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Clinical Study

# Effects of levetiracetam on mu rhythm in persons with epilepsy

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ABSTRACT

Mu rhythm can be suppressed by movements, the so called event-related desynchronization (ERD). Levetiracetam (LEV) is a newer type of antiepileptic drug. A previous study reported that LEV might enhance mu rhythm and caused mu status in one subject. The main purpose of this study was to investigate the effects of LEV on EEG frequency contents and ERD. Seventeen patients with epileptic foci outside the Rolandic area were recruited. The following studies were performed before and after chronically taking LEV. An electroencephalogram (EEG) with 10 minutes of resting state and 5 minutes covering 10 right thumb movements were recorded. Reaction time was evaluated with a simple visual reaction time test. EEG data were analyzed by S-transformation and relative band powers were calculated. The results showed that the relative powers of theta, alpha and beta band in frontal (F3 and F4) and occipital (O1 and O2) leads and mu band in the centro-parietal (C3, C4, P3 and P4) leads were not changed by chronically taking LEV. No mu status was observed in any subject. However, the mean group ERD was enhanced at C3, Cz and P4 leads. Reaction time was similar before and after taking LEV. In conclusion, chronically taking LEV did not change the frequency contents of EEG and did not cause drowsiness, but enhanced ERD. The results suggest that chronically taking medication, such as LEV, is a plausible method to broaden the applicability of ERD-based brain-computer interfaces.



## 1. Introduction

Mu rhythm is an alpha-range electroencephalographic (EEG) activity recorded at the Rolandic area from the scalp when the subject is in a relaxed and eye-opened state, and is suppressed by movements of the contralateral limbs, especially the thumb.[1] The suppression is called event-related desynchronization (ERD)[2], because it is believed that the motor attempt disrupts the synchronization of cortical cells and causes the suppression of mu rhythm. That motor imagination without actual movement also causes suppression of mu rhythm[3] implies that ERD can be produced by patients with motor deficits but a lesion is outside the cerebral cortex; for example, in the white matter or spinal cord. Many brain-computer interface (BCI) systems,[4–6] which aim to build an artificial connection between the human brain and the environment, take the advantage of this property and utilize mu rhythm as the control source. We have also developed such a system.[7] However, there are some practical difficulties with using ERD. Mu rhythm is more prominent in adolescents, is visually detectable in only <10% of adults[8] and is not detectable even after extensive signal processing in 10% of adults. In addition, the physiological wax-and-wane time course, similar to that observed in alpha rhythm, makes the detection of mu rhythm more difficult, further limiting the applicability of the mu-based BCI systems. Mu rhythm is more visible in many pathological conditions, but only a few physiological factors enhance mu rhythm, including light drowsiness, ocular motility[8] and paucity of motor drive. Although biofeedback training of subjects may increase the detectability of mu rhythm,[9] the training process itself is rather time consuming.

Levetiracetam (LEV) is one of the newer antiepileptic drugs (AED).[10] Since its approval for clinical use in 1999 in the USA, LEV has become widely used and is effective in partial and generalized epilepsy syndromes. Its advantages include multiple antiepileptic mechanisms and linear pharmacokinetics. Side effects include somnolence, dizziness, headache, diplopia and pruritus.[10,11] One study reported that chronic use of LEV induced mu-status, such as continuous mu wave, in a person with epilepsy in light drowsiness.[12] If this observation can be confirmed as universal, LEV or related drugs, such as piracetam, may be used to enhance mu rhythm and broaden the applicability of BCI. To our knowledge, there is no drug proven to enhance mu wave *per se*, without indirectly doing so through associated drowsiness. The

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main purpose of this study is to investigate the chronic effects of LEV on mu rhythm and to evaluate whether LEV could be a candidate drug that can improve ERD detection.

## 2. Methods

### 2.1. Participants

The inclusion criteria for the subjects included: (i) having partial epilepsy without epileptic foci in the Rolandic area, (ii) not using LEV before this study and needing to add an additional AED for seizure control, (iii) being aged between 20 years and 60 years old, and (iv) having a clear consciousness and being willing to cooperate. Patients with complex partial seizure due to seizure foci at the mesial temporal area were preferred and patients with cortical lesions were avoided. The reason that we chose the persons with epilepsy as the study group was solely ethical, not theoretical. We assumed that the response of mu rhythm to LEV in these patients was identical to that in a general population. The study protocol was approved by the National Cheng Kung University Hospital ethics committee with regard to human subject study. Before the experiment began, the purpose, the potential hazards and the experimental procedures were fully explained to each subject. All participants signed written informed consent forms.

### 2.2. Experimental setup and procedure

In a standard room used for clinical electrophysiological study, scalp EEG data were recorded with a digital EEG machine (Profile, Medelec, Oxford Instruments, Surrey, England) through standard Ag–AgCl cup electrodes at a sampling rate of 256 Hz and an amplification of 10,000. A monopolar montage of 21 channels (19 EEG, one electrocardiography and one electromyography [EMG]), with the average serving as the reference, was adopted throughout the study. The surface EMG channel was used to record the movements of thumb abductors.

Two sessions of EEG examination were performed, one before and the other after taking LEV. After the completion of the first EEG session, the patients started to take LEV. The dosage was titrated up at a rate of 500 mg per week until the daily dose was 2000 mg (1000 mg twice daily) and the final dosage was maintained for at least 4 weeks. The second EEG session was performed afterwards. Most patients had their second EEG session 12 weeks after the first session. Both EEG sessions were performed by the same technician in the morning between 8 a.m. and 9 a.m. On the day of the second EEG session, LEV was taken 30 minutes before the EEG examination.

For every session involving an EEG examination, each patient, lying in a bed-chair, was asked to stay relaxed, maintain clear consciousness and to blink naturally during the first 10 minutes. The purpose of this section was to record EEG during a resting state. Then, over the next 5 minutes, the subject was asked to quickly swing their right thumb up and relax once after hearing a cue, which was given verbally by the examiner. The cues were given at intervals of approximately 20 s to 30 s to prevent patients from expecting the cue. In total, 10 cues were given in a session. The purpose of this section was to evaluate ERD.[13] The last section was the reaction time (RT) test. A simple visual RT test as an indicator of drowsiness was performed with the software, Presentation (www.neurobs.com), on a laptop computer. The subject was instructed to push the left mouse button with the right hand when a white rectangle ($15\ cm^2 \times 13\ cm^2$) appeared on the computer screen. There was no warning signal before the appearance of the white rectangle. The RT was defined as the average of ten test trials.

### 2.3. Data processing

The initial 10 minutes of EEG data was first visually inspected and a contiguous EEG data of 8 minutes was chosen for frequency domain analyses. This section represented the resting background state without thumb movements. The purpose of this section was to test whether LEV changed background activity or the proportion of different rhythms (such as theta, alpha and beta). The next 5 minutes involved the thumb movements. The purpose of this second section was to test specifically whether LEV affected ERD. The EMG channel was first processed by the standard algorithm to obtain an EMG envelop and, then, EEG segments of 4 s centered on the time of the EMG peak were collected.

For the frequency domain analyses, discrete S-transformation[14,15] was adopted (Equations 1 and 2):

$$S[j,n] = \sum_{m=0}^{N-1} F[m+n] \cdot e^{-2\pi^2 m^2/n^2} \cdot e^{i2\pi mj/N} \quad n \neq 0 \tag{1}$$

**Table 1**
Demographic characteristics and data on the effects of levetiracetam in persons with epilepsy

| Patient no. | Age (year) | Sex | Sz year (year) | Sz focus by EEG[a] | Brain imaging | AED before LEV | Improvement by LEV |
|---|---|---|---|---|---|---|---|
| 1 | 53 | F | 7 | S2, Fp2F4 | Normal | CBZ | Y |
| 2 | 41 | F | 19 | S1, S2 | Normal | VPA, LTG | Y |
| 3 | 35 | M | 35 | Fp1F3, S2, Fp2F4 | Normal | CBZ, LTG | Y |
| 4 | 55 | F | 19 | S1, S2 | Normal | CBZ | N |
| 5 | 58 | M | 39 | S1 | L FT EM | CBZ | Y |
| 6 | 50 | M | 39 | S2 | R MTS | CBZ, VPA | N |
| 7 | 30 | F | 26 | S1, S2 | L MTS | CBZ, TPM | Y |
| 8 | 28 | M | 22 | T4T6 | R F ESS | CBZ, LTG | N |
| 9 | 48 | F | 36 | S1, S2 | Normal | CBZ | N |
| 10 | 28 | F | 20 | F3, F4 | Normal | LTG | N |
| 11 | 23 | F | 20 | S1, S2 | Cerebellar atrophy | CBZ, TPM, VGB | N |
| 12 | 26 | F | 12 | S1 | L MTS | CBZ | N |
| 13 | 25 | M | 14 | F7 | Normal | CBZ, LTG | Y |
| 14 | 30 | F | 20 | S1, S2 | Normal | CBZ, PHB | Y |
| 15 | 44 | F | 11 | S1 | L BG & F EM | CBZ, VPA, TPM, | Y |
| 16 | 51 | M | 23 | T3T5 | L MTS | CBZ | Y |
| 17 | 28 | M | 18 | T6 | Normal | LTG, VPA | N |

[a] Abbreviations refer to standardized system of nomenclature for EEG electrodes[1] except S1 = left sphenoidal lead, S2 = right sphenoidal lead. AED = antiepileptic drug, BG = basal ganglia, CBZ = carbamazepine, EEG = electroencephalography, EM = encephalomalacia, ESS = enlarged subarachnoid space, F = frontal, FT = fronto-temporal, L = left, LEV = levetiracetam, LTG = lamotrigine, MTS = mesial temporal sclerosis, N = no, PHB = phenobarbital, R = right, Sz = seizure, S1 = left sphenoidal lead, S2 = right sphenoidal lead, TPM = topiramate, VGB = vigabatrin, VPA = valproic acid, Y = yes.