Brain activations in errorless and errorful learning in patients with diffuse axonal injury: A functional MRI study

Abstract

Primary objective: Errorless learning has been reported to be effective in the rehabilitation of patients with impaired cognitive functions following brain injury. We compared brain activations in errorless learning (EL) and errorful learning (EF) in patients with diffuse axonal injury (DAI) using a functional magnetic resonance imaging (fMRI).

Methods and procedures: The participants were 13 patients with DAI. Thirteen healthy individuals were evaluated as a control group. The participants learned words under the EL and EF conditions in advance and performed the recognition task during fMRI scanning.

Main outcomes and results: EL in the control group was significantly faster than EF (p = 0.005), but not in the DAI group. EL in the DAI group scored significantly higher than EF (p = 0.026). An fMRI showed significant activations in the posterior cingulate gyrus (BA 31) and precuneus (BA 7) in the control group when EF > EL, but in the precuneus (BA 7, 31) and bilateral inferior parietal lobules (BA 39, 40) in the DAI group.

Conclusions: These results indicate the disadvantage of EF and advantage of EL to DAI patients. The findings also reflect brain plasticity in patients with DAI in the chronic phase.

Keywords: diffuse axonal injury, errorless learning, errorful learning, fMRI

Introduction

Traumatic brain injury (TBI), which is often a result of traffic accidents, is a major cause of death in young adults, and is a significant cause of sequelae. There are two categories of TBI: focal injuries and diffuse injuries. Diffuse brain injuries comprise classical brief cerebral concussion and more prolonged posttraumatic coma, also known as diffuse axonal injury (DAI) [1]. DAI leads to various impairments of cognitive functions; of these, memory and executive function impairments are observed most frequently [2], but impairments of attention, data processing speed, and social behaviour are also noted. Memory disturbances pose many problems for DAI patients to adjust with daily living and social life. Therefore, rehabilitation for memory disturbances is important in the overall rehabilitation of cognitive functions. Errorless learning (EL), which circumvents the trial-and-error process, is an effective strategy for enhancing the learning ability of patients with memory impairment.

EL is a learning method in which errors are avoided as much as possible in the acquisition process of new skills or information. Since Baddely & Wilson [3] reported the effectiveness of EL for the treatment of patients with amnesia, the technique has been applied to the rehabilitation of patients with various memory impairments, and many reports have been published to date [4-10].

In learning under an errorful condition (in which errors may occur and learning happens through trial and error), patients with memory impairments are unable to eliminate errors, and as a result, erroneous information is reinforced. Therefore, errorful learning (EF) has come to be considered less efficient than EL [3]. This hypothesis has not been fully validated, although several theoretical grounds have been presented based on neuro-psychological approaches [11, 12]. In addition, there are only two ERP studies [13, 14] and no PET/fMRI studies that have addressed the differences between errorless and errorful learning. Rodriguez-Fornells et al. [13] contrasted event-related brain potentials to items that had been learned under errorless and errorful conditions. They evaluated the executive system for memory retrieval under the two learning conditions, however, their study did not provide much information about the relationship between the advantage of EL and activated regions of the brain. In their study, the accuracy was greater in the EL condition, but correct responses were more frequent in the EF condition, further research is needed to clarify the benefits of the EL [10].

Clarification of the mechanism of the effect of EL and its differences compared with EF is important for evaluating the pathology of memory impairments such as DAI and the rehabilitation of patients with these conditions. There has been no report evaluating the effectiveness of EL using functional magnetic resonance imaging (fMRI). The aims of this study were to clarify the differences in brain activations between the EL and EF using fMRI and to compare brain activations between DAI patients and healthy individuals.

Methods

Participants

Thirteen patients with DAI but without local brain injuries participated in this study. They all fulfilled the Gennarelli’s classification[1], which is a criteria for DAI. Diagnosis was confirmed by the presence of traumatic microbleeds in conventional MRI T2*-weighted images. Patients with local brain injuries were excluded. Higher cognitive functions of the DAI patients were evaluated using the Revised Wechsler Adult Intelligence Scale, the Trail Making Tests A and B and the Rivermead Behavioral Memory Test. Thirteen healthy controls approximately matched regarding educational background, age and gender participated in the study. Table 1 compares the characteristics of both the groups. All participants were right-handed as assessed using the Edinburgh Handedness Inventory [15] and were native speakers of Japanese. Informed consent was obtained from each participant according to the instructions of the Ethical Review Board, Hiroshima Higher Brain Function Center.

Word stimuli

A list of word stimuli was prepared by selecting 3-kana-letter Japanese words at random from those that appear frequently (frequency ≥ 100) in 'Nihongo-no Goitokusei' (Lexical Properties of Japanese) in the Nippon Telegraph And Telephone Database Series Volume 7 [16].

Learning trials (Learning phase)

Learning trials were performed under the EF and EL conditions, and the order of trials under both conditions was counterbalanced in all participants. Under the EF condition, a question, for example, 'I am thinking of a 3-letter word starting with [i]. Can you guess what it is?' was asked. After three guessing trials, they were told, 'The answer was [i-chi-go] (strawberry). Please remember it.' The participants were thus informed of the answers (target words) and asked to memorize them. Under the EL condition, they were asked, for example, ‘I am thinking of a 3-letter word starting with [ta]. It is [ta-ba-ko] (cigarette). Please remember it.’ The participants were thus guided to memorize five target words, respectively.

Scanned recognition task (Test phase)

The recognition tasks were divided into the following two types of test trials. Under the EF condition, six words consisting of two target words learned in the EF phase and four non-target words (words that the participants themselves guessed in the EF phase, i.e., errors) were used as lures [12] and were presented at random in each block. Under the EL condition, six words consisting of two target words learned under the EL phase and four non-target words (other words starting with the same letters as the target words learned in the EL phase were selected randomly from the prepared word pool) were presented randomly in each block. One block consisted of 10 volumes (2.2 s/vol), and six words/22 s/block were presented as word stimuli at equal intervals visually on a screen using a video projector. The trial tasks were arranged in a block design of the RABRBAR/RBARABR pattern [R: Simply seeing letters unrelated to the targets and non-targets (rest condition). A/B: Performing recognition tasks under the EF or EL condition], and the order of tasks was counterbalanced in all participants (see Figure 1). The reaction time (RT) and percentage of correct answers (accuracy) were determined.

Comparisons of RT and accuracy between the control group and the DAI group were performed by the Wilcoxon’s rank sum test. In the two participants groups with RT and accuracy, the effects of the EL condition were evaluated using the Wilcoxon's signed rank test.

Image data acquisition

A 1.5-T MRI system (Magnetom Symphony, Siemens, Erlangen, Germany) was used to acquire 20 T2*-weighted transverse echo-planar images (FOV, 192 × 192 mm; matrix size, 64 × 64 mm; in-plane resolution, 3 × 3 mm^2; flip angle, 90° ; TE, 60 ms) with blood oxygenation level-dependent contrast. Echo-planar images represented 6.0 mm thick axial slices obtained every 6 mm, continuously acquired during a 2.5 min session using an interleaf method. An automatic shimming procedure was conducted before each session. Seventy-one functional volumes were collected from each participant within a single scanning session, with an effective repetition time of 2.2 s/vol. The first volume obtained was discarded to allow for T1 equilibration effects. Image processing was carried out using SPM2 (Wellcome Department of Imaging Neuroscience, London, UK; see http://www.fil.ion.ucl.ac.uk/spm) implemented in MATLAB 6.5 (Mathworks, Sherborn, MA). Images were realigned to the first volume by rigid body transformation and interpolated synchronously over time to correct for phase advance during acquisition. The images were then normalized to standard stereotactic space using the Montreal Neurological Institute (MNI) template. Normalized images of 3 × 3 × 6 mm^3 were spatially smoothed using a Gaussian kernel of FWHM 8-8-15 mm [17, 18]. Treating the volumes as a time series, the data were high-pass filtered to 1/128 Hz.

Image data analysis

Data were analyzed with SPM2 using a random-effects model implemented in a procedure. Model estimation was convolved with a canonical haemodynamic response function at a fixed effects level based on the General Lineal Model. Random-effects analyses were conducted at a second stage for every contrast according to the proposed hypotheses. Task-related group activation tested the null hypothesis to show that patients and controls had identical group means. Clusters of voxels, which had a peak Z-score > 3.1 (amplitude threshold uncorrected $p < 0.001$, extent threshold corrected $p < 0.05$) were considered to show considerable activation. Contrasts of activation between controls and patients with DAI during the experimental task also tested the null hypothesis to show that patients and controls had identical group means. Clusters of voxels, which had a peak Z-score > 3.1 (amplitude threshold uncorrected $p < 0.001$, extent threshold corrected $p < 0.05$) were considered to show considerable activation.

Anatomical identification was carried out by superimposing the maxima of activation foci on the MNI template and normalized structural images of each participant. Activation foci were labelled using the Talairach atlas [19].

Results

Behavioural data

Mean reaction time

The mean reaction times in the recognition tasks using the words learned under the EF and EL conditions were 1151 SD 146 ms and 1036 SD 115 ms, respectively, for the control group and

1575 SD 216 ms and 1516 SD 351 ms, respectively, for the DAI group. The reaction time was significantly shorter in the control group under both conditions ($Z = -3.89$, $p < 0.0001$) ($Z = -3.48$, $p = 0.0004$). It was shorter under the EL condition in the control group ($p = 0.005$), but no significant difference was noted in the DAI group ($p = 0.207$) (see Table 2).

Mean percentage of correct answers

In the control group, the mean percentages of correct answers on recognition tasks using the words learned under the EF and EL conditions were 94.2 SD 8.7% and 91.8 SD 7.7%, respectively. In the DAI group, they were 73.8 SD 17.7% and 83.5 SD 15.9%, respectively. The mean percentage of correct answers was significantly higher in the control group under the EF condition ($Z = 2.99$, $p = 0.0027$), but no significant difference was noted between the two groups under the errorless condition ($Z = 1.45$, $p = 0.138$). It was higher under the EL condition in the DAI group ($p = 0.026$), but no significant difference was noted in the control group ($p = 0.674$) (see Table 2).

Neuroimaging data

We identified the regions of the brain that required more activation for EF than EL by subtracting brain activities during word recognition tasks under the EL condition from those under the EF condition. The results are shown in Table 3 and Figure 2. Significant activations were observed in the posterior cingulate gyrus (BA 31) and precuneus (BA 7) in the control group, but in the precuneus (BA 7, 31) and bilateral inferior parietal lobules (BA 7, 39, 40) in the DAI group.

When brain activities during word recognition tasks under the EF condition were subtracted from those under the EL condition, no region with significant activations was noted in the control or the DAI group.

We performed group analysis in the control and DAI groups concerning differences in brain activities during word recognition tasks under the EF and EL conditions, but no region with significant activations was noted.

Discussion

In this study, we have demonstrated the differences in brain activations related to memory acquired by EF and that by EL using recognition tasks. In healthy adults, greater activations of the precuneus and posterior cingulate gyrus were more necessary for recognition via EF than that via EL. We also examined DAI patients approximately matched for age and gender using the same recognition tasks. In the DAI patients, greater activation of the precuneus was necessary for the recognition of words learned by EF than those learned by EL, similar to healthy controls, but the bilateral posterior parietal cortices were also activated, unlike healthy controls. These results suggest that greater activations of the precuneus and posterior cingulate gyrus are needed for EF, and may explain the poor performance in EF and effectiveness of EL in patients with memory impairments such as DAI. In addition, they suggest that DAI patients compared with healthy individuals show the recruitment of the bilateral posterior parietal cortices to perform EF at a level as nearly equal as possible to that of the healthy individuals.

EL has been proposed and widely performed as an effective learning method in patients with memory impairments. Although no clear conclusion has been reached concerning the advantage of EL, there have been few neuroimaging studies in which differences in the memory system involved in EF and EL were evaluated from a neuroanatomical viewpoint. The notable characteristic in the current work is that it is the first to clarify differences in brain activations in EL and EF using fMRI and to compare brain activations between DAI patients and healthy adults. We aimed to identify regions of the brain activated in the recognition of words learned by EF (i.e., discrimination between target words and lures) and to evaluate their differences compared with the regions activated in the recognition of words learned by EL (ordinary old/new discrimination). The term 'lure' was used by Page et al. [12] to describe words used to prime the participants by advance exposure as errors under an EF condition and used as non-target words. In this study, a list of stimuli was prepared, following the experimental design of Page et al.

When EF > EL, significant activities were observed in the posterior cingulate gyrus (BA 31) and precuneus (BA 7) in the normal control group and also in the precuneus (BA 7, 31) in the DAI group. The functions of the posterior cingulate gyrus remain unclear compared with those of the anterior cingulated gurus. The retrosplenial cortex located posterior to the posterior cingulate gyrus is considered to be related to memory based on clinical reports that memory disturbances are caused by injuries to this region [20, 21]. In addition, stimuli related to emotion activate the posterior cingulate gyrus and retrosplenial cortex, and Maddock [22] suggested that the retrosplenial cortex functions as a region of interaction between emotion and episodic memory.

The precuneus plays a more general role in episodic retrieval and can be divided functionally into anterior and posterior parts [23]. Moreover, the posterior part of the precuneus is activated more in source recognition than in item recognition [24]. Patients with memory impairment in whom episodic memory is impaired may remember that words presented as stimuli were those presented in the learning phase; however, because of the impairment of source monitoring, the patients may find it difficult to judge whether the words were target words. Thus, because discrimination between targets and errors (lures) in EF requires source recognition using episodic memory before and after learning, the precuneus may be increasingly activated in EF.

Alzheimer's disease causes marked recent memory disturbance and decreases in the circulation and metabolism of the posterior cingulate gyrus and precuneus early after the onset has been reported [25]. Patients with Alzheimer's disease are considered to be at a disadvantage in EF, which requires the activities of these regions, and EL is expected to be effective for them. Indeed, the effectiveness of EL has been established. Grandmaison and Simard [26] performed a meta-analysis of five studies concerning the effects of EL in patients with Alzheimer's disease and reported that significant improvements were noted after training.

There have been several reports on brain circulation and metabolism in DAI patients, and the posterior cingulate gyrus was one of the regions that showed reduced circulation and metabolism [27, 28]. In addition, EF, which requires activities of the posterior cingulate gyrus and surrounding areas, may be difficult for DAI patients. Consistent with this view, we presently observed that the percentage of correct answers was significantly higher in EL than in EF for the DAI patients. This result supports findings from previous reports that EL is also effective in DAI patients.

We subtracted the brain activities of DAI patients during EL from those during EF, and clarified that the bilateral inferior parietal lobules (BA 7, 39, 40) as well as the precuneus (BA7, 31) were significantly activated during EF and that EF requires activities of wider areas of the brain. The parietal lobule is known to be involved in working memory, but was once considered to contribute little to explicit memory. However, Wagner et al. [29] analyzed several recent studies of episodic retrieval using fMRI and reported that the posterior parietal cortex, including regions within the intraparietal sulcus extending laterally to the inferior parietal lobule, as well as the precuneus and posterior cingulate gyrus plays an important role in episodic memory retrieval. These areas are the same as those observed in EF > EL in DAI patients. Therefore, activities of the parietal lobules are considered important in EF.

In DAI patients, a different procedure may be used in the process of memory, and a different circuit of memory may be formed compared with healthy individuals. Therefore, the activation of the bilateral parietal lobes observed in the DAI patients may indicate activities of different regions of the brain for EF. There have been some reports on such relocalization in patients with brain dysfunctions including neuroimaging studies of patients with stroke [30] and multiple sclerosis [31]. There is also the possibility that DAI patients with hypoactivities of the posterior cingulate gyrus and precuneus compared with healthy individuals perform tasks of EF by compensatory mobilization of the parietal lobe areas, important for episodic retrieval and remaining relatively intact. However, in the current study, the DAI subjects performed more poorly than the control subjects, these recruited regions may reflect more of 'attempted' compensation than successful compensation [32]. Levine et al. [33] studied functional neuroanatomical regions that support memory retrieval in patients with moderate to severe TBI using positron emission tomography. The activities of the frontal lobes, anterior cingulate gyrus, and occipital lobes were increased compared with those in healthy controls. They concluded that TBI patients execute memory tasks using an altered functional neuroanatomical network and that these changes reflect either cortical disinhibition attributable to disconnection or compensation for inefficient mnemonic processes. Maruishi et al. [34] evaluated brain activities during the Paced Visual Serial Attention Test, which is an attention task for patients with pure DAI. Compensatory activities were observed in the right inferior frontal gyrus and right middle frontal gyrus in DAI patients compared with healthy controls, and they considered that these findings indicate the adaptive capacity of the neuronal system and plasticity of the brain in the course of recovery from DAI.

A limitation of this study was that no significant difference was observed in group analysis, while the activated regions of the brain differed clearly between the groups. The small number of participants may have affected the results. Differences in brain activations are considered to have been very weak because similar recognition tasks were used under both errorful and errorless conditions.

We found that EF is disadvantageous and EL is advantageous for DAI patients. This difference arises because the circulation and metabolism of the posterior cingulate gyrus and precuneus are reduced, and episodic retrieval related their activities are required more for EF. In addition, in DAI patients, the activities of the bilateral inferior parietal lobules are recruited to obtain maximum performance under the EF conditions. These results confirm that DAI patients have greater difficulty with the EF condition compared with healthy individuals, and suggest the adaptability and plasticity of the neuronal system in the recovery phase of DAI.

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Figure legends

Figure 1: Schematic representation of the experimental block design paradigm.

Figure 2: Averaged activation maps showing BOLD signal increases for comparison between errorful learning (EF) and errorless learning (EL) for each group.

(a) Subtracted activation during EL from activation during EF in the controls. The activated regions including cingulate gyrus (BA 31) and precuneus (BA 31, 7).

(b) Subtracted activation during EL from activation during EF in the patients with DAI. The activated regions including right inferior parietal lobules (BA 7, 40, 39) left inferior parietal lobules (BA 40, 39), and precuneus (BA 31, 7).

Table 1

Characteristics of DAI patients and healthy controls

Characteristics	Patients with DAI (n = 13)		Controls (n = 13)		
	Mean	SD	Mean	SD	*p* value
Sex					
Male(female)	10(3)		11(2)		0.62
Age (years)	27.8	10	22.4	2.47	0.08
Education (years)	14	2.96	14.7	0.63	0.44
Time from onset (months)	32.9	28.9	NA	NA	
GCS score	8.7	3.5	NA	NA	
Duration of unconsciousness (day)	19.2	21.2	NA	NA	
WAIS-R					
FSIQ	90.4	15.7	NA	NA	
VIQ	89.2	15.5	NA	NA	
PIQ	93.4	17.6	NA	NA	
Trail Making Test-A	102.9	23.9	NA	NA	
Trail Making Test-B	106.9	32.4	NA	NA	
RBMT					
Profile score	18.1	3.9	NA	NA	
Screening score	7.8	2.6	NA	NA	

DAI, diffuse axonal injury; NA, not available; GCS, Glasgow Coma Scale; WAIS-R, Wechsler Adult Intelligence Scale Revised; FSIQ, full-scale intelligence quotient; VIQ, verbal intelligence quotient; PIQ, performance intelligence quotient; RBMT, Rivermead Behavioral Memory Test

Table 2

Mean (SD) of reaction times and accuracy

	Reaction time (ms)			Accuracy (%)		
	EF	EL	**p* value	EF	EL	**p* value
Control	1151 (146)	1036 (115)	0.005	94.2 (8.7)	91.8 (7.7)	0.674
DAI	1575 (216)	1516 (351)	0.207	73.8 (17.7)	83.5 (15.9)	0.026
p value	< 0.0001	0.0004		0.0027	0.138	

EF, errorful learning; EL, errorless learning; DAI, diffuse axonal injury

*Wilcoxon's signed rank test.

Table 3

Brain regions activated by errorful learning versus errorless learning

Brain regions (Brodmann area)	MNI template			Z score
	X	Y	Z	
Controls				
Right cingulate gyrus (BA 31)	4	-27	35	4
Left precuneus (BA 31)	0	-45	34	3.57
Left precuneus (BA 7)	0	-62	44	3.73
	-2	-72	36	3.13
Patients with DAI				
Right inferior parietal lobule (BA 7)	40	-68	44	4
Right inferior parietal lobule (BA 40)	59	-51	38	3.58
Right inferior parietal lobule (BA 39)	51	-62	38	3.46
Left inferior parietal lobule (BA 40)	-44	-52	47	3.96
Left inferior parietal lobule (BA 39)	-38	-66	35	3.85
	-35	-60	40	3.75
Left precuneus (BA 31)	-6	-65	27	3.66
Left precuneus (BA 7)	-6	-62	34	3.56
Right precuneus (BA 7)	8	-58	36	3.6

Figure 1

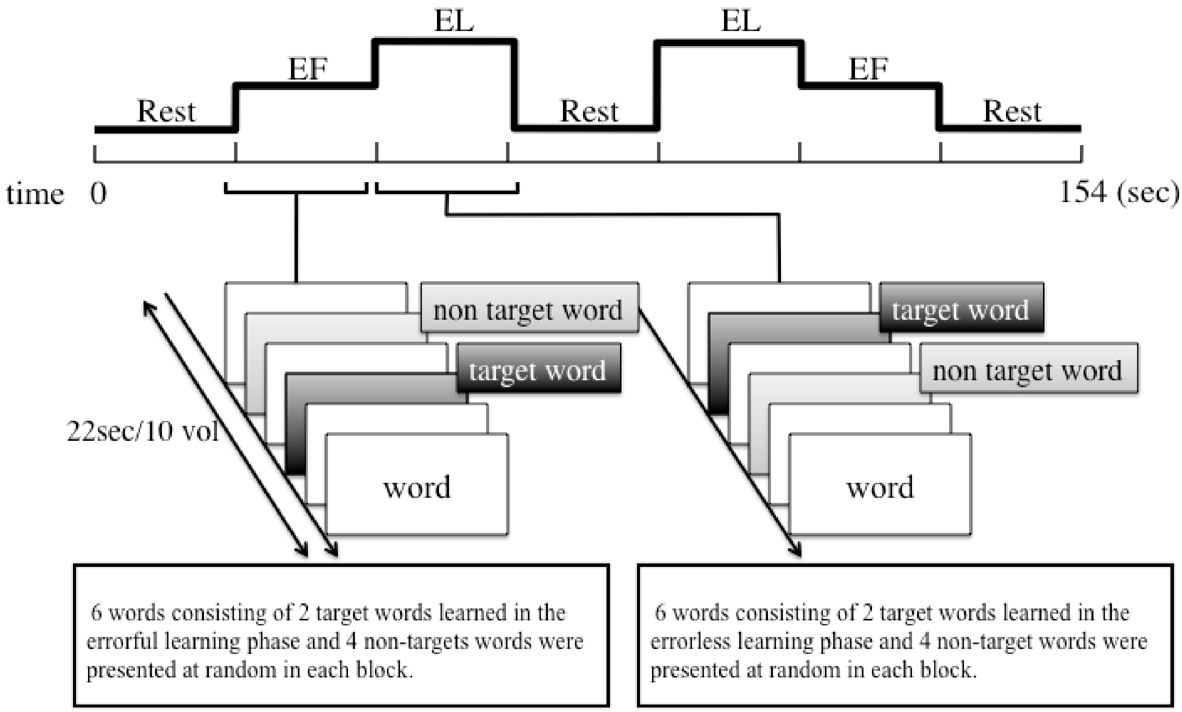
EL
EL
EF
EF
Rest
Rest
Rest
time 0
154 (sec)
22sec/10 vol
non target word
target word
word
target word
non target word
word
6 words consisting of 2 target words learned in the errorful learning phase and 4 non-targets words were presented at random in each block.
6 words consisting of 2 target words learned in the errorless learning phase and 4 non-target words were presented at random in each block.

Figure 2