Brain & Development 41 (2019) 334–340

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Original article

Novel method using Hjorth mobility analysis for diagnosing attention-deficit hyperactivity disorder in girls

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Received 29 September 2018; received in revised form 3 November 2018; accepted 13 November 2018

Abstract

Background: Attention-deficit hyperactivity disorder (ADHD) is a common childhood neuropsychiatric disorder. Diagnosis of ADHD is based on core symptoms or checklists; however, practitioner subjectivity inevitably results in instances of over- or under-diagnosis. Although an elevated theta/beta ratio (TBR) of the electroencephalography (EEG) band has been approved by the Food and Drug Administration as a factor that may be used in diagnosis of ADHD, several studies have reported no significant differences between the TBR of patients with ADHD and controls.

Purpose: In this study, a method was developed based on Hjorth Mobility (M) analysis of EEG to compare patients with ADHD and controls.

Methods: Differences in the presentations of ADHD between boys and girls are well established; therefore, separate investigations are required. The present study enrolled 30 girls with ADHD and 30 age-matched controls.

Results: The results revealed that the control group had significantly higher Hjorth M values in most brain areas in EEG readings compared with the values for the ADHD group. Compared with TBR, our method revealed a greater number of more significant differences between the girls in the ADHD group and the controls. Moreover, our method can produce the higher average sensitivity (0.796), average specificity (0.796), average accuracy (0.792), and average area under the curve of receiver operating characteristic curve (AUC) value (0.885). Therefore, compared with TBR, Hjorth M possessed the better potential for differentiating between girls with ADHD and controls.

Conclusion: The proposed method was more accurate than the TBR in diagnosing ADHD. Therefore, Hjorth M may be a promising tool for differentiating between children with ADHD and controls.

Keywords: ADHD; EEG; TBR; Hjorth M; Girls

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1. Introduction

Attention-deficit hyperactivity disorder (ADHD) is a common childhood developmental condition character-

https://doi.org/10.1016/j.braindev.2018.11.006

ized by behaviorally inappropriate symptoms of inattention and/or hyperactivity–impulsivity [1]. The prevalence of ADHD in school children is 3%–7%, and it is more commonly diagnosed in boys than in girls (reported ratios range between 3:1 and 9:1) [1,2]. Compared with boys with ADHD, girls with ADHD are less hyperactive, more inattentive, and more likely to develop depressive and anxiety disorders [3,4]. Moreover, a study reported that girls with ADHD are relatively likely to demonstrate high emotional reactivity and excessive talking as opposed to excess motor activity [4]. These sex-associated differences suggest that the mechanisms underlying ADHD differ between the sexes. To elucidate sex-dependent characteristics of ADHD, only girls were included in this study.

Diagnosis of ADHD mostly depends on criteria from the Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition) (DSM-V). Some physicians also use checklists as tools for diagnosing ADHD. However, the subjectivity involved in determining criteria or using checklists can lead to over- or under-diagnosis [5,6]. To overcome this problem, some researchers have used quantitative electroencephalography (QEEG) to assist diagnosis. The most consistent finding in initial studies was relatively high absolute power in the theta EEG band in children with ADHD [7–10]. A reduced beta band was also observed in some studies [11,12]. The theta/beta ratio (TBR) was subsequently approved by the Food and Drug Administration (FDA) of United States as a tool for diagnosing ADHD (regulation number: 882.1440) [13]. The TBR represents the ratio of the spectral power in the theta frequency band (4–7 Hz) relative to the power in the beta frequency band (13–21 Hz) and is sometimes measured at a single electrode site (Cz) during rest. However, in recent years, elevated TBR has not been replicated in at least five studies with both children and adults [14–19]. In a cross-sectional analysis, Buyck and Wiersema used logistic regression and reported that the TBR was only 49.2%–54.8% accurate in predicting ADHD in a patient [17], whereas Liechti et al. demonstrated that the TBR was 53% accurate if considered only in terms of diagnostic prediction [18]. Furthermore, in the largest TBR study, no significant differences were observed between 562 children, adolescents, and adults with ADHD compared with 309 controls, although modest heterogeneity and psychiatric comorbidity were attributed to ADHD subtypes [19].

Hjorth parameters were proposed by Hjorth for the quantitative description of EEG when EEG signals are considered as time series [20]. "Hjorth M" represents mobility, which is one Hjorth parameter. Mobility in EEG is defined as the square root of the ratio of activity of the first derivative of the EEG amplitude to the activity of the EEG amplitude in a given period. Hjorth parameters are considered suitable for analyzing nonstationary EEG signals. The parameters have been used in quantitative EEG studies to evaluate driver drowsiness [21], the effect of alcohol on the human brain [22], and the effect of antiepileptic drugs in patients with epilepsy [23]. Because the findings regarding the use of the TBR in patients with ADHD have been inconsistent, Hjorth M values between girls with ADHD and controls were compared in the present study.

2. Materials and methods

2.1. Research participants

We hypothesized that distinct mechanisms underpin ADHD in male and female patients; therefore, the study cohort comprised 42 ADHD females, and 30 girls with inattention type ADHD and 30 age-matched controls were selected for analysis in this study. All of the children were examined by a pediatric neurologist or psychiatrist and received EEG examinations. None of the girls were taking medication at the time of testing. Children with histories of epilepsy, mental retardation, drug abuse, head injury, or psychotic disorders were excluded. Diagnoses of ADHD were made according to the DSM-V criteria. Three ADHD subtypes exist. Depending on presented symptoms, patients are diagnosed with ADHD of an inattentive, hyperactive/impulsive, or combined subtype. Patients diagnosed with the inattentive subtype mainly exhibit inattentive symptoms and few or no hyperactive symptoms; those diagnosed with the hyperactive/impulsive subtype mainly exhibit hyperactive or impulsive symptoms and few or no inattentive symptoms; and those diagnosed with the combined subtype exhibit both inattentive and hyperactive symptoms. In the present study, written informed consent was obtained from a family member or legal guardian for each participant. This study was approved by the Institutional Review Board of the Kaohsiung Medical University Hospital (KMUIRB-SV(I)-20150052).

2.2. EEG recordings

Identical equipment and procedures were used in the EEG recordings for the ADHD and control groups. The patients with ADHD underwent EEG examinations with their eyes closed for 20 min prior to receiving any treatment. The subjects were tested in a quiet, air-conditioned room that contained the person conducting the experiment and the recording equipment. All recordings were made during daylight hours (between 08:00 a.m. and 05:00p.m.). EEG data were digitally obtained using 21 electrodes at a sampling rate of 256 Hz (EBNeuro Mizar 33, Florence, Italy). Amplifier characteristics were bandpass filtered between 0.5 and 60 Hz with 10,000 times gain, and electrodes were arranged based on the International 10–20 system.

2.3. EEG feature extraction

In this study, 18 channels of monopolar montage were adopted for EEG analysis: "FP1," "FP2," "F7," "F3," "FZ," "F4," "F8," "T3," "T5," "T4," "T6," "C3," "C4," "P3," "PZ," "P4," "O1," and "O2." To enable unbiased comparison of the EEG data, the EEG segment of each participant was acquired from artifact-free sections of the corresponding EEG recording conducted when she was awake. For each EEG segment, two feature descriptors, namely Hjorth M and the TBR, were employed for extracting the corresponding features. Hjorth M is used to describe the statistical property of a signal in a time domain, and it is defined as the square root of the ratio of the variance of the first derivative of the signal and that of the signal. Where $\boldsymbol{x}(t)$ is the sample sequence of a channel signal, the corresponding Hjorth M $HjorthM(\boldsymbol{x}(t))$ may be calculated using the following equation:

$$HjorthM(\boldsymbol{x}(\boldsymbol{t})) = \sqrt{\frac{var(\boldsymbol{x}'(t))}{var(\boldsymbol{x}(t))}}$$

where $\boldsymbol{x}'(t)$ is the corresponding first derivative of $\boldsymbol{x}(t)$, and $var(\boldsymbol{x}(t))$ and $var(\boldsymbol{x}'(t))$ are the variances of $\boldsymbol{x}(t)$ and $\boldsymbol{x}'(t)$, respectively. Additionally, the corresponding TBRs, $TBR(\boldsymbol{x}(t))$, are calculated using the following equation:

$$TBR(\boldsymbol{x}(t)) = \frac{RelPow\theta(\boldsymbol{x}(t))}{RelPow\beta(\boldsymbol{x}(t))}$$

where $RelPow\theta(\boldsymbol{x}(t))$ and $RelPow\beta(\boldsymbol{x}(t))$ are the relative power of the $\boldsymbol{x}(t)$ theta and beta bands, respectively. To extract the corresponding features of each channel signal of each EEG segment, values of the two aforementioned feature descriptors were computed in a window-by-window manner. The widow size was set to 5 s. The average of all values of Hjorth M/TBR corresponding to the same channel was then calculated. Finally, an averaged Hjorth M/TBR feature vector with 18 dimensions corresponding to the 18 channels was obtained for each subject.

2.4. Classification analysis

A classification analysis was made for comparing the discriminant power of Hjorth M with that of TBR. For the dataset composed of 60 subjects' averaged feature vectors related to one of descriptor, Hjorth M or TBR, and the corresponding labels (ADHD or Control), it was randomly spilt into a training set and a test set in a size ratio of 9:1. The above splitting of dataset was repeated 20 times and therefore 20 training sets and the corresponding 20 test sets were obtained. Then, a classification model was trained on each training set by the logistic regression with principle component analysis (PCA)-based feature reduction [24]. Moreover, 10-fold cross-validation approach was applied for turning parameters in each model training process. After that, label predictions (ADHD or control) were made on the corresponding test set. The prediction results of each test set were further evaluated by four performance indices, including accuracy, area under the curve of receiver operating characteristic curve (AUC), sensitivity, and specificity. Note that the higher the above indices are, the better the model is. Finally, values of each performance index corresponding to 20 test sets were aggregated by calculating the mean for representing the classification performance of the corresponding dataset.

2.5. Statistical analysis

All statistical analyses were conducted using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA). Data are presented as mean ± standard deviation. A comparison between ADHD and control EEG features was conducted using the two-sample t test, and $p < 0.05$ was considered statistically significant. Cohen's effect size was calculated to compare the classification power between Hjorth M and the TBR.

3. Results

To reduce the confounding effect of different types of ADHD, only ADHD girls with the inattention subtype were enrolled in this study. The mean age of the ADHD group was 7 years, 10 months (± 2 years, 2 months) and that of the control group was 8 years, 1 month (± 2 years, 0 months). No significant difference was evident in the age distributions of the groups.

3.1. Comparison of Hjorth M between the ADHD and control groups

We compared Hjorth M between the ADHD and control groups. All average Hjorth M values, except T3, in different EEG channels were higher in the controls than in the patients with ADHD. Significant differences in average Hjorth M values were identified in the following 12 of the 18 EEG channels: F3 ($p = 0.019$), Fz ($p = 0.041$), F4 ($p = 0.007$), C3 ($p = 0.017$), C4 ($p = 0.011$), T5 ($p = 0.001$), P3 ($p = 0.001$), Pz ($p = 0.004$), P4 ($p = 0.002$), T6 ($p = 0.020$), O1 ($p = 0.001$), and O2 ($p = 0.001$) (Table 1).

3.2. Comparison of TBR between ADHD and control groups

The TBR value in the O1 channel only was significantly different between the ADHD and control groups ($p = 0.040$). However, TBR values in other 17 channels

Table 1
Comparison of Hjorth M between ADHD and control groups in different channels.

Channel	ADHD	Control	p value
FP1	66.380 ± 15.380	72.698 ± 16.202	0.133
FP2	65.845 ± 15.509	72.307 ± 14.902	0.111
F7	67.190 ± 17.797	70.886 ± 13.170	0.372
F3	69.499 ± 16.648	79.901 ± 16.087	0.019*
FZ	59.637 ± 12.605	66.948 ± 13.950	0.041*
F4	69.891 ± 15.444	80.781 ± 14.462	0.007*
F8	67.298 ± 17.272	71.455 ± 13.986	0.318
T3	77.903 ± 26.222	75.730 ± 14.117	0.696
C3	75.196 ± 15.690	85.834 ± 17.387	0.017*
C4	73.917 ± 15.303	85.073 ± 16.788	0.011*
T4	71.667 ± 17.021	78.436 ± 16.877	0.134
T5	66.270 ± 11.805	78.619 ± 15.916	0.001*
P3	67.498 ± 11.846	80.106 ± 16.031	0.001*
PZ	63.983 ± 10.854	73.857 ± 13.925	0.004*
P4	66.514 ± 11.634	78.026 ± 15.228	0.002*
T6	66.590 ± 14.376	75.860 ± 15.043	0.020*
O1	64.366 ± 12.201	77.711 ± 17.328	0.001*
O2	64.633 ± 12.111	77.805 ± 16.699	0.001*

*$p < 0.05$.

in the present study demonstrated no significant difference between ADHD and control groups (Table 2). The results showed that the p values of the Hjorth M in the 12 channels compared with TBR in one channel were lower than 0.05 between the ADHD and control groups (Fig. 1A, B).

3.3. Comparison of classification power between Hjorth M and the TBR with Cohen's effect size and classification performance in the ADHD and control groups

Effect size is the magnitude of the difference between groups, whereas absolute effect size is the difference between the average or mean outcomes in two intervention groups. Cohen established the effect size classifications of small (d = 0.2), medium (d = 0.5), and large (d = 0.8) [25]. The Cohen's effect size for use of Hjorth M was higher than that for use of the TBR in classifying the ADHD and control groups (Table 3). In particular, in channels T5, P3, P4, O1, and O2, the values of the Cohen's effect size of Hjorth M were higher than 0.8 (Fig. 2). Moreover, compared with TBR-related feature descriptors, Hjorth M-related descriptors can produce the higher average sensitivity (0.796 versus 0.464), average specificity (0.796 versus 0.742), average accuracy (0.792 versus 0.575), and average AUC value (0.885 versus 0.633).

Table 2
Comparison of TBR between ADHD and control groups in different channels.

Channel	ADHD	Control	p value
FP1	10.962 ± 6.401	10.559 ± 5.240	0.794
FP2	10.906 ± 6.364	10.232 ± 4.807	0.651
F7	11.086 ± 7.559	10.214 ± 4.622	0.598
F3	10.042 ± 6.737	8.107 ± 4.030	0.190
FZ	12.571 ± 7.688	10.725 ± 4.862	0.279
F4	9.355 ± 5.894	7.785 ± 3.941	0.238
F8	11.066 ± 7.665	10.192 ± 4.539	0.599
T3	10.329 ± 6.992	10.162 ± 4.507	0.914
C3	9.611 ± 5.194	8.694 ± 3.933	0.452
C4	9.679 ± 5.369	8.562 ± 3.949	0.370
T4	10.929 ± 6.430	9.883 ± 4.823	0.486
T5	14.354 ± 7.832	10.919 ± 6.294	0.071
P3	12.732 ± 6.534	9.715 ± 4.871	0.051
PZ	14.702 ± 8.473	11.618 ± 5.564	0.107
P4	13.419 ± 7.715	10.292 ± 4.969	0.072
T6	15.043 ± 8.847	12.363 ± 6.994	0.206
O1	16.277 ± 9.129	11.893 ± 6.546	0.040*
O2	16.383 ± 10.940	12.202 ± 6.764	0.085

*$p < 0.05$.

4. Discussion

This study used a Hjorth M-based EEG analytic method to identify differences between girls with ADHD and controls. Compared with the TBR in this study, significant differences were observed in the selected Hjorth M-related features between the patients with ADHD and the controls.

Hjorth M represents mobility, which is a Hjorth parameter. Mobility in EEG is defined as the square root of the ratio of activity of the first derivative of the EEG amplitudes to activity of the EEG amplitudes in a given period. The feature of mobility is highly dependent on the first derivative, which indicates the instantaneous slope of EEG signals [26]. In other words, mobility is a measure of the standard deviation of the slope with reference to the standard deviation of the amplitude. It is expressed as a ratio per time unit and may also be treated as a mean frequency [20]. In a study, EEG features with Hjorth parameters were compared in patients with uremic encephalopathy before and after hemodialysis. The researchers observed a significant increase in Hjorth M after hemodialysis, and this increase was correlated with improvement in visual discrimination, memory, and maximal tapping speed [27]. Researchers used Hjorth parameters to evaluate the drowsiness status in a simulated driving environment. The result showed that the Hjorth M increased as drowsiness status decreased [21]. In our previous study, a significant increase in Hjorth M was observed in the antiepileptic drugs (AED) effective group when compared with the ineffective group in patients with epilepsy [23]. The current study demonstrated that Hjorth M values in all EEG channels, except T3, were higher in controls than in patients with ADHD. Studies have indicated that subjects with higher Hjorth M values might have higher cognitive functions than those with lower values and lower Hjorth M value might be associated with inattention in girls with ADHD.

In this study, we discovered that the EEG Hjorth M over the bilateral dorsolateral prefrontal cortex (F3, F4)

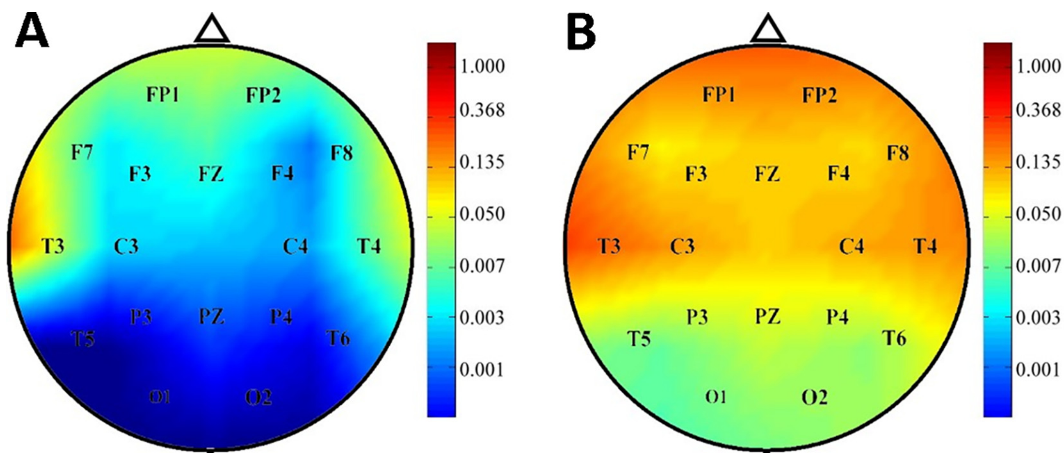

Fig. 1. Comparison of p values of Hjorth M and the TBR between the ADHD and control groups. Hjorth M values were significantly higher in the control group than in the ADHD group for 12 of 18 EEG channels (A). Only the TBR value in the O1 channel was significantly different between the ADHD and control groups (B).

Table 3
Comparison of classification power between Hjorth M and TBR with Cohen's effect size in ADHD and control groups in different channels.

Channel	Effective size of Hjorth M	Effective size of TBR
FP1	0.393	0.068
FP2	0.418	0.117
F7	0.232	0.137
F3	0.625	0.343
FZ	0.541	0.282
F4	0.716	0.308
F8	0.260	0.137
T3	0.101	0.028
C3	0.632	0.196
C4	0.683	0.233
T4	0.393	0.181
T5	0.867	0.475
P3	0.879	0.515
PZ	0.778	0.423
P4	0.835	0.474
T6	0.619	0.330
O1	0.876	0.543
O2	0.888	0.452

was significantly lower in the girls with ADHD than in the controls. This study enrolled patients with the inattention subtype of ADHD. Attention is a complex function involving intricate neuronal systems. Sustained attention, which is mostly related to vigilance, depends on the integrity of the prefrontal cortex [28]. Researchers noted that rats with frequent prefrontal interictal spikes appeared relatively inattentive and made more omission errors [29]. The researchers proposed that impaired prefrontal function was associated with inattention. In a functional, near-infrared spectroscopy study, Miao et al. demonstrated that children with ADHD exhibited reduced activity in the left prefrontal cortex during the go/no-go task compared with controls [30]. The go/no-go test requires the high-level cognitive functions of decision-making, response selection, and response inhibition [31]. The aforementioned findings suggest that patients with ADHD exhibit lower prefrontal activity than controls. In this study, in addition to relatively low activity in the prefrontal cortex, significantly lower Hjorth M values were noted in the central, temporal, parietal, and occipital areas in the patients with ADHD compared with the controls. This suggested that the neural network involved in the inattention subtype of ADHD is not limited to the prefrontal cortex. Neurophysiological studies on nonhuman primates have reported that spatial attention appears to be controlled by structures such as the prefrontal cortex [32], lateral intraparietal area in the parietal cortex [33], and superior colliculus [34]. Evidence suggests that one or more of these structures drives the selection of stimuli for attention within the posterior visual cortex [35].

Several studies have used the TBR as a measure to determine whether children have ADHD [36–39]. One study compared the TBR between girls with ADHD and controls; according to the results, the girls with ADHD exhibited globally reduced relative delta and beta activity and globally increased relative theta activity and TBR compared with the controls [40]. The TBR has been approved by the FDA as a tool for diagnosing ADHD [13]. However, studies have revealed that only 38% and 26% of patients with ADHD significantly different from controls based on the TBR [14,41]. Our study showed that the p values of the Hjorth M in the 12 channels compared with TBR in one channel were lower than 0.05 between the ADHD and control groups. Moreover, the Cohen's effect sizes of Hjorth M in all EEG channels were higher than those of the TBR in classifying the ADHD and control groups. This finding indicated that Hjorth M was more effective than the TBR in identifying girls with ADHD.

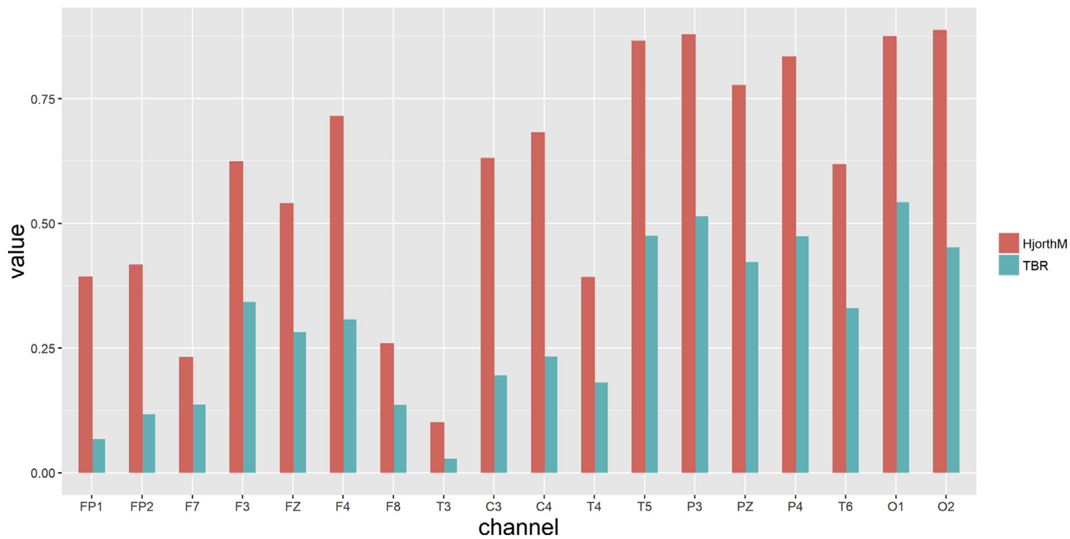

Fig. 2. Comparison of classification power between Hjorth M and the TBR with Cohen's effect sizes in the ADHD and control groups. The Cohen's effective sizes of Hjorth M in all EEG channels were higher than those of the TBR in classifying the ADHD and control groups. Cohen's effect sizes of Hjorth M were larger than 0.8 in T5, P3, P4, O1, and O2 channels.

5. Conclusions

In present study, we found that average Hjorth M values in most EEG channels were significantly higher in controls than in girls with ADHD. The lower Hjorth M values might be associated with inattention in these girls. The proposed method was more accurate than the TBR in diagnosing ADHD. Therefore, Hjorth M may be a promising tool for differentiating between children with ADHD and controls.

Acknowledgments

We would like to thank the participants and their families. This study was partly supported by the Kaohsiung Medical University Hospital (grant numbers KMUH102-2T09, 106CM-KMU-11, and KMUH106-6R47) and the Ministry of Science and Technology, Taiwan (grant numbers MOST 106-2314-B-037 -080 -MY2, 106-2221-E-214 -048, and MOST 107-2221-E-214 -028).

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