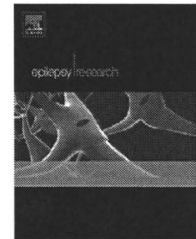
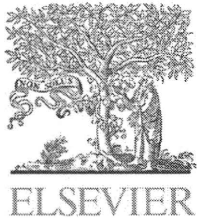


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Abnormal mismatch negativity for pure-tone sounds in temporal lobe epilepsy

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Summary Auditory processing abnormalities in temporal lobe epilepsy (TLE) were assessed by investigating mismatch negativity (MMN) in a group of 20 TLE patients and 20 healthy control subjects. MMN is an event-related potential (ERP) component that reflects pre-attentive sensory memory function. A passive oddball paradigm using frequency changes in sinusoidal tones was employed to evoke MMN. MMN at frontocentral sites was enhanced in TLE patients relative to controls, while mismatch signals at mastoid sites (i.e., mismatch positivity; MMP) did not differ between the two groups. In the MMP temporal range, greater positivity at mastoid sites in response to standard stimuli was observed in TLE patients than in controls. Both MMN and MMP were significantly delayed in the TLE group. These findings demonstrate that TLE patients have impaired pre-attentive processing of pure-tone sounds. Enhanced frontocentral MMN may reflect hyperexcitability of the frontal lobes in compensation for dysfunction of the temporal lobes. Larger positivity at the mastoids in response to standard stimuli may be attributed to poor neuronal adaptation in the temporal lobe. Taken together, results suggest that evaluation of MMN/P is a useful physiological tool for identifying pre-attentive auditory memory dysfunction in TLE.

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Introduction

Temporal lobe epilepsy (TLE) is often associated with memory impairment due to damage in the hippocampus and surrounding structures (Dietl et al., 2008; McCagh et al., 2009). It has been repeatedly shown that both short-term and long-term memory are impaired in TLE (Butler and Zeman, 2008; McCagh et al., 2009). However, little is known concerning dysfunction in initial sensory memory encoding in TLE.

Mismatch negativity (MMN) is an early auditory event-related potential (ERP) elicited when infrequent ("deviant") sounds occur in a sequence of repetitive ("standard") sounds (Näätänen et al., 1978). It has been proposed that MMN automatically arises if there is mismatch between the physical features of a deviant stimulus and a neuronal sensory-memory trace produced by repetitive standard stimuli (Näätänen et al., 1989). MMN is believed to reflect the earliest cortical event in the cognitive processing of auditory information (Pfefferbaum et al., 1995) and thus to be a part of auditory pre-attentive memory (Cowan et al., 1993). MMN can be elicited even in the absence of attention, and effects of motivation are minimal (Näätänen, 2000). MMN has therefore received considerable interest because of its potential application to clinical research, and has been studied in various populations including newborns (Stefanics et al., 2009) and children (Milovanov et al., 2009) as well as in disorders such as schizophrenia (Kasai et al., 2002; Salisbury et al., 2007) and Alzheimer's disease (Pekkonen et al., 2001). Focusing on pre-attentive processes may be the only means of assessing cognitive function in patients with advanced cognitive decay who are unable to perform traditional cognitive tasks.

To date, the extant literature evaluating MMN response in epilepsy patients is limited and discrepant, with some studies pointing to attenuated or delayed MMN, whereas others report enhanced MMN. For example, Lin et al. (2007) investigated the magnetic equivalent of mismatch negativity (MMNm) in intractable TLE patients using magnetoencephalography (MEG). Longer MMNm latencies were observed in patients than in healthy controls. The authors also evaluated inter-trial phase coherence as indexed by phase-locking factors using wavelet-based analyses. For patients who became seizure-free after removal of right temporal epileptic foci, phase-locking in response to deviant stimuli was enhanced and more strongly distributed in frontotemporal regions. Such findings suggest that successful surgery may improve auditory change detection. Borghetti et al. (2007) demonstrated similar improvements in drug-resistant epilepsy patients who underwent vagus nerve stimulation (VNS). Prior to VNS implantation, MMN latencies in some patients were abnormally late and attenuated relative to controls. After implantation, however, these patients exhibited a major reduction in MMN latency and increase in amplitude, suggesting a positive effect of VNS on pre-attentive processes.

In the pediatric field, MMN has been shown to be absent or prolonged for speech (but not tones) in patients with benign childhood epilepsy with centro-temporal spikes (BCECTS) (Boatman et al., 2008; Duman et al., 2008). Patients with BCECTS with atypical features and learning difficulties have

also been shown to exhibit attenuated MMN amplitudes (Metz-Lutz and Filippini, 2006). Furthermore, Honbolygó et al. (2006) found that in Landau-Kleffner syndrome, MMN was obtained for phoneme differences but was absent for stress pattern differences.

In contrast to findings of attenuated MMN amplitudes and delayed latencies, Usui et al. (2009) observed distinctively large N100m signals, the magnetic counterpart of N1/N100, in autosomal-dominant lateral temporal lobe epilepsy with seizures provoked by auditory stimuli. Similarly, Gene-Cos et al. (2005) reported that MMN amplitudes tended to be larger in patients with epilepsy than in healthy controls. Furthermore, work from our own laboratory has shown extremely large MMN amplitudes in response to high-frequency deviants in a patient with frontal lobe epilepsy with seizures provoked by high-frequency auditory stimuli (Miyajima et al., 2009). One could hypothesize that the higher amplitudes observed in epileptic patients indicate increased activation of the same neuronal population as in controls, or that extra neuronal circuits are activated in epileptic patients (Myatchin et al., 2009).

Taken together, the existing literature provides discrepant accounts of how MMN is affected in epilepsy patients. Furthermore, most studies in adult epileptics have not focused on patients with specific types of epileptic syndromes or epileptogenic regions. To this end, the broad aim of the current study was to better characterize potential differences in cortical activation patterns between TLE patients and controls during pre-attentive auditory processing. Specifically, we employed a passive oddball task and evaluated whether frontal and mastoid mismatch components were equally affected by TLE. If a single auditory cortex generator is responsible for any potential abnormalities in TLE, we hypothesized that similar MMN changes should be expected across electrode locations, given that frontal and mastoid electrodes are approximately equidistant from Heschl's gyrus (Baldeweg et al., 2002).

In addition to characterizing MMN differences between TLE patients and controls, a secondary objective was to investigate whether MMN abnormalities, if present in TLE patients, were associated with epileptic seizures. Specifically, we evaluated whether mismatch components differed between patients who experienced at least one seizure in the months leading up to the experiment and patients who were seizure-free during the same time period.

Methods

Subjects

Twenty TLE patients (8 females and 12 males; mean age 33.9 ± 10.0 (SD) years) and 20 comparable healthy control subjects (10 females and 10 males; mean age 34.0 ± 7.8 years) participated in this study as volunteers.

Epilepsy patients were recruited from Tokyo Medical and Dental University Hospital and Hara Clinic, a specialized epilepsy clinic certified as a training facility by The Japan Epilepsy Society. All patients had partial seizures with features strongly suggestive of a TLE diagnosis, including simple partial seizures characterized by autonomic and/or psychic symptoms, certain phenomena such as olfactory and auditory sensations, and complex partial seizures beginning with motor arrest followed by orolimentary automatism

Table 1 Clinical information for healthy controls and TLE patients.

Variables	Controls (n = 20)			TLE patients (n = 20)			
	Mean	(SD)	Range	Mean	(SD)	Range	
Age (years)	34.0	(7.8)	23–50	33.9	(10.0)	20–50	NS
Education (years)	16.6	(3.3)	12–22	14.5	(1.7)	12–16	NS
Gender (male/female)	10/10			12/8			
Duration of epilepsy (years)	NA			13.7	(9.8)	3–33	
Age of onset (years)	NA			20.1	(11.4)	0–45	
Side of epileptic focus (left/right/bilateral or undetermined)	NA			9/4/7			
Seizure status (intractable/remission)	NA			12/8			
Number of AED	NA			1.8	(1.0)	1–4	

AED, antiepileptic drug; NA, not applicable; NS, no significant difference.

(Commission on Classification and Terminology of the International League Against Epilepsy, 1989). Diagnoses were based on a combination of clinical symptoms, EEG, and structural/functional imaging data. Exclusion criteria for both groups included comorbid psychiatric disease, substance abuse or dependence, and reports of hearing or vision problems at the time of the experiment. Additional exclusion criteria for the control group included a history of psychiatric disease, history of traumatic brain injury with any known cognitive consequences or loss of consciousness, history of convulsions other than simple febrile seizures, and psychiatric disease or epileptic disorder in first-degree relatives.

Table 1 summarizes the subjects' clinical characteristics. Patients were divided into two subgroups, an intractable subgroup and a remission subgroup. The intractable subgroup experienced at least one seizure within a 20-month period prior to the experiment, while the remission subgroup was completely seizure-free during this time. All patients were treated with at least one anti-epileptic drug (AED), e.g., carbamazepine or phenytoin, for seizure control.

The study was approved by the Ethics Committee at Tokyo Medical and Dental University. Written informed consent was obtained from each participant after thoroughly describing the experiment.

Procedure

Subjects were presented with auditory stimulus sequences consisting of 600 standard stimuli and 150 deviant stimuli delivered in random order. Fifty deviant stimuli were presented to each subject in a single block, and each subject completed three blocks. The experimental conditions were designed to elicit MMN in response to changes in frequency of pure tones. To this end, stimuli consisted of pure tones presented for 100 ms each, with a rise/fall time of 5 ms and a stimulus onset asynchrony (SOA) of 500 ms. Standard stimuli (1000 Hz) comprised 80% of all trials, while deviant stimuli (1050 Hz) comprised 20%. The standard pure tone frequency of 1000 Hz is commonly used in psychoacoustic and electrophysiological studies, and was chosen because it does not directly correspond to the fundamental of any musical note. Stimuli were delivered binaurally via earphones at 90 dB as subjects watched a silent film while seated and were instructed to ignore auditory stimuli.

ERP recording

EEG was recorded using a portable bio-amplifier recording device (Polymate AP-1532 with silver/silver chloride electrodes, or Polymate AP-216 with active electrodes, TEAC Corporation, Japan) from the midline (Fz, Cz, Pz, and Oz) and bilateral mastoids. The tip of the nose served as the reference for all electrodes. Two electrodes

were placed above the left eye and below the right eye to monitor the electrooculogram (EOG). Impedance between the electrodes and skin did not exceed 5 kΩ. The sampling rate was 1000 Hz for each channel and the recording bandwidth was between 0.05 Hz and 300 Hz.

Data analysis

Data analysis focused on a 600 ms time window ranging from 100 ms pre-stimulus to 500 ms post-stimulus onset. The pre-stimulus baseline was corrected separately for each channel according to the mean EEG amplitude over the 100 ms period. Averaging and artifact rejection were performed off-line. Trials with excessive movement activity or with EOG activity exceeding 100 μV peak-to-peak were excluded from analysis. Average waveforms were obtained separately for deviant and standard stimuli, with a minimum of 100 deviant trials for each subject.

Because MMN is known to show inverted polarity at mastoid locations, the term 'mismatch positivity' (MMP) has been adopted to describe the mismatch component at this location (Baldegeweg et al., 1999). For this reason, we use the term MMP when describing mastoid findings, and MMN for findings at all other electrode locations.

Statistical analyses

The mean amplitudes of standard and deviant waveforms were defined as the average amplitude for each waveform 100–250 ms post-stimulus onset (the range in which MMN/P is typically found). MMN/P peak latency was defined as the latency of the peak showing maximal negativity/positivity 100–250 ms post-stimulus onset for the deviant – standard difference waveform.

Mean amplitudes for standard and deviant waveforms were first analyzed using three-way repeated-measures analyses of variance (ANOVA), with separate ANOVAs conducted for sites with negative and positive polarity. For both ANOVAs, factors included the between-subjects factor GROUP (TLE and control), and two within-subject factors STIMULUS (standard and deviant) and SITE (for sites with negative polarity: Fz and Cz; for sites with positive polarity: left and right mastoid). Additional two-way ANOVAs with one between-subject factor GROUP (TLE and control), and one within-subject factor SITE (for sites with negative polarity: Fz and Cz; for sites with positive polarity: left and right mastoid) followed separately for standard and deviant waveforms.

MMN/P peak latencies based on the difference waveform were examined using two-way repeated-measures ANOVAs with one between-subject factor GROUP (TLE and control), and one within-

Table 2 Mean amplitudes of standard, deviant and difference (MMN) waveforms as well as MMN peak latencies in controls and TLE patients.

Variables	Site		Controls (n=20)		TLE patients (n=20)	
			Mean	(SD)	Mean	(SD)
Mean amplitude (µV)						
Standard	Frontocentral	Fz	0.17	(0.70)	0.17	(1.31)
		Cz	0.15	(0.69)	0.07	(1.12)
	Mastoid	L	-0.22	(0.66)	0.43	(0.56)
		R	-0.31	(0.67)	0.42	(0.59)
Deviant	Frontocentral	Fz	0.11	(0.73)	-0.56	(1.59)
		Cz	0.24	(1.07)	-0.55	(1.39)
	Mastoid	L	0.13	(0.60)	0.49	(0.98)
		R	0.16	(0.56)	0.45	(1.20)
MMN	Frontocentral	Fz	-0.05	(0.73)	-0.75	(0.84)
		Cz	-0.10	(1.19)	-0.64	(0.93)
	Mastoid	L	0.35	(0.51)	0.06	(0.91)
		R	0.47	(0.58)	0.02	(0.63)
Peak latency (ms)						
MMN	Frontocentral	Fz	133	(28)	179	(36)
		Cz	141	(42)	171	(41)
	Mastoid	L	145	(31)	157	(53)
		R	150	(33)	185	(39)

subject factor SITE (for sites with negative polarity: Fz and Cz; for sites with positive polarity: left and right mastoid).

Finally, to explore whether potential abnormalities in TLE patients were associated with epileptic seizures, the TLE group was divided into two subgroups, an intractable subgroup and a remission subgroup. Mean amplitudes for standard and deviant waveforms were first analyzed using three-way ANOVAs with one between-subjects factor SUBGROUP (intractable and remission), and two within-subject factors STIMULUS (standard and deviant) and SITE (for sites with negative polarity: Fz and Cz; for sites with positive polarity: left and right mastoid). When a three-way ANOVA yielded a significant interaction or trend for an interaction between factors, a two-way ANOVA was performed for the relevant factors. MMN/P peak latencies based on the difference waveform were examined using two-way repeated-measures ANOVAs with one between-subjects factor SUBGROUP (intractable and remission), and one within-subject factor SITE (for sites with negative polarity: Fz and Cz; for sites with positive polarity: left and right mastoid).

With respect to all analyses, statistics for sites showing a negative mismatch component were limited to Fz and Cz because MMN typically is largest at midline frontocentral sites. As anticipated, visual inspection of difference waveforms at Pz and Oz revealed small and obscure mismatch signals such that it was difficult to determine individual peaks. MMN typically reverses polarity at nose-referenced mastoid sites. To this end, evaluation of waveforms at mastoid sites enabled comparison of polarity with waveforms at Fz and Cz, providing additional assurance that the observed negativity at these sites was a "true" mismatch response (Näätänen et al., 2007).

Results

Fig. 1 presents grand-averaged ERP waveforms for standard and deviant stimuli in TLE patients and controls at Fz, Cz, and left and right mastoids, with associated mean amplitudes presented in Table 2. Although statistical analyses

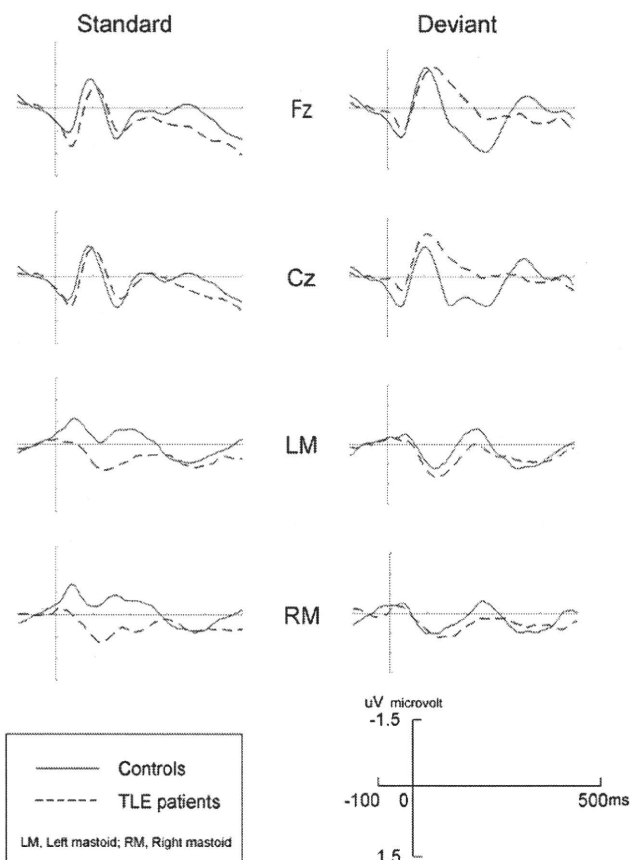


Figure 1 Comparison between grand-averaged ERPs for standard and deviant stimuli in controls and TLE patients. Solid line, control group; striped line, epilepsy group.

Table 3 Mean amplitudes of standard deviant and difference (MMN) waveforms as well as MMN peak latencies in TLE intractable and remission subgroups.

Variables	Site		Intractable (n = 12)		Remission (n = 8)	
			Mean	(SD)	Mean	(SD)
Mean amplitude (μ V)						
Standard	Frontocentral	Fz	0.23	(0.64)	0.08	(0.61)
		Cz	0.12	(1.46)	-0.01	(0.53)
	Mastoid	L	0.45	(0.68)	0.40	(0.36)
		R	0.43	(0.70)	0.43	(0.39)
Deviant	Frontocentral	Fz	-0.60	(1.91)	-0.51	(1.06)
		Cz	-0.66	(1.50)	-0.38	(1.29)
	Mastoid	L	0.36	(1.09)	0.70	(0.82)
		R	0.36	(1.06)	0.57	(0.53)
MMN	Frontocentral	Fz	-0.82	(0.84)	-0.63	(0.87)
		Cz	-0.78	(0.85)	-0.38	(1.03)
	Mastoid	L	-0.10	(0.96)	0.09	(0.90)
		R	-0.06	(0.73)	0.02	(0.58)
Peak latency (ms)						
MMN	Frontocentral	Fz	183	(34)	149	(72)
		Cz	172	(43)	148	(73)
	Mastoid	L	165	(64)	126	(59)
		R	193	(45)	147	(64)

for mean amplitude were performed based upon standard and deviant waveforms, we also present grand-averaged MMN/P waveforms (i.e., difference waveforms) in Fig. 2 for ease of comparing mismatch signals across groups. For the

same reason, MMN/P mean amplitudes also are presented in Table 2, with mean amplitude defined as the average amplitude of the deviant – standard difference waveform 100–250 ms post-stimulus onset. Peak latencies for the difference waveform are also reported in Table 2. Finally, Table 3 presents data relevant to the TLE subgroup analysis, including mean amplitudes of standard, deviant and difference (MMN/P) waveforms, as well as peak latencies of the MMN/P waveform.

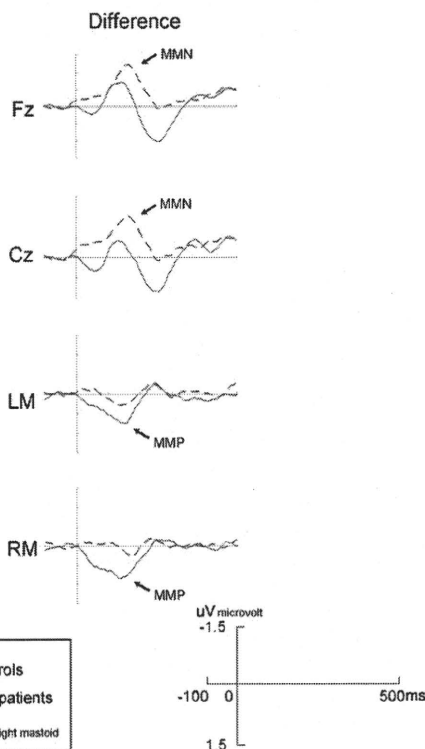


Figure 2 Deviant minus standard difference waveforms in controls and TLE patients. Solid line, control group; striped line, epilepsy group.

Frontocentral sites

A 2 (GROUP: TLE vs. control) \times 2 (STIMULUS: standard vs. deviant) \times 2 (SITE: Fz vs. Cz) repeated-measures ANOVA examining mean amplitudes for standard and deviant stimuli in the range of 100–250 ms revealed a significant main effect of STIMULUS [$F(1, 38) = 5.05, p < 0.05$], such that deviant amplitudes were greater than standard amplitudes. A significant interaction between STIMULUS and GROUP was also found [$F(1, 38) = 5.74, p < 0.05$], indicating that the difference between deviant and standard amplitudes in TLE patients was greater than that in controls. Stated another way, MMN was enhanced in TLE patients relative to controls (see Figs. 1 and 2 and Table 2). Separate 2 (SITE: Fz vs. Cz) \times 2 (GROUP: TLE vs. control) repeated-measures ANOVAs for deviant and standard mean amplitudes showed no significant main effects or interactions. Additionally, visual inspection of waveforms revealed that deviant waveforms in TLE patients were still negative at a latency of 200 ms, whereas in controls deviant waveforms shifted from negative to positive around 150 ms, effectively leading to prolonged MMN duration in TLE patients (see Fig. 1 and Table 2).

With respect to MMN peak latency (based on the deviant–standard difference waveform), a two-way repeated measures ANOVA revealed a significant main effect of GROUP [$F(1, 38)=12.45, p<0.01$], such that MMN peak latency was delayed in patients compared with controls. No significant main effect of SITE or interaction between GROUP and SITE was observed.

Mastoid sites

A three-way repeated-measures ANOVA examining mean amplitudes for standard and deviant stimuli revealed significant main effects of both GROUP [$F(1, 38)=7.14, p<0.05$] and STIMULUS [$F(1, 38)=5.08, p<0.05$]. Collapsed across stimulus type and site, mean amplitudes were greater in TLE patients than controls; collapsed across group and site, deviant amplitudes were greater than standard amplitudes. No significant interaction between factors was observed. In addition, separate two-way repeated-measures ANOVAs were performed for deviant and standard amplitudes. No significant main effects of GROUP or SITE or an interaction between factors were found for deviant stimuli. Conversely, for standard stimuli a main effect of GROUP was found [$F(1, 38)=13.65, p<0.001$], with TLE patients showing greater mean amplitudes than controls (see Fig. 1 and Table 2). No main effect of SITE or an interaction between GROUP and SITE was found for standard stimuli.

A two-way repeated measures ANOVA for MMP peak latency based on the difference waveform revealed a significant main effect of GROUP ($F(1, 38)=4.39, p<0.05$) and SITE ($F(1, 38)=7.65, p<0.01$), indicating that MMP peak latency was delayed in TLE patients relative to controls, and that both groups displayed delayed MMP peak latencies in the right relative to left mastoid (see Fig. 2 and Table 2). There was a trend toward a significant interaction between GROUP and SITE [$F(1, 38)=3.88, p=0.056$], although the difference did not reach a significant level.

MMN/P and epileptic seizures

At frontocentral sites, a 2 (STIMULUS: standard vs. deviant) \times 2 (SITE: Fz vs. Cz) \times 2 (SUBGROUP: intractable vs. remission) repeated-measures ANOVA for mean amplitudes of standard and deviant waveforms in the range of 100–250 ms revealed a significant main effect of STIMULUS [$F(1, 38)=9.44, p<0.01$], such that deviant amplitudes were greater than standard amplitudes (see Table 3). No main effect of GROUP or interaction between STIMULUS and SUBGROUP was observed. For MMN peak latency, a 2 (SITE: Fz vs. Cz) \times 2 (SUBGROUP: intractable vs. remission) repeated measures ANOVA revealed no significant main effects or interactions.

At mastoid sites, a three-way repeated measures ANOVA for mean amplitudes of standard and deviant stimuli revealed no significant main effects or interactions between factors. With respect to MMP peak latency, a two-way repeated measures ANOVA revealed a significant main effect of SITE [$F(1, 18)=7.06, p<0.05$], reflecting longer latencies in both groups for right than left mastoid (see Table 3). No main effect of SUBGROUP or interaction between SITE and SUBGROUP was observed.

Discussion

In response to a passive auditory oddball task, patients with TLE exhibited patterns of cortical activity that differed from control subjects in several ways. First, at frontocentral sites, MMN was enhanced in TLE patients relative to controls, as revealed by a significant GROUP by STIMULUS interaction for mean amplitude. Secondly, at mastoid sites, TLE patients showed greater standard waveform amplitudes than controls. Finally, in addition to amplitude differences between groups, analyses revealed longer MMN/P peak latencies in TLE patients relative to controls at both frontocentral and mastoid sites.

A number of researchers have noted that mismatch potentials recorded from mastoid electrodes may exhibit characteristics different from those of MMN recorded from frontal electrodes (Baldeweg et al., 2002; Sato et al., 2002). Early studies of MMN identified a single dipole generator within the bilateral superior temporal gyri (STG) in the vicinity of Heschl's gyri (Scherg et al., 1989). Toward the mastoids, an inversion of polarity is typically observed and has been considered evidence for the generation of MMN in the temporal lobe (Sams et al., 1985). However, more recently it has been suggested that the single dipole model may not account for all the data, and that more than one source may contribute to the scalp MMN (Giard et al., 1994). To this end, multichannel MEG and EEG studies (Rinne et al., 2000) as well as intracranial recordings (Rosburg et al., 2005) have identified additional generators in the frontal cortex. In the latter study, MMN was observed in two patients at electrode contacts over lateral inferior frontal cortex and in one patient in a frontal interhemispheric electrode strip, providing evidence for the participation of frontal gyri in MMN generation. Recent observations have led to the view that temporal electrodes mainly detect mismatch sources in the superior temporal lobe, including perhaps its lateral surface, while electrodes over the frontal scalp may detect signals from putative frontal generators (Escera et al., 2003; Näätänen et al., 2007).

In addition to debate surrounding the number of MMN generators, the specific neural mechanisms underlying MMN generation also remain controversial. Two major competing hypotheses, the model adjustment hypothesis and the adaptation hypothesis, are considered below in relation to the current findings.

To date, the most commonly suggested mechanism underlying MMN generation is a pre-attentive sensory memory mechanism (Tiitinen et al., 1994) posited to automatically compare present auditory input and memory traces of previous sounds (Näätänen et al., 2007). More specifically, it has been suggested that MMN may reflect on-line modifications of a perceptual model that is updated when auditory input does not match its predictions (Näätänen and Winkler, 1999), a hypothesis known as the model-adjustment hypothesis. Based on this model, MMN is thought to result from two underlying functional processes: a sensory memory mechanism arising from temporal generators and an automatic attention-switching process arising from frontal generators (Giard et al., 1990). Providing support for this model, Escera et al. (2003) demonstrated evidence for prefrontal cortex involvement in providing top-down modulation of a deviance detection system in the temporal cortex. With respect to

the current study, findings of enhanced MMN at frontocentral sites in TLE patients might thus be interpreted as frontal lobe hyperexcitability to compensate for temporal lobe dysfunction. That is, a larger number of synchronously activated frontal neurons may be required for successful automatic attention-switching in TLE patients than in controls, due to impairment of a initial sensory memory mechanism in the temporal lobe.

An alternative mechanism recently proposed by Jääskeläinen et al. (2004) suggests that MMN results from a much simpler mechanism of local neuronal adaptation in the auditory cortex. According to the adaptation hypothesis, reduced responsiveness in the auditory cortex during continuous stimulation is sufficient to explain the generation of an apparent MMN. In the current study, although deviant – standard differences (i.e., MMP) at mastoid sites did not significantly differ between the two groups, greater standard waveform amplitudes were observed in patients than in controls. With respect to the adaptation hypothesis, such findings may reflect poor neuronal adaptation in the temporal lobe such that repeated presentation of standard stimuli does not lead to reduced responses. In other words, processing resources may continue to be allocated in TLE patients despite the repetitive nature of the standard stimuli (Myatchin et al., 2009). TLE may be characterized by excitability of the temporal lobe despite stimulus repetition, which might be related to epileptogenesis of the temporal cortex. The current results suggest that adaptation mechanism of the temporal cortex for stimuli that are subsequently repeated may be impaired in TLE.

It also bears noting that longer latency components such as P3a may have affected the pre-stimulus baseline period, in turn affecting MMN/P amplitudes given that epochs were baseline-corrected. Specifically, because we chose a short SOA (500ms), standard trials preceded by a deviant trial may have had different pre-stimulus baseline periods than those preceded by another standard trial. Although P300 abnormalities in TLE are controversial, studies in chronic TLE patients typically report trends toward lower P300 amplitudes relative to controls (e.g., Drake et al., 1986; Tuunainen et al., 1995; Abubakr and Wambacq, 2003). To avoid potential confounds related to P3a, future studies should exclude standard trials preceded by deviant trials from averaging.

In addition to amplitude differences between TLE patients and controls, a second key difference was an increase in MMN/P latency in TLE patients, consistent with previous reports (Lin et al., 2007; though see Duncan et al., 2009, for reports of normal auditory P300 latencies in patients with complex partial seizures). Because ERPs provide a chronological measure of brain function and ERP latencies are thought to indicate timing of covert neuronal events in which certain subroutines in the brain are activated (Kok, 1997), increased MMN/P latencies in TLE patients in the current study may be the result of an early but not later slowing in auditory information processing speed.

Furthermore, in TLE patients the MMN component persisted longer at frontocentral sites than in controls, consistent with previous findings by Gene-Cos et al. (2005). The authors argue that prolonged MMN duration might point to difficulty mainly in "the closure mechanism of the MMN

process". They suggest that this information processing dysfunction could be related to concentration and memory difficulties observed in TLE patients, given that patients may spend more time evaluating stimulus novelty than controls and may experience difficulty switching attention from one stimulus to another difficult (Piazzini et al., 2006). Such findings in epilepsy patients are in agreement with previous studies in which barely discriminable tones elicited delayed MMN peaks (Näätänen and Alho, 1995; Inouchi et al., 2004) with delays increasing as the magnitude of deviation decreased (Yabe et al., 2001; Inouchi et al., 2004).

Interestingly, collapsed across subject groups, MMP was delayed in the right mastoid compared with the left. Because of the small number of patients whose epileptic focus was clearly lateralized, statistical analyses could not be conducted to evaluate the relationship between MMP latency and laterality of epileptic focus. Furthermore, given that laterality effects have not been reported previously with respect to MMP latency in healthy adults, further investigation is warranted before drawing strong conclusions about this finding.

Finally, our patient subgroup analysis investigating the relationship between seizures and MMN/P did not reveal any significant differences between groups, suggesting that the occurrence or absence of seizures in the months leading up to the experiment did not significantly affect MMN/P.

Because all patients were being treated with AEDs at the time of data collection, it bears noting that use of AEDs may have affected MMN/P amplitudes and latencies. It has been shown, for example, that anti-epileptic medication can have an effect on motor reaction times and on latencies in ERP studies (Lagae, 2006; Myatchin et al., 2009), as well as an overall dampening effect on amplitudes (Rosburg et al., 2005). Benzodiazepines, which are also used as AEDs, have been found to reduce MMN amplitude (Rosburg et al., 2004). To this end, the current finding of enhanced MMN amplitudes in TLE patients cannot be explained as a simple dampening effect of AEDs, though further studies will be required to better address the effects of AEDs on MMN. Finally, although all patients reported normal hearing levels, it is possible that MMN/P was affected by subclinical differences in auditory discriminative abilities between patients and controls.

Taken together, results from the present study reveal clear cortical abnormalities in TLE patients that have not been well-characterized previously by conventional EEG. In TLE patients, enhanced MMN at frontocentral sites and greater positivity at mastoid sites of standard waveforms may be interpreted in terms of increased activation of the same neuronal population as in controls, or activation of extra neuronal circuits. In conclusion, the current study extends previous findings of impaired short and long-term memory in TLE patients (Butler and Zeman, 2008; McCagh et al., 2009) by revealing that initial sensory memory is impaired in TLE as well. Our findings indicate that MMN/P can be useful as a physiological probe of pre-attentive sensory memory for tones in TLE.

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■原著

動かしているが使えない —両手動作時に左手の空振りを呈した一症例—

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要旨：両手動作時の左手に特異な障害を呈した症例を報告した。症例はくも膜下出血後脳梗塞を併発し、右頭頂葉病変を認めた。左半側空間無視や運動消去はなかったが、視・聴・触覚の左の消去現象を呈した。左手は高次体性感覚障害と拙劣に加え、両手動作の際、あたかも対象を操作しているかのように動作を継続するものの、実際には対象を把持せず、空振りのような動作が観察された。4年後、両手動作時の左手の障害と消去現象は並行して消失したが、左手の高次体性感覚障害と拙劣は残存した。これまで高次体性感覚障害を伴う病巣対側上肢の拙劣症の報告はあるが、両手動作時の異常の記載はない。また本例は左半側空間無視や運動消去は呈していない。本例の障害は、4年後とともに消失した多様式消去現象と関連し、能動的動作時に内発的に生じる体性感覚に対する消去現象により説明できる可能性が考えられ、右頭頂皮質病巣が関与しているものと思われた。

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Key Words : 高次体性感覚障害, 拙劣, 消去現象, 頭頂葉

higher somatosensory disturbance, clumsiness, extinction phenomenon, parietal lobe

はじめに

頭頂葉は、中心後回の一次体性感覚野に入力された情報を階層的に処理し、さらには同側の視覚情報や聴覚情報のみならず、対側からの情報も統合する「連合野の連合野」として知られている。またこの後方連合野は前頭連合野と連絡し、運動出力とも密接に関係している。そのため、頭頂葉が損傷されるとさまざまな症状を呈する。たとえば、皮質性感覚障害、肢節運動失行（運動拙劣症）、把握障害、視覚性運動失調、自己身体定位障害が出現し、とくに右半球損傷では半側空間無視、半身無視、着衣失行などが認められる（平山ら2009）。

今回われわれは、右頭頂葉の梗塞後にこれまで報告のない特異な両手動作時の左手の障害を呈し

た症例を報告する。本報告にあたり、記載内容、画像の使用、報告内容について、症例本人に口頭と文書で説明を行い、署名による同意を得た。

I. 症 例

40歳代後半、右利き男性。大学卒。特記すべき既往歴はなかった。

現病歴：右内頸動脈瘤破裂によりくも膜下出血を発症、当日開頭動脈瘤頸部クリッピング術が施行された。第10病日、血管攣縮により右中大脳動脈・後大脳動脈境界領域に脳梗塞を発症し、第31病日に水頭症に対し脳室腹腔短絡術が施行された。第70病日、明らかな運動麻痺や感覚障害などもなく、自宅退院となった。その後、発症から8ヵ月後に、「左手がうまく使えない」と訴えがあり、外来を再診した。その後、心筋梗塞のため他院で加

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療することとなり通院は中断していたが、復職を前に発症4年後に再度外来受診した。

Ⅱ. 発症8ヵ月後の所見

1. 神経学的所見

脳神経・小脳系の異常は認めず、視力・視野・眼球運動も問題なかった。随意運動は、左右ともに良好で麻痺は認めなかった。握力は右40kg・左20kgで、左上肢の筋力低下を認めた。体性感覚は「左手がちょっと鈍い」という日もあれば、「左右差はない」という日もあり、症例の表現は一定しなかったが、筆で軽く触れられた刺激の有無の判断は常に可能であった。また痛覚・温度覚も正常であった。深部感覚は、母指探しテストでは左上肢でごくわずかなずれを認めたが、運動覚に問題はなかった。

2. 神経心理学的所見 (表1・表2・表3)

神経心理学的検査結果を表1に、消去検査結果

を表2に、高次体性感覚検査の結果を表3に示す。

意識は清明で、見当識、コミュニケーションに問題はなく、検査にも協力的であった。記憶は日常生活上、問題はなかった。視覚による物品の弁別・呼称、形・色・奥行き認知は問題なく、図形模写や構成にも問題はなかった。星抹消検査では少数の見落としを認めたが左右に偏りはなく、線分二等分や図形模写でも半側空間無視は確認されなかった。日常生活でも左身体をどこかにぶつけることや髭のそり残しなどのエピソードもなかった。一方で、視覚・触覚・聴覚の左消去現象を認めた(表2)。動作時の運動無視、両手同時の上肢挙上や交互運動での運動消去は認めなかった。行為については、日常生活や訓練場面での物品操作の誤りはなく、模倣・言語指示からのジェスチャーや手指パターン模倣も両手とも問題なかった。着衣も可能であった。また、注視下でも周辺視野でも上肢の到達運動障害はなく、プレシェーピン

表1 神経心理学的検査所見 (発症8ヵ月後)

MMSE		27/30
RCPM		29/36
WAIS-R	4下位検査による推定IQ	96~101
	知識	(評価点) 10
	数唱	10
	理解	8
	類似	8
	絵画完成	10
	積み木模様	5
	符号	10
Ray-Osterrieth	模写	36/36
	複雑図形	遅延再生 (5分後)
		17/36
星抹消検査		31/36
RBMD	標準プロフィール点	19/24
	スクリーニング点	8/12
Word Fluency	カテゴリー (動物・果物・乗物)	19・10・10
	語頭音 (し・い・れ)	7・8・7

MMSE : Mini-Mental State Examination

RCPM : Raven's Coloured Progressive Matrices

WAIS-R : Wechsler Adult Intelligence Scale-Revised

RBMT : Rivermead Behavioral Memory Test

グにも問題なかった。しかし、後述する左手の拙劣を認めた。

症例自身は検査を実施するまで明らかな感覚障害の自覚はなかったが、左手の二点識別覚・書字知覚・触点定位・皮膚運動方向覚 (Benderら1982)・立体覚の障害を認めた (表3)。二点識別覚は左手で示指指先・手掌面ともに右手に比べ識別可能な距離が延長し、とくに手掌では7cmでも困難であった。書字知覚では1から5の数字を手掌面にペン先で書いて検査したが、左手ではまったく判別できなかった。触点定位は上肢の任意の部位を検者が指で軽く触れ、触れられた反対側の手で同じ場所を示させた。皮膚運動方向覚は、手掌面にペン先で縦・横・斜めの線を描き、その方向を口頭で答えてもらった。立体覚の検査は立方体や球など一辺が2.5~4cmの5種類の木製の積

表2 消去検査時の正答数

		8ヵ月後	4年後
視覚	左一側	10/10	10/10
	右一側	10/10	10/10
	両側同時	3/10	10/10
触覚	左一側	10/10	10/10
	右一側	10/10	10/10
	両側同時	3/10	10/10
聴覚	左一側	10/10	10/10
	右一側	10/10	10/10
	両側同時	4/10	10/10

各感覚様式について、一側刺激と両側同時刺激をランダムにそれぞれ10回提示した。触覚では手掌面を軽く触った。触覚・聴覚の検査は閉眼で実施した。

表3 高次体性感覚検査結果

		右手	左手 (8ヵ月後)	左手 (4年後)
二点識別覚	示指の識別閾値	0.3cm	1.0cm	1.2cm
	手掌の識別閾値	1.0cm	7cm以上	4cm
書字知覚 (数字)	正答数	5/5	0/5	3/5
触点定位 (上肢)	ずれの距離	0~1cm以内	5~10cm	3~10cm
皮膚運動方向覚 (手掌面)	正答数	6/6	1/6	1/6
立体覚 積み木	正答数 (正答率)	7/7 (100%)	4/7 (57%)	8/10 (80%)
	日用品	正答数 (正答率)	10/10 (100%)	6/10 (60%)

木を2セット準備し、1セットを机上に並べ、手に持たせたものと同じ物を選択させた。同様に日用品はブラシ・鉛筆・鍵などの5つについて実施した。日用品の立体覚検査で正答した物品は、「冷たいから金属…スプーン」など、材質や大きさの質感などから推測した回答であった。

3. 左手の拙劣

日常生活で「左手がうまく使えない」場面を症例にたずねると、自宅で赤ん坊を両手で抱きあげる時、左手で持っているはずの赤ん坊の頭がはずれていて落としそうになったことや、またそれに気をつけすぎて赤ん坊だけでなく座っていた椅子まで一緒に左手が持ち上げていたことなどのエピソードを述べた。また、洗濯物をたたもうとしても、どうしてもうまくたためないと述べた。

診療場面で観察した左手の拙劣は、手袋を左手にはめようとする一つ一つの穴に2本の指を入れることや、左手を手探りでポケットに入れられないことであり、肢節運動失行様であった。これらの症状は視覚による代償で改善した。左手一側の動作は、キャッチボールなどの粗大運動、目視下でペグを穴に差し込むなどの比較的容易な巧緻動作は問題なく可能であった。しかし、指先だけでペグを回転させるなどのより巧緻な作業はやや拙劣であった。

一方、両手動作では、目視下であっても左手で押さえる、つまむなどの動作が不良で、作業が進まないことが観察された。症例の左手は動作が停滞することなく合目的に動いており、右手に合わせて協調的に動きを継続しているが、いつの間にか左手が対象から離れていることや、適切な位

置を保っていないことに気づかずに動作を続けることが観察された。たとえば洋服やタオルをたたむ動作では、タオルの端を持つ動きをしているものの、左手はタオルを持たずに空振りしたまま動作を続けることや、端だけでなくほかの部分も一緒に持ったまま動作を続けることがあった(図1)。また、ボルトとナットを組み合わせる作業でも、目視による代償が可能な眼前で行っているにも関わらず、左手はボルトを把持した形でひねる動作をしているが、指はボルトからはなれていることがあった。症例は「うまくいかない」とは述べたが、左手の空振りや不適切な把持が原因であることには気づいていなかった。また、左手を見ながら動作を行うよう指示し、適切な位置を把持させて作業を再開しても、作業経過中に不適切な把持

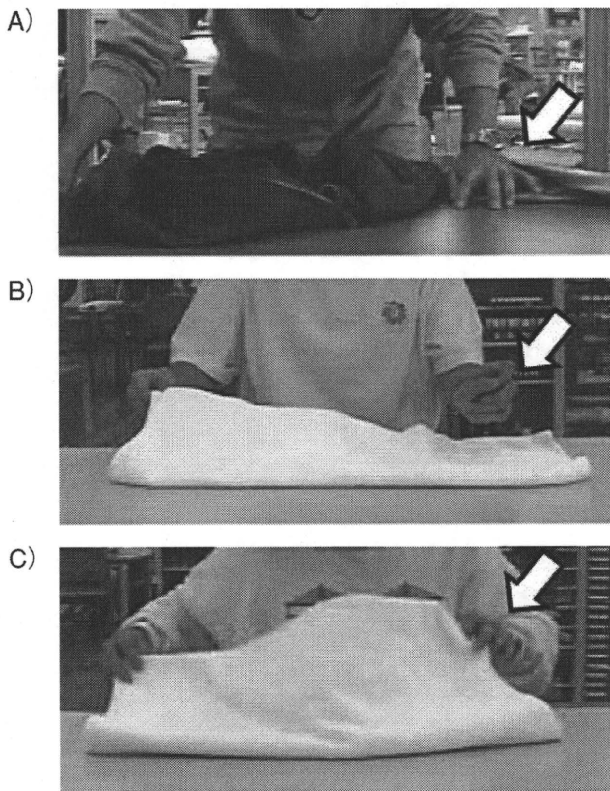


図1 発症8ヵ月後の両手動作時の左手の異常
(動画から抽出)

- A) 衣服(黒色)を机上に広げようと左手を動かしているが左手は衣服を捉えておらず、空振りした。
B) タオルをたたむ際、左手はタオルを把持せず作業を継続した。
C) タオルをたたむ際、端ではない部分も把持しているが持ち直すことなく作業を継続した。

になり、改善しなかった。

Ⅲ. 発症4年後の所見

1. 神経学的所見

左手の握力が8ヵ月後の20kgから29kgへと改善していた。その他は特記すべき変化を認めなかった。

2. 神経心理学的所見

発症後8ヵ月後に認めた左側の視覚・聴覚・触覚の消去現象は消失していた(表2)。また、両手動作時の左手の使用障害も消失していた。日常生活においても、とくに困ることはないとのことであった。

一方、左上肢の高次体性感覚障害は、書字知覚と立体覚は多少改善していたものの、右手と比較すると成績は不良で、障害は残存していた(表3)。また、ポケットや手袋に手を入れることや巧緻動作は視覚の代償が必要で、片手使用時の拙劣は残存していた。

Ⅳ. 脳画像所見

1. 頭部CT(図2)

頭部CTでは、右半球に上側頭回から下・上頭頂小葉、側脳室前角外側の低吸収域を認めた。左半球では、前方のシャントチューブに加え、角回にも淡い低吸収域を認めた。発症後4年の時点でも、8ヵ月後と比較して低吸収域に著明な変化はなかった。

2. 脳血流SPECT(図3)

脳血流SPECTでは、頭部CTで認めた低吸収領域の周囲を含む広範な右頭頂側頭葉と、右前頭葉下部の血流低下を認めた。また左角回にも血流低下を認めた。8ヵ月後と4年後を比較すると、両側側頭葉底面、右中前頭回、左頭頂側頭移行部、左前頭前野、両側帯状回、両側小脳の血流に軽度の改善があったが、右頭頂側頭部の血流低下は残存しており、大きな変化はなかった。

Ⅴ. 考 察

1. 高次体性感覚障害を伴う拙劣症について

求心性の体性感覚障害の関与する病巣対側上肢の肢節運動失行や拙劣症は、中心後回を含む一側

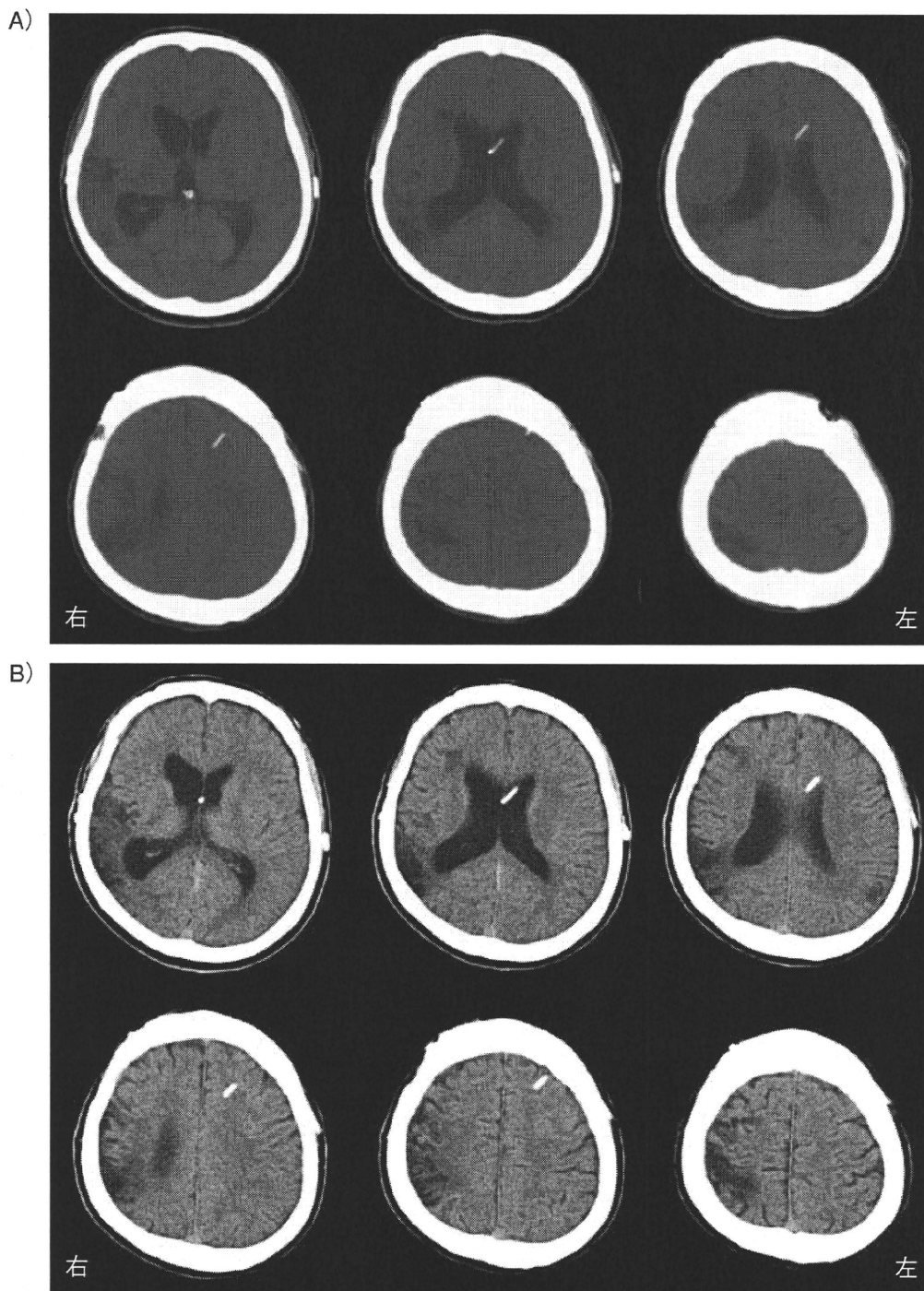


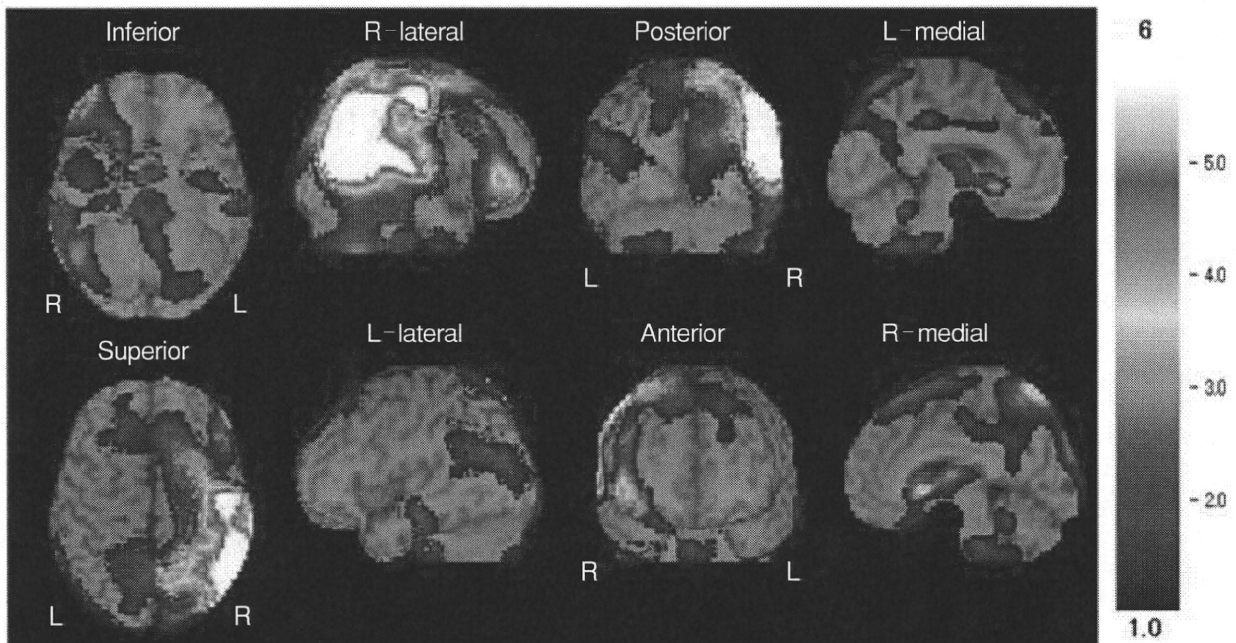
図2 CT画像

A) 発症8ヵ月後, B) 発症4年後

の頭頂葉病変を有する症例で報告されている (Yamadori 1982, 河村ら 1986, 下村ら 1988, Motomuraら 1990, Binkofskiら 2001, Valenzaら 2001, 鈴木ら 2003)。また, 頭頂葉損傷による高次の触覚認知障害例でも, 病巣と反対側上肢の拙劣が報告されている (Bohlhalterら 2002)。これ

らの症例の特徴は, 病巣の反対側上肢の筋力・分離運動や表在知覚・位置覚に問題がないにもかかわらず, 対象の操作が拙劣になること, 二点識別や立体覚などの高次体性感覚障害を伴うことである。拙劣は視覚により手指動作の補正が可能だが, 病巣が後方に伸展し拙劣も重度であった症例では,

A)



B)

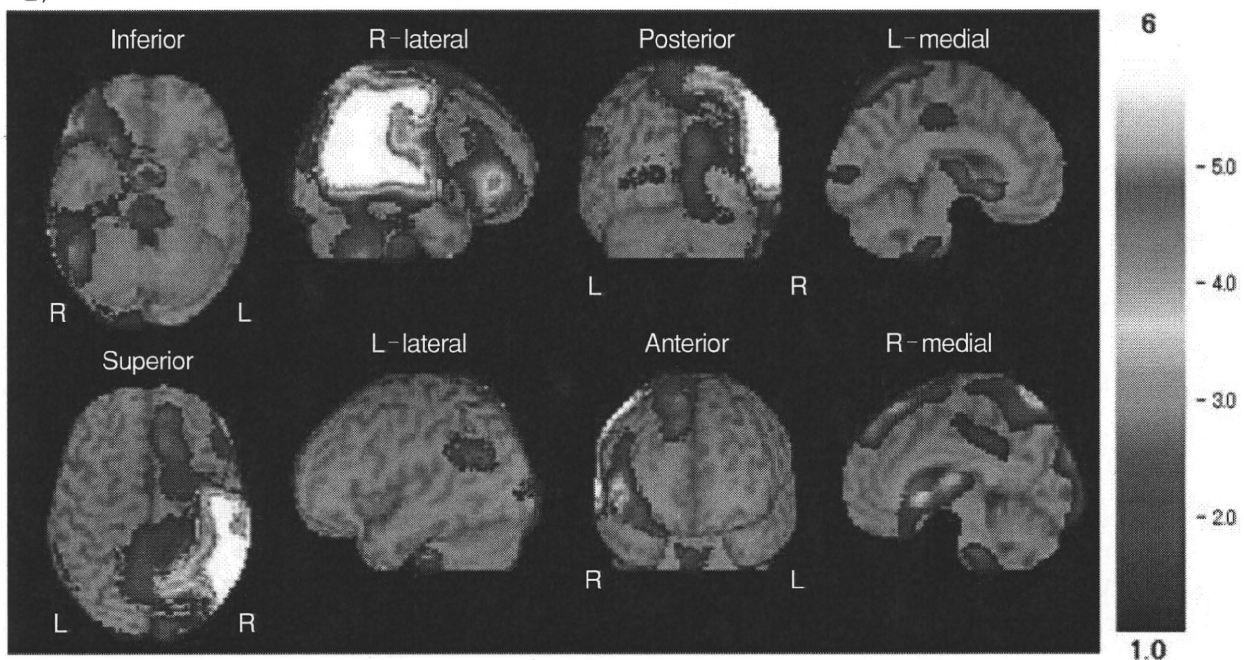


図3 99mTc-ECD SPECT e-ZIS 解析

A) 発症8ヵ月後, B) 発症4年後

視覚補正の効果がなかったとの報告もある（細見ら 2005）。

本例は、発症後8ヵ月・4年の両時点において、左手は、表在知覚や位置覚にはほとんど問題はなかったが、立体覚を含む高次の体性感覚障害を呈していた。また運動機能が保存されていたにもか

かわらず、手袋やポケットに手を入れることが不良で、巧緻動作もやや拙劣であった。よって本例の左手は、高次体性感覚障害を伴う肢節運動失行あるいは拙劣症であったと考えて矛盾はないと思われる。しかし、変性疾患を除く中心領域後方病変による拙劣症の報告では、両手動作時における

一側肢の障害や拙劣の悪化などの記載はない。また本例は、当初より左手一側でもペグ操作が可能なほど運動機能は保存されており、かつ視覚補正による改善も認めたことから、症例の両手動作時の障害は拙劣症だけでは説明できないと考えられる。

2. 本例の両手動作時の左手の障害について

本例の障害のもっとも特異な点は、左手はあたかも対象を操作しているかのように動かすものの、実際には対象を把持せず動作を続けていたことである。

Ghikaら(1998)は、頭頂葉に限局病変のある発症後1~3週の脳卒中症例32名について、運動に関する症候を検討した結果、全例に両手動作障害を認めたとしている。しかし、その内容は病巣対側上肢の不使用傾向であり、本例の呈した障害とは異なる。

本例は、図形模写や抹消検査で検出されるような左半側空間無視は認めず、日常生活でも身体の左側をぶつけるといったエピソードもなかった。また、左手の不使用や運動無視も認めず、両手動作中も左手の動きは減弱することなく、動きそのものも途切れなかった。つまり本例の両手動作時の左手の障害は、半側空間無視、半側身体無視、運動無視、運動消去により説明できる障害ではなく、これらとは異なる障害であると考えられる。

一方で、本例は両手動作中に左手が適切に対象を把持していないことを指摘しても改善しなかった。また、4年後における両手動作時の左手の障害の回復と並行して、視覚・触覚・聴覚の消去現象が消失していた。これらの現象からは、本例の左手の障害に、左側に対する何らかの注意の障害が関係している可能性が考えられる。

感覚性の消去現象は、臨床的には比較的急性期に生じる現象で、半側空間無視とともに観察されることが多いが、それぞれが独立して観察されることもある(Cocchiniら1999)。よって、発症8ヵ月後に本例で半側空間無視は認めなかったものの左の消去現象が陽性であったことは珍しいこととは言えない。しかし、消去現象を認めた症例のうち、消去側の手の両手動作時の障害の記述は、われわれが検索した限りでは見つけられず、特異

な現象であると思われる。

本例の呈した両手動作時の障害は、運動自体は継続されており、その際に生じる体性感覚の入力を無視しているかのようなようであった。われわれはこの障害を、これまで報告のない、運動時に生じる能動的で内発的な感覚に対する消去現象(active touch neglect)であったと考える。一般に、消去現象は、被験者に対し受動的な感覚刺激を与え、その刺激を感じた側を答えさせることで検査する。よって、検査では被験者にとって外部から受動的に入力された感覚に対する消去しか検出することはできない。一方、通常能動的な動作を行うときは、運動によって生じる内発的な体性感覚の入力を伴う。それは触覚系に加え、運動感覚や固有感覚であり、自分で運動をすることでしか得られない特殊な感覚である(Gibson 1983, 岩村 2001)。この能動的な動作に伴う内発的な体性感覚の消去は、他の感覚消去と同様の方法では検出できない。この消去現象は、入力される感覚の問題であって、運動消去のように出力そのものが減弱することとはまったく異なる現象である。おそらく、臨床場面では、本例の呈したような左手の障害を観察し、推察する以外、発見する方法はないものと思われる。

本例の左手の障害に関するもう一つの説明として、単に多様式感覚の消去現象と高次体性感覚障害が重複して生じた現象である可能性も考えられる。本例では多様式の消去現象と高次体性感覚障害を随伴しているため、両者の関係性を検証することはできない。今後同様の障害を呈する症例を発見し、詳細に検討することで、何らかの示唆が得られる可能性があると思われる。

3. 病巣との関係

本例の病巣は、CT上両側性で、右側は頭頂-側頭皮質と前頭葉皮質下、左側は頭頂領域に低吸収域を認め、SPECTでも複数領域の血流低下を認めている。そのため、本例の呈した障害はこれらの複合した病変による偶発的な現象であった可能性もある。しかし、現症として左半球病変による症状は呈していないこと、上頭頂小葉病変で生じる可能性が高い視覚運動失調も認めなかったこと、観察された障害は高次感覚障害、拙劣、感覚消去、

両手動作時の左手の障害のみであったことを考えると、本例の障害を生じさせた主たる病巣は中心後回と下頭頂小葉を中心とする右頭頂葉領域であると考えられる。しかし、明らかな半側空間無視、半身無視は認めていない。

Bartolomeoら(2007)、Doricchiら(2008)は、半側空間無視を脳内ネットワークの離断症候群として再考し、皮質下線維束の重要性を強調している。彼らは、皮質領域に生じた病変では、その領域そのものと、線維連絡のある遠隔皮質の機能のみが障害されるが、皮質下病変では密に隣り合った線維束まで影響を受けるため、その線維と連絡のある皮質領域すべての機能障害を引き起こすこととなり、結果としてより重篤な障害を呈するとしている。本例の右頭頂病変は皮質に限局していたため、左側への注意の障害が比較的軽度で、運動と感覚を統合する頭頂葉の機能の中でも、体性感覚に関連した障害だけが顕著に発現した可能性が考えられる。

頭頂葉後方に病変を有し、触覚性の消去現象を呈した症例では、両側同時刺激時も病巣側の一次感覚領域の賦活があることがfMRIで確認されている(Kobayashiら2005, Sarriら2006)。これは、感覚自体は入力されているが、それに対する注意を向ける機構が頭頂葉後方にあることを示している。本例ではおそらく、頭頂葉後方病変により、物体の弁別や認知、それに関わる運動感覚の処理そのものの障害も存在していたが、体性感覚に対する注意も同様に障害されていた可能性がある。本例においては、両者が脳内でどのように処理されていたのかは明らかではない。今後、頭頂葉損傷例のさらなる神経心理学的検討と脳機能画像研究により、これらの脳内メカニズムが解明されることを期待したい。

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Abstract

Moving but not Using
— a case with missing object due to inattention to moving left hand during
bimanual movements —

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We reported a unique patient who showed inattention to the left hand during bimanual movements following a right parietal lobe lesion despite absence of unilateral neglect and motor extinction. The patient was a man in his late forties who suffered from cerebral infarction at watershed area of the right middle and posterior cerebral arteries, which was followed by subsequent subarachnoid hemorrhage secondary to a ruptured right internal carotid artery aneurysm. Eight months after the onset, neuropsychological examination disclosed that he had left side visual/auditory/tactile extinction, left hand clumsiness, and impairments of higher somatosensory functions including two-point discrimination and stereognosis, while his touch, pain, temperature and position senses on the left hand were intact. The patient presented with a unique failure on his left hand during bimanual movements despite absence of unilateral neglect and motor extinction. Although he performed as if his left hand could manipulate an object, the left hand caught only the air and missed the object. Re-examination following 4 years demonstrated that higher somatosensory disturbances and left hand clumsiness remained unchanged. However, his left hand movements during bimanual activities improved and multimodal extinctions dissolved as well. Although limb-kinetic apraxia following a deficit in the higher order sensory system is well known, there has been no report that the apraxia coincided with deterioration of contralesional hand clumsiness during bimanual activities. We conclude that his multimodal extinctions affected bimanual movements. Furthermore, we suggest that his unique left hand failure is accounted by inattention to somatosensory information that could arise intrinsically or spontaneously within active and voluntary bimanual movements, resulting from lesions involving the right parietal lobe posterior to primary sensory area.

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