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Neuropsychological performance in patients with focal drug-resistant epilepsy and different factors that affect their performance

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Abstract

Background: Drug-resistant epilepsy (DRE) accounts for nearly 30% of patients with epilepsy, which is associated with high incidence of cognitive comorbidity. The aim of this work was to study the role of neuropsychological assessment in patients with epilepsy, and different factors that affect their performance in patients with multiple factors (focal onset DRE).

Methods: 118 patients were recruited from Kasr Alainy hospital, epilepsy outpatient clinic with focal DRE. The patients' demographic and clinical data were collected, Electroencephalograph (EEG) interictal/ictal (when available), and brain imaging (MRI epilepsy protocol). Neuropsychological assessment by Wechsler Adult Intelligence Scale (WAIS-IV), proposed neurocognitive assessment battery and mood assessment was done. Their performance in neuropsychological assessment was correlated with the collected data. Concordance between different assessment modalities and brain lesion were done.

Results: Among recruited patients, 67.3% of patients showed Full-scale Intelligence Quotient (FSIQ) was less than average. FSIQ score significantly correlated with years of education, and number of anti-seizure medications (ASMs). Neurocognitive assessment battery could achieve cognitive profile of the patients but with poor lateralizing value. Executive function was the most affected cognitive domain. History of status epilepticus significantly affect FSIQ and executive function performance. Fifty-six percent of patients had depression. Among the analyzed factors, FSIQ and lesional brain imaging significantly affected neurocognitive performance of studied patients. Clinical semiology had better concordance in lateralization (74.7%) and localization (69.5%) with brain imaging compared to ictal EEG. Among patients who had ictal EEG recording, 36.4% patients (25% were temporal lobe) had complete concordance, while 38.6% patients had partial concordance.

Conclusions: Among analyzed factors, FSIQ was the most significant determinant of studied population's neurocognitive performance. Clinical semiology were the best correlated with brain lesion. Complete concordance was best detected at the temporal lobe.

Keywords: Focal epilepsy, Drug-resistant epilepsy neuropsychological assessment, Performance, Factors, Concordance

Background

Cognitive impairment shows a high incidence rate in people with epilepsy (PWE), it includes both cognitive functions and intelligence quotient (IQ) performance. It is one of the common and troubling comorbidities in PWE [1, 2].

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Neuropsychological assessment is developing to become part of routine assessment, presurgical and postsurgical assessment in PWE. Neuropsychological assessment in routine epilepsy care provides comprehensive and objective assessment of cognitive and psychological functions in PWE. Its role may be diagnostic, prognostic or differentiating. Diagnostic role is guided by cognitive or behavior impairment to localize seizure network or epilepsy syndrome. Prognostic role includes the assessment of effect of seizures, medications on the individual cognitive functioning. In addition, it could provide psychoeducation to patients, their families about the implication of assessment and cognitive, behavioral or psychological treatment to aid in daily functioning. Differentiating role between neurological, psychological and social factors causing the clinical presentation at certain time [3, 4].

Recognition of determinants of cognitive impairment is usually challenging, especially in retrospective assessment in patients with long standing epilepsy. Despite the common finding is that longer duration of epilepsy associated with worse cognitive performance [5].

In drug-resistant epilepsy (DRE) variable factors would affect cognition. Intellectual abilities are usually formed based on learning and memory mechanism during childhood, while early onset of epilepsy and frequent seizure occurrence interfere markedly with these mechanisms during critical period of brain development, which lead to failure of acquisition of such functions [6].

This work aimed to study the value of neuropsychological assessment in people with DRE, and the relationship between intelligence and cognitive performance among those patients, in addition to assessing the effect of different factors on patients' performance. In this study, focal onset seizures were specifically included to assess the impact of focality on cognitive function either specific or global.

Methods

Study design and participants: this cross-sectional study was conducted over duration of 15 months, from September 2019 to November 2020. All patients with DRE [7], who visited the epilepsy outpatient clinic of Cairo University Hospitals during the period of the study, were included. Both males and females aged ≥ 16 years, can read, write, do simple calculation and had focal onset seizures [8] were included; while those with uncontrolled seizures due to non-compliance, or received anti-seizure medications (ASMs) less than 1 year were excluded from the study, as shown in Fig. 1.

All patients were subjected to the following as shown in Fig. 1.

History taking and clinical assessment

They include demographics, age at onset, duration of illness, and ASMs regimen. Seizure semiology was documented as described by a reliable witness or home video record of the seizures or seizures recorded in the Cairo University Epilepsy Unit (CUEU). Documented semiology was analyzed according to the new International League against epilepsy (ILAE) classification [9]. Etiology of epilepsy was classified as structural, infectious, immune, unknown, metabolic and genetic to conform to the aforementioned ILAE classification, which was found in 81 (68.6%), 12 (10.2%), 2(1.7%), 23 (19.5%), 0 (0%), and 0 (0%) patients, respectively. All included patients were subjected to detailed neurological examination.

Video electroencephalography (EEG)

Video EEG was performed for all included patients with the help of a well-trained EEG technician at CUEU. Nihon Kohden Neurofax EEG apparatus (Tokyo, Japan) was used. Electrode placement was done according to the international 10–20 system; Additional electrodes at T1/T2 positions and for ECG recording [10]. The occurrence of seizures during the recording was documented for detailed semiology analysis.

An expert neurophysiologist assessed all recordings: presence or absence of interictal epileptiform discharge (IEDs), localization and lateralization of IEDs if present, localization and lateralization of seizure onset during ictal recording.

Epilepsy-protocol MRI—brain

It was performed on a 1.5 T General Electric (GE) Signa clinical scanner (Milwaukee, WI, USA). The MRI HARNESS protocol were implemented for assessment of PWE, that included: three dimension (3D) T1-weighted sequence, 3D fluid attenuation inversion recovery (FLAIR) sequences and 2D coronal T2-weighted sequence acquired perpendicular to the hippocampus, [11].

Brain lesion was assessed according to the anatomical localization to be further analyzed in relation to the electro-clinical data. Concordance of lateralization and localization between MRI brain and both clinical semiology and video EEG was done, based on assumption that brain lesion is the epileptogenic focus [12]. In addition, complete concordance was established when the three modalities [seizure semiology, ictal EEG, and brain
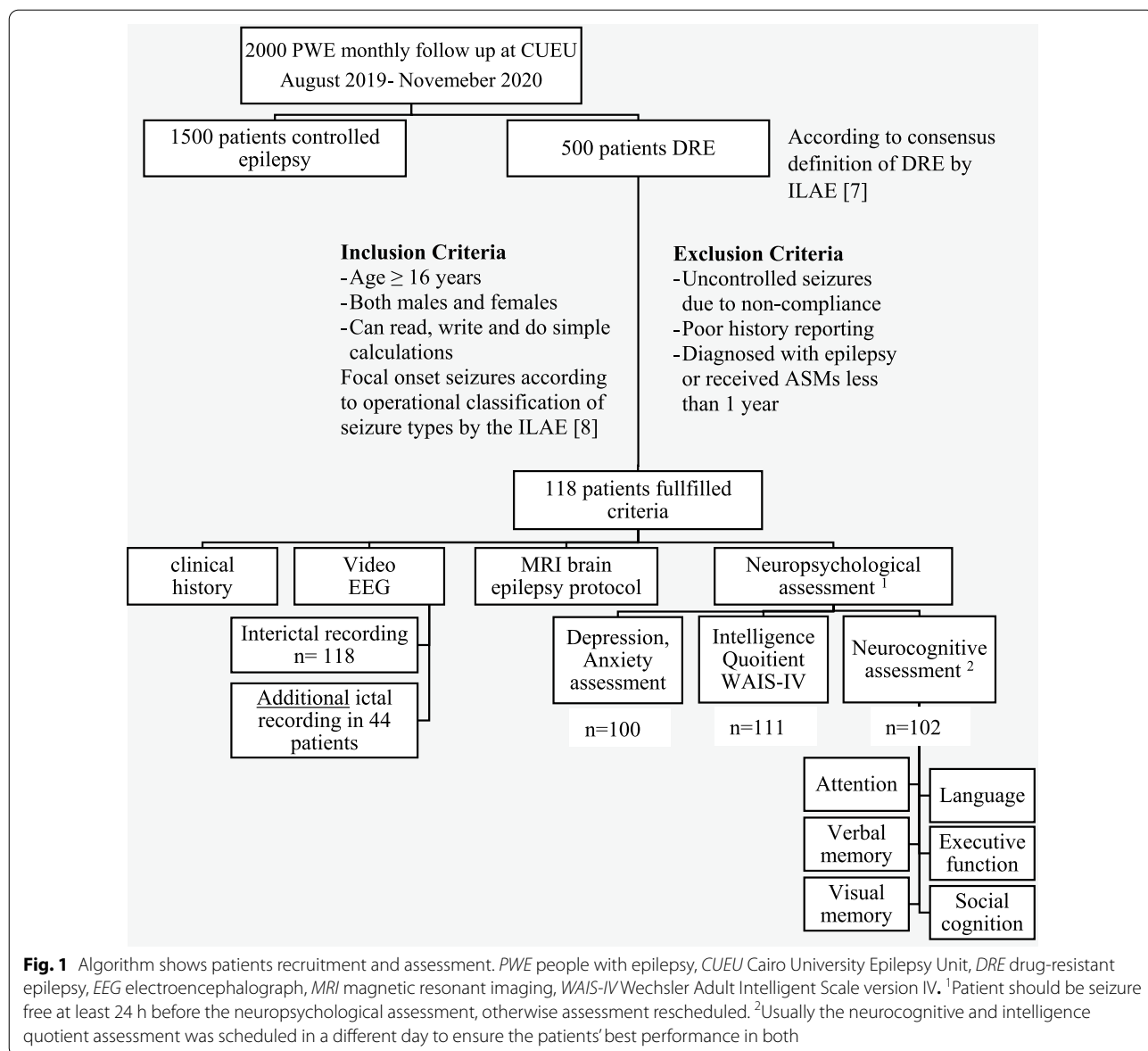
Fig. 1 Algorithm shows patients recruitment and assessment. *PWE* people with epilepsy, *CUEU* Cairo University Epilepsy Unit, *DRE* drug-resistant epilepsy, *EEG* electroencephalograph, *MRI* magnetic resonant imaging, *WAIS-IV* Wechsler Adult Intelligent Scale version IV. [1]Patient should be seizure free at least 24 h before the neuropsychological assessment, otherwise assessment rescheduled. [2]Usually the neurocognitive and intelligence quotient assessment was scheduled in a different day to ensure the patients' best performance in both

imaging] are concordant regarding both lateralization and localization, while partial concordance was established when only two modalities were concordant [13].

Neuropsychological assessment
Comorbid depression and anxiety
Beck Depression Inventory (BDI) questionnaire—Arabic version [14] was used for screening of depression among our patients, with a cut-off point of 16 [15]. Beck Anxiety Inventory [16], Arabic translation [17] was used for screening of anxiety among our patients.

Wechsler Adult Intelligence Scale-version IV (WAIS-IV) [18]
A trained and specialized psychologist performed it. Full-Scale Intelligence Quotient (FSIQ) is the sum of the scores derived from the Verbal IQ (VIQ) and the Performance IQ (PIQ). The VIQ based on the total combined performance of the Verbal Comprehension Index (VCI) and Working Memory Index (WMI). The PIQ based on the total combined performance of the Perceptual Reasoning Index (PRI) and Processing Speed Index (PSI).

Neurocognitive assessment
Arabic neuropsychological assessment battery was constructed. This battery was selected according to ILAE 2015 recommendations where different cognitive and

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psychological domains to be covered [4]. All the subtests of this battery were well-known, reliable, valid tests; non-cultural, non-educational dependent, and either adopted into Arabic language or non-language dependent. It covers most of cognitive domains in patients with epilepsy that included attention, verbal and visual memory, executive function, language, and social cognition.

Digit span forward and backward [19]

It measures active attention, working memory. Scored by the longest digit string could be recalled forward and backward. Normal score is 5–8 digits forward (cut-off < 5), 4–6 digits backward (cut-off < 3).

Paired Associate Learning Test (PAT) [20, 21]

It assess of episodic verbal memory and recall. The test uses the concept of semantic cueing.

Brown Location Test (BLT) [22]

It assesses visual–spatial learning and memory. Computer version of the test was used after approval of the author Franklin C. Brown permission. Scoring: correct answers of each trial were recorded and compared to the normative data in terms of standard deviation from normal. Score was considered abnormal if Z-score < − 0.6 SD [23].

Benton Visual Retention Test (BVRT) [24]

It assesses visual perception, visual memory, and visuo-constructive abilities. Scoring: number of correct reproductions. Normal score based on age and full-scale IQ. Cut-off value: 4 or more points below the expected correct score is a strong indication of impairment.

Language battery: figurative interpretation [25]

It assesses language comprehension by interpret meaning of 12 sentences from 3 choices. Scoring: given 2 points for choice of the correct answer (metaphor meaning) for each sentence and zero for other choices. Judgment on sentence [25]: it measuring language expression by assessing each sentence regarding the integrity in form and content. Scoring: give one point for each correct answer regarding integrity of the form and content, and third point if both answers were correct in the same sentence. Score would be 20 points for form, 20 points for content and total 60 points.

Controlled Oral Word Associate Test (COWAT) [26], Arabic version [27]

It assesses executive function phonemic and semantic fluency. Phonemic fluency: the patient asked to say as many words as possible beginning with a specified letter

set Haa (ح), Meem (م), Seen (س) during a fixed period time (usually: 1 min). These letters are equivalent to English letters H, M, and S. Semantic fluency: the patient was asked to say names in a specific category (animals), as many as possible, within a 1-min interval. Scoring of the total number of all admissible words with cut-off value 11 words each [27].

Trail Making Test (TMT) [28, 29]

It assesses attention, speed, and mental flexibility. The time required to complete each trail A and B was recorded in seconds. With cut-off value range Trail A < 29 s, Trail B < 75 s.

Social cognition [30]

It assesses ability for facial emotion expression processing. This task was carried out with pictures derived from the software developed by Ekman. Participants were asked to identify the emotion that best described the facial expression from different emotions (happy, sad, angry, afraid, surprised and disgusted) plus neutral expressions. Number of correctly chosen emotion for each emotion.

Ethical statement All the participants gave their written informed consent to join the study. The ethical committee of Faculty of medicine Cairo University approved the study.

Data will be analyzed using SPSS (statistical package for the social science) version 28, produced by IBM Corporation in USA, May 2021. Numerical data were presented by mean and standard deviation or median and range as appropriate. Qualitative data were expressed as number and frequencies (percentages). Comparison between two groups using Student T test for continuous data, comparing more than 2 groups ANOVA test will be used. Pearson's and Spearman correlation were used for examining the relation between continuous and ordinal variables. Regression analysis was done to predict factors affecting tests response. P value less than 0.05 was considered significant.

Results

Demographics and clinical characteristics of the study population

One hundred eighteen patients with DRE were included. Their ages ranged from 16–58 years with mean age of 28.4 ± 9.5 years. The study included 75 males (63.5%) and 43 females (36.4%). Mean years of education was 10.1 ± 4.5 years. Clinical characteristics of the studied group are shown in Table 1.

Table 1 Clinical characteristics of the recruited patients

Patients (n = 118)	
Age at onset [mean ± SD]	14.2 ± 11.4
Duration of illness [mean ± SD]	14.1 ± 8.9
Frequency of seizures/month [mean ± SD]	8.7 ± 14.2
History of status epilepticus [*n* (%)]	46 (39%)
Neurological deficit [*n* (%)]	17 (14.4%) [1]
Number of ASMs [mean ± SD]	2.7 ± 1
Clinical seizure semiology	
State of awareness	Focal aware [*n* (%)]	18 (15.3%)
	FWIA [*n* (%)]	100 (84.4%)
Seizure onset	Motor [*n* (%)]	77 (65.3%)
	Non-motor [*n* (%)]	41 (34.7%)
Focal to bilateral tonic clonic (TC) [*n* (%)]		94 (79.7%)

ASMs anti-seizure medications, *FWIA* focal with impaired awareness.

[1] 16 patients had hemiparesis and only one patient had hemianopia

Table 2 Percentage of lateralization and localization of epileptogenic focus according to different assessment modalities, and percent of concordance with brain imaging

		Semiology	Video EEG		Brain imaging
			Ictal (n = 44)	Interictal (n = 118)	
Lateralization	Right	46 (39%)	14 (36.4%)	23 (19.5%)	43 (36.4%)
	Left	49 (41.5%)	8 (18.2%)	26 (22%)	45 (38.1%)
	Multifocal or bilateral	–	6 (13.6%)	18 (15.3%)	4 (3.4%)
	Undetermined	23 (19.5%)	16 (36.4%)	51 (43.2%)	26 (22%)[1]
Lateralization	Temporal	68 (57.6%)	15 (34.4%)	47 (39.8%)	53 (44.9%)
	Frontal	29 (24.6%)	11 (9.3%)	11 (9.3%)	15 (12.7%)
	Parieto-occipital	12 (10.2%)	2 (1.7%)	2 (1.7%)	11 (9.3%)
	Insula	3 (2.5%)	–	–	4 (3.4%)
	Multifocal or hemispheric	–	5 (9.1%)	7 (5.9%)	7 (5.9%)
	others	–	–	–	5 (4.2%)[2]
	Undetermined	6 (5%)	16 (36.4%)	51 (43.2%)	23 (19.5%)[3]

[1] 23 patients had Normal MRI and 3 patients had hypothalamic hamartoma

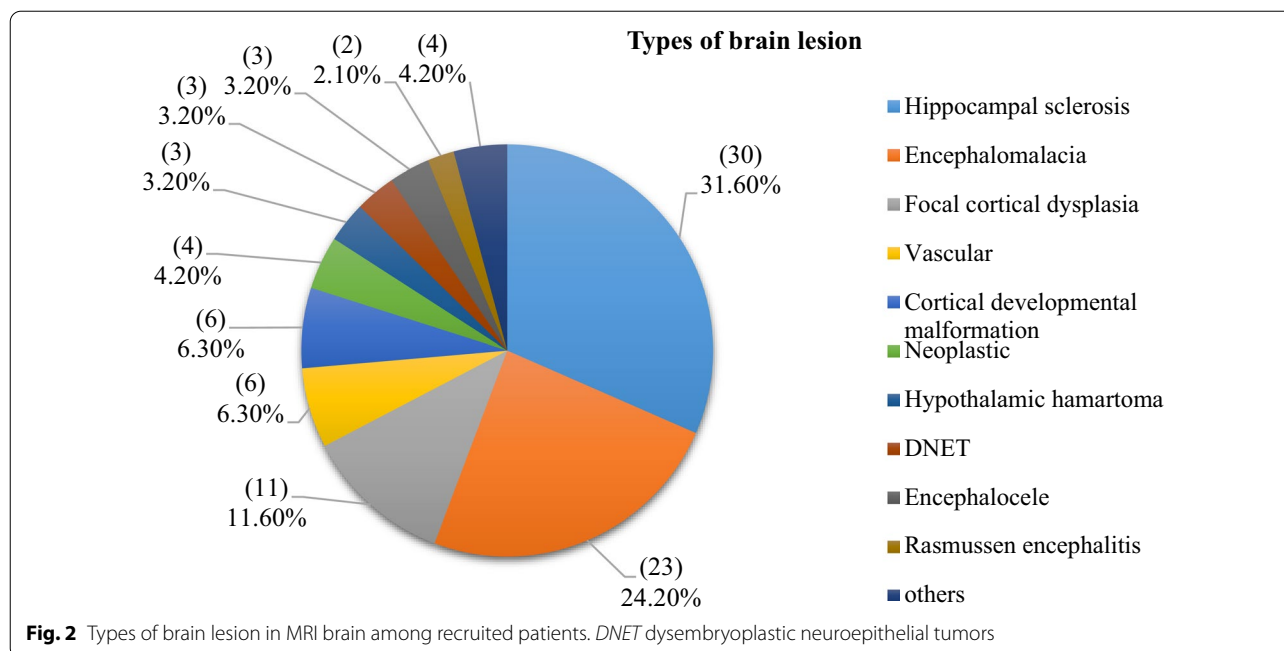[2] Patients had thalamic, subependymal lesion and hypothalamic hamartoma

[3] Patients had Normal MRI

Lateralization and localization value by different assessment modalities

History of clinical semiology of seizures, video EEG, and brain imaging were done to all patients. Video EEG recording could capture the ictal event in 44 (37.3%) patients. Interictal recording showed epileptiform discharge in 62 (52.5%) patients. Brain imaging could detect lesion in 95 (80.5%) patients. Lateralizing and localizing value of each modality were assessed, as shown in Table 2.

Concordance between different assessment modalities (clinical semiology and video EEG) with lesional brain imaging were assessed, as shown in Table 2. Clinical semiology showed the highest percent of concordance with brain imaging (74.7%, 69.5%) followed by ictal EEG recording (45.9%, 35%), regarding lateralization and localization, respectively. Rather than the interictal showed the least concordance (33.7%, 35.8%). Complete concordance between clinical semiology, brain imaging and ictal EEG were achieved in 13 (35%) patients that included eight patients with temporal localization, frontal localization in 4 patients, and occipital in only one patient, while 20 (54.1%) patients achieved partial concordance.

Fig. 2 Types of brain lesion in MRI brain among recruited patients. *DNET* dysembryoplastic neuroepithelial tumors

Type of brain lesion by MRI brain

Patients' imaging was done for all included patients. Lesional MRI brain was found in 95 patients (80.5%). The most common lesion was hippocampal sclerosis (31.6%), as shown in Fig. 2.

Neuropsychological assessment

Comorbid depression and anxiety: Screening of depression and anxiety was done for 100 patients during the session of neuropsychological assessment. Beck Depression Inventory showed that 56% of patients had depression (BDI score ≥ 16). Beck Anxiety Inventory showed that 7% of patients had severe anxiety, 21% had moderate and 72% had low anxiety. Intelligence quotient: WAIS-IV was done for 111 patients (7 patients dropped out during pandemic). Neurocognitive assessment: neuropsychological assessment was done for 102 patients (16 patients dropped out during pandemic). Patients' performance was the worst in executive function among different tests, as shown in Table 3.

Relation of patients' performance in neuropsychological assessment battery to other factors

Demographic and clinical characteristics

Different factors (age, years of education, age of onset, duration of illness, frequency of seizures, number of ASMs, and FSIQ score) were correlated with patients' performance scores, as shown in Table 4. It showed that years of education directly correlate significantly with performance in WAIS-IV and neurocognitive battery. The number of ASMs inversely correlates with performance in WAIS-IV, as well as executive function subtests. Moreover, IQ scores showed highly significant direct correlation with neurocognitive assessment battery.

Clinical data of seizure semiology

Recruited patients were classified according to epilepsy history. Patients with history of status epilepticus showed significantly worse performance in WAIS-IV compared to those with no history of status epilepticus. History of focal to bilateral tonic clonic showed no significant difference compared to those with no history apart from digit span backward (p = 0.04). Type of seizure either aware or impaired awareness showed no significant difference among subgroups, as shown in Table 5.

Depression

Patients with depression features according to BDI showed no difference from those who had no depression, as shown in Table 5.

Investigations

Patients with lesional brain imaging and abnormal interictal EEG showed no significant difference in performance compared to those with non-lesional MRI and normal interictal EEG. Localized brain lesion in MRI: Patients with localized brain lesion (either temporal,

Table 3 Patients' performance in WAIS and neurocognitive battery tests

Intelligence Quotient (WAIS-IV)

		Score mean ± SD	Mental retarded	Borderline	Below average	Average	Above average	Superior	Talented
Verbal IQ	VCI	91.2 ± 15.7	5 (4.5%)	21 (18.9%)	32 (28.8%)	36 (32.4%)	8 (7.2%)	8 (7.2%)	1 (0.9%)
	WMI	83.4 ± 14.3	11 (9.9%)	38 (34.2%)	32 (28.8%)	23 (20.7%)	5 (4.5%)	1 (0.9%)	1 (0.9%)
Performance IQ	PRI	87.6 ± 12.9	4 (3.6%)	24 (21.6%)	41 (36.9%)	36 (32.4%)	2 (1.8%)	–	-
	PSI	81 ± 13.5	20 (18.2%)	36 (32.4%)	23 (20.7%)	31 (27.9%)	1 (0.9%)	–	-
FSIQ		84.9 ± 14.2	9 (8.2%)	34 (30.6)	31 (27.9%)	29 (26.1%)	5 (4.5%)	3 (2.7%)	–

Neurocognitive assessment battery

		Score mean ± SD	**Normal**	**Abnormal**
Attention digit span	Forward	6.6 ± 2.3	70 (68.6%)	32 (31.4%)
	Backward	3.6 ± 1.96	45 (44.1%)	57 (55.9%)
Verbal memory PAT		10.99 ± 4.3	48 (47.1%)	54 (52.9%)
Visual memory: BLT[1]	Learning trials	− 1.9 ± 1.2	15 (14.7%)	87 (85.3%)
	Short delayed recall	− 1.9 ± 1.04	12 (11.8%)	90 (88.2%)
	Long delayed recall	− 1.9 ± 1.1	14 (13.7%)	88 (86.3%)
Visual memory: BVRT		4.3 ± 2.3	68 (66.7%)	34 (33.3%)
Language assessment battery		–	35 (34.3%)	67 (65.7%)
Executive function/verbal fluency COWAT	Phonemic	14.6 ± 8.99	6 (5.9%)	96 (94.1%)
	Categorical	13.9 ± 5.7	71 (69.6%)	31 (30.4%)
Executive function	TMT-A	57.95 ± 30.8[3]	11 (10.8%)	91(89.2%)[2]
	TMT-B	92.7 ± 46.2[3]	28 (27.5%)	74 (72.5%))[2]
Social cognition Ekman emotion recognition	Happy	7.9 ± 0.2	–	–
	Sad	4.7 ± 2.3	–	–
	Fear	2.3 ± 1.9	–	–
	Surprise	7.02 ± 1.6	–	–
	Anger	5.1 ± 2.7	–	–
	Disgust	6.04 ± 2.1	–	–
	Neutral	6.2 ± 2.1	–	–

VCI verbal comprehensive index, *PRI* perceptual organization index, *WMI* working memory index, *PSI* processing speed index, *FSIQ* Full-Scale Intelligence Quotient, *SD* standard deviation, *PAT* Paired Associate Test, *BLT* Brown Location Test, *BVRT* Benton Visual Retention Test, *COWAT* Controlled Oral Word Association Test, TMT: Trail Making Test

[1] Scoring by Z-score calculated according to age group

[2] Included those could perform the test but exceeded the cut-off time, and those who failed to perform it

[3] Mean score of patients who performed normally and those did it correctly, but exceeded the cut-off time

frontal, or parieto-occipital) were compared in their performance. There were no significant differences among these subgroups as shown in Table 5.

Multivariate analysis

Different variables were analyzed regrading effect on neurocognitive tests: [age of onset, duration of illness, seizure frequency, number of ASMs, years of education, FSIQ, lesional brain imaging, abnormal interictal EEG, and depression]. The proposed neurocognitive assessment battery scored by individualized total score. Each test with impaired performance scored one and the higher the score the more impairment detected.

Age of onset was correlated with patients' performance (*P* value = 0.045). Yet on multivariate stepwise regression analysis, only Intelligence Quotient and lesional brain imaging could predict performance in neuropsychological tests. The lower IQ leads to worse performance in neurocognitive tests, as shown in Table 6 and Fig. 3.

Discussion

Intelligence comprises mental representations (such as propositions or images) of information and processes that can operate on such representations. The basic cognitive processes are the building blocks of intelligence. When evaluating overall IQ test scores or other assessments of performance, there is a risk of arriving at

Table 4 Correlation of demographic and clinical data with performance in neuropsychological tests

			Age	Years of education	Age of onset	Duration of illness	Frequency of seizure	Number of ASMs	FSIQ Score
FSIQ Score		*r* value	0.07	0.46	0.13	-0.09	0.05	-0.33	
		P value	0.63	<0.001*	0.35	0.54	0.73	0.02*	
Digit span	Forward	*r* value	− 0.2	0.4	− 0.08	− 0.11	0.13	− 0.13	0.49
		P value	0.15	0.003*	0.58	0.42	0.37	0.34	<0.001*
	Backward	*r* value	− 0.04	0.44	− 0.03	− 0.01	0.05	− 0.21	0.64
		P value	0.78	<0.001*	0.83	0.95	0.73	0.13	<0.001*
Verbal memory Verbal PAT		*r* value	− 0.08	0.41	0.13	− 0.24	− 0.03	− 0.21	0.65
		P value	0.57	0.003*	0.35	0.09	0.81	0.13	<0.001*
Visual memory	Learning trials	*r* value	− 0.11	0.31	0.12	− 0.25	0.02	− 0.1	0.47
		P value	0.45	0.03*	0.39	0.08	0.9	0.46	<0.001*
	Short delayed recall	*r* value	0.1	0.34	0.21	− 0.14	0.1	− 0.2	0.5
		P value	0.49	0.01*	0.14	0.31	0.49	0.15	<0.001*
	Long delayed recall	*r* value	0.08	0.26	0.23	− 0.19	0.03	− 0.31	0.46
		P value	0.59	0.07	0.09	0.17	0.84	0.03*	<0.001*
Visual memory: BVRT		*r* value	− 0.12	0.38	0.06	− 0.19	0.04	− 0.18	0.59
		P value	0.39	0.01*	0.69	0.18	0.76	0.2	<0.001*
Executive function/verbal fluency COWAT	Phonemic	*r* value	0.13	0.6	0.12	− 0.01	0.1	− 0.34	0.67
		P value	0.37	<0.001*	0.4	0.92	0.5	0.01*	<0.001*
	Categorical	*r* value	− 0.07	0.44	− 0.02	− 0.05	0.05	− 0.27	0.61
		P value	0.64	0.001*	0.9	0.72	0.75	0.05	<0.001*
Executive function	TMT A^2	*r* value	− 0.12	− 0.44	− 0.04	− 0.08	− 0.1	0.33	− 0.61
		P value	0.39	<0.001*	0.79	0.59	0.5	0.02*	<0.001*
	TMT− B^2	*r* value	0.04	− 0.22	0.19	− 0.18	0.06	0.36	− 0.58
		P value	0.78	0.12	0.17	0.2	0.67	0.01*	<0.001*

ASMs anti-seizure medications, *FSIQ* Full-Scale Intelligence Quotient, *PAT* Paired Associate Test, *BLT* Brown Location Test, *BVRT* Benton Visual Retention Test, *COWAT* Controlled Oral Word Association Test, *TMT* Trail Making Test

*P value < 0.05 is considered significantly different

[1] Scoring by Z-score calculated according to age group

[2] Included only patients who performed the test within cut-off time normally and those did it correctly but exceeded the cut-off time

conclusions that are misleading. By using cognitive analysis, the test interpreter is able to determine the degree to which the poor score stems from [31].

Cognitive impairment frequently occurs in epilepsy patients. Patients with DRE have poor drug responsivity and higher seizure frequency which consequently lead to brain damage and may have implications on cognitive status [32]. One of the challenges in interpreting cognitive performance in PWE is the timing of assessment. If patient is assessed during adulthood, it becomes unclear whether this cognitive impairment represents developmental decline in cognitive functioning due to the early interruption of network development by epileptogenesis or it occurred later during course of disease.

In the proposed neuropsychological battery, DRE patients showed cognitive impairment in all assessed domains. Executive functions were the most affected domains (COWAT Phenomic (94.1%) of patients were abnormal, while in TMT-A (89.2%), TMT-B (72.5%)),

followed by visuospatial learning and memory tested by Brown Location Test (BLT learning (85.3%), short delayed recall (88.2%), long delayed recall (86.3%)), while impaired performance was (52.9%) in Verbal PAT, and (65.7%) language. In addition, the presence of IEDs was associated with significant worse performance in executive function (TMT-B) that agreed with Liu and colleagues. IEDs affect the cognitive performance by disturbing the default mode network, which is important for cognitive development [33]. This model could explain the high prevalence of impairment in executive functions in our study.

Presumed hypothesis was proposed by earlier studies, that cognitive impairment has a structure–function relationship as an example frontal lobe epilepsy (FLE) would have impaired executive function and temporal lobe epilepsy (TLE) would have impaired memory. However, later studies disapproved with this postulation and showed that cognitive impairment, in patients with focal epilepsy,

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Table 5 Comparison of neuropsychological performance according to different factors

		Seizure state of awareness	History of bilateral TC	History of status epilepticus	Depression	Brain imaging	Interictal EEG	Anatomical location of brain lesion
		P1	P2	P3	P4	P5	P6	P7
FSIQ score		0.9	0.86	0.02*	0.58	0.64	0.18	0.3
Digit span	Forward	0.4	0.76	0.4	0.58	0.9	0.07	0.38
	Backward	0.98	0.04	0.05	0.79	0.37	0.59	0.25
Verbal memory Verbal PAT total		0.4	0.59	0.19	0.58	0.63	0.06	0.79
Visual memory: BLT[1]	Learning trials	0.99	0.24	0.12	0.47	0.27	0.54	0.49
	Short delayed recall	0.5	0.38	0.03*	0.5	0.38	0.06	0.33
	Long delayed recall	0.8	0.55	0.03*	0.97	0.44	0.3	0.74
Visual memory: BVRT		0.5	0.4	0.38	0.39	0.16	0.15	0.52
Executive function/verbal fluency COWAT	Phonemic	0.7	0.8	0.17	0.69	0.79	0.55	0.15
	Categorical	0.4	0.6	0.39	0.86	0.11	0.18	0.02*
Executive function	TMT-A[2]	0.4	0.96	0.18	0.28	0.17	0.27	0.42
	TMT-B[2]	0.6	0.32	0.74	0.9	0.26	0.004*	0.61

FSIQ: Full-Scale Intelligence Quotient, PAT: Paired Associate Test, BLT: Brown Location Test, BVRT: Benton Visual Retention Test, COWAT: Controlled Oral Word Association Test, TMT: Trail Making Test

P1: P value of comparison between patients with focal aware versus those with focal with impaired awareness seizures

P2: P value of comparison between patients with history of focal to bilateral TC versus those with no history of bilateral TC

P3: P value of comparison between patients with history of status epilepticus versus those with no history of status epilepticus

P4: P value of comparison between patients had depression versus those had no depression

P5: P value of comparison between patients with lesional versus non-lesional brain imaging

P6: P value of comparison between patients with abnormal versus normal interictal EEG

P7: P value of comparison between patients classified according to the different anatomical location of brain lesion (right temporal, left temporal, right frontal, left frontal, parieto-occipital).

[1] Scoring by Z-score calculated according to age group

[2] Included only patients who performed the test within cut-off time normally and those did it correctly but exceeded the cut-off time

Table 6 Multivariate analysis of different variables effect on neurocognitive performance

	Unstandardized coefficients		R square	P value
	B	Std. error		
(Constant)	10.66	0.66	0.475	< 0.001
IQ subgroups	− 2.01	0.22		< 0.001*
Brain imaging lesional or not	1.21	0.56		0.033*

*P value < 0.05 is considered significantly different

were not limited to pathophysiological boundaries. In case of patients with TLE, memory impairment was the common feature, but not the only feature. Nevertheless, generalized affection of cognitive functions (IQ, memory, executive, language, and other abilities) was found. Cognitive abilities depend on disrupted neural network, not only location of brain lesion, and related pathophysiology [34]. This agreed with our results that location of brain lesion could not achieve significant difference across neurocognitive tests, apart from categorical verbal fluency. Patients with left temporal and bilateral frontal lobe lesions showed significant difference performance compared to those with right temporal and parieto-occipital lobes lesion; this agreed with Metternich and colleagues [35].

Moreover, performance in neuropsychological tests is affected by several factors other than location of the lesion, as education level, intellectual abilities. Accordingly, sensitivity of lateralizing value of neuropsychological assessment was much lower than semiology, EEG and MRI, which does not preclude its value in presurgical evaluation. Occasionally discordant neuropsychological assessment with EEG and MRI might predict unfavorable postoperative outcome according compensatory adequacy, and functional reserve [36].

Children with DRE had poorer performance in IQ tests and lower IQ score compared to those with controlled epilepsy, while adults with epilepsy might have cognitive decline with disease [2]. The results of this study were
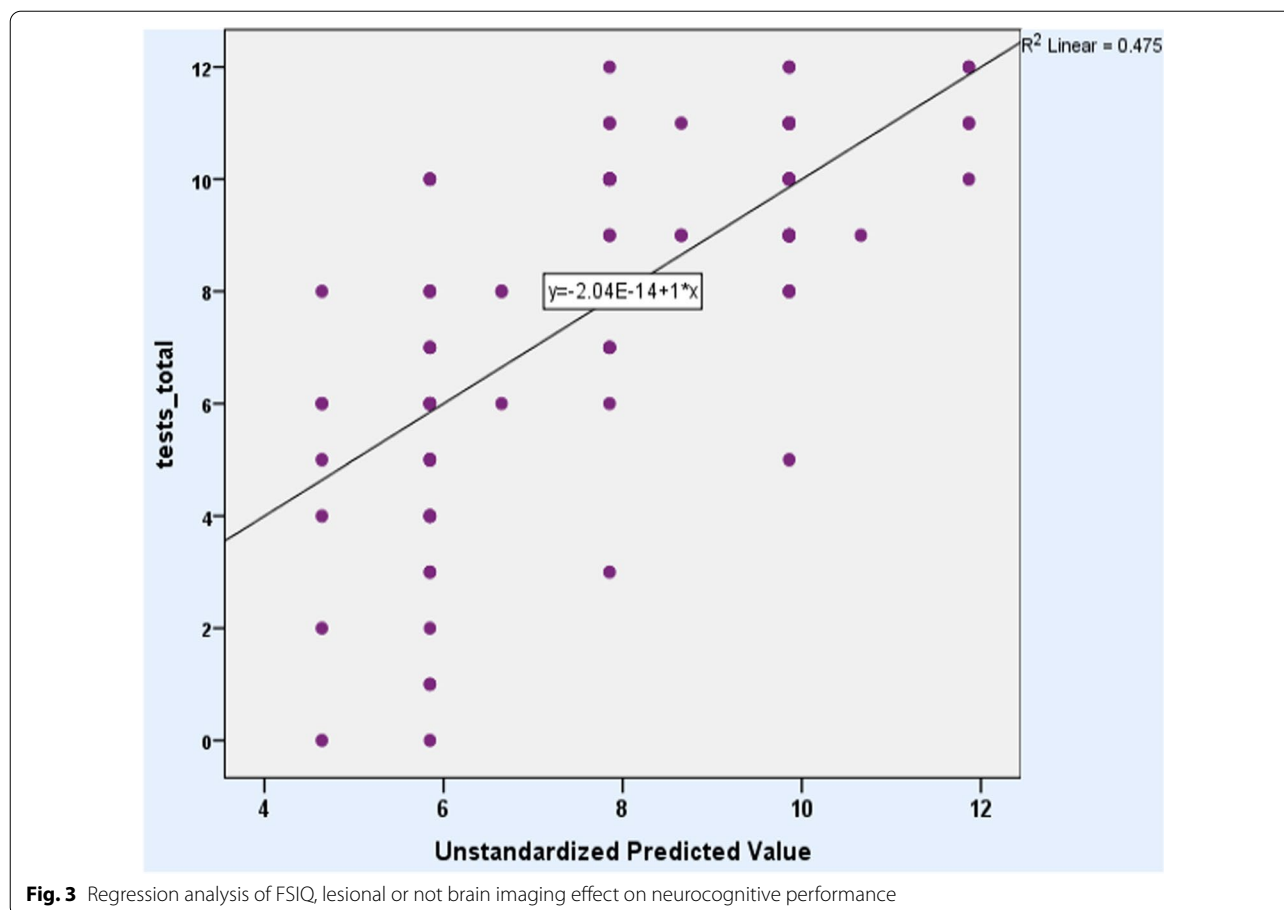
Fig. 3 Regression analysis of FSIQ, lesional or not brain imaging effect on neurocognitive performance

similar to other studies that found patients with low IQ had a low cognitive function; high percent of recruited patients in our study had IQ lower than average (66.7%), yet still patients with normal IQ can perform poorly in neurocognitive assessment.

Intellectual abilities are usually formed based on learning and memory mechanism during childhood. Meta-analysis was conducted on the effect of education on IQ performance; it showed that years of education correlate significantly with IQ score. Early onset of epilepsy and frequent seizure occurrence interfere markedly with these mechanisms during critical period of brain development, which lead to failure of acquisition of such functions [6, 37]. The earlier age of epilepsy onset was associated with marked increased risk of intellectual impairment compared to control group. In addition, cognitive abilities impairment manifested later after epilepsy manifestation [38].

Several studies were conducted to assess factors that affect IQ in children with epilepsy and showed that younger age of onset, number of ASMs, frequent seizures significantly associated with low IQ [6, 39]. This would explain the significant correlation in our study between

lower years of education and number of ASMs and poor performance in neuropsychological assessment (including FSIQ and neurocognitive assessment battery). The number of ASMs was associated with lower years of education and showed significant impact on executive functions; similar to pervious findings by Witt and colleagues [40]. Nevertheless, age of onset did not achieve significant correlation with neuropsychological performance. This could be attributed to the wide range of age of disease onset (0.5–53 years) included in this study.

Reduced intellectual ability affects interpretation of neurocognitive assessment (memory, language, executive function) [41]. This agreed with our finding, as multivariate analysis of factors that affect neuropsychological assessment showed that FSIQ and lesional brain imaging were the only factors that significantly affect performance in neurocognitive assessment. That is why neurocognitive assessment awaited role for lateralization could not be achieved in patients with low FSIQ.

In this study, history of status epilepticus showed significant difference in IQ performance compared to those with no history of status epilepticus, in addition to poor performance in delayed recall of brown location test.

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Different studies were conducted, using different neuropsychological tests, to assess long-term cognitive consequence of status epilepticus and variable results were found. Cognitive consequence was found in about 30% of assessed children, while status epilepticus showed no consequence in adults. However, drug-resistant epilepsy was more likely to affect cognitive performance than status epilepticus. So the impact of status epilepticus on cognitive performance in DRE is still controversial [42].

Few years ago, social cognition impairment became extensively studied. As this impairment would cause psychosocial difficulties, social maladaptation and markedly affect interpersonal relationships. Accordingly, studies were directed to assess the burden of this impairment and its relation to epileptic condition either its due to condition itself or consequence of seizure, underlying lesion or treatment [30, 43]. Social cognition impairment might be explained by the involvement of network responsible for social perception in mesial prefrontal cortex, superior temporal lobe and temporal pole. These areas are responsible on interpretation of others mental state, so they require involvement of amygdala to interact to others [30].

Social cognition assessment in our population showed that fear emotion recognition was the most impaired in all other studied emotions, this agree with all previous studies assessed social cognition showed that fear emotion recognition was impaired in patients with TLE more than patients with idiopathic generalized epilepsy (IGE), who showed impairment in both anger and fear. Also fear recognition was found more in TLE patients with ictal fear aura [44, 45].

On the other hand, in this study, seizure semiology could lateralize epileptogenic focus in 80.5% of patients and localize in 97.5% of patients, while brain imaging, ictal and interictal EEG was able to lateralize (74.5%, 54.6% and 41.5%) and localize (72.7%, 45.4% and 50.8%) epileptogenic focus in lower percent of patients, respectively. This finding was nearly on agreement with Elwan and colleagues; that evaluated the lateralizing and localizing value of seizure semiology in patients who became completely seizure free post-resective epilepsy surgery [46]. And concordance of assessment modalities with brain imaging, showed that clinical semiology had better concordance with brain imaging compared to ictal EEG, that disagree with Abdulghani and colleagues that showed that ictal EEG was better than clinical semiology [12]. This could be explained by the classification of clinical semiology according to operational classification of seizure types by the ILAE that allowed better lateralization and localization of epileptogenic focus [7]. Complete concordance between the three assessment modalities were achieved in 35% of patients which is similar to the ratio reported by a previous study assessed concordance between the noninvasive tests (35%) [13]. Nevertheless, the rate of our patients who had partial concordance (54.1%) was slightly lower than the rate scored by their peers in the study mentioned above (56.7%) [13]. Complete concordance between the three assessment modalities (seizure semiology, ictal EEG, and brain imaging) represents a straightforward approach for resective epilepsy surgery with high success rate [47]. Moreover, Cendes and colleagues reported that concordance was best detected at temporal lobe lesion [48], which showed total agreement with our results as the epileptogenic focus in most of patients who achieved complete concordance was detected at the temporal level.

Morad and colleagues stated that no clear evidence that longstanding epilepsy alone is the main cause of progressive and irreversible cognitive impairments. Several determinants of continuous decline were identified as seizure frequency, bilateral TC seizures, ASMs, IEDs, underlying brain lesion and neuro-developmental effects, poor cognitive baseline, which are also marker for more severe epilepsy and cognitive decline [43, 49].

Similarly, our studied population showed significant correlation between years of education and number of ASMs and neuropsychological performance (including IQ and neurocognitive battery), but no correlation with other factors (age of onset, seizure type, bilateral tonic clonic seizures, seizure frequency and depressed mood).

Conclusions
In this study, neuropsychological assessment succeeded to delineate the cognitive profile of recruited patients, as well as the impact of different factors on performance. This would direct clinicians to the importance of cognitive assessment in patients with drug-resistant epilepsy and the importance of aggressive treatment to minimize the adverse effects of epilepsy on cognition. This would represent a leap in developing the medical care and management provided to this group of patients in particular, and all epileptic patients in general. Eventually, this presented study achieves the proposed aim of work, and started the main step of pragmatic roadmap for neuropsychological assessment of epileptic patients in low/middle-income countries (Additional file 1).

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Intelligence Quotient; PRI: Perceptual Reasoning Index; PSI: Processing Speed Index; PWE: People with epilepsy; SD: Standard deviation; SPSS: Statistical Package for the Social Science; TC: Tonic clonic; TLE: Temporal lobe epilepsy; VCI: Verbal Comprehension Index; VIQ: Verbal Intelligence Quotient; WAIS-IV: Wechsler Adult Intelligence Quotient version IV; WMI: Working Memory Index; 3D: Three dimensions.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s41983-022-00523-4.

> **Additional file 1.** Detailed comparison of neuropsychological performance according to the different factors (Clinical data, investigation, anatomical location of brain lesion and depression).

Availability of data and materials
All datasets generated and analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
All procedures performed in the study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments. Research committee ethically approved the study; and the faculty of medicine Cairo University ethical committee reviewed and approved the study 24/8/2019 (ethical committee approval number: md-64-2019). Written informed consent was obtained from all participants involved in this investigation prior to the conduct of any study-related activities.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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References
1. Berg AT, Langfitt JT, Testa FM, Levy SR, DiMario F, Westerveld M, et al. Global cognitive function in children with epilepsy: a community-based study. Epilepsia. 2008;49(4):608–14.
2. Kim EH, Ko TS. Cognitive impairment in childhood onset epilepsy: Up-to-date information about its causes. Korean J Pediatr. 2016;59(4):155–64.
3. Baxendale S, Wilson SJ, Baker GA, Barr W, Helmstaedter C, Hermann BP, et al. Indications and expectations for neuropsychological assessment in epilepsy surgery in children and adults: executive summary of the report of the ILAE Neuropsychology Task Force Diagnostic Methods Commission: 2017–2021. Epilepsia. 2019;60(9):1794–6.
4. Wilson SJ, Baxendale S, Barr W, Hamed S, Langfitt J, Samson S, et al. Indications and expectations for neuropsychological assessment in routine epilepsy care: report of the ILAE Neuropsychology Task Force Diagnostic Methods Neuropsychological. Epilepsia. 2015;56(5):674–81.
5. Helmstaedter C, Witt JA. Epilepsy and cognition—a bidirectional relationship? Seizure. 2017;49:83–9. https://doi.org/10.1016/j.seizure.2017.02.017.
6. Berg AT, Zelko FA, Levy SR, Testa FM. Age at onset of epilepsy, pharmacoresistance, and cognitive outcomes: a prospective cohort study. Neurology. 2012;79(13):1384–91.
7. Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Hauser WA, Mathern G, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia. 2010;51(6):1069–77.
8. Fisher RS, Cross JH, D'Souza C, French JA, Haut SR, Higurashi N, et al. Instruction manual for the ILAE 2017 operational classification of seizure types. Epilepsia. 2017;58(4):531–42.
9. Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, et al. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58(4):512–21.
10. Tsuchida TN, Acharya JN, Halford JJ, Kuratani JD, Sinha SR, Stecker MM, et al. American clinical neurophysiology society: EEG guidelines introduction. J Clin Neurophysiol. 2016;33(4):301–2.
11. Bernasconi A, Cendes F, Theodore WH, Gill RS, Koepp MJ, Hogan RE, et al. Recommendations for the use of structural magnetic resonance imaging in the care of patients with epilepsy: a consensus report from the International League Against Epilepsy Neuroimaging Task Force. Epilepsia. 2019;60(6):1054–68.
12. Abdulghani KO, Gaber AA, Abdulaziz AA, Afeefy HH, Alloush TK, Zaki AA, et al. Value of seizure semiology and ictal source analysis in lateralizing and localizing the epileptic zone. Egypt J Neurol Psychiatry Neurosurg. 2015;52(4):223–7.
13. Bochynska A, Konopko M, Iwanek A, Sledz H, Ryglewicz D, Rola R, et al. Noninvasive presurgical assessment in partial refractory epilepsy—Extend of concordance between diagnostic evaluations. Experience in a tertiary care center. J Neurol Sci. 2017;381:336–7.
14. Fawzi MH, Fawzi MM, Abu-Hindi W. Arabic version of the Major Depression Inventory as a diagnostic tool: reliability and concurrent and discriminant validity. East Mediterr Heal J. 2012;18(4):304–10.
15. de Oliveira GN, Lessa JMK, Gonçalves AP, Portela EJ, Sander JW, Teixeira AL. Screening for depression in people with epilepsy : Comparative study among Neurological Disorders Depression Inventory for Epilepsy (NDDI-E), Hospital Anxiety and Depression Scale Depression Subscale (HADS-D), and Beck Depression Inventory (BDI). Epilepsy Behav. 2014;34:50–4.
16. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. J Consult Clin Psychol. 1988;56(6):893–7.
17. Al-Shatti TS. Psychometric properties of the Arabic version of the beck anxiety inventory in the state of Kuwait. Univ Bahrain Sci. 2015;16(2):448–9.
18. Holdnack JA, Zhou X, Larrabee GJ, Millis SR, Salthouse TA. Confirmatory Factor Analysis of the WAIS-IV/WMS-IV. Assessment. 2011;18(2):178–91.
19. Byab B. Memory span : a review of the literature. Psychol Bull. 1938;35(1):1.
20. Wechsler D. A standardized memory scale for clinical use. J Psychol Interdiscip Applied. 1945;19:87–95.
21. Strauss E, Sherman EMS, Spreen O. A compendium of neuropsychological tests: administration, norms, and commentary Vol. 41. 3rd ed. Oxford: Oxford University Press; 2006. p. 1856–1856.
22. Brown FC, Roth RM, Saykin AJ, Beverly-Gibson G. A new measure of visual location learning and memory: development and psychometric properties for the brown location test (BLT). Clin Neuropsychol. 2007;21(5):811–25.
23. Brown FC, Hirsch LJ, Spencer DD. Spatial memory for asymmetrical dot locations predicts lateralization among patients with presurgical mesial

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temporal lobe epilepsy. Epilepsy Behav. 2015;52:19–24. https://doi.org/10.1016/j.yebeh.2015.08.020.

24. Benton AL. The revised visual retention test: clinical and experimental applications. 4th ed. New York: Psychological Corporation; 1974. p. 32–41.

25. Yusuf GS. Language comprehension and production tests battery. Cairo: Center for Psychological Research and Studies, Faculty of Arts, Cairo University; 2002. p. 28–34.

26. Benton AL, Hamsher KD, Sivan AB. Multilingual aphasia examination. 3rd ed. Lutz: Psychological Assessment Resources Inc; 1994. p. 50–6.

27. Farghaly M, Hussein M, Hegazy M, Sabbah A. Testing of verbal fluency in egyptians : cultural and educational challenges. Cogn Behav Neurol. 2018;31(3):133–41.

28. Reitan R. Validity of the Trail Making test as an indicator of organic brain damage. Percept Mot Skills. 1958;8(3):271–6.

29. Lezak MD, Howieson DB, Loring DW, Fischer JS. Neuropsychological Assessment. USA: Oxford University Press; 2004. p. 959–64.

30. Amlerova J, Cavanna AE, Bradac O, Javurkova A, Raudenska J, Marusic P. Emotion recognition and social cognition in temporal lobe epilepsy and the effect of epilepsy surgery. Epilepsy Behav. 2014;36:86–9.

31. Sternberg RJ. Handbook of intelligence. Cambridge: Cambridge University Press; 2000. p. 421–44.

32. Gavrilovic A, Toncev G, Matic TB, Vesic K, Zivojinovic JI, Gavrilovic J. Impact of epilepsy duration, seizure control and EEG abnormalities on cognitive impairment in drug-resistant epilepsy patients. Acta Neurol Belg. 2019;119(3):403–10. https://doi.org/10.1007/s13760-019-01090-x.

33. Liu XY, Shi T, Yin WN, Ren ZY, Deng Y-L, Chen S-D. Interictal epileptiform discharges were associated with poorer cognitive performance in adult epileptic patients. Epilepsy Res. 2016;128:1–5. https://doi.org/10.1016/j.eplepsyres.2016.09.022.

34. Hermann B, Loring DW, Wilson S. Paradigm shifts in the neuropsychology of epilepsy. J Int Neuropsychol Soc. 2017;23(9–10):791–805.

35. Metternich B, Buschmann F, Wagner K, Schulze-Bonhage A, Kriston L. Verbal fluency in focal epilepsy: a systematic review and meta-analysis. Neuropsychol Rev. 2014;24(2):200–18.

36. Kim H, Yi S, Son EI, Kim J. Lateralization of epileptic foci by neuropsychological testing in mesial temporal lobe epilepsy. Am psychological Assoc. 2004;18(1):141–51.

37. Ritchie SJ, Tucker-Drob EM. How much does education improve intelligence? A meta-analysis. Psychol Sci. 2018;29(8):1358–69.

38. Sorg AL, von Kries R, Borggraefe I. Cognitive disorders in childhood epilepsy: a comparative longitudinal study using administrative healthcare data. J Neurol. 2022. https://doi.org/10.1007/s00415-022-11008-y.

39. Mohamed IN, Osman AH, Mohamed S, Hamid EK, Hamed AA, Alsir A, et al. Intelligence quotient (IQ) among children with epilepsy: National epidemiological study – Sudan. Epilepsy Behav. 2020;103:106813. https://doi.org/10.1016/j.yebeh.2019.106813.

40. Witt JA, Elger CE, Helmstaedter C. Adverse cognitive effects of antiepileptic pharmacotherapy: Each additional drug matters. Eur Neuropsychopharmacol. 2015;25(11):1954–9. https://doi.org/10.1016/j.euroneuro.2015.07.027.

41. Baxendale S, Mcgrath K, Thompson PJ. Epilepsy and IQ : the clinical utility of the Wechsler Adult Intelligence Scale—Fourth Edition (WAIS—IV) indices in the neuropsychological assessment of people with epilepsy. J Clin Exp Neuropsychol. 2014; 36(2): 137–143.

42. Sculier C, Gaínza-Lein M, Sánchez Fernández I, Loddenkemper T. Long-term outcomes of status epilepticus: a critical assessment. Epilepsia. 2018;59:155–69.

43. Witt JA, Helmstaedter C. Cognition in epilepsy: current clinical issues of interest. Curr Opin Neurol. 2017;30(2):174–9.

44. Realmuto S, Zummo L, Cerami C, Agrò L, Dodich A, Canessa N, et al. Social cognition dysfunctions in patients with epilepsy: evidence from patients with temporal lobe and idiopathic generalized epilepsies. Epilepsy Behav. 2015;47:98–103.

45. Reynders HJ, Broks P, Dickson JM, Lee CE, Turpin G. Investigation of social and emotion information processing in temporal lobe epilepsy with ictal fear. Epilepsy Behav. 2005;7(3):419–29.

46. Elwan S, Alexopoulos A, Silveira DC, Kotagal P. lateralizing and localizing value of seizure semiology: comparison with scalp EEG, MRI and PET in patients successfully treated with resective surgery. Seizure Eur J Epilepsy. 2018;61:203–8.

47. Zijlmans M, Zweiphenning W, Klink N. Changing concepts in presurgical assessment for epilepsy surgery. Nat Rev Neurol. 2019;15(10):594–606.

48. Cendes F, Li LM, Craig W, Andermann F, Dubeau F, Arnold DL. Is Ictal recording mandatory in temporal lobe epilepsy? Not when the interictal electroencephalogram and hippocampal atrophy coincide. Arch Neurol. 2000;57(4):497–500.

49. Morad O, Abdellatif MG, Arafa AG, Amin AE. Cognitive implications in epilepsy. Sohag Med J. 2019;24(1):57–63.

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