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# Seizure frequency and risk of cognitive impairment in people living with epilepsy in a sub-urban community in South Eastern Nigeria

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ABSTRACT

This study is aimed at assessing the impact of seizure frequency on the cognitive performance of epileptic adult patients in a rural community in South Eastern Nigeria. A total of 51 patients with epilepsy (33 males and 18 females) with a mean age of 30.7 ± 12.1 years and 51 age and sex matched controls participated in this study. The cognitive performances of the people with epilepsy and controls were assessed using the Community Screening Interview for Dementia (CSID) and the computerized cognitive assessment test battery, the FePsy. The control group performed better in almost all the neurocognitive tests compared with the low seizure frequency (LSF) and high seizure frequency (HSF) groups. Analysis of covariance revealed that patients with LSF performed better (p = 0.04) in visual reaction time – dominant hand (VRT-D) compared with the HSF group. There was lack of significant differences in mean total CSID scores and mean sub-total scores for language, memory, orientation, attention, constructional praxis, auditory reaction time-dominant hand and non-dominant hand, VRT – non-dominant hand and figure recognition. HSF patients indicated significantly greater prevalence (80% vs. 20%; p = 0.020) and risk (OR, 8.0; 95% CI, 1.8–33.8)) of memory impairment, but not in the other neurocognitive domains compared with the LSF group. In conclusion, the present study indicated that adults with epilepsy performed poorly in a wide range of neurocognitive variables compared with the controls. However, no significant adverse effects of high seizure frequency were observed on almost all the neurocognitive variables.



## 1. Introduction

Epilepsy is a group of neurological diseases characterized by recurrent, unprovoked seizures [1]. It is one of the most common diseases of the nervous system that affects people of all ages and the commonest neurological disorder encountered in sub-Saharan Africa [1,2]. It imposes enormous adverse effects on the physical, psychological, social, and economic well being of individuals and families [3,4]. These effects include social stigmatization, poor quality of life, lower educational achievement, worse employment outcomes, learning disabilities, morbidity and preventable mortality [5,6].

Neurocognitive impairment is frequent in patients with epilepsy [7]. Some degree of cognitive dysfunction has been observed in children and adults with epilepsy [8–11]. The most prominent feature of epilepsy is seizures, which are reported to cause cognitive, neuropsychological, morphological and functional changes within the brain [12]. Although the underlying causes of cognitive impairment in people with epilepsy are generally complex and multifactorial, seizure frequency has been established as a significant factor associated with cognitive impairment [13]. On the other hand, lack of significant adverse effects of seizures on intellectual performance of children has been previously reported in studies assessing the effects of seizure frequency on cognitive performance of patients with epilepsy [14,15]. In adult patients, memory difficulties, mental slowness and attention deficits are the most cognitive complaints [13]. Of these three factors, memory appears to be the most vulnerable cognitive function associated with epileptic seizures in adults [16].

There are few studies assessing the relationships between seizure frequency and cognitive performance of adult patients and these studies mainly focused on urban populations and could not control for other seizure variables affecting cognitive functions. The present study therefore is aimed at assessing the relationships between seizure frequency, studied as a main factor, and the cog-

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nitive performance of epileptic adult patients in a rural community in South Eastern Nigeria after controlling for other seizure variables such as seizure types, anti-epileptic drug load, duration of epilepsy, duration of therapy, age at onset of seizures. In addition, we determined the incidence and risk of cognitive impairment in patients with high seizure frequency compared with those with low seizure frequency. It is believed that understanding of the impact of seizure frequency on the cognitive function of adults with epilepsy, as well as the associated risk of cognitive impairment across a wide range of neuropsychological domains, would help guide treatment selection in this population.

## 2. Methods

### 2.1. Study area

The study was carried out in Ukpo, a sub-urban community in Anambra state, South-East of Nigeria. It has a population of 14,300 with estimated 65% above the age of 18 years [17]. The Ukpo community population comprises of indigenes and non-indigenes who are predominantly traders and farmers and who can speak native Igbo, English and 'pidgin' English languages. The temperature of this area ranges between 29 °C and 35 °C. The traditional rulers and heads of schools were informed of the study and preliminary sensitization and consultations were made with the community leaders, the herbalists, opinion leaders, the clergy men and school heads before commencement of the study.

### 2.2. Participants

A total of 51 patients with epilepsy (33 males and 18 females) with a mean age of 30.7 ± 12.1 years participated in this study. Fifty one healthy controls matched in age and gender (mean age, 31.4 ± 12.8 years; 33 males and 18 females) were also recruited for the study. The PWE were selected by snowball method from the Ukpo community. The controls were recruited from the neighborhood of the PWE in the community and had neither personal nor family history of seizures. All patients completed a structured questionnaire designed to obtain demographic information such as age, sex, level of education, age at onset of seizures, history of fever, head injury, drug or alcohol abuse, systemic diseases that can result in symptomatic seizures, and seizure type, seizure frequency and duration of illness. The seizure types were classified clinically based on the International League Against Epilepsy (ILAE) classifications [18]. The selected patients had clinical diagnosis of epilepsy with characteristic history collaborated with eye witness with EEG confirmation. The duration of epilepsy was estimated as the historic time interval between the first attack ever and the initial presentation at the neurology clinic of Nnamdi Azikiwe University Teaching Hospital, Nnewi. Informed consent was obtained from each subject before commencement of the study. The ethical committee of the Nnamdi Azikiwe University Teaching Hospital gave approval for the study.

### 2.3. Recruitment of patients with epilepsy

The patients with epilepsy were selected using the snowball sampling technique. The snowball sampling (or chain sampling, chain-referral sampling, referral sampling) is a non-probability (convenience) sampling technique where existing study subjects recruit future subjects from among their acquaintances. Thus the sample group is said to grow like a rolling snowball. It is used in recruiting people who are difficult to identify or have to meet certain criteria to participate. The first phase of this method involved identifying people who knew those with epilepsy in the community. These individuals included herbalists, community leaders, opinion leaders, the clergy and school heads, who assisted in identifying PWE. The second phase of the recruitment method was asking those identified as people with epilepsy to assist in identifying other people with the disease. This continued until enough sample size of identified PWE was gathered for the research.

Using the snowball method, 75 persons were identified with epilepsy in the community. The inclusion criteria included patients who were; >16 years of age, without impairment of consciousness or awareness, without seizures associated with fever, infection, head injury, cerebrovascular diseases, malignancies, brain tumour, drug or alcohol abuse. Patients who had no visual and hearing impairment (because of interference with psychometric analysis) including those who were able to understand, communicate and follow instructions for the psychometric test were also included in the study. Of the 75 persons identified as PWE, 18 were aged <16 years; 2 had hearing and speech impairments; 2 had severe physical disability, and 2 were severely mentally impaired (they could not cope with the cognitive assessment). The remaining 51 satisfied the inclusion criteria and thus formed the sample of the study. The study lasted for a period of 6 months.

### Study design and protocols

The study was designed to determine the impact of seizure frequency on cognitive performances of PWE and also assess the risk of high seizure frequency in the development of cognitive impairment. Patients with epilepsy were therefore classified into a "high" seizure frequency (HSF) subgroup (seizures occurring >2 times per month) and a "low" seizure frequency (LSF) subgroup (seizures occurring ≤2 times monthly). The cut-off for seizure frequency between the two groups was chosen based on median (50th percentile) of the seizure frequency per month. The control data was primarily for the purpose of determining the cognitive impairment cut-offs for the study. The cognitive performances of the PWE and controls were assessed using (a) the computerized cognitive assessment test battery, the FePsy and (b) Community Screening Interview for Dementia (CSID). The choice of CSID as a cognitive test is because of its suitability for use by non-specialists in poor cross-cultural settings. It combines culture and education-fair cognitive testing of the participants. For example it consists of a cognitive test for non-literate and literate populations and an informant interview regarding performance in everyday living.

### Assessment of seizure frequency

In this study, a trained health professional collected the seizure frequency data by using a purposeful interview on the patients' disease course, as well as by examining the patients' seizure diaries. Patient-reported seizure counts represent a key outcome measure for individual treatments and clinical studies in epileptology, hence the need for daily diary of seizure which is a reliable method for securing data on seizure counts. The seizure counts were reported as number of seizures per specified time period (e.g., number per day, week, month, 2 months, 3 months and 6 months) by the patient (who recognized all seizures) when capable or by family or caregivers if unable in order to reduce documentation failures resulting from postictal seizure unawareness. The seizure counts per month were then documented in order to determine the cut-off for seizure frequency classification and descriptive data (mean, standard deviation) for the total sample and sub-groups.

### 2.6. Cognitive testing

#### 2.6.1. a) The community screening interview for dementia

The CSID instrument takes an average of 15 min to administer and comprises 48 items with 32 items for cognitive tests and 16 items for informant interview [19]. The cognitive test covers the domains of memory (recall, registration), language (expression, naming, repetition and fluency), attention and calculation, orientation (to place and time), praxis and abstract thinking [19]. CSID has been used in many populations from different socioeconomic backgrounds and has been translated and used among the African Americans, Chinese, Taiwanese and Nigerian Yorubas [20].

The CSID was translated into the traditional Igbo language and back translated to ensure consistency. The translation was done by an Igbo language university graduate secondary school teacher who holds a first degree in Igbo language. The CSID was administered to all PWEs and controls by one of the authors. The administration of the CSID was done in a room free of noise, movements and other distractions. The CSID administration per participant took between 15 and 25 min. The subtotal scores for each cognitive domain were calculated and the aggregate score was also calculated. Cognitive impairment cut-offs were determined by subtracting 2 standard deviations (SD) from mean values of the control subjects' subtotal scores of language, memory, orientation, and attention domains and total CSID score as previously documented by Salawu et al. [21]. The cut-off values therefore were; 12.14 for language score, 3.72 for memory score, 4.15 for orientation score, 1.70 for attention score and 23.02 for total CSID score. Therefore any value below these cut offs were considered as cognitively impaired. In contrast, 2SD was added to the mean control praxis score to obtain the cut-off score of 4.57 because the cognitive performance is inversely related to the praxis score. Any value above this cut-off was considered impaired.

#### 2.6.2. (b) The computerized cognitive assessment test battery, the FePsy

The Iron Psychology (acronym FePsy) is a neuropsychological test battery which had been utilized in the study of cognitive function in various patients groups in Nigeria [22,23]. The 'Fepsy' consists of reaction time tasks, recognition memory tests, visual scanning task, seashore rhythm test, abstraction task and Corsi block task [24]. In the present study, we assessed for the simple reaction time and recognition memory of subjects. Details of how the FePsy instrument is administered on the patients has been described elsewhere [24].

### 2.7. The simple reaction time

This has two components- the visual and auditory reaction time. The essence of this task is to assess the mental (psychomotor) speed of the individual. The reaction time for simple auditory and visual stimuli were measured. In the visual version, the testee was expected to react as quickly as possible on seeing a white square in the middle of the computer screen by pressing the space bar. The auditory version involves the presentation of sound stimuli of 800 Hz generated by the computer and the testee was asked to react as quickly as possible on hearing the sound by pressing the space bar.

The two tests were done using the dominant hand and non dominant hands. It had two phases: the learning phase and the test phase. In the learning phase (trial run) the candidate was taught how to do the test according to the instructions in the computer screen. In the test phase, the candidate carried out the instructions exactly as taught. Failure to do this after three consecutive trials disqualified the candidate for the test. The interstimulus interval was randomly varied from 2.5 to 4 s. For both the dominant and non-dominant hands of each subject, 30 stimuli were presented for the auditory version and another 30 stimuli for the visual version. The results showed accuracy and speeds of response in milliseconds. The evaluation of the results was done within the context of speed of information processing and alertness functions. The average of the scores in milliseconds was then analyzed and recorded automatically by the computer. The normal control reference values of auditory reaction times for both dominant and non-dominant hands were 492.02 ms and 484.85 ms respectively. Anybody that scored above this had abnormal score. For visual reaction times the values were 464.71 and 542.26 ms for dominant and non-dominant hands respectively.

### *The recognition memory task*

This comprised the words and figures sections which were presented simultaneously to assess recall. The study items consisted of 4 figures (nonsense figures) or 6 words which were presented for 1 s each. In this test, the participant was shown an array of words and figures respectively and was expected to be able to detect among subsequent words and figures, the words/figures, that appeared before. The test comprised of the learning phase and the test proper. Accordingly, the research team administered the learning phase to the participant, before the test phase. This sub-task took a minimum of 20 min to be administered per participant.

As mentioned earlier, the task was divided into a study phase in which the material to be remembered was presented and a test phase in which recognition (recall of study items) was tested. In the study phase, the subject was presented with 3 or 4 figures, or 4 or 6 words to study and memorise. In the recognition phase, different sets of 3 or 4 figures or 4 or 6 words were presented again and one of these matched one of the study items. The testee was required to identify the word or figure in the second presentation that matched one of the study items presented initially.

Patients with primary and secondary education were tested using the 3 figures and 4 words for visual and verbal memory respectively, while those in tertiary education were tested using the 4 figures and 6 words. Words were randomly selected from a pool of about 100 words. Figures were randomly built up from basic elements of triangles (D) and rectangles () and were difficult to label. However, only very few patients were able to perform the word recognition task due to poor lexical knowledge and word-finding difficulties, thus word recognition data was excluded in the final analysis. The results were calculated as a percentage of correct responses. The evaluation of the recognition task was performed in the context of the recognition process within the memory function. The cut-off values for figure recognition was 59.73 as set by the control group.

### *Data analysis*

Descriptive data were expressed as mean and standard deviation for continuous variables and as percentages for categorical variables. Comparative analyses of cognitive scores between the control and the two seizure frequency groups were done using one way analysis of variance (ANOVA), while the comparative analysis between the LSF and HSF groups was done using student's *t*-test. Comparison of categorical variables between the LSF and HSF groups were analyzed using chi-square test. Pearson's partial correlation test was used to relate seizure frequency with neurocognitive variables. Logistic regression test was performed to determine the risk of cognitive impairments across cognitive domains. Statistical significance was set at $P < 0.05$. All statistics were done using SPSS for windows (version 20.0).

## 3. Results

Table 1 shows the demographic characteristics of the study population. The mean age of the PWE was 30.7 ± 12.1 years (LSF = 32.3 ± 15.3 and HSF = 28.6 ± 12.5 years) while that of the control was 31.4 ± 12.8 years. The mean age did not differ significantly (p = 0.77) between the control and PWE as well as between the LSF and HSF groups (p = 0.35) respectively. Gender (males, n = 33; females, n = 18) were matched between the controls and the PWE. Similarly, the frequency of participants by level of education (non-formal, n = 5 vs. 5, p = 1.0; primary, n = 18 vs. 24, p = 0.35; secondary, n = 25 vs. 19, p = 0.36; tertiary, n = 3 vs. 3, p = 1.0) did not differ significantly between the control and PWE. A greater number of the LSF (n = 19) and HSF (n = 14) patients were males, while equal number (n = 9) of females participated in both sub-groups. Privately employed persons (n = 12) dominated the LSF group, while students (n = 14) dominated the HSF group. Those with secondary education (n = 13) had the largest number of participants among the LSF group, while a greater number (n = 14) of the HSF group were those with primary education.

The clinical characteristics of the PWE are summarized in Table 2. Majority (n = 29, 56.8%) of the PWE had generalized seizures, while 22 (43.2%) had partial seizures. A greater number (n = 20) of the patients with generalized seizure had secondary generalized seizures while majority (n = 16) of the cases with partial seizures were of the complex type. Among the LSF group, majority (55.6%) had secondary generalized seizures, while most (45.8%) of the HSF group, had complex partial seizures. A greater occurrence (n = 29; 56.9%) of the epileptic condition was idiopathic (LSF, n = 20 and HSF, n = 9). Eighteen (35.3%) of the epileptic cases were cryptogenic, while 4 (7.8%) were provoked (metabolic abnormalities and reactions to medication). Polytherapy was used in majority (n = 26, 51%) of the patients (LSF = n = 11; HSF, n = 15), monotherapy was used in 21 (41.2%) of the PWE (LSF = n = 12; HSF, n = 9) and 4 patients (LSF, n = 4; HSF, n = 0) had no AED. No significant differences were observed in age of onset of epilepsy, duration of illness and duration of therapy between the LSF and HSF groups. Seizure frequency expectedly was greater (p < 0.001) in the HSF group (13.50 ± 11.06) compared with the LSF group (1.35 ± 0.72).

The descriptive data of the seizure frequency of the total sample and sub-groups of PWE is summarized in Table 3. Majority (31.4%) of the PWE experienced several seizures per week, followed by those who had several seizures per month (29.4%). Very few (3.9%) of the PWE had seizures once in 3 months or once in 6 months. Majority (51.8%) of the LSF group had several seizures per month, while most HSF patients (62.5%) had several seizures per week. It is noteworthy that for the sake of convenience in data analysis, the above seizure frequency data was converted to number of seizures per month and the seizure frequency groups reduced to two (LSF, ≤2 seizures/month ad HSF, >2 seizures/month).

Table 4 presents the neurocognitive test results for the control and the patients' sub-groups. The control group performed better in total CSID score and subtotal scores for language, memory, attention, constructional praxis and figure recognition compared with the LSF and HSF groups respectively. The control group also performed better in ART-D, ART-ND, VRT-D and VRT-ND compared with the HSF group but not the LSF group. No significant differences were observed in orientation score between the control and the two seizure frequency groups. Analysis of covariance controlling for seizure types, etiology of epilepsy, type of anti-epileptic drug, duration of epilepsy, duration of therapy, age at onset of seizures, revealed lack of significant differences in mean total CSID scores (p = 0.86) and mean sub-total scores for language (p = 0.76), memory (p = 0.17), orientation (p = 0.77), attention (p = 0.49), constructional praxis (p = 0.31), ART-D (p = 0.71), as well as ART-ND (p = 0.28), VRT-ND (p = 0.09) and figure recognition (p = 0.78). In contrast, mean score for VRT-D was significantly greater (p = 0.04) in the HSF group compared with the LSF group. The correlation between seizure frequency and each cognitive domain is summarized in Table 5. Pearson's partial correlation test controlling for seizure types, etiology of epilepsy, type of anti-epileptic drug, duration of epilepsy, duration of therapy, age at onset of seizures, revealed no significant associations between seizure frequency and language (p = 0.433), memory (p = 0.078), orientation (p = 0.247), attention (p = 0.887), constructional praxis (p = 0.252), total CSID (p = 332), ART-D (p = 0.774), ART-ND (p = 0.668), VRT-D (p = 0.877), VRT-ND (p = 0.817) and figure recognition (p = 0.203).

Table 6 shows the incidence of cognitive impairment in both LSF and HSF across all cognitive domains. Cognitive impairment was found in all cognitive domains of both groups. The HSF group indicated significantly greater prevalence of memory impairment compared with the LSF group (80% vs. 20%; p = 0.020). In contrast, no significant differences were observed in the prevalence of cognitive impairment between the LSF and HSF groups in the other neurocognitive domains. Furthermore, logistic regression analysis indicated that patients with high seizure frequency were not at greater risk of cognitive impairment compared with those with

Table 1
The demographic characteristics of the study population.

| Characteristics | Controls n = 51 | Patients with epilepsy | | | Statistical analysis (LSF vs. HSF) | |
|---|---|---|---|---|---|---|
| | | All n = 51 | Low seizure frequency n = 27 | High Seizure frequency n = 24 | Statistics | P |
| Age (years) | | | | | | |
| Mean ± SD | 31.4 ± 12.8 | 30.7 ± 12.1 | 31.1 ± 15.7 | 30.1 ± 12.3 | t = 0.25 | 0.80 |
| Gender | | | | | | |
| Males | 33 | 33 | 17 | 16 | $\chi^2$ = 0.07 | 0.78 |
| Females | 18 | 18 | 10 | 8 | | |
| Occupation | | | | | | |
| Publicly Employed | 4 | 6 | 4 | 2 | $\chi^2$ = 3.24 | 0.35 |
| Privately Employed | 30 | 18 | 11 | 7 | | |
| Students | 8 | 21 | 8 | 13 | | |
| Unemployed | 9 | 6 | 4 | 2 | | |
| Level of Education | | | | | | |
| Non-Formal | 5 | 5 | 3 | 2 | $\chi^2$ = 4.45 | 0.34 |
| Primary | 18 | 24 | 9 | 15 | | |
| Secondary | 25 | 19 | 13 | 6 | | |
| Tertiary | 3 | 3 | 2 | 1 | | |

Abbreviations: LSF = Low Seizure Frequency, HSF = High Seizure Frequency; SD = Standard Deviation.

Table 2
The clinical characteristics of patients with epilepsy.

| | All PWE n = 51 | Low seizure frequency n = 27 | High seizure frequency n = 24 | Statistical analysis (LSF Vs. HSF) | |
|---|---|---|---|---|---|
| | | | | Statistics | P |
| | n (%) | n (%) | n (%) | | |
| Seizure Type | | | | | |
| Simple Partial | 6 (11.8) | 2 (7.4) | 4 (16.7) | | |
| Complex Partial | 16 (31.4) | 5 (18.5) | 11 (45.8) | | |
| Primary Generalized | 20 (39.2) | 15 (55.6) | 5 (20.8) | $\chi^2 = 7.87$ | 0.049 |
| Secondary Generalized | 9 (17.6) | 5 (18.5) | 4 (16.7) | | |
| Etiology | | | | | |
| Idiopathic | 29 (56.9) | 20 (74.1) | 9 (37.5) | | |
| Cryptogenic | 18 (35.3) | 4 (14.8) | 14 (58.3) | $\chi^2 = 10.58$ | 0.005 |
| Provoked | 4 (7.8) | 3 (11.1) | 1 (4.2) | | |
| AED | | | | | |
| No AED | 4 (7.8) | 4 (14.8) | 0 (0) | | |
| Monotherapy | 21 (41.2) | 12 (44.4) | 9 (37.5) | $\chi^2 = 4.88$ | 0.08 |
| Polytherapy | 26 (51.0) | 11 (40.7) | 15 (62.5) | | |
| Age at Epilepsy Onset (Mean ± SD) | 18.7 ± 15.5 | 20.3 ± 16.5 | 16.8 ± 14.5 | t = 0.81 | 0.42 |
| Duration of Epilepsy Mean ± SD | 12.0 ± 9.9 | 10.8 ± 8.9 | 13.3 ± 10.8 | t = —0.90 | 0.37 |
| Duration of Therapy Mean ± SD | 6.7 ± 6.4 | 7.0 ± 7.2 | 6.3 ± 5.5 | t = 0.38 | 0.70 |
| Seizure Frequency Mean ± SD | 7.1 ± 9.7 | 1.35 ± 0.72 | 13.50 ± 11.06 | t = —5.69 | <0.001 |

Abbreviations: PWE = Patients with Epilepsy; AED = Anti Epileptic Drugs; LSF = Low Seizure Frequency, HSF = High Seizure Frequency; SD = Standard Deviation; $\chi^2$ = Chi square

Table 3
Descriptive data for seizure frequency of people with epilepsy.

| Seizure frequency | All PWE n = 51 | | | Low seizure frequency n = 27 | | | High seizure frequency n = 24 | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | % | Median (Range) | N | % | Median (Range) | N | % | Median (Range) |
| Once/day | 3 | 5.9 | 1.0 (0) | 0 | 0 | 0 (0) | 3 | 12.5 | 1.0 (0) |
| Once/week | 4 | 7.8 | 1.0 (0) | 0 | 0 | 0 (0) | 4 | 16.7 | 1.0 (0) |
| Several/week | 15 | 29.4 | 3.0 (10.0) | 0 | 0 | 0 (0) | 15 | 62.5 | 3.0 (10) |
| Once/month | 6 | 11.8 | 1.0 (0) | 6 | 22.2 | 1.0 (0) | 0 | 0 | 0 (0) |
| Several/month | 16 | 31.4 | 2.0 (1.0) | 14 | 51.8 | 2.0 (0) | 2 | 8.3 | 2.0 (11) |
| Once/2 months | 3 | 5.9 | 1.0 (0) | 3 | 11.1 | 1.0 (0) | 0 | 0 | 0 (0) |
| Once/3 months | 2 | 3.9 | 1.5 (1.0) | 2 | 7.4 | 1.5 (1.0) | 0 | 0 | 0 (0) |
| Once/6 months | 2 | 3.9 | 1.0 (0) | 2 | 7.4 | 1.0 (0) | 0 | 0 | 0 (0) |
| Total | 51 | 100 | 2.0 (11) | 27 | 100 | 2.0 (1.0) | 24 | 100 | 2 (11) |

Table 4. The CSID and FePsy test scores compared between the low and high frequency seizure groups.

| Tests | | Control | PWE | | Statistical analysis (LSF vs. HSF) | |
|---|---|---|---|---|---|---|
| | | | Low seizure frequency | High seizure frequency | Unadjusted t-stat ; (p-value) | Adjusted‡ F-stat; (p-value) |
| CSID | Language | 25.53 ± 5.87*λ | 20.03 ± 8.08 | 19.87 ± 6.82 | 0.07; (0.93) | .09; (0.76) |
| | Memory | 8.43 ± 1.97*λ | 6.25 ± 2.34 | 4.45 ± 3.06 | 2.37;(0.02) | 1.94; (0.17) |
| | Orientation | 5.61 ± 0.98 | 5.40 ± 0.75 | 5.08 ± 1.31 | 1.09; (0.27) | 0.08; (0.77) |
| | Attention | 4.52 ± 1.39*λ | 3.6 ± 1.1 | 3.50 ± 1.58 | 0.42; (0.67) | 0.46; (0.49) |
| | Constructional Praxis | 1.92 ± 1.35*λ | 3.11 ± 1.15 | 3.33 ± 1.34 | —0.63; (0.52 | 1.05; (0.31) |
| | Total CSID | 42.18 ± 8.12*λ | 31.92±10.59 | 29.95 ± 11.77 | 0.62; (0.53) | 0.03; (0.86) |
| | ART-D | 358.40 ± 66.81 λ | 944.6 ± 259.6 | 1023.0 ± 373.1 | -0.77; (0.44) | 0.14; (0.71) |
| PePsy | ART-ND | 357.05 ± 63.90 λ | 829.3 ± 228.3 | 1009.3 ± 479.9 | -1.53; (0.13) | 1.19; (0.28) |
| | VRT-D | 331.05 ± 66.83 λ | 807.6 ± 241.7 | 1043.3 ± 338.9 | -2.86; (0.006) | 4.22; (0.04) |
| | VRT-ND | 361.60 ± 90.33 λ | 825.7 ± 289.2 | 1042.1 ± 330.1 | -2.47; (0.01) | 2.96; (0.09) |
| | Figure Recognition | 76.45 ± 8.36*k | 43.8 ± 14.3 | 40.5 ± 16.2 | 0.49; (0.62) | 0.08; (0.78) |

Abbreviation: CSID = Community Screening Interview for Dementia; ART – D: Auditory reaction time dominant, ART – ND: Auditory reaction time-nondominant, VRT – D: Visual reaction time dominant, VRT – ND: Visual reaction time – nondominant.
‡ Adjusted for seizure types, etiology, type of anti-epileptic drug, duration of epilepsy, duration of therapy, age at onset of seizures.
* Significant difference ($p < 0.05$) between LSF group and control; k Significant difference ($p < 0.05$) between the HSF group and control

low seizure frequency in the total CSID (p = 0.83) as well as in language (p = 0.57), orientation (p = 0.34), attention (p = 0.24), constructional praxis (p = 85), ART-D (p = 0.81), ART-ND (p = 0.37), VRT-D (p = 0.73), VRT-ND (0.73) and figure recognition (p = 0.08) domains respectively. In contrast, the HSF group was eight times at greater risk (OR, 8.0 (95% CI, 1.8–33.8); p = 0.002) of memory impairment compared with the LSF group. However, Cohen's Kappa test indicated very low effect size (-0.115) of differences in the prevalence of memory impairment between the two groups.

## 4. Discussion

The principal findings of the present study indicated that both LSF and HSF patients performed poorer in most cognitive domains

Table 5
Correlation between seizure frequency and cognitive variables in the total patient sample.

| Test | Seizure Frequency vs. | Unadjusted Correlation | | Adjusted Correlation‡ | |
|---|---|---|---|---|---|
| | | Coefficient (R) | P-Value | Coefficient (R) | P-Value |
| CSID | Language | —0.152 | 0.286 | —0.118 | 0.433 |
| | Memory | —0.308 | 0.028* | —0.263 | 0.078 |
| | Orientation | —0.129 | 0.366 | —0.174 | 0.247 |
| | Attention | —0.082 | 0.566 | —0.021 | 0.887 |
| | Constructional Praxis | 0.267 | 0.058 | 0.172 | 0.252 |
| | Total CSID | —0.171 | 0.229 | —0.146 | 0.332 |
| FePsy | ART-D | 0.342 | 0.033* | —0.078 | 0.774 |
| | ART-ND | 0.397 | 0.012* | —0.116 | 0.668 |
| | VRT-D | 0.109 | 0.452 | 0.042 | 0.877 |
| | VRT-ND | 0.097 | 0.504 | —0.063 | 0.817 |
| | Figure Recognition | 0.303 | 0.338 | 0.336 | 0.203 |

Abbreviation: CSID = Community Screening Interview for Dementia; ART – D: Auditory reaction time – dominant, ART – ND: Auditory reaction time-nondominant, VRT – D: Visual reaction time – dominant, VRT – ND: Visual reaction time – nondominant.
* Significant association.
‡ Adjusted for seizure types, etiology, type of anti-epileptic drug, duration of epilepsy, duration of therapy, age at onset of seizures.

Table 6
The incidence and risk of cognitive impairment according to seizure frequency of patients with epilepsy.

| Cognitive variables | Cognitive impairment | Seizure frequency | | Total | $X^2$ | Risk | Kappa | P-value |
|---|---|---|---|---|---|---|---|---|
| | | Low | High | | | OR(95%CI) | | |
| Language | Absent | 23 | 19 | 42 | 0.31 | 1.5(0.3–6.4) | —0.017 | 0.574 |
| | Present | 4 | 5 | 9 | | | | |
| Memory | Absent | 24 | 12 | 36 | 9.25 | 8.0(1.8–33.8) | —0.115 | 0.002 |
| | Present | 3 | 12 | 15 | | | | |
| Orientation | Absent | 24 | 19 | 43 | 0.90 | 2.1(0.4–9.9) | —0.026 | 0.341 |
| | Present | 3 | 5 | 8 | | | | |
| Attention | Absent | 26 | 21 | 47 | 1.36 | 3.7(0.3–38.3) | —0.023 | 0.244 |
| | Present | 1 | 3 | 4 | | | | |
| Constructional praxis | Absent | 23 | 20 | 43 | 0.03 | 1.1(0.2–5.2) | —0.005 | 0.856 |
| | Present | 4 | 4 | 8 | | | | |
| Total CSID | Absent | 22 | 19 | 41 | 0.04 | 1.1(0.3–4.6) | —0.006 | 0.835 |
| | Present | 5 | 5 | 10 | | | | |
| ART-D | Absent | 6 | 6 | 12 | 0.05 | 0.8(0.2–3.1) | 0.012 | 0.815 |
| | Present | 21 | 18 | 39 | | | | |
| ART-ND | Absent | 6 | 8 | 14 | 0.78 | 0.5(0.1–1.9) | 0.045 | 0.375 |
| | Present | 21 | 16 | 37 | | | | |
| VRT-D | Absent | 3 | 2 | 5 | 0.11 | 1.3(0.2–9.0) | —0.013 | 0.739 |
| | Present | 24 | 22 | 46 | | | | |
| VRT-ND | Absent | 3 | 2 | 5 | 0.11 | 1.3(0.2–9.0) | —0.013 | 0.739 |
| | Present | 24 | 22 | 46 | | | | |
| Figure Recognition | Absent | 14 | 18 | 32 | 2.91 | 0.3(0.1–1.1) | 0.072 | 0.088 |
| | Present | 13 | 6 | 19 | | | | |

Abbreviations: CSID = Community Screening Interview for Dementia; $V^2$ = Chi square; OR = Odds Ratio.

of CSID and FePsy tests when compared with controls. In addition, we observed no significant adverse effects of high seizure frequency on most of the neurocognitive variables after controlling for confounding seizure variables such as seizure types, etiology of epilepsy, type of anti-epileptic drug, duration of epilepsy, duration of therapy and age at onset of seizures. However, patients with high frequency seizure performed worse on visual reaction time (dominant hand) and indicated greater prevalence and risk of memory impairments compared with those with low seizure frequency.

The present study which indicated poorer cognitive performance in the two subgroups of PWE (LSF and HSF) compared with the control, confirms that epilepsy is associated with cognitive dyfunction. A previous study [25] has shown that epileptic patients with more frequent seizures performed worse on tests of cognitive functions compared with those with less frequent seizures. Similarly, studies have shown that the higher the frequency of seizure the more the cognitive dysfunctions [26,27]. It is noteworthy that the underlying causes of cognitive impairment in PWE are generally complex and multifactoral. This suggests that the present finding may reflect the combined influence of several factors and not necessarily seizure frequency per se. Besides epileptic seizure frequency, the etiology of epilepsy, seizure type, age at onset of epilepsy, duration of epilepsy and anti-epileptic drugs could affect the cognitive function in people with epilepsy [28].

In the present study, we limited our findings to the role of seizure frequency, as one of the underlying factors associated with cognitive impairment in people with epilepsy. Our data indicated lack of significant differences between the two seizure frequency groups in a wide range of neurocognitive variables such as language, memory, orientation, attention and construction subscales of the CSID and total CSID, visual reaction time (non-dominant hand), auditory reaction time (dominant and non-dominant hand) as well as figure recognition. Furthermore, in the total PWE sample, no significant relationships were observed between seizure frequency and cognitive variables such as total CSID and subscale scores for language, memory, orientation, attention, construction, visual reaction time (dominant and non-dominant hand) and figure recognition. These findings suggest that frequent seizure attacks may not necessarily have negative impact on all cognitive

performance of epileptic patients. This is not so surprising since there is no difference in education level or employment statuses across the groups, suggesting patients with higher seizure frequencies may not lack good quality of life. Moreover, previous studies [29,30] have demonstrated no significant relationship between cognitive decline and seizure frequency among adults with epilepsy. On the other hand, a recent study [31] found that individuals with greater seizure frequency performed more poorly on cognitive tests. Similarly, some cross-sectional studies have reported the contributions of seizure frequency on cognitive performance of patient subgroups either statistically or by strategic comparisons [32,33].

Our data further indicated that PWE with higher seizure frequency performed worse on visual reaction time (dominant hand) when compared to those with lower seizure frequency. This finding suggests delayed visual reaction time or poor psychomotor speed in the high seizure frequency group relative to the low seizure frequency group. It remains unknown whether high seizure frequency is related to delay in visual reaction time. However, a previous study has reported lack of significant effect of seizure frequency on visual reaction time [23].

The relationship between cognitive impairment and seizure frequency is complex and not well understood and has proven very difficult to substantiate. Cross-sectional studies show contradicting results of association between cognitive impairment and seizure related variables. Some cross-sectional neuropsychological studies have provided some evidence of a relationship between cognitive impairment and seizure frequency [12,34], while others found that seizure frequency was not related to cognitive impairment [32,33]. In this study, cognitive impairment was found in all domains of cognitive function for both low and high seizure frequency groups. However, apart from memory no other cognitive domain indicated significant difference in the prevalence of cognitive impairment between the two seizure frequency groups. Logistic regression also indicated greater risk of memory impairment in patients with higher seizure frequency compared with the lower frequency group. However, when subjected to further tests using Cohen's Kappa test, the size effect of the differences in memory impairment between the two groups was very trivial in spite of the statistical significance. Data obtained under conditions of extremely low effect size between groups may not be clinically meaningful. Moreover, there were methodological limitations of not adequately characterizing the cumulative burden of the patient's condition since not all confounding variables that affect cognition were considered during our data analysis. These factors therefore make the estimation of relationship between seizure frequency and cognitive performance very difficult and calls for caution in the interpretation of the present result/data and avoidance of any generalized conclusions.

### *4.1. Limitations of study*

This study is limited primarily by its relatively small sample size and cross-sectional design which may hinder its generalization. It is also thought that small sample size may have contributed to the absence of correlations in the total patient sample and lack of significant differences between the two seizure frequency groups. Furthermore, we could not include in our analysis other relevant confounders such as the pre-comorbid affection of patients (e.g. depression and anxiety) prior to cognitive test, since these factors are associated with seizure frequency. Another limitation of ours is the impossibility to control factors such as recall bias by informants during the CSID test which may lead to possible errors in CSID scores. Similarly, the effects of the recall bias by informants and pre-seizure cognitive levels of patients may not be ruled out as possible reasons for lack of significant differences in cognitive variables between the two seizure frequency groups. It is noteworthy that the confounders of cognition such as seizure types, etiology, type of anti-epileptic drug, duration of epilepsy, duration of therapy, age at onset of seizures were controlled for in our analysis. This is one of the strengths of our study.

## 5. Conclusion

The present study indicated that a wide range of neurocognitive variables such as total CSID scores, subtotals of language, memory, attention, orientation, constructional praxis scores and psychomotor tests (visual reaction time (non-dominant hand), auditory reaction time (dominant and non-dominant hand)) as well as figure recognition, were not affected by increased seizure frequency. However, the low seizure frequency group performed significantly better than the high frequency group in one of the neurocognitive tests - visual reaction time (dominant hand), thus suggesting poor psychomotor speed patients with high seizure frequency. The incidence and risk of memory impairment was greater in the high seizure frequency group compared with the low seizure patients. We believe this study will add to existing knowledge on the impact of seizure frequency on cognitive function of adults with epilepsy, thus assisting in the differential diagnosis of cognitive complaints and improve the design of treatment studies for people with epilepsy. Future studies should control for more confounding variables in a larger sample size to help elucidate the relative impact of seizure frequency on cognitive outcomes.

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