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Decreased bimanual coordination is related to abnormal regional slow wave activity in epileptic patients

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ABSTRACT

Electroencephalographic slow wave activity (SWA, 1-4 Hz) in non-deep sleep has been classified as a "pathological state" of the neural tissue. Decreased bimanual coordination and slow wave activity can be observed in brain diseases like stroke and neurological degenerative disorders. We set out to investigate the relation of decreased coordination of spontaneous hand movements to regional slow wave activity in epileptic patients without motor deficits. In 153 patients with focal or generalized epileptic seizures we measured the occurrence of regional SWA by means of 24-hour video-electroencephalography (EEG) recordings and the spontaneous hand movements using actiwatches on either wrist. It was found that the coordination of spontaneous hand movements of daily living was impaired in patients with regional slow wave activity as compared with patients without regional slow wave activity. In contrast, the amount of movement activity did not differ between the two hands. Also, there were no differences in patients with epileptic discharges as compared with patients without epileptic discharges. These findings indicated that decreased spontaneous bimanual coordination is related to regional slow wave activity but not to decreased movement generation or the presence of epileptic discharges.

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KEYWORDS: electroencephalogram, bimanual coordination, epileptic discharges, slow wave activity.

INTRODUCTION

Bilateral arm movements play an important role in daily activities including the use of fork and knife for eating, opening boxes, and lacing shoes [1]. Usually the actions of the hands are highly coordinated with one hand leading the action in a task-dependent manner [2]. Following stroke or in neurodegenerative disorders, bimanual coordination is often profoundly impaired [3-6]. However, similarly to the typical neurological examination, the studies on bimanual coordination employed comparatively simple movement tasks and these tasks were performed on an instructing command [2, 7]. These relatively simple schematic tasks may not reflect the coupling of spontaneous bimanual movements as they occur in daily living. In fact, spontaneous hand movements have enjoyed little interest in clinical neurology, although dedicated measuring devices allowing continuous movement activity, such as the so-called actiwatches, have been marketed recently and shown to have a high potential for identifying even subtle abnormalities of hand and arm movements [8].

Slow wave rhythm is a normal pattern in electroencephalography (EEG) characterizing deep sleep [9]. However in non-deep sleep, slow wave activity (SWA, 1-4 Hz) has been shown to occur in a generalised fashion in patients with mental disorders [10], neurodegenerative disorders [11, 12], toxic and metabolic encephalopathy [13] and patients with seizures [14]. In patients with Alzheimer's disease, the greater slowing of EEG pattern suggested more severe cognitive deficits [15, 16]. Regional SWA reflecting pathological or 'dysfunctional' neural tissue [17, 18] was found to signify structural brain lesions [19-21]. Moreover, regional SWA was described to predict poor functional recovery from stroke [17, 22]. In sum, SWA is considered as a kind of non-epileptiform abnormal discharge despite being non-specific [23, 24].

Regional abnormal SWA and decreased bimanual coordination have been observed in degenerative neurological disorders such as Parkinson's disease [3, 25]. Recently, we reported SWA expression and disturbance of bimanual coordination after stroke [26]. Specifically, it was found that in patients with brain infarcts decreased spontaneous movement activity was indicated by an abnormal interictal EEG pattern, e.g. regional SWA. Here, we wondered if regional SWA may be related to impaired bimanual coordination also in patients with epileptic seizures who had no neurological motor deficit. In this prospective study we investigated the spontaneous movements of the two hands in daily living using actiwatches, whilst simultaneously the EEG was recorded in these patients using the 24-hour video-EEG. We hypothesized that there is a relation between abnormal spontaneous bimanual coordination and regional SWA in epileptic patients that present with no focal neurological deficit.

PATIENTS AND METHODS

Participants

This prospective clinical study was performed in the Centre of Neurology and Neuropsychiatry of the LVR Klinikum Düsseldorf from March 2013 until June 2016. 153 subjects who had focal or generalized epileptic seizures participated in this study. The patients were treated with anti-epileptic drugs according to the treatment guidelines of the International League against Epilepsy [27]. Inclusion criteria were that the participants showed no dysfunction in daily living and no motor deficit or psychiatric illnesses. All patients had monitoring of heart rate, blood pressure, blood oxygen saturation, measurement of body temperature, and testing of blood samples including blood sugar levels. According to the specific status of individuals, the patients received antiepileptic drug treatment with levetiracetam, valproate, lamotrigin, lacosamid or lorazepam. All the patients had brain magnetic resonance imaging (MRI) that was read by neuroradiologists.

Procedures

In addition to a routine 20-channel EEG involving a 5-min episode of hyperventilation, the patients had a 24-hour video-EEG concurrent with actigraphy recordings with actiwatches on both hands. Measurements with the 24-hour video-EEG and actiwatch recordings were identical in all the patients. Informed consent was obtained from each patient before the investigation. The study was approved by the Ethics Committee of the Heinrich-Heine University Düsseldorf (#4206).

EEG data acquisition

EEGs were recorded using a nineteen-channel analogue recorder (Nihon Kohden EEG-1200) according to the international 10-20 system [28] continuously for 24 hours. In addition, a video camera (Nihon Kohden) located on the ceiling above the patient recorded the behavioral data. EEG and video data were recorded in a time-locked fashion. The electrodes were placed using a quantified ruler. The impedances of the electrodes were kept at less than 10 kΩ. Filter settings were set at 0.3-40 Hz. To score sleep stages, two electrooculographic channels were placed laterally to the orbita on each side. The EEG and video data were displayed simultaneously off-line on a personal computer for formal and statistical analysis. Unipolar reference montages (reference electrodes: Cz, average electrode) as well as bipolar montages were used (longitudinal: Fp2-F4, F4-C4, C4-P4, P4-O2; Fp2-F8, F8-T8, T8-P8, P8-O2 (accordingly on the left side) to assess sleep stages, focal SWA, and epileptiform discharges. Following the EEG recording, the sleep and

EEG pattern were evaluated by two reviewers. Only when the two reviewers reached an agreement, the data would be brought into the final statistical analysis. The sleep parameters including sleep latency, total sleep time (TST), wake after sleep onset (WASO), sleep efficiency, and sleep architecture including the proportion of non-rapid eye movement sleep (NREM) and the proportion of rapid eye movement sleep (REM), and EEG pattern including abnormal SWA and interictal epileptiform discharge were assessed from the EEG recordings. In this study, abnormal regional SWA was defined as in [17, 29]. It had to occur in the 1-4 Hz range repeatedly during the waking periods or in the non-deep sleep stage.

Actigraphy

To investigate the spontaneous movement activity of both hands continuously, recordings with actiwatches (Cambridge Neurotechnology, Cambridge, UK; http://camntech.co.uk) were done. These small light-weight devices of the size of a watch were equipped with movement-sensitive sensors that recorded movements in the three dimensions of space. An actiwatch was attached to both lower forearms close to the wrist like a watch to synchronously record the movements of both hands continuously for 24 h. Activity was binned into minutes in which the movement activity was integrated by each device (Actiwatch Activity & Sleep Analysis 5.42, Cambridge Neuro-technology). Before the recording started, the actiwatches were calibrated to have the same sensitivity. Data were analyzed off-line using SPSS Statistics 17.0 (SPSS Inc., 2009) software. The movement artifacts due to nursing were eliminated from the data. The temporal coordination of movements of the two hands was studied using the Spearman's rank correlation coefficient (r_s) of the synchronously recorded movement counts. It was calculated for the entire 24 hours (r_{s24h}), for day time (r_{sd}) and for sleep time (r_{ss}). The relative movement activity of the left hand compared to right hand was calculated using the mean counts of two hands for the entire 24 hours (RMA_{24h}), daytime (RMA_d), and sleep time (RMA_s).

Statistical evaluation

All data were presented with descriptive statistics as means ± standard deviation (SD). Group comparisons of the quantified items were based on the t-test. The Mann-Whitney test was used to assess group differences in numeric variables. All tests were 2-sided with $P < 0.05$ considered statistically significant. Statistical analysis was performed using SPSS Statistics 17.0 (SPSS Inc., 2009).

RESULTS

153 patients with epileptic seizures, aged 41 ± 17 years were included in the study. 34 patients aged 44 ± 6 years had regional SWAs (SWA group), 119 patients aged 40 ± 17 years showed no SWAs (no SWA group) during wakefulness. The neurological status, the sex ratios and ages of the two groups showed no differences (Table 1). Examples of regional SWA are provided in figure 1.

An example of the actigraphic recordings is given in figure 2. It is apparent that activity counts were mostly similar for both hands but there were also discrepancies with more activity in one or the other hand. The main finding was that the patients in the SWA group in comparison with those in the no SWA group showed a significantly lower bimanual coordination (r_s) in day time and in sleep time, and also for the entire 24-hour recording time. In contrast, the two groups did not differ concerning the relative movement activity of the two hands in any of the three recording episodes (Table 1). Thus, the amount of movement activity was similar between the two hands but desynchronized in time. In an additional analysis we found that regional SWA over the left or right hemisphere showed no impact on the relative movement activity of the two hands ($p > 0.05$). In the SWA group, MRI was abnormal in 23 of 34 patients showing the following abnormalities: cerebrovascular disease (n = 11), perinatal hypoxia (n = 2), degenerative cerebral atrophy (n = 3), postencephalitic lesions (n = 3), arachnoidal and choriodal cysts (n = 2), and amygdalohippocampectomy (n = 2).

The sleep parameters including sleep latency, wake after sleep onset, total sleep time, and sleep efficiency were evaluated using the video-EEG data. We found no significance differences in these sleep parameters between the two groups. However, the sleep architecture of the two groups

Table 1. Movement activity and sleep characteristics in the SWA patients and no SWA patients.

	SWA group (n = 34)	No SWA group (n = 119)	*p*
Male: female	17:17	53:66	0.574
Age (years, mean ± SD)	44 ± 6	40 ± 17	0.212
Movement parameters			
r_{s24h} (mean ± SD)	0.734 ± 0.125	0.803 ± 0.091	0.005**
r_{sd} (mean ± SD)	0.675 ± 0.119	0.731 ± 0.115	0.014*
r_{ss} (mean ± SD)	0.672 ± 0.179	0.742 ± 0.146	0.041*
RMA_{24h} (mean ± SD)	1.193 ± 0.652	0.998 ± 0.309	0.101
RMA_d (mean ± SD)	1.193 ± 0.665	0.995 ± 0.323	0.070
RMA_s (mean ± SD)	1.198 ± 0.577	1.084 ± 0.449	0.223
Sleep parameters			
Sleep latency (min, mean ± SD)	24.6 ± 21.0	21.0 ± 18.9	0.350
WASO (min, mean ± SD)	119.9 ± 76.1	100.1 ± 61.5	0.123
TST (min, mean ± SD)	412.2 ± 99.6	413.0 ± 95.6	0.978
Sleep efficiency (%, mean ± SD)	72.9 ± 14.1	77.0 ± 10.9	0.077
Sleep architecture			
NREM (%, mean ± SD)	67.6 ± 12.0	67.7 ± 10.4	0.606
REM (%, mean ± SD)	7.1 ± 4.8	9.1 ± 5.6	0.038*
With epileptic discharge (n)	7	19	0.556

Note: $^{**}p < 0.01$, $^{*}p < 0.05$, r_{s24h} = bimanual Spearman's rank correlation coefficient of 24 hours, r_{sd} = bimanual Spearman's rank correlation coefficient of daytime (24 hours minus the time in bed in the night), r_{ss} = bimanual Spearman's rank correlation coefficient of the night(from sleep onset to sleep end), RMA_{24h}, RMA_d, RMA_s = relative movement activity of the left hand compared to right hand in 24 hours, in daytime and sleep time (from sleep onset to sleep end). WASO = wake after sleep onset, TST = total sleep time, NREM = non-rapid eye movement sleep, REM = rapid eye movement sleep. SD = standard deviation.

showed significant differences in the proportion of REM sleep: the SWA group showed lower proportion of REM sleep. In the SWA group, there were only 7 (20.6%) patients with interictal epileptiform discharge activity.

To investigate the influence of interictal epileptiform discharge activity on spontaneous hand movement, we divided the patients into two groups: one group with epileptiform discharge activity and another group with no epileptiform discharge activity. Both, the bimanual coordination and the relative movement activity between two hands showed no differences between the two groups (Table 2). However, we found differences between the two groups in sleep architecture. In detail, the patients with epileptiform discharges showed a higher percentage of NREM sleep and a decreased percentage of REM sleep (Table 2). These findings in patients with interictal epileptic discharge were different from those findings in patients with abnormal SWAs. Thus, in contrast to regional SWA that showed a prominent impact on the bilateral coordination of spontaneous arm movements, the interictal epileptic discharge affected the sleep architecture, but not the amount and coordination of hand movement activity.

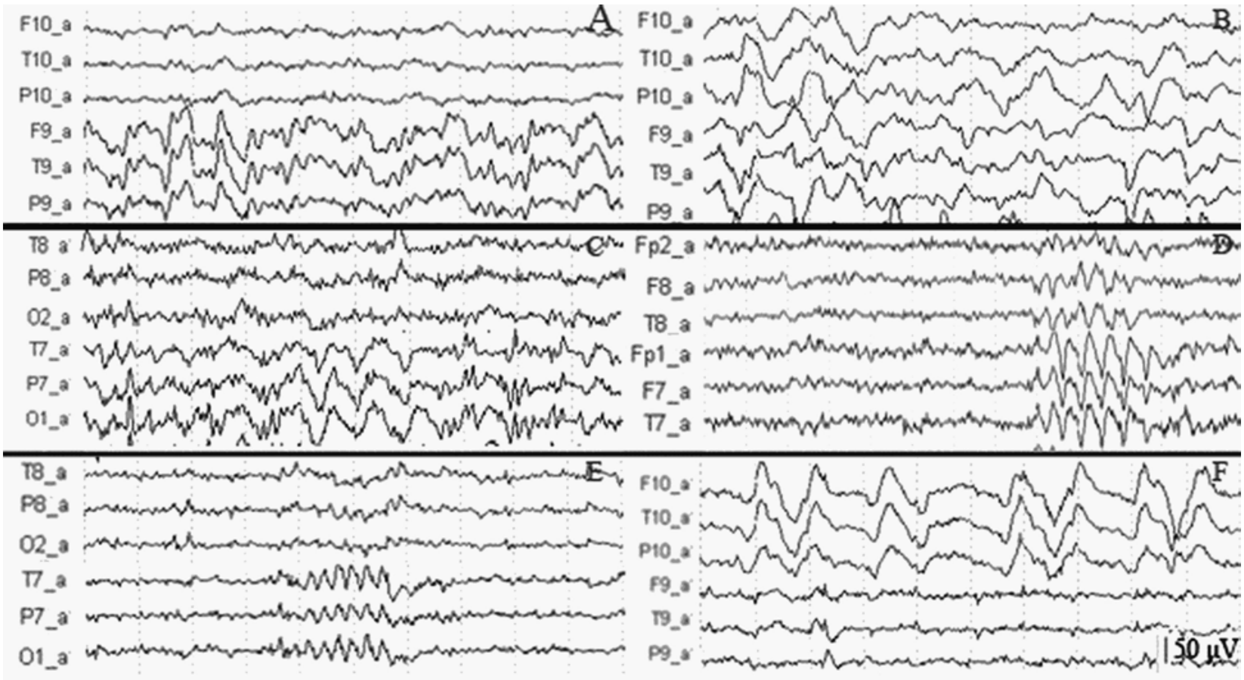

Figure 1. Six examples with typical regional SWA. A-F typical regional SWA is featured with 1-4 Hz asymmetrical and repeated occurrence in non-deep sleep periods. Filters: 0.3-40 Hz.

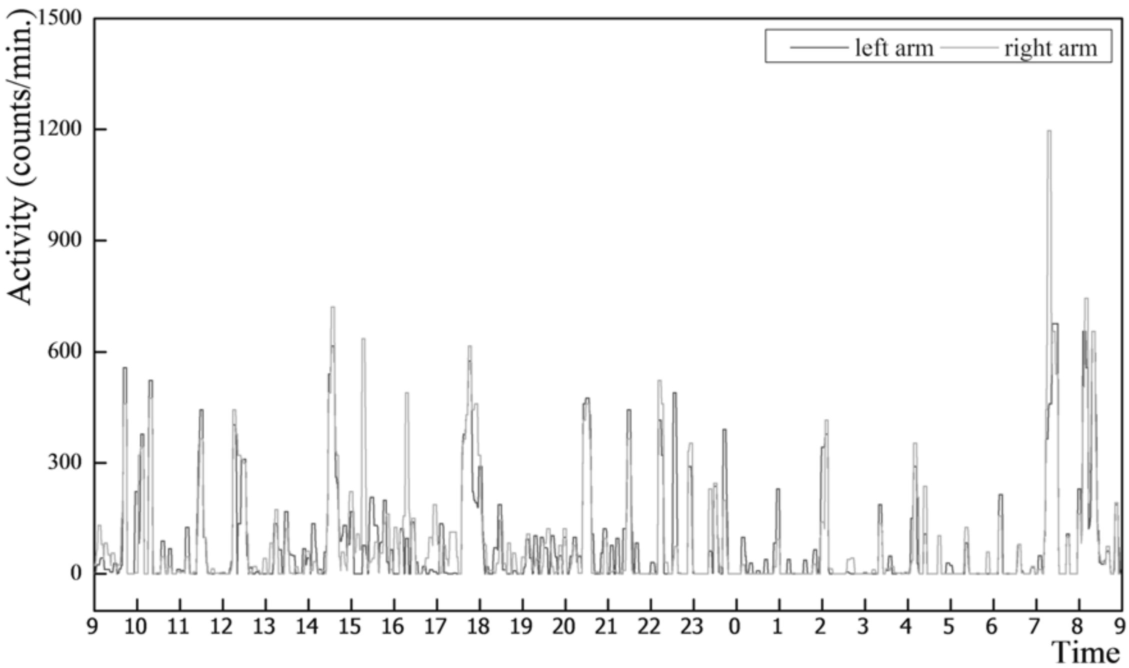

Figure 2. Movement count-time curves of a patient without regional SWA as obtained from bimanual synchronous actigraphy recording. The Spearman's rank correlation coefficient (r_s) between the two hands was calculated by using the activity data obtained by bimanual actigraphy recording. Greater movement differences between the two hands resulted in lower r_s.

Table 2. Movement activity and sleep characteristics in the patients with epileptic discharges compared with patients without epileptic discharges.

	Epileptic discharge group (n = 26)	**No epileptic discharge group (n = 127)**	***p***
Male : female (ratio)	8:18	62:65	0.093
Age (years, mean ± SD)	41 ± 17	41 ± 17	0.870
Movement parameters			
r_{s24h} (mean ± SD)	0.809 ± 0.065	0.784 ± 0.109	0.558
r_{sd} (mean ± SD)	0.748 ± 0.090	0.712 ± 0.122	0.230
r_{ss} (mean ± SD)	0.746 ± 0.127	0.723 ± 0.161	0.699
RMA_{24h} (mean ± SD)	1.034 ± 0.445	1.080 ± 0.229	0.074
RMA_d (mean ± SD)	1.036 ± 0.460	1.086 ± 0.246	0.074
RMA_s (mean ± SD)	1.159 ± 0.325	1.090 ± 0.507	0.109
Sleep parameters			
Sleep latency (min, mean ± SD)	19.2 ± 13.9	22.4 ± 20.3	0.418
WASO (min, mean ± SD)	113.5 ± 58.1	102.6 ± 68.5	0.447
TST (min, mean ± SD)	446.1 ± 78.9	405.7 ± 98.5	0.052
Sleep efficiency (%, mean ± SD)	76.6 ± 10.1	75.9 ± 12.1	0.729
Sleep architecture			
NREM (%, mean ± SD)	71.7 ± 10.2	66.8 ± 10.7	0.002**
REM (%, mean ± SD)	5.6 ± 4.3	9.3 ± 5.5	0.035*

Note: ***p* <0.01, **p* <0.05. The abbreviations are same as in table 1.

DISCUSSION

In the present study, we used 24-hour actigraphy measurements and video-EEG recording to explore the relation of regional SWA and bimanual coordination of spontaneous hand movements in patients suffering from epileptic seizures. The major novel finding was that the patients with regional SWA showed decreased bimanual coordination of spontaneous hand movements employed in activities of daily living. Notably, the decreased coupling of hand movement activity was not related to interictal epileptiform discharges. Moreover, the relative movement activity between the two hands was not significantly different between SWA group and no SWA group. This corresponded to the neurological examination which disclosed that the patients with SWAs had no motor deficit and to the fact that the patients enrolled in the study showed no overt or subclinical motor deficit in daily living. Our findings indicated that the cerebral abnormality in the SWA patients affected the temporal interlimb coordination but not the amount of spontaneous hand movement activity suggesting that focal SWA and interictal epileptiform discharges had different pathological causes. Thus, in accordance with previous studies, regional SWA was a marker of a pathological state rather than of a global process such as aging despite being non-specific [18]. On the contrary, interictal epileptic discharges signified seizure activity in patients with manifest or suspected epilepsy but not a focal lesion of brain tissue. This result might indicate that the EEG is a sensitive tool to demonstrate different categories of brain dysfunction.

It was noted that the majority of patients with abnormal SWAs had abnormalities in MRI, although they exhibited no overt neurological motor deficit. In a previous study, we have found that decreased bimanual coupling was related to the occurrence of abnormal SWA in acute stroke patients [26]. Moreover, the decreased bimanual coordination and increased abnormal SWA was found in neurodegenerative diseases [3, 4, 25]. These findings are not unexpected considering that extensive cortical networks including premotor cortex, parietal cortex, mesial motor cortices, specifically the supplementary motor area, cingulate motor cortex, primary motor cortex, basal ganglia, and cerebellum were found to contribute to bimanual coupling tasks [30-32]. Accordingly, abnormalities involving these areas cause decreased bimanual coordination and abnormal SWA. It should be emphasized that enrolled in the present study were patients with focal or generalized epileptic seizures. There is only very little evidence of motor deficits in patients with seizures. For example, children with generalized epilepsy were reported to show deficits in executive functions and motor coordination [33]. Notably, however, in this study we focused on the coordination of spontaneous movements rather than on forelimb movements performed on command as usually studied in neurology and dedicated motor testing.

In the present study, the novel method of actigraphy was used to explore spontaneous bimanual coordination. By nature, the two hands are used mostly together to execute bimanual movements in daily living [1]. The actiwatches count the activities of both hands synchronously. Thus, when subjects show dysfunction in bimanual coordination, they tend to use two arms in a form of non-synchronized movements. In contrast, there was no decrease of movement activity between the two arms which would reflect a motor deficit. Rather, the Spearman's rank correlation coefficient allowed to quantitatively characterize the coordination of spontaneous hand movements. It should be noted that the actiwatches recorded lifting, lowering and positioning movements as well as rotations of the hand. As they are instrumental for object handling and manipulations which are performed by skilled finger movements, we studied an important indicator of hand use in activities of daily living. This was different from previous simple or schematic tasks that studied bimanual coordination, as those movements were performed on command by the experimenters. To our knowledge our study was the first to directly score the bimanual coordination in daily living in epileptic patients. As the Spearman's coefficient was found to be decreased in the SWA patients, we were able to demonstrate that they exhibited a deficit of synchronization (in-phase and anti-phase movements) in spontaneous hand movements employed in daily living. As the calculation of the Spearman's rank correlation coefficient is straight forward, accelerometry with actiwatches might be used in many more neurological conditions.

CONCLUSION

This study combining actigraphy measurements and video-EEG recordings found that epileptic patients with SWA showed lower movement coordination between two hands than those patients without SWA. This abnormality in spontaneous bilateral hand movements was not due to a neurological motor deficit or related to abnormal interictal epileptic activity.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

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