Original Article

Internal Tempo during the Interictal Period in Patients with Temporal Lobe Epilepsy: Dependence on the Laterality of Epileptiform Discharges

Masanori Saito¹⁾

¹Department of Psychiatry, Kitasato University School of Medicine, Kanagawa, Japan

Key words: Temporal lobe epilepsy, interictal epileptiform discharge, laterality, time estimation

Accepted May 22, 2014 ; Published online August 13, 2014

Abstract

Purpose: To investigate the internal tempo of passage of time in patients with temporal lobe epilepsy (TLE), and to assess possible dependence on the laterality of interictal epileptiform discharges (IEDs).

Methods: A verbal estimation task was administered to 30 right-handed patients with TLE in whom unilateral IEDs were repeatedly observed on interictal scalp electroencephalogram.

Results: Patients with IEDs on the right side showed a significantly longer subjective duration of one minute than did patients with IEDs on the left.

Discussion: IEDs on the non-dominant side may interfere with the activities of the supratemporal gyrus on the ipsilateral side during mental counting. However, the locus and nature of the internal clock that generates internal tempo remain unknown.

Introduction

Distortion of the perception of time is a form of disturbance in the internal tempo of time passage, and may occur during psychic seizures and auras [1]. Because the temporal lobes are thought to be involved in generating distortion of sense of time [2, 3], the temporal lobes may be involved in the generation or regulation of internal tempo during interictal periods. However, little is known on how interictal epileptiform discharges (IEDs)—as opposed to seizure discharges—affect the sense of time.

Prospective time estimation may reflect the internal tempo of passage of time [4]. Using this method, key data was obtained suggesting that the laterality (dominant or non-dominant side) of IEDs recorded at temporal lobe electrodes on scalp electroencephalogram (EEG) may affect the internal tempo differently.

Methods

Subjects

Patients with epilepsy who visited the Neuropsychiatric Center of Kitasato University East Hospital were screened. The diagnosis of epileptic syndromes was based on the patient's clinical history, seizure semi-ology, serial interictal electroencephalography (EEG), and magnetic resonance imaging (MRI) workup. Psychopathological phenomena were screened using the Mini International Neuropsychiatric Interview (MINI) [5]. Patients over 60 years of age were additional-

ly assessed using the revised version of the Hasegawa Dementia Scale (HDS-R).

Of 512 patients with epilepsy who regularly visited our center, 121 were diagnosed with temporal lobe epilepsy (TLE) based on seizure symptoms [6] and detection of IEDs over the anterior temporal or mid-temporal lobe. Of these patients with TLE, 47 showed IEDs on only one side in the two most recent consecutive EEG recordings. Among them, 17 patients were excluded because of marked psychopathological symptoms in 11 (eight had mental retardation, two had psychotic symptoms, and one had manic episodes), left-handedness in three, and refusal to participate in three. The remaining 30 patients (17 males and 13 females; age, 22.3–75.2 years; all right-handed) were enrolled in this study. In these 30 patients, the most recent EEGs were recorded 23.5 ± 67.4 days (-91 to 168 days) before the first verbal estimation task (described below) was administered. Among the 30 patients, 16 had IEDs on the left side only (the peak of distribution of interictal spikes or sharp waves was located at the F7 or T3 electrode), and the remaining 14 had IEDs on the right side only (the peak was at either the F8 or T4 electrode).

Of the 16 patients in whom IEDs were detected on the left side only, three had left temporal lesions (hippocampal sclerosis, a history of brain contusion, or atrophy). On the other hand, of 14 patients in whom IEDs were detected on the right side, only one had right hippocampal sclerosis. The remaining 26 patients showed no lesion on MRI. The sex ra-

tio, age, duration of disease, the frequency of all seizures including aura, and the frequency of alpha rhythm in the two groups are shown in Table 1. None of the patients had familial TLE.

Informed Consent

All subjects were fully informed of the content of this study and provided written consent prior to enrollment. All the procedures in this study were approved by the Ethical Committee of Kitasato University School of Medicine.

Assessment of Hand Preference

Hand preference was assessed using a 13-item questionnaire, adapted from Chapman and Chapman [7] for the average Japanese lifestyle. This questionnaire requires the subjects to indicate which hand they usually use for the following actions: drawing, writing, using a bottle opener, throwing, using a hammer, using a toothbrush, using a screwdriver, using an eraser on paper, using a racket, using scissors, holding a match when striking it, stirring a can of fluid, and using chopsticks. Each item was scored as “1” for right, “2” for either, or “3” for left. Thus, the total score ranged between 13 (strongly right-handed) and 39 (strongly left-handed). Patients who scored between 13 and 17 were classified as right-handed, according to the criteria described by Nalcaci et al. [8].

Task

A verbal estimation task [4] was adminis-

tered. First, all subjects were shown a digital watch, which provided the same counting frequency for all subjects to model. The subjects were then requested to count to 60 silently, at a rate of one count per second. Some subjects repeated this task one to six months after the first trial.

Statistical Analyses

All the clinical data and duration of the subjective one-minute counting task were stored and analyzed using SPSS 13.0J. A non-parametric test (Kruskal-Wallis) was used to examine the relationship of the subjective one-minute duration with the side of epileptogenic focus and sex. Spearman rank correlation coefficient was used to assess the correlation between the subjective one-minute duration and age, duration of disease, or frequency of recent seizures. The test-retest reproducibility was also assessed using the Spearman coefficient. Regression analyses were conducted to identify factors that affect the subjective one-minute duration. *P* values were calculated using the Monte Carlo method.

Results

Table 1 shows the IED laterality, age, sex, aura symptoms, medication, and subjective one-minute duration. Two patients, a 71.7 year-old man and a 41.9 year-old woman, reported nausea as aura that was not localized to any part of the body.

Eleven of 30 patients refused to perform a retest, mainly because they thought that they could not perform as accurately as requested

by the investigator. None of the antiepileptic drugs prescribed to the patients correlated significantly with performance on the verbal estimation task.

As shown in Table 2, the subjective one-minute duration was significantly longer in patients with right temporal IEDs than in those with left temporal IEDs (Kruskal-Wallis test, $p = 0.038$). No sex difference in the subjective one-minute duration was observed (Kruskal-Wallis, $p = 0.530$). Age (Spearman rank correlation, $r = -0.167$; $p = 0.379$), disease duration ($r = -0.090$, $p = 0.635$), and recent seizure frequency ($r = -0.039$, $p = 0.839$) did not correlate significantly with the subjective one-minute duration.

In a regression analysis using the polytomous universal model, a significant model was identified in which the subjective one-minute duration was a variable and laterality of the epileptogenic focus was a factor (chi square = 4.769, $df = 1$, $p = 0.029$). No significant model was obtained when sex and/or age were added as cofactors. The test-retest reproducibility of the subjective one-minute counting results was sufficient ($n = 25$, Spearman, $r = 0.485$, $p = 0.014$).

Discussion

Simmel and Counts [9] conducted a seminal study on estimating perceived temporal intervals in patients with TLE. By comparing the accuracy of estimations of various time spans (0.5, 1, 2, 5, 15, 30 and 60 min) in patients with TLE (before and after temporal

lobectomy), patients with neurosis and normal subjects, they found no significant differences in time estimation among the different groups and concluded that an anterior temporal lobectomy does not affect time estimation. However, the question of whether time estimation was influenced by the laterality of the epileptogenic foci or IEDs in patients with TLE remained unanswered.

It is of special interest to know whether aura, if present, affects the results. Two patients with IEDs on the right side, a 41.2 year-old man and a 41.9 year-old woman, reported that they occasionally felt that time passed slowly during auras. Although their subjective one-minute duration seems to be prolonged, the results obtained from only two persons cannot be generalized. In fact, some other patients showed even more prolonged estimation.

The present data suggests that the subjective one-minute duration differs in patients with TLE according to the laterality of IEDs. Laterality appears to be the only significant factor. The subjective one-minute duration was longer among patients with right-sided (non-dominant) IEDs. However, whether the laterality of the epileptogenic focus or the laterality of the IEDs affects the subjective one-minute duration could not be determined. The reasons are (1) the laterality of IEDs on daytime EEGs sometimes differed from the laterality of ictal onset [10], and (2) the side of ictal onset was confirmed to be ipsilateral to interictal IEDs in only some patients (eight with left-sided IEDs and six with right-sided

IEDs).

Verbal estimation of a one-minute span may become more precise upon retesting. As shown in Tables 1 and 2, both groups seemed to estimate more accurately on retest than in the first trial, even though the test-retest intervals were more than one month. A previous study reported that repetition effect was observed for verbal estimates of intervals ranging from 8 to 54 s repeated over several months, and concluded that the effect was more similar to habituation than to sensory adaptation [11]. Therefore, the patients who performed the one-minute task in the present study could possibly have habituated. However, the precise reason why the laterality of IEDs affected the performance of only the first one-minute task remains uncertain.

The task employed in this study partly resembles the “Continuation (C)” conditions of Rao et al.’s study [12], in which healthy subjects are requested to continue to tap their index finger after the pacing tones are discontinued. In the study of Rao et al. [12] using functional magnetic resonance imaging, “C” condition produced equivalent activation within various regions, including the right superior temporal gyrus and the right inferior frontal gyrus, which are functionally interconnected with the auditory cortex. Taken together, these findings suggest that IEDs detected over the non-dominant temporal lobe may interfere with the activities of the superior temporal gyrus on the ipsilateral side during mental counting.

The laterality of the TLE focus affects the

Wechsler intelligence factors [13]; while left mesial TLE is associated with deficits in verbal intelligence, right mesial TLE is related to nonverbal intelligence. Although “a verbal estimation task” was used in the present study, it remains unclear whether the data reflects purely the “verbal” aspect of internal tempo.

The present data does not provide any direct evidence for the existence of an internal clock. Although the task differs from that used in the present study, Conditt and Mussa-Ivaldi [14] showed that time and time-dependent dynamics are not explicitly represented within the neural structures that are responsible for motor adaptation. The anatomical identity of the internal clock that generates internal tempo remains uncertain.

Due to the methodological limitations of this study, it was not possible to classify the subjects into subgroups using, for example, the 1989 ILAE classification (amygdalo-hippocampal seizures or lateral temporal seizures) [15], or the classification of whether seizure onset was limited to medial or lateral structures [6]. Such classification would be helpful in clarifying the relation between internal tempo and semiology in the future.

Another limitation of this study is that the detailed cognitive status of each patient, including intelligence and memory performance, was not determined. Although all patients had undergone cognitive screening processes, whether the cognitive status differs between patients with IEDs on the right side and those with IEDs on the left is not known.

Table 1. Patient profile and subjective one-minute duration

Side of IED	Age	Sex	Perceived Content of Aura	Medication(daily dose in mg)	Subjective one minute (sec)	Subjective one minute-retest (sec)
Left	28.2	M	None	CBZ(400),ZNS(200)	37.2	
Left	29.2	M	Epigastric sensation	PHT(250)	72.1	63.1
Left	37.2	M	Faint	PRM(750)	67.0	68.8
Left	44.7	M	None	CBZ(800)	103.2	65.2
Left	46.7	M	None	CBZ(1000),AZA(250)	51.1	49.9
Left	56.5	M	Fungus-like smell, Happy feeling	PHT(250),VPA(400)	47.0	
Left	67.0	M	None	VPA(1200)	23.2	
Left	71.7	M	Nausea	CBZ(600),PRM(450)	37.7	59.5
Left	25.1	F	Faint	CBZ(400)	54.9	
Left	28.5	F	Difficulty in hearing speech	None	73.2	49.4
Left	44.2	F	None	CBZ(800),VPA(1400),PRM(700)	36.8	
Left	48.8	F	Faint, Musical hallucination	CZP(0.5)	100.2	52.5
Left	54.3	F	Faint	PHT(150),CBZ(1200)	38.1	
Left	55.4	F	None	PHT(300),VPA(1200),PB(100)	40.4	78.7
Left	56.2	F	Somewhat strange feeling	PHT(220),PB(120)	69.7	84.9
Left	67.4	F	None	PHT(300),PB(100)	24.9	22.3
Right	22.3	M	None	CBZ(200)	65.3	
Right	35.3	M	Epigastric sensation	PHT(300),VPA(1600),GBP(2400)	71.8	65.3
Right	40.4	M	Fear, Visual hallucination	VPA(1200),ZNS(200),CLB(7.5)	91.4	
Right	41.0	M	Palpitation	VPA(1200)	79.1	65.4
Right	41.2	M	Slow time passage, Loneliness	PHT(300),CBZ(800),ZNS(100),GBP(2400)	74.1	68.3
Right	47.1	M	Dizzy strange feeling	PB(140)	52.7	37.0
Right	50.4	M	None	PHT(225),CBZ(900),AZA(750),ZNS(300)	54.4	
Right	52.7	M	None	PHT(200)	92.3	63.5
Right	75.2	M	None	PHT(150),CBZ(600),PB(150),CLB(20)	89.5	72.0
Right	41.9	F	Nausea, Slow time passage(rare)	CZP(1.5)	65.3	
Right	50.0	F	None	CBZ(800),ZNS(100),CLB(10)	45.8	63.7
Right	51.7	F	Epigastric sensation	PHT(270),CBZ(600)	43.3	32.9
Right	58.4	F	Chest sensation (warm, ascending)	PHT(100),CBZ(400)	92.2	64.6
Right	65.5	F	Fear	PHT(250),CBZ(1000),CZP(4)	94.8	

Table 2. Results of statistical analyses on two groups

Side of interictal epileptiform discharge	Left	Right	p value (Kruskal-Wallis)
Number of Patients	16 (8 males, 8 females)	14 (9 males, 5 females)	
Age (mean±SD, years)	47.56±14.90	48.07±13.06	0.92
Duration of disease (mean±SD, years)	24.1±14.85	25.21±13.22	0.83
Seizure frequency (mean±SD, times/month)	7.2±13.2	1.6±2.6	0.72
Frequency of alpha rhythm (mean±SD, Hz)	9.4±1.1	8.8±1.3	0.20
Subjective one minute duration (mean±SD, sec)	54.79±24.21	72.29±18.31	0.038
Subjective one minute duration, retest (mean±SD, sec)	59.43±17.55	59.19±14.03	0.97

References

- [1] Williams D. The structure of emotions reflected in epileptic experiences. *Brain* 1956;79:29-67.
- [2] Mullan S, Penfield W. Illusion of comparative interpretation and emotion. *AMA Arch Neurol Psychiatry* 1959; 81:269-284.
- [3] Hara S, Ryu R, Hara T. A case of distortion of time sense with right (non-dominant) temporal focus. *Seishin Igaku* 1991; 33: 53-58. (in Japanese)
- [4] Kinsbourne M, Hicks RE. The extended present: Evidence from time estimation by amnesics and normals. In: Vallar G, Shallice T (eds), *Neuropsychological impairments of short-term memory*. Cambridge University Press 1990, Cambridge, pp319-329.
- [5] Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry*. 1998;59 Suppl 20:22-33.
- [6] Maillard L, Vignal J-P, Gavaret M, Guye M, Biraben A, McGonigal A, Chauvel P, Bartolomei F. Semiologic and electrophysiologic correlations in temporal lobe seizure subtypes. *Epilepsia* 2004;45:1590-9.
- [7] Chapman LJ, Chapman JP. The measurement of handedness. *Brain Cogn*. 1987;6:175-183.
- [8] Nalcaci E, Kalaycioglu C, Cicek M, Genc Y. The relationship between handedness and fine motor performance. *Cortex* 2001;37:493-500.
- [9] Simmel ML, Counts S. Clinical and psychological results of anterior temporal lobectomy in patients with psychomotor epilepsy. In: Baldwin M, Bailey P (eds), *Temporal lobe epilepsy*. Charles C Thomas Publisher 1958, Springfield, Illinois, pp530-550.
- [10] Malow BA, Selwa LM, Ross D, Aldrich MS. Lateralizing value of ictal spikes on overnight sleep-EEG studies in temporal lobe epilepsy. *Epilepsia*, 1999;40:1587-1592.
- [11] Hicks RE, Allen DA. The repetition effect in judgments of temporal duration across minutes, days, and months. *Am J Psychol* 1979;92:323-333.
- [12] Rao SM, Harrington DL, Haaland KY, Bobholz JA, Cox RW, Binder JR. Distributed neural systems underlying the timing of movements. *J Neurosci* 1997;17:5528-5535.
- [13] Kim H, Yi S, Son EI, Kim J. Differential effects of left versus right mesial temporal lobe epilepsy on Wechsler intelligence factors. *Neuropsychology* 2003;17:556-65.
- [14] Conditt MA, Mussa-Ivaldi FA. Central representation of time during motor learning. *Proc Natl Acad Sci USA* 1999;96:11625-11630.

- [15] Commission on Classification and Terminology of ILAE. Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia* 1989;30:389-399.