ISSN: 2476-8642 (Print)
ISSN: 2536-6149 (Online)
www.annalsofhealthresearch.com
African Index Medicus, Crossref, Index Copernicus
& Google Scholar
C.O.P.E & Directory of Open Access Journals

Annals of Health Research

VOLUME 7
NO. 2
APR. - JUN., 2021

IN THIS ISSUE

PUBLISHED BY THE MEDICAL
AND DENTAL CONSULTANTS ASSOCIATION
OF NIGERIA, OOUTH, SAGAMU, NIGERIA.
www.mdcan.oouth.org.ng

CC BY-NC

Annals of Health Research
Volume 7, Issue No 2: 165-178
June 2021
doi:10.30442/ahr.0702-08-127

ORIGINAL RESEARCH

Electroencephalographic Correlates of Cognition among Nigerian Women with Epilepsy on Anti-epileptic Monotherapy

Ogunjimi L*[1], Alabi A[1], Osalusi B[2], Muritala A[1], Aderinola A[1], Ogunniyi A[3]

[1]Department of Pharmacology and Therapeutics, [2]Department of Medicine, Obafemi Awolowo College of Health Sciences, Olabisi Onabanjo University, Sagamu Ogun State, Nigeria
[3]Department of Medicine, University College Hospital, Ibadan, Oyo State, Nigeria

*Correspondence: Dr LO Ogunjimi, Department of Pharmacology and Therapeutics, Obafemi Awolowo College of College Health Sciences, Olabisi Onabanjo University, Sagamu, Ogun State, Nigeria.
E-mail: luqmanogunjimi@yahoo.com; ORCID – https://orcid.org/0000-0001-9185-9774.

Abstract

Background: The prospect of EEG as a potential biomarker for detecting a cognitive decline in those living with epilepsy has not been extensively studied.
Objective: To determine the relationship between electroencephalographic (EEG) changes and cognitive functions in Women with Epilepsy (WWE).
Methods: The study involved 100 adult WWE aged between 16 and 40 years on Levetiracetam (LEV) or Carbamazepine (CAB) monotherapy. Zung Self-Reporting Depression Scale (ZSRDS) was used to assess the mood of participants while the Community Screening Interview for Dementia (CSID) was used to assess various cognition domains.
Results: The frequency of Periodic Epileptiform Discharges (PED) ($p = 0.008$), delta waves and theta waves ($p = 0.004$) were higher in WWE with Cognitive Impairment (CI) compared to those without CI. Lower cognitive scores were seen among those with delta wave across the domains of cognition with statistical significance for language fluency ($p = 0.039$), language comprehension ($p = 0.000$), and total CSID ($p = 0.000$). WWE with PED had a lower mean total CSID score compared to those without PED ($p = 0.019$). The absence of alpha wave ($p = 0.027$), presence of delta wave ($p = 0.013$), slow frequency ($p = 0.015$) and PED ($p = 0.031$) were EEG predictors of cognitive impairment. Medication type ($p = 0.016$) and depression ($p = 0.001$) were the clinical predictors of cognitive impairment in WWE.
Conclusion: The frequencies of PED and slow waves were higher in WWE with CI while the absence of alpha wave, presence of delta wave and PED were EEG predictors of CI.

Keyword: Anti-Epileptic Drug, Cognition, Electroencephalography, Epilepsy, Nigeria, Women.

Introduction

The EEG has been identified as a potential biomarker for detecting cognitive decline and for classifying its severity in a healthy individual and those with neurodegenerative disease, specifically Alzheimer's disease. [1 -3] However, this potential benefit has not been fully explored as a potential biomarker for detecting a cognitive decline in those living with epilepsy. Epileptogenesis-related neuronal plasticity, reorganization, sprouting, and impairment of

cellular metabolism are fundamental determinants of progressive cognitive deterioration. [3] Furthermore, transient disruption of cognitive encoding processes may occur with paroxysmal, focal or generalized epileptiform discharges which are associated with memory impairments, mental slowing, communicative and behavioural disturbances and attention deficits, both in children and adults with epilepsy. [3]

Identified biomarkers of cognitive decline on EEG include an increase of theta relative power, a decrease of gamma relative power and an increase of high alpha bands as compared to low alpha bands, hippocampal theta synchronization, whole theta/gamma ratio and alpha B/alpha Z ratio. [2, 4] The Amygdalo-Hippocampal (AHC) network is a key structure in the generation and synchronization of theta rhythm. [5] Theta synchronization in AHC appears to improve communication during memory retrieval. On the other hand, the retrieval of hippocampus-dependent memory is provided by the integrity of CA3-CA1 interplay, coordinated by gamma oscillation. [5, 6] Excess of theta waves on resting EEG has been linked to cognitive decline in healthy adults. [1, 7] Age and gender are significant factors that have been associated with cognitive impairment with a high prevalence rate in females. [1, 8 - 12] Gender differences in cognitive performance have been reported in diseases that target the integrity of the hippocampus like epilepsy. [11, 12] Among females, the focus has been on older adults, especially postmenopausal women, with less attention on the reproductive age group. A decline in cognition among postmenopausal women has been described, relative to the reproductive age group and this has been linked to the high level of circulating endogenous oestrogen. [13] It has been postulated that the effect of older enzyme-inducing agents and newer non-enzyme inducing Anti-Epileptic Drugs (AEDs) on cognitive functions vary. [14] Early detection of cognitive impairment in WWE using EEG biomarkers allows for prompt interventions to improve the overall quality of life. Therefore, this study aimed to determine the relationship between EEG changes and cognitive functions in WWE of reproductive age.

Methods

The hospital-based, comparative, cross-sectional study was conducted between 19th August 2015 and 18th August 2016. The study was carried out at the Medical Out-Patient Department of the University College Hospital, Ibadan (UCH), which is an 850-bed tertiary health facility located in Ibadan, south-west Nigeria. A pre-established interviewer-based questionnaire was used to obtain baseline information which included socio-demographic characteristics and medical history related to epilepsy, age of onset, aetiology, duration of epilepsy, frequency and types of AED, from WWE attending the clinic. [15]

Using the clinic attendance record as the sampling frame, patients on AED monotherapy without a prior medical record of cognitive impairment were consecutively recruited, once informed consent is secured. The study comprised 100 WWE, 50 of which received Carbamazepine (CBM) monotherapy and 50 received Levetiracetam (LVM) monotherapy. The choice of CBM was driven by the fact that it is one of the oldest drugs and commonly used agent in the environment, while LVM is a relatively new drug with an increasing rate of usage and neuroprotective properties. Excluded from the study were subjects with prior use of any other AED, alternative medicine or herbs, previous diagnosis of primary and secondary hypogonadism, chronic medical illness, background psychiatric disorder and pregnancy. Patients with cognitive impairment based on their medical record were, also excluded from the study.

The diagnosis of epilepsy was clinical but supported by the electroencephalographic (EEG) features. Using the international 10-20 electrode placement, an awake EEG was carried out on all cases and controls using a Phoenix digital 16-channel electroencephalography machine. Classification and reporting of EEG records were done following standard international criteria by two neurologists who were blinded to the clinical and neuroimaging findings of the patients and worked independently. [17-18] Epileptiform abnormalities were defined as sharps with accompanying slow waves complexes, or spikes with accompanying slow-wave discharges that are distinct from the normal background activity. [18] Sharps were defined as transient, clearly distinguishable from background activity, with pointed peaks and duration of 70-200 milliseconds. [18, 19] Spikes were defined as transient, clearly distinguishable from background activity, with pointed peaks and a duration of 20-70 milliseconds. [18] Fast frequency was defined as alpha waves at frequencies of 8 – 13 per second and beta waves at frequencies greater than 13 per second. [16, 18, 19] Theta waves were defined as frequencies between 4 – 7 waves per second and delta waves as frequencies up to 4 waves per second. [16] Periodicity was defined as the repetition of a waveform with relatively uniform morphology and duration with a quantifiable inter-discharge interval between consecutive waveforms and recurrence of the wave at nearly regular intervals. Discharges were referred to as waveforms with no more than three phases (crosses the baseline no more than twice) or any waveform lasting 0.5 seconds or less, regardless of the number of phases. Bursts were defined as waveforms lasting more than 0.5 seconds and having at least four phases (crosses the baseline at least three times. [16]

The Cognitive Screening Instrument for Dementia (CSID), a previously validated instrument in the environment was used to assess global cognitive functioning and various sub-cognition domains. [20] It is a culturally acceptable, paper and pen-based global cognitive function screening instrument, developed by Ibadan- Indianapolis Dementia Project for assessing language, memory, calculation, orientation and attention sub-domains. A score of two standard deviations below the mean score of the age-matched population was taken as cognitively impaired. The Zung Self-Rating Depression Scale (ZSRDS) with a minimum possible score of 20 and a maximum score of 80 was used to screen for depression. [21, 22] ZSRDS consists of 20 items with Likert type scale after each item and the score for each item ranges from 1 to 4. A score > 50 defined depression on the scale. [22, 23]

Sample size determination

Pocock's formula for two-group comparisons was used to calculate the minimum sample size with mean total CSID scores in epilepsy obtained from a previous local study and the expected difference in CSID score of 3.0 was postulated. [24] Due to the non-parametric distribution of the variables and the suspicion of a small dataset, bootstrap resampling methods based on observations (B=1000 bootstrapped samples) were carried out to evaluate the effect of various factors on CSID scores.

Ethical considerations

Ethical clearance was obtained from the joint institution review committee of the UCH and the College of Medicine, the University of Ibadan with UI/UCH Ethics Committee certificate number UI/EC/15/077.

The study participants were fully informed on the research protocol detailing the purpose, method, risks and benefits of the research. Each of the participants voluntarily gave written informed consent.

Data analysis

The data were entered into Microsoft Excel for cleaning and were transferred to Statistical

Package for Social Science Version 22. The Pearson Chi-Square test was used to compare categorical variables while the Student's t-test was used to compare two observed means. The Non-parametric bivariate analysis was used to determine potential predictors to be selected for multivariate analysis. The level of statistical significance was set at a p-value of <0.05.

Results

Relationship between age, age of onset, medication, depression and different domains of cognition in WWE

Tables Ia and Ib shows there were no correlation between the age, age of onset and different cognitive domains in WWE. However, there was a significant association between depression and immediate recall (p = 0.000), semantic memory (p = 0.000), attention and calculation (p = 0.000), orientation (p = 0.003) and total CSID (p = 0.000). Furthermore, there was a significant association between fluency (p = 0.032), registration (p = 0.002), semantic memory (p = 0.013), attention and calculation (p = 0.031) and total CSID (p = 0.009).

Table Ia: Relationship between Age, age of onset, medication, depression and different domains of cognition

	Percentage	*Language (Naming)*	*Language (definition)*	*Language (repetition)*	*Language (Fluency)*	*Language Compreh-ension*	*Memory (Delayed Recall)*
Age (Years)							
15-25	44.0	6.91±0.42	4.84±0.64	1.00±0.22	4.66±0.89	4.73±0.79	1.84±0.37
26-35	30.0	6.60±1.00	4.67±0.71	1.00±0.00	4.50±0.86	4.63±0.76	1.83±0.59
36-45	26.0	6.81±0.57	4.92±0.27	1.00±0.00	4.81±0.49	4.81±0.40	1.81±0.40
F-Test		1.854	1.397	0.000	1.046	0.434	0.045
p-value		0.162	0.252	1.000	0.355	0.649	0.956
Age at Onset (Years)							
1-15	34.0	6.78±0.68	4.81±0.47	1.00±0.00	4.64±0.76	4.56±0.88	1.83±0.56
16-20	42.0	6.81±0.74	4.81±0.77	1.00±0.22	4.62±0.91	4.81±0.63	1.86±0.35
21-45	24.0	6.76±0.62	4.81±0.40	1.00±0.00	4.71±0.64	4.81±0.40	1.81±0.40
F-Test		0.056	0.033	0.000	0.130	1.069	1.204
p-value		0.982	0.992	1.000	0.942	0.366	0.313
ZUNG Score							
Depressed	14.00	6.57±1.16	4.64±0.84	1.07±0.27	4.36±1.08	4.64±1.15	1.86±0.77
Not depressed	86.00	6.83±0.58	4.83±0.55	0.99±1.08	4.70±0.74	4.73±0.60	1.83±0.38
F-Test		1.664	1.276	4.246	2.230	0.198	0.058
p-value		0.200	0.261	0.042	0.139	0.658	0.809
Medication							
CAB	50.00	6.84±0.65	4.70±0.76	1.00±0.20	4.48±0.91	4.62±0.75	1.84±0.51
LEV	50.00	6.74±0.72	4.92±0.34	1.00±0.00	4.82±0.63	4.82±0.63	1.82±0.39
F-Test		0.529	3.469	0.000	4.731	2.078	0.049
p-value		0.469	0.066	1.000	0.032	0.153	0.826

CAB-Carbamazepine; LEV-Levetiracetam

Comparison of the electroencephalographic patterns in cognitively impaired and non-cognitively impaired WWE

Table II shows that the frequency of delta waves and theta waves were 75% and 75% in WWE with cognitive impairment compared to 25% and 25% respectively in those without cognitive impairment (p = 0.004).

Table Ib: Relationship between Age, age of onset, medication, depression and different domains of cognition

	Percentage	*Memory (Registration)*	*Memory (Immediate Recall)*	*Memory (semantic)*	*Attention & Calculation*	*Orientation (time)*	*Orientation (place)*	*CSID*
Age (Years)								
15-25	44.0	3.70±0.51	5.43±0.97	7.84±1.60	7.16±1.18	3.95±0.21	5.93±0.25	69.86±5.68
26-35	30.0	3.60±0.67	5.50±0.67	8.17±1.21	7.40±1.07	3.93±0.37	6.23±1.92	70.07±6.27
36-45	26.0	3.42±0.81	5.31±0.97	8.08±1.16	7.46±0.86	4.00±0.00	6.00±0.00	69.92±4.79
F-Test		1.543	0.272	0.548	0.801	0.539	0.739	0.012
p-value		0.219	0.762	0.580	0.452	0.585	0.480	0.988
Age at Onset (Years)								
1-15	34.0	3.64±0.59	5.42±1.08	7.64±1.73	7.22±1.20	3.94±0.23	6.22±1.69	69.61±5.75
16-20	42.0	3.52±0.71	5.38±0.94	8.24±1.05	7.33±1.05	3.95±0.31	5.90±0.48	70.00±5.93
21-45	24.0	3.67±0.66	5.48±0.93	8.10±1.22	7.43±0.93	4.00±0.00	6.00±0.00	70.29±4.93
F-Test		0.426	0.159	1.472	0.196	0.256	0.582	0.112
p-value		0.735	0.923	0.227	0.899	0.857	0.628	0.953
ZUNG Score								
Depressed	14.00	3.43±0.76	4.29±1.44	6.21±1.71	5.86±1.51	3.79±0.58	5.64±0.84	63.79±8.71
Not Dep	86.00	3.63±0.63	5.60±0.74	8.29±1.07	7.55±0.76	3.99±0.11	6.10±1.08	70.94±4.20
F-Test		1.129	27.959	37.381	42.611	9.065	2.303	24.335
p-value		0.291	0.000	0.000	0.000	0.003	0.132	0.000
Medication								
CAB	50.00	3.40±0.73	5.32±1.08	7.66±1.35	7.08±1.10	3.94±0.31	6.10±1.50	68.50±6.26
LEV	50.00	3.80±0.49	5.52±0.86	8.34±1.33	7.54±0.99	3.98±0.14	5.98±0.14	71.38±4.45
F-Test		10.316	1.050	6.421	4.796	0.676	0.316	7.026
p-value		0.002	0.308	0.013	0.031	0.413	0.575	0.009

Not Dep- Not Depressed; CSID-Cognitive Screening Instrument for Dementia; CAB-Carbamazepine; LEV-Levetiracetam

Table II: Comparison of EEG background changes between women with epilepsy that were cognitively impaired and not cognitively impaired

Variables	*Categories*	*Cognitive Impairment*	*No cognitive Impairment*	*Statistics*	*p-value*
Background (n, %)	Delta	9 (75.0)	3 (25.0)	$\chi^2 = 15.622$	0.004
	Theta	15 (75.0)	5 (25.0)		
	Alpha	4 (22.2)	14 (77.8)		
	Intermixed	10 (50.0)	10 (50.0)		
	Intermixed slow	21(70.0)	9 (30.0)		
Frequency (n, %)	Fast	18 (42.9)	24 (57.1)	$\chi^2 = 7.801$	0.005
	Slow	41 (70.7)	17 (29.3)		
Slowing (n, %)	Absent	23 (50.0)	23 (50.0)	$\chi^2 = 2.852$	0.091
	Present	36 (66.7)	18 (33.3)		
Epileptiform (n, %)	Nil	7 (50.0)	7 (50.0)	$\chi^2 = 2.763$	0.251
	Focal	22 (52.4)	20 (47.6)		
	Generalized	30 (68.2)	14 (31.8)		
Periodic Epileptiform Discharge (n, %)	Absent	36 (50.7)	35 (49.3)	$\chi^2 = 6.965$	0.008
	Present	23 (79.3)	6 (20.7)		

The frequency of fast frequency and slow frequency were 42.9% and 70.7% in WWE (p = 0.005) while the frequency of periodic epileptiform pattern was 79.3% compared to 20.7% in those without cognitive impairment (p = 0.008).

Background EEG changes versus cognitive status in WWE

Consistently, the highest score was seen among cases with alpha rhythm while it was lowest among those with delta rhythms across the domains of cognition and this difference was statistically significant for language fluency (p = 0.039), language comprehension (p = 0.00), memory delayed recall (p = 0.004), memory immediate recall (p = 0.046), semantic memory (p = 0.001) and total CSID (p = 0.000) (Table IIIa and IIIb).

Table IIIa: Relationship between background, EEG changes and different domains of cognition

Background	*Language (Naming)*	*Language (definition)*	*Language (repetition)*	*Language (Fluency)*	*Language Compreh-ension*	*Memory (Delayed recall)*	*Memory (Registration)*
Delta	6.33±1.30	4.42±0.90	1.00±0.00	4.25±0.87	3.75±1.21	1.75±0.45	3.33±0.65
Theta	6.75±0.64	4.95±0.22	1.00±0.00	4.90±0.31	4.90±0.31	1.70±0.47	3.50±0.83
Alpha	7.00±0.00	5.00±0.00	1.00±0.00	5.00±0.00	5.00±0.00	2.11±0.47	3.83±0.51
Intermixed	7.00±0.00	4.80±0.89	1.00±0.32	4.55±1.15	4.95±0.39	1.90±0.31	3.65±0.59
Intermixed slow	6.73±0.74	4.77±0.50	1.00±0.00	4.50±0.86	4.67±0.66	1.73±0.45	3.60±0.62
F-Test	2.419	2.165	0.000	2.627	10.224	2.941	1.240
p-value	0.054	0.079	1.000	0.039	0.000	0.024	0.299

Table IIIb: Relationship between background, EEG changes and different domains of cognition

Background	*Memory (Immediate Recall)*	*Memory (semantic)*	*Attention and Calculation*	*Orientation (time)*	*Orientation (place)*	*CSID*
Delta	4.67±1.30	6.58±2.23	6.75±1.48	3.67±0.65	5.58±0.90	63.67±10.43
Theta	5.55±0.76	7.95±1.10	7.55±0.83	4.00±0.00	6.00±0.00	70.90±3.11
Alpha	5.72±0.96	8.72±0.75	7.67±0.91	4.00±0.00	6.00±0.00	72.94±2.39
Intermixed	5.35±1.09	8.15±1.09	7.30±1.03	4.00±0.00	5.95±0.22	70.55±4.70
Intermixed slow	5.50±0.78	8.07±1.23	7.17±1.09	4.00±0.00	6.33±1.83	69.60±4.31
F-Test	2.529	5.263	1.760	5.971	1.183	6.476
p-value	0.046	0.001	0.143	0.000	0.323	0.000

CSID-Cognitive Screening Instrument for Dementia

Epileptiform pattern versus cognitive state in WWE

The presence of epileptiform patterns showed a significant association with language definition (p = 0.046), language fluency (p = 0.015) and attention and calculation (p = 0.034). WWE with a periodic pattern on EEG had a lower mean total CSID score of 67.92±7.20 compared to a score of 70.77±4.60 among those without a periodic pattern on EEG (p = 0.019). In the language subdomain, the mean score of 22.35±2.06 among WWE with the presence of periodic pattern was higher compared to 21.28±2.71 among WWE without a periodic pattern (p = 0.034) (Tables IV and V).

Table IV: Relationship between the presence of epileptiform pattern and cognitive changes on EEG

Cognitive domains	*NEP (n = 14)*	*FEP (n = 42)*	*GEP (n = 44)*	*F-Test*	*p-value*
Language (Naming)	6.86±0.53	6.88±0.45	6.68±0.88	0.983	0.378
Language (definition)	4.79±0.43	4.98±0.15	4.66±0.83	3.169	0.046
Language (repetition)	1.00±0.00	1.02±0.15	0.98±0.15	1.155	0.319
Language (Fluency)	4.64±0.63	4.83±0.58	4.48±0.98	2.202	0.116
Language Comprehension	4.36±0.93	4.93±0.34	4.64±0.81	4.367	0.015
Memory (Delayed recall)	2.07±0.62	1.81±0.40	1.78±0.42	2.479	0.089
Memory (Registration)	3.71±0.47	3.69±0.64	3.48±0.70	1.413	0.248
Memory (Immediate Recall)	5.14±1.35	5.60±0.86	5.34±0.94	1.396	0.252
Memory (semantic)	7.64±1.82	8.31±1.05	7.82±1.47	1.949	0.148
Attention & Calculation	7.29±1.27	7.62±0.82	7.02±1.15	3.509	0.034
Orientation (time)	3.93±0.27	4.00±0.00	3.93±0.33	0.983	0.378
Orientation (place)	5.93±0.27	5.98±0.15	6.14±1.59	0.329	0.720
Total CSID	69.21±6.80	71.40±3.83	68.77±6.36	2.595	0.080

NEP-No Epileptiform Pattern, FEP-Focal Epileptiform Pattern, GEP-Generalized Epileptiform Pattern
CSID-Cognitive Screening Instrument for Dementia

Frequency versus cognitive state in WWE

The mean total CSID score and memory subdomain score were higher among WWE with the presence of fast frequency on EEG compared to those with slow frequency on EEG (p = 0.01 and 0.03 respectively) (Table VI).

Time of onset of epilepsy versus cognitive changes in WWE

There was no significant relationship between the time of onset of epilepsy and cognitive changes except for the language naming subdomain (p = 0.004) (Table VII).

The clinical and EEG predictors of cognitive impairment in WWE

The presence of alpha wave (p = 0.027), delta wave (p = 0.013), frequency (p = 0.015) and periodic epileptiform discharge (p = 0.031) were EEG predictors of cognitive impairment while medication type (p = 0.016) and depression (p = 0.001) were the clinical predictors of cognitive impairment in WWE (Table VIII).

Table V: Relationship between the presence of periodic epileptiform discharge on EEG and cognitive function

Cognitive Domain	*Absent PED (n = 71)*	*Present PED (n = 29)*	*F-Test*	*p-value*
Language (Naming)	6.82±0.62	6.72±0.84	0.374	0.542
Language (definition)	4.87±0.56	4.66±0.67	2.788	0.098
Language (repetition)	0.99±0.12	1.03±0.19	2.439	0.122
Language (Fluency)	4.76±0.76	4.38±0.82	4.908	0.029
Language Comprehension	4.82±0.59	4.48±0.87	4.912	0.029
Memory (Delayed recall)	1.80±0.40	1.90±0.56	0.890	0.348
Memory (Registration)	3.68±0.63	3.41±0.68	3.420	0.067
Memory (Immediate Recall)	5.49±0.88	5.24±1.18	1.372	0.244
Memory (semantic)	8.18±1.30	7.55±1.48	4.474	0.037
Attention & Calculation	7.39±1.02	7.10±1.18	1.530	0.219
Orientation (time)	3.99±0.12	3.90±0.41	2.839	0.095
Orientation (place)	5.99±0.12	6.17±1.98	0.632	0.429
Total CSID	70.77±4.60	67.90±7.20	5.706	0.019

PED- Periodic Epileptiform Discharges
CSID-Cognitive Screening Instrument for Dementia

Discussion

This study demonstrated that changes in the background EEG pattern can predict a cognitive outcome. The alpha wave was associated with a good outcome while the delta wave was associated with a poor outcome. Previous studies have been able to identify EEG as a reliable biomarker that helps in detecting cortical abnormalities associated with cognitive decline and dementia. This study also confirms the previous hypothesis that periodic epileptiform discharges are associated with cognitive impairment or diseases associated with cognitive decline such as ischaemic stroke, viral encephalitis, Prion disease and acute repetitive seizures. PLED (Periodic Lateralizing Epileptiform Discharge) often are manifestations of increased neuronal excitability, irrespective of the underlying aetiology. [16, 25, 26] Van der Hiele *et al.* described EEG as a marker of future cognitive performance with increased theta activity during

eye closure and less alpha reactivity during eyes opening and memory activation indicating lower global and executive performance. A combination of information from EEG, MRI and neuropsychology is being proposed as a general model for decline cognitive performance in a heterogeneous population. [4]

Consistently, from the findings in the present study, higher scores were recorded among cases with alpha rhythm while lower scores were recorded among those with delta rhythms across the domains of cognition. This was significant for language fluency, language comprehension, memory delayed recall, memory immediate recall, semantic memory and total CSID - which is a measure of global cognitive function.

Table VI: Relationship between frequency pattern on EEG and cognitive changes

Frequency	*Fast Frequency*	*Slow frequency*	*F-Test*	*p-value*
Language (Naming)	7.00±0.00	6.64±0.87	7.212	0.009*
Language (definition)	4.88±0.63	4.76±0.57	1.020	0.315
Language (repetition)	0.98±0.15	1.01±0.13	2.054	0.155
Language (Fluency)	4.81±0.74	4.53±0.82	2.965	0.088
Language Comprehension	4.88±0.40	4.60±0.84	3.972	0.049*
Memory (Delayed recall)	1.90±0.30	1.78±0.53	2.013	0.159
Memory (Registration)	3.79±0.52	3.47±0.71	6.196	0.014*
Memory (Immediate Recall)	5.62±0.79	5.28±1.07	3.073	0.083
Memory (semantic)	8.45±0.94	7.67±1.55	8.386	0.005*
Attention & Calculation	7.38±0.96	7.26±1.15	0.316	0.575
Orientation (time)	4.00±0.00	3.93±0.32	1.984	0.162
Orientation (place)	6.24±1.54	5.90±0.45	2.555	0.113
Total CSID	71.62±3.36	68.72±6.53	6.910	0.010*

CSID-Cognitive Screening Instrument for Dementia

This finding agrees with the previous finding that EEG measures obtained during recall or recognition were largely reliable and helpful in predicting cognitive decline. The predictive value of EEG changes as biomarkers can be enhanced by performing a specific task during acquisition. [4, 6, 27] EEG correlates of cognitive ability are age-dependent with expected moderate changes in alpha and Theta-Alpha ratio. However, adults who did not show the age-related changes are likely to exhibit cognitive deficits when compared to those that exhibited the age-related changes. [6]

In the present study, while the presence of epileptiform pattern was comparable in WWE with or without cognitive impairment, there was a significant association between language

(comprehension and definition), attention and calculation sub-domain and sub-type of epileptiform discharges. There was a significant difference between the two groups with regards to periodic epileptiform discharges. Indeed, growing pieces of evidence are linking epileptiform discharges on EEG and cognitive disorders. Epileptiform discharge leads to dysfunctional memory encoding and consolidation process. An unexplored therapeutic potential in treating cognitive disorders might be the modulation of epileptiform discharges and neuronal excitability. [28] Therefore, it is reasonable to consider the role of AEDs in controlling neuronal toxicity and epileptiform discharges associated with cognitive impairment.

Table VII: Relationship between the time of onset of epilepsy and cognitive changes

Duration of Epilepsy	*<1 month*	*1-6 months*	*6 months-1 year*	*2-5 years*	*>5 years*	*F-Test*	*p-value*
Language (Naming)	5.83±1.33	7.00±0.00	7.00±0.00	6.94±0.25	6.74±0.80	4.211	0.004*
Language (definition)	4.67±0.82	5.00±0.00	4.83±0.39	4.87±0.34	4.76±0.77	0.366	0.833
Language (repetition)	1.00±0.00	1.00±0.00	1.00±0.00	1.03±0.18	0.98±1.47	0.659	0.622
Language (Fluency)	4.50±1.22	4.80±0.45	4.83±0.58	4.68±0.70	4.59±0.88	0.329	0.858
Language Comprehension	4.67±0.82	4.80±0.45	4.92±0.29	4.87±0.43	4.57±0.89	1.203	0.315
Memory (Delayed recall)	1.83±0.41	1.60±0.55	1.83±0.39	1.90±0.30	1.80±0.54	0.557	0.694
Memory (Registration)	3.83±0.41	3.40±0.89	3.83±0.39	3.61±0.67	3.52±0.69	0.860	0.491
Memory (Immediate Recall)	5.83±0.41	5.80±0.45	5.50±0.90	5.45±0.89	5.28±1.12	0.706	0.590
Memory (semantic)	8.83±0.41	8.00±1.00	8.17±1.11	8.06±1.24	7.80±1.61	0.836	0.506
Attention & Calculation	8.00±0.00	6.80±1.30	7.33±0.98	7.39±0.92	7.22±1.21	1.037	0.392
Orientation (time)	4.00±0.00	4.00±0.00	4.00±0.00	4.00±0.00	3.91±0.35	0.789	0.535
Orientation (place)	6.00±0.00	6.00±0.00	6.00±0.00	5.97±0.18	6.11±1.57	0.089	0.986
Total CSID	71.67±4.08	70.00±3.81	71.17±4.04	70.06±4.93	69.30±6.66	0.429	0.787

Cognitive Screening Instrument for Dementia

However, the role of AEDs is limited by the poor tolerability, narrow therapeutic index and worsening cognitive function. These drugs exert widespread effects on neuronal networks and cause a range of undesired side effects such as sedation and cognitive deficits. [6] Newer AEDs have more selective targets modulating excitability in discreet neuronal circuits and are better positioned for the potential treatment of interictal epileptiform discharges associated with cognitive impairment. [28]

The finding from the present study revealed that LEV performed better on assessing memory domain and overall global cognitive function. This is in tandem with many animal and clinical studies showing the cognitive enhancing effect of LEV, a function it was initially developed for

from Piracetam. It acts on synaptic vesicle protein and has better tolerability compared to CAB and other conventional AEDs that works on postsynaptic receptors or ion channels. [29] LEV action includes modulation of hippocampal activities, enhancement of executive function, working memory, fluid intelligence, verbal fluency psychomotor speed with fewer untoward neurophysiological and neuropsychological effect compared with CAB. It has been postulated synaptic vesicle 2A (SV2A) is an emerging biomarker of synaptopathy-associated neuropsychiatry disorders with cortical hyperactivity such as epilepsy and Alzheimer's disease. Therefore, reducing SV2A activity might be a good therapeutic end-point in epilepsy and Alzheimer disease. The ability of LEV to modulate SV2A remains underutilized as a potential therapeutic endpoint.

Table VIII: Relationship between the clinical and EEG predictors of cognitive impairment

Variables	*B*	*S. E*	*Wald*	*p-value*	*Odds ratio*	*95% C I*	
						Lower	**Upper**
Medication							
CAB	-0.116	0.048	5.782	0.016	0.891	0.811	0.979
LEV	Reference						
ZUNG score							
Depressed	-0.189	0.058	10.676	0.001	0.828	0.739	0.927
Not Depressed	Reference						
Background							
Delta	-0.126	0.057	4.897	0.027	0.881	0.788	0.986
Theta	0.068	0.070	0.962	0.327	1.071	0.934	1.227
Alpha	0.311	0.125	6.146	0.013	1.365	1.067	1.746
Intermixed	0.047	0.066	0.498	0.480	1.048	0.921	1.192
Intermixed-slow	Reference						
Periodicity							
Absent	0.088	0.041	4.649	0.031	1.092	1.008	1.182
Present	Reference						
Frequency							
Fast	0.129	0.053	5.862	0.015	1.138	1.025	1.263
Slow	Reference						

B-Regression Coefficient; S.E - Standard Error; CI-Confidence Interval

In the present study, 14% of the patients with WWE had depression, and depression showed a negative relationship with total cognition score and its sub-domain, especially memory, orientation, attention and calculation. Cognitive deficit has been identified as a primary mediator in major depressive disorder and it has been proposed that cognitive dysfunction may improve after the treatment of depression but the symptoms persist. [30-32] Difficulties in thinking, learning, executive function, concentrating decision making process and memory are major cognitive deficits in patients with depression. Recent studies are now linking mutation on the short allele of 5′ promoter polymorphism of serotonin transporter gene (5-HTTPLR) to the onset of depression, cognitive biases in depression and clinical response in both remission and response rate. [31, 32] Till date, only duloxetine and vortioxetine, unlike other available antidepressant drugs have pro-cognitive effect as the cognitive aspect of depression is generally less addressed. [30, 31]

This study has a few limitations. The conventional qualitative EEG was used in the present study because of the non-availability of quantitative EEG. Therefore, the Theta-Alpha Ratio and other ratios could not be calculated. Furthermore, while Pocock's formula for two-

group comparisons was used to calculate the sample size, using the mean total CSID scores, bootstrap resampling was done due to the non-parametric distribution of variables and the suspicion of a small dataset. In addition, even though the participants had neuroimaging preferably MRI, the EEG changes and imaging findings could not be correlated.

Conclusion

The study demonstrated that changes in background EEG pattern can predict the cognitive outcome; alpha wave was associated with the good cognitive outcome while delta wave was associated with poor cognitive outcome. The study also confirmed the previous hypothesis that periodic epileptiform discharges are predictive of cognitive impairment. The EEG has been underutilized as a screening tool in detecting a decline in cognitive functioning, as such awareness needs to be created in this regard to reduce the overall burden of cognitive impairment.

Acknowledgement: The authors acknowledged Dr (Mrs) Mojisola Olushola-Bello and David Oboh for their roles in image reporting and acquisition. Mrs Tosin Elegbede, Miss Onafowokan Oyinkansola and Stella Adeyemo are also appreciated for their assistance with data collection.

Authors' Contributions: OL and OA conceived the study. All the authors participated in the study design, data collection and interpretation and made a significant revision of the draft manuscript for sound intellectual content. OL performed the statistical analysis. OL and OA were involved in manuscript drafting. All the authors approved the final version of the manuscript.

Conflict of Interest: None.
Funding: Self-funded.
Publication History: Submitted 12 March 2021**; Accepted** 09 May 2021.

References

1. Yassine IA, Eldeeb WM, Gad KA, Ashour YA, Yassine IA, Hosny AO. Cognitive functions, electroencephalographic and diffusion tensor imaging changes in children with active idiopathic epilepsy. Epilepsy Behav 2018; 84: 135–141. https://doi.org/10.1016/j.yebeh.2018.04.024

2. Nemtsas P, Birot G, Pittau F, Michel CM, Schaller K, Vulliemoz S, *et al.* Source localization of ictal epileptic activity based on high-density scalp EEG data. Epilepsia 2017; 58: 1027–1036. https://doi.org/10.1111/epi.13749

3. Landi S, Petrucco L, Sicca F, Ratto GM. Transient cognitive impairment in epilepsy. Front Mol Neurosci [Internet]. 2019 Jan 7 [cited 2020 Mar 19];11. https://doi.org/10.3389/fnmol.2018.00458

4. Höller Y, Butz KHG, Thomschewski AC, Schmid EV, Hofer CD, Uhl A, *et al.* Prediction of cognitive decline in temporal lobe epilepsy and mild cognitive impairment by EEG, MRI, and Neuropsychology. Comput Intell Neurosci [Internet]. 2020 May 20 [cited 2021 Feb 26]; 2020. https://doi.org/10.1155/2020/891961

5. Ferrara NC, Trask S, Pullins SE, Helmstetter FJ. The dorsal hippocampus mediates synaptic destabilization and memory lability in the amygdala in the absence of contextual novelty. Neurobiol Learn Mem 2019; 166: 107089. https://doi.org/10.1016/j.nlm.2019.107089

6. Trammell JP, MacRae PG, Davis G, Bergstedt D, Anderson AE. The relationship of cognitive performance and the Theta-Alpha Power Ratio is age-dependent: An EEG study of short term memory and reasoning during task and resting-state in healthy young and old adults. Front Aging Neurosci [Internet]. 2017 [cited 2021 Feb 28]; 9. Available from: https://www.frontiersin.org/articles/10.3389/fnagi.2017.00364/full

7. Sánchez-Moguel SM, Alatorre-Cruz GC, Silva-Pereyra J, González-Salinas S, Sanchez-Lopez J, Otero-Ojeda GA, *et al.* Two different populations within the healthy elderly: Lack of conflict detection in those at risk of cognitive decline. Front Hum Neurosci. 2017; 11: 658. https://doi.org/10.3389/fnhum.2017.00658

8. Hamson DK, Roes MM, Galea LAM. Sex hormones and cognition: Neuroendocrine influences on memory and learning. Compr Physiol 2016 13; 6: 1295–1337. https://doi.org/10.1002/cphy.c150031

9. Hirnstein M, Hugdahl K, Hausmann M. Cognitive sex differences and hemispheric asymmetry: A critical review of 40 years of research. Laterality 2019; 24: 204–252. https://doi.org/10.1080/1357650X.2018.1497044

10. Hyde JS. Sex and cognition: gender and cognitive functions. Curr Opin Neurobiol 2016; 38: 53–56. https://doi.org/10.1016/j.conb.2016.02.007

11. Wang J, Xiao LD, Wang K, Luo Y, Li X. Gender differences in cognitive impairment among rural elderly in China. Int J Environ Res Public Health 2020; 17: 3724. https://doi.org/10.3390/ijerph17103724

12. Duarte-Guterman P, Yagi S, Chow C, Galea LAM. Hippocampal learning, memory, and neurogenesis: Effects of sex and estrogens across the lifespan in adults. Horm Behav 2015; 74: 37–52. https://doi.org/10.1016/j.yhbeh.2015.05.024

13. Rubin LH, Carter CS, Drogos LL, Pournajafi-Nazarloo H, Sweeney JA, Maki PM. Effects of sex, menstrual cycle phase, and endogenous hormones on cognition in schizophrenia. Schizophr Res 2015; 166: 269–275. https://doi.org/10.1016/j.schres.2015.04.039

14. Huang YH, Chi NF, Kuan YC, Chan L, Hu CJ, Chiou HY, *et al.* Efficacy of phenytoin, valproic acid, carbamazepine and new antiepileptic drugs on control of late-onset post-stroke epilepsy in Taiwan. Eur J Neurol 2015; 22: 1459–1468. https://doi.org/10.1111/ene.12766

15. Ogunjimi L, Yaria J, Makanjuola A, Ogunniyi A. Sexual dysfunction among Nigerian women with epilepsy. Epilepsy Behav 2018; 83: 108–112. https://doi.org/10.1016/j.yebeh.2018.02.004

16. Hirsch LJ, LaRoche SM, Gaspard N, Gerard E, Svoronos A, Herman ST, *et al.* American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2012 version. J Clin Neurophysiol 2013; 30: 1–27. https://doi.org/10.10197/WNP.0b013e3182784729

17. Beniczky S, Hirsch LJ, Kaplan PW, Pressler R, Bauer G, Aurlien H, *et al.* Unified EEG terminology and criteria for nonconvulsive status epilepticus. Epilepsia 2013; 54 (Suppl 6): 28–29. https://doi.org/10.1111/epi.12270

18. Maganti RK, Rutecki P. EEG and epilepsy monitoring. Continuum (Minneap Minn) 2013; 19: 598–622. https://doi.org/10.1212/01.CON.0000431378.51935.d8

19. Bermeo-Ovalle A. Bringing EEG back to the future: Use of cEEG in Neurocritical Care. Epilepsy Curr 2019; 19: 243–245. https://doi.org/10.1177/1535759719858350

20. Hall KS, Gao S, Emsley CL, Ogunniyi AO, Morgan O, Hendrie HC. Community screening interview for dementia (CSI 'D'); performance in five disparate study sites. Int J Geriatr Psychiatry 2000; 15: 521–531. https://doi.org/10.1002/1099-1166(200006)15

21. Jokelainen J, Timonen M, Keinänen-Kiukaanniemi S, Härkönen P, Jurvelin H, Suija K. Validation of the Zung self-rating depression scale (SDS) in older adults. Scand

J Prim Health Care 2019; 37: 353–357. https://doi.org/10.10197/WNP.0b013e3182784729

22. Dunstan DA, Scott N. Clarification of the cut-off score for Zung's self-rating depression scale. BMC Psychiatry 2019; 19: 177. https://doi.org/10.1186/s12888-019-2161-0

23. Dunstan DA, Scott N, Todd AK. Screening for anxiety and depression: reassessing the utility of the Zung scales. BMC Psychiatry 2017; 17: 329. https://doi.org/10.1186/s12888-017-1489-6

24. Sunmonu TA, Komolafe MA, Ogunrin AO, Ogunniyi A. Cognitive assessment in patients with epilepsy using the Community Screening Interview for Dementia. Epilepsy Behav 2009; 14: 535–539. https://doi.org/10.1186/s12888-019-2161-0

25. Lin L, Drislane FW. Lateralized Periodic Discharges: A Literature Review. J Clin Neurophysiol 2018; 35:189–198. https://doi.org/10.1097/WNP.0000000000000448

26. Hartl E, Rémi J, Stoyke C, Noachtar S. What is the "L" in LPDs? Localized as well as lateralized. Acta Neurologica Scandinavica 2017; 136: 160–163. https://doi.org/10.1111/ane.12730

27. Johnson L, Yao J, Zou L, Xiao T, Loprinzi PD. Mental Imagery and acute exercise on episodic memory function. Brain Sci 2019; 9: 237. https://doi.org/10.3390/brainsci9090237

28. Horvath AA, Csernus EA, Lality S, Kaminski RM, Kamondi A. Inhibiting epileptiform activity in cognitive disorders: Possibilities for a novel therapeutic approach. Front Neurosci [Internet]. 2020 Oct 15 [cited 2021 Feb 28];14. https://doi.org/10.3389/fnins.2020.557416.

29. Löscher W, Gillard M, Sands ZA, Kaminski RM, Klitgaard H. Synaptic Vesicle Glycoprotein 2A ligands in the treatment of epilepsy and beyond. CNS Drugs 2016; 30: 1055–1077. https://doi.org/10.1007/s40263-016-0384-x

30. Perini G, Cotta Ramusino M, Sinforiani E, Bernini S, Petrachi R, Costa A. Cognitive impairment in depression: recent advances and novel treatments. Neuropsychiatr Dis Treat 2019; 15: 1249–1258. https://doi.org/10.2147/NDT.S199746

31. Polito L, Davin A, Vaccaro R, Abbondanza S, Govoni S, Racchi M, *et al.* Serotonin transporter polymorphism modifies the association between depressive symptoms and sleep onset latency complaint in elderly people: results from the "InveCe.Ab" study. J Sleep Res 2015; 24: 215–222. https://doi.org/10.1111/jsr.12248

32. Margoob MA, Mushtaq D. Serotonin transporter gene polymorphism and psychiatric disorders: Is there a link? Indian J Psychiatry 2011; 53: 289–299. https://doi.org/10.4103/0019-5545.91901

This is an Open Access document licensed for distribution under the terms and conditions of the Creative Commons Attribution License (http://creativecommons.org/licenses/by-nc/4.0). This permits unrestricted, non-commercial use, reproduction and distribution in any medium provided the original source is adequately cited and credited.