Rehabilitation of the Tohoku University Hospital.

On neurological examination she had anisocoria (right>left), right facial weakness, slurred speech, trunkal ataxia, and limb ataxia (left>right). Sensation, motor strength and deep tendon reflexes were normal.

Neuropsychological examination revealed good orientation to time and place. Attention was normal. No aphasia, agnosia, visuoconstructive impairment, spatial neglect or apraxia was observed. On memory testing her immediate memory was normal (forward digit span of 6). However, she showed difficulty in memorizing current information. Also she was completely amnesic for the events that had happened during one and a half months following the accident. In addition, there was a patchy and fragmental retrograde amnesia of about 2 years preceding the accident.

A T2-weighted MRI of the brain showed high intensity areas in the bilateral frontal white matter, in the posterior end of the body of the corpus callosum, and the left upper cerebellar peduncle. Single photon emission tomography (SPECT) showed mild but diffuse decrease of the blood flow in the right hemisphere, and right cerebellum. EEG showed predominance of 8 to 10 Hz basic waves with occasional 7 Hz diffuse θ waves, which showed no change throughout the hospital stay.

When she was discharged home on December 8th, 1997, her anterograde memory was judged to be normal, and the amnesia for remote memories had shrunk considerably, but amnesia for events during 6 months immediately preceding the ictus persisted.

**Case 2**

On July 16, 1996, a 23-year-old right-handed female employee of a newspaper company suddenly developed a confusional episode. Next morning she was found having grand mal seizures and was admitted to a hospital. Viral encephalitis was suspected. But no elevation of titer for any virus was found in the cerebrospinal fluid collected on two occasions. When her consciousness cleared on the third hospital day, she was found having a severe amnesia both in anterograde and retrograde direction. On August 5, 1997, she was transferred to the Department of Rehabilitation of the Tohoku University Hospital for further evaluation and treatment of the amnesia.

On admission no neurological physical signs were noted. She was alert and cooperative. No aphasia, agnosia or apraxia was present. Attention was good with a forward digit span of 8. Spatial memory span for places tested with serial pointing of 9 locations drawn on a sheet of paper was 7. However, she could not recall any of the three words that had been given five minutes before. Her remote memory for events was defective for 2 to 3 years preceding the present illness. Older memories were retrieved well.
The amnesia showed a slow but definite improvement during the hospital stay and she was discharged home on October 26th. Even after the discharge her memory continued to recover. Fourteen months after the onset her anterograde memory was judged to be within normal range for verbal as well as nonverbal materials. However even at this point her retrograde amnesia of about 14 months persisted without amelioration.

A T2 weighted MRI taken at the acute stage at the previous hospital showed high signal intensities in the bilateral caudate nuclei, thalami, and medial temporal lobes (MTLs) including the amygdala, hippocampi and parahippocampal gyri. Another MRI taken one-month post onset revealed lesions only in the bilateral MTLs, more marked in the right. A SPECT study at this period showed a decrease of the blood flow in the bilateral MTLs. The final MRI taken 3 months after the onset revealed no abnormal signals. A SPECT taken a year later was almost normal with a minimal perfusion deficit in the right MTL. EEG showed normal electrical activities and no seizure discharges were detected.

Common clinical profile of the two cases

State of the anterograde amnesia. Originally both suffered from a disturbance of consciousness eventually evolving into the clinical state of global amnesia. Gradually memorizing capacity for current events recovered to the normal level. Case 1 recovered her memorizing capacity during the 3.5 months' stay in our hospital. Recovery of the anterograde amnesia in Case 2 was slower requiring for about 14 months. For each case, general cognitive state at the stage when their anterograde memory became normal was assessed by Wechsler Adult Intelligence Scale (WAIS), and the state of memory by Auditory Verbal Learning Test (AVLT), Rey-Osterreith Complex Figure Test (ROCF) and Wechsler Memory Scale (WMS). All were within normal range.

The detail of AVLT performance is shown in Fig. 1, and all the data are summarized in Table 1.

State of the retrograde amnesia. Even after having recovered normal cognitive abilities, both cases were left with a period of retrograde amnesia for autobiographical epi-

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**Fig. 1.** Results of Auditory Verbal Learning Test. Trials were repeated 5 times. Sixth trial was tested after interruption. □, the scores of Case 1; ○ those of Case 2.
Table 1. Summary of neuropsychological data of the two cases

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<tr>
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<th>Case 1</th>
<th>Case 2</th>
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<tr>
<td>WAIS-R</td>
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<tr>
<td>VIQ</td>
<td>94</td>
<td>109</td>
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<td>PIQ</td>
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<td>FIQ</td>
<td>82</td>
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<td>AVLT</td>
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<td>Mean 1-5</td>
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<td>Trial 6 (delay)</td>
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<td>14</td>
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<td>Copy</td>
<td>36</td>
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<td>Delay (30 min)</td>
<td>29</td>
<td>32</td>
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<tr>
<td>WMS-R</td>
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<td>MQ</td>
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All data were at the time when antegrade amnesia cleared behaviorally. The case 2's WAIS was taken 1.5 months after the onset, and AVLT was taken 14 months after the onset. All the scores are considered to be within normal range. WAIS-R, Wechsler Adult Intelligence Scale Revised; VIQ, verbal IQ; PIQ, performance IQ; FIQ, full IQ; AVLT, Auditory Verbal Learning Test. Score is a mean of 5 trials. Delay means a score after interference and delay of 30 minutes. ROCF, Rey-Osterreith Complex Figure Test. WMS-R, Wechsler Memory Scale Revised; MQ, Memory Quotient.

Sodes immediately preceding the onset of the present illness. To evaluate this purely selective (or isolated) and temporally limited (or focal) memory disturbance as objectively as possible, we collected detailed personal histories from their parents, siblings, colleagues and friends and made a chronological chart for important personal events and tested these items by interview.

Case 1 initially showed approximately two years' loss of remote memory, which subsequently contracted to about 6 months. Case 2 had a difficulty in remembering personal events for over two years preceding the encephalitis, which finally shrank to about 14 months. However it has to be noted that this loss was by no means complete and there existed gray zones.

Case 1 was a student and had many seasonal events. A clinical practice at a hospital that began 3 days prior to the onset of the present illness was completely forgotten. The same was true for a cherry-blossom party held 18 days before the onset. A month before the onset she had a clinical practice course at another hospital, but none of the events was remembered. Two months prior to the onset she had a car trip with 9 close friends. She did remember that she traveled with friends by car. She also correctly remembered 5 of the 9 friends. But she could not remember any of the places they stopped at or stayed overnight. Four months prior to the accident she had another clinical practice course at another hospital for 3 weeks. None of the events could be remembered. In November 1994, 17 months prior to the onset she participated in a cookout party held at a riverside. She remembered correctly they did a mass game there, but could not remember when and where it happened. Neither could she remember whether they cooked or not at the occasion. In August 1994, 21 months before the onset she went to a beach with 8 friends. She could only remember the fact that she went with about 10 friends to a beach, but could not remember where they went and what they did. Recollection of an entrance ceremony of her nursing college 25 months prior to the onset was very vague. She remembered she had attended a graduation ceremony of a senior high school 26 months before the accident but again no details could be retrieved. Beyond this point, her memory about school events and travels with her friends or family were mostly correct. This case's retrograde amnesia slowly contracted. She became able to remember the content of the graduation day from the senior high school correctly as well as the beach event. By December it became limited to about 6 months preceding the illness.

Case 2 graduated from a university in March of 1995 and had been working as a secretary at a newspaper company for 15 months when the confusional episode developed. She had no memory at all what she did.
in long holidays in May, 2 months prior to the onset. However, she did remember correctly that no new colleagues joined her in April 1996, 3 months prior to the onset. In Japan, newly recruited from schools start their career from the first of April en masse. She also remembered that she had started the study of book keeping at a night school in the same year, but could not remember when she started and in what day of the week she attended. She had no recollection at all about a party held by the company for new employees in April of the last year, 14 months before the onset. She had a vague memory of a trip to Hawaii with friends sometime before the graduation of the university, but no details could be retrieved. Events during the rest of the life at the university and the senior high school were recollected much more correctly. Over the months after the discharge her retrograde amnesia showed slight but definite shrinkage. Thus she became able to remember most of the events of the university life correctly. At the latest evaluation her patchy retrograde amnesia probably extended for about 14 months preceding the disease onset.

Memory for remote public events was also assessed. Both were tested with 20 items for each decade with 2 items for each year. The result of Case 1 was considered to be normal for the items before 1994. Case 2 showed fair retrieval for events up to the eighties, and the first half of the nineties. But recall for events in 1995 and 1996 was vague and poor. For instance she remembered a big earthquake in Kobe area in 1995 (death toll reached more than 6000), but no details were recalled. Thus both showed poor recollection for events of the past 2 years before the ictus.

Based on these results we can safely estimate that for both cases retrograde amnesia affected not only the memories for autobiographical events but also those for public events approximately to the same degree and for the same duration.

State of the postictal amnesia. In this paper we call a recollection difficulty about events that happened to a patient after an ictus “postictal amnesia” (Fukatsu et al. 1998). Russel (1971) called it posttraumatic amnesia because he dealt with traumatic patients. It should be distinguished from anterograde amnesia in its current usage since the term has been used with implicit agreement that it means an amnesic state for ongoing events which is not caused by general cognitive disturbances (Shimamura 1989). While the term postictal amnesia is used here as a descriptive term referring to a postmorbid amnesic period resulting from any cognitive troubles including coma. In other words anterograde amnesia means ongoing amnesic process, while postictal amnesia describes a past state in retrospect. It necessarily follows that the state of anterograde amnesia can be assessed objectively, but that of postictal amnesia can only be assessed based on a patient’s statement.

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<th>Table 2. Memory profiles of 2 cases</th>
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<td><strong>Age/Sex</strong></td>
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<td>Case 2</td>
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*Imaging data were those at the last evaluation. RA, duration of retrograde amnesia in years; SRA, duration of shrinkage of RA; AA, presence of anterograde amnesia; PIA, duration of estimated postictal amnesia in years in months; Dx, Diagnosis; bil F, bilateral frontal lobe; CC, corpus callosum; lt, left; CP, cerebellar peduncle; H, cerebral hemisphere; mT, medial temporal lobe.
Case 1 was brought to a hospital in coma. Her posttraumatic amnesia extended for about 4 months. It was dense for events of the first one and a half month and patchy for the rest. Case 2 was initially in epileptic status, and left with postictal amnesia of about 3 months. These data are summarized in Table 2.

**DISCUSSION**

There are common features in these two cases of isolated focal retrograde amnesia. Both suffered from an acute cerebral disorder. Both were left with a period of postictal amnesia of several months. While their anterograde amnesia ameliorated fully, retrieval difficulty of personal events that had taken place during 6 (Case 1) and 14 (Case 2) months preceding the onset of the present illness persisted. The duration of amnesia for public events was roughly equivalent. Both showed contraction of the retrograde amnesia starting from the remote end. Within the retrograde amnesic period, not all the memories were lost. Fragments of events could be retrieved. There were also differences. Case 1 suffered from a trauma, and case 2 a viral encephalitis. In the last MRI of Case 2 the initially observed signal changes in the bilateral basal ganglia and MTLs were no more demonstrated. It was judged to be normal. In Case 1 multiple white matter lesions persisted. The results of SPECT studies were also different.

As for the reason of this selective non-availability of the relatively recent portion of the premorbid memories that must have been encoded normally, two types of explanation have been proposed. The first explanation presumes that memory contents for these events of the recent past are destroyed. Most of the currently dominant theories more or less adopt this idea. It is mainly based on clinical experiences of amnesic cases resulting from the MTL lesions (Bechterew 1900; Corkin et al. 1997). This theory argues that an episodic memory is represented and stored in a distributed network involving the neocortex and MTL. This memory network for the episode remains active for a few years. Over this period the MTL system keeps exerting its influence on the network in such a way to consolidate it into a durable one. Past this critical period, only the neocortical system becomes its bearer. This would beautifully explain the temporally graded retrograde amnesia often observed in MTL amnesia (Squire 1992; Squire and Alvarez 1995). Retrograde amnesia for recent events is the result of a failure to form a long lasting memory trace because they cannot be consolidated without the help of the MTL system. A more elaborate theory proposes that the MTL system produces index code for binding various information stored in widely distributed neocortical areas (Nadel and Moscovitch 1997). They further assume this indexing system in the MTL recruits new neurons whenever an episodic memory is retrieved. Thus they hypothesize neurons involved in indexing the episodic memory increase in number as time passes since the chances that it is remembered would increase. The presence of retrograde amnesia for recent past is the reflection of the small number of indexing neurons and their vulnerability, while the persistence of events of the remote past is the reflection of the large number of indexing neurons and its durability. However, if memory content itself were broken by a damage, shrinking of retrograde memory would not have been possible even if it is represented in a distributed way. Shrunk portion of the past memory must have been intact. Further, the theory takes the participation of the MTL system in memory-trace formation for granted. For the cases that show no clear evidence of permanent MTL damage like the present cases, it is difficult to apply.

The second explanation assumes that memory contents themselves are not destroyed directly by a damage, but they are lost from retrieval because of the lack of necessary
amount of activation. This "activation" theory was proposed by Symonds among others (Symonds 1966). He presumed that memory traces have the intrinsic tendency to decay. If a certain amount of activation were supplied, they would gain the resistance to decay. In the similar line of reasoning but with a bit of amendment, if we presume that memory traces do not decay or perish as Symonds suggested, but are only left dormant because of the lack of appropriate activation, many of the present symptoms can neatly be explained. If we further presume that availability or retrievability of a particular memory trace to consciousness is a function of the amount and length of activation it has received, the sudden cessation of memory-activation caused by an ictal process would exert memory traces of the recent origin more damage than the old ones. Continued lack of activation caused by the prolongation of postictal amnesia would further weaken these memory traces, resulting in temporally graded retrograde amnesia. When anterograde amnesia recovers, we presume retrograde activation of memory also recovers. Summation of the effect of premorbid activation and renewed activation would lead to the recovery of relatively recent memories that have been kept at the subthreshold level. Unstable memories at the threshold level may fluctuate in their availability, resulting in fragmented recall. This hypothesis is summarized as a schema in Fig. 2.

Is separation of memory trace (contents) and its activation tenable? Three evidences may be quoted in favor of this stand. (1) We know that even severe amnesias, if their amnesia is pure, can have a normal short-term memory, which means that they can encode, store, and retrieve new information if these processes were completed in a short period. If their attention is not distracted, they can keep these memories rather long (Milner et al. 1968). This suggests that stored information (memory trace) and its holding mechanism (activation) are different. (2) Recently we have encountered a rare case of amnesia with a bilateral basal forebrain damage who was able to encode and store episodic memories that had happened during a behaviorally severe amnesic period, clearly demonstrating memories and its availability are dissociable (Fukatsu et al. 1998). (3) Neurophysiological studies indicate that memory can be acquired and stored in the neocortical association areas alone. MTL systems can be viewed as a kind of memory controller (Sakai et al. 1994).

The MTLs are not the only region known to produce amnesic syndrome with temporally graded retrograde amnesia. Lesions in the diencephalon (Victor et al. 1971; Harding et al. 2000) and basal forebrains (Damasio et al. 1985; Fukatsu et al. 1998) can produce severe global amnesia. These amnesias are also characterized with intact short-term memory like the cases with MTL lesions. Above all, some reports of isolated retrograde amnesia with relatively short temporal gradient like ours (less than 2 years) have shown no definite lesions at least in MRI. Sometimes EEG or SPECT studies indicated some pathologies outside of these memory related areas (Yoneda et al. 1992; Hokkannen et al. 1995; Ishihara et al. 1997).

It is likely that one of the possible functions of these amnesia-causing regions is to supply memory-specific activation to the memory traces newly formed in the neocortical network. These areas may not be concerned with storage of memory contents themselves. Of course, this hypothesis cannot be applied to all types or aspects of retrograde amnesia. Cases of life-long loss of autobiographical memory, or dense retrograde amnesia with temporal gradient of more than 5 years constitute a clearly different pathological category, and should be interpreted in terms of other mechanisms.

We also have to admit that this activation hypothesis is based on the fragile evidence derived from only a couple of cases. There certainly are dense evidences that the MTL system is most critical for memory formation.
Fig. 2. A schema of stabilization of memory traces by activation. Uppermost arrow toward right represents the flow of physical time. Oblique arrow toward the lower right represents the flow of events in the real life. Horizontal lines represent the state of episodic memory trace at a specific date. Normally, a newly formed episodic memory (solid line) is constantly activated for a certain period of time (gray line with solid arrow head) and is changed into stable memories. When “activation systems” are damaged, memory activation stops (leftward arrow with broken line) resulting in decay of recent memories (retrograde amnesia shown as broken solid line) as well as failure to build new memories for current events (anterograde amnesia: thin broken line). When memory activation recovers, anterograde memories become normal and some of the old memories also become available because the sum of the old (solid arrow head) and new activation (open arrow head) reaches a threshold (shrunk retrograde amnesia). The portion where the sum of activation does not reach the threshold remains unavailable to consciousness resulting in isolated focal amnesia. For instance at date “a,” memory function is normal. At date “b” a brain damage occurs resulting in dysfunction of memory system. Activation stops. At date “c” the patient is in the state of global amnesia. Amnesia extends both for anterograde and retrograde direction. At date “d” anterograde memory starts to recover. Activation resumes. At date “e” the patient accumulates normal anterograde memory. Thanks to the resumption of activation, retrograde memory with a minimum activation at the premorbid period comes to life, leaving the last portion of the weakest activation dormant.

But we have to be careful to conclude that these areas are the sole structures responsible for human memory. Accumulation of similar cases like ours and development of experimental studies simulating a retrograde amnesia is necessary to confirm the present hypothesis.
Acknowledgments

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