Research Article   OMICS International

Impaired Executive Function by Interictal Epileptiform Discharges in Patients with Idiopathic Generalized Epilepsy

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Abstract

Objective: Many patients with Idiopathic Generalized Epilepsy (IGE) exhibit cognitive deficits. Interictal Epileptiform Discharges (IEDs) may contribute to cognitive impairment in epilepsy; however, the relationship between IEDs and cognitive impairment is unclear.

Methods: In this study, we analysed executive function in three groups: IGE patients with IEDs, IGE patients without IEDs and healthy controls. Executive function was assessed using the Stroop Test, the Verbal Fluency Test, the Digit Span Test and Wisconsin Card-Sorting Test.

Results: The IGE patients with IEDs performed worse on executive function tests compared with patients without IEDs. Furthermore, the IGE patients without IEDs performed worse compared with healthy controls. There were significant differences between the three groups in performance on the Stroop Test, the Digit Span Test (forward and backward), Verbal Fluency Test (animals, fruits) and the subscales of WCST (Categories Completed, Correct Response, Total Errors and Preservative Errors).

Conclusion: These results suggest that executive function in patients with IGE is impaired and is further impaired by IEDs. Future studies should determine whether well-controlled patients with IGE could benefit from antiepileptic treatment.

Keywords: Sexecutive function; Interictal Epileptiform Discharges (IED); Idiopathic Generalized Epilepsy (IGE); Epilepsy; Cognition

Introduction

Epilepsy is a common brain disorder that is characterized by recurrent and spontaneous seizures that result from abnormal and excessive synchronization of neuronal activity. Epileptiform discharges are abnormal neuronal discharges seen on Electroencephalogram (EEG) as a result of transient synchronous depolarisation of neurons [1]. Findings from published work suggest that these discharges are not mere biomarkers of epilepsy but have important behavioural and cognitive consequences [2-4]. Niemann et al. established an independent relationship between cognitive impairment and the percentage of epileptiform discharges for a large number of factors such as the duration of epilepsy and the aetiology [5]. Evidence suggests that there is a relationship between epileptiform discharges and both learning difficulties and behavioural regression [6]. Epileptiform discharges not accompanied by obvious clinical events are generally regarded as subclinical or interictal. Investigations have confirmed the occurrence of cognitive deficits during Interictal Epileptiform Discharges (IEDs) [4,7]. Epileptiform discharges can result in Transitory Cognitive Impairment (TCI), with the type of deficit dependent on where in the cortex the Epileptiform discharges arises [8]. Furthermore, disruption of sleep architecture by epileptiform discharges may be an important factor contributing to cognitive impairment in children with epilepsy [9]. Although the most prominent effects of IEDs are attention and motor speed, transitory cognitive impairment is not simply inattention [10]. Focal discharges have been temporally linked to material-specific deficits, depending on the hemisphere and the particular brain region [11].

Executive functions are integral to higher level and complex cognitive processes and are thought to be responsible for the ability to plan and form abstract concepts and goals, carrying out goal-directed plans, adjust to changing demands and new instructions, and controlling attention, impulsivity, and emotions [12,13]. The Wisconsin Card Sorting Test is one of the most widely used executive tests [14]. Executive functions are important in everyday life and learning processes and are the most common cognitive domain affected in patients with temporal and extra temporal epilepsy [15].

Idiopathic Generalized Epilepsy (IGE) is typically associated with normal intelligence, but many patients' exhibit specific, frontal-lobe cognitive deficits [16-18]. A meta-analysis found that IGE patients demonstrated significantly lower scores on tests across all cognitive factor-domains except visual-spatial abilities [3] and increasing seizure frequency was significantly associated with worse outcomes [19]. Epilepsy is not understood as a disorder affecting one discrete brain region but as a disorder of widespread brain networks [20]. Although the neuropsychological and behavioural correlates of IGEs are less studied compared to temporal lobe epilepsy, compelling evidence implicates localized frontal lobe dysfunction in some IGE syndromes [21,22]. In this study, we investigated executive function in patients with IGE to determine the relationship between IEDs and executive function.

Materials and Methods

Patients

All patients evaluated in the epilepsy specialist clinic of the First Affiliated Hospital of Anhui Medical University in 2014 were considered for participation in the present study. A total of 38 right-handed patients (19 males and 19 females) with IGE met the criteria and agreed to participate. All patients were seizure free for at least half a year. To be included in the study, patients had to: (a) Have been diagnosed with IGE as defined by the Commission on Classification and Terminology of the International League against Epilepsy [23]; (b) Have a normal cognitive ability, as determined by MoCA (Montreal Cognitive Assessment, patients with MoCA scores below 26 were excluded); (c) Have more than 5 years of education; (d) Have normal or corrected vision; and (e) Have the ability to understand the procedures of the experiment. Patients with evidence of other neurological or psychiatric disorders, as determined by a medical history, physical examination or neuroimaging, were excluded. All patients were interviewed during 24 h ambulatory EEG recording (including hyperventilation and all EEG recordings captured sleep). Medical records were also reviewed to obtain their demographic(gender, age, education) and clinical information(age at seizure onset, disease duration, seizure free duration, history of antiepileptic drug therapy and current dosages, previous EEG findings and neuroimaging findings). Based on the results of the EEG monitoring, the patients were divided into two groups: patients without IEDs and patients with IEDs. In group without IEDs, 12 patients were juvenile myoclonic epilepsy, 2 patients were childhood absence epilepsy and 1 patient was GTCS only. In group with IEDs, 15 patients were juvenile myoclonic epilepsy, 2 patients were childhood absence epilepsy, 3 patients were juvenile absence epilepsy, 2 patients were epilepsy with myoclonic absences and 1 patient was GTCS (generalized tonic-clonic seizures) only.

Additionally, we included a group of Healthy Controls (HC), which included 24 participants (9 males and 15 females) who were matched to the patient group on age, gender and education.

This study was approved by the ethics committee of Anhui medical university and all participants provided written informed consent to participate in the study.

Background tests

All patients completed the MoCA Beijing version. The Beck Depression Inventory (BDI, translated into Chinese) and Hamilton Anxiety Scale (HAMA, translated into Chinese) were administered to obtain measurements of depressive and anxiety symptoms in both the patients with IGE and the healthy controls.

Executive function tests

Executive function was assessed using the Stroop Test, the Verbal Fluency Test (using animal, fruit and word categories), the Digit Span Test (forward and backward) and the Wisconsin Card-Sorting Test [24]. All patients completed executive function assessment during the 24 h ambulatory EEG recording.

The Stroop Test evaluates the ease with which a person can maintain a goal in mind and suppress a habitual response in favour of a less familiar one. It also assesses selective attention, susceptibility to interference and cognitive flexibility. The difference (in seconds) between the execution time of the third (words) and the first (colours) tasks was evaluated [25].

The Verbal Fluency Test (using semantic categories of animals and fruits, and phonemic categories) evaluates the spontaneous production of words under restricted search conditions. The generation of words belonging to a certain category within 1 min is used to assess verbal association fluency and mental retrieval from long-term memory [26].

In the Digit Span (DS) Test (forward and backward), a string of digital numbers is presented beginning with length of 3 digits forward or 2 digits backward. In the DS forward, the participant must listen to a digit span at a speed of one digit per second and repeat it forward. The DS backward follows the same procedure as the DS forward except the participant must repeat the span backward. Two trials were presented at each length. The test was halted when the participant failed to recall both sequences at a single sequence length [27].

The Wisconsin Card-Sorting Test (WCST) requires participants to match cards to one of four target cards. The examinee was not told how to match the cards but was informed if their particular match on each response was correct or incorrect. The sorting principles include colour, shape and number. The sorting principles are changed during the course of the test and the examinee had to use examiner feedback to arrive at a correct solution. The 128-card, hand-administered version of WCST was used. Scores used for analysis were the number of categories completed, correct responses, preservative responses and preservative errors [24].

Statistical analysis

Statistical analyses were performed using SPSS version 20.0 for Windows. A Chi-square test was performed for the variable of gender. Non-parametric statistics (Kruskal-Wallis test) were performance for the variables of age, education, MoCA, BDI and HAMA. The variables of age at seizure onset, disease duration, seizure-free time, and the daily dose of Valproic Acid (VPA) and Lamotrigine (LTG) were assessed using non-parametric statistics (Mann-Whitney test). An Analysis of Covariance (ANCOVA) was used to compare the variables of the Stroop Test, Digital Span Test (forward and backward), Verbal Fluency Test and WCST across the three groups and the daily dose of VPA were used as a covariant. Pairwise comparisons were tested using the Least Significance Test. A $p < 0.05$ was considered to be statistically significant.

Results

Demographic variables and background tests

All IGE patients were being treated with Antiepileptic Drugs (AEDs) and were well controlled. All patients were seizure free for at least half a year. Of the IGE patients in this study, 20 patients used VPA (sodium valproate, produced by Sanofi Co. Ltd.) only, 16 patients used LTG (lamotrigen, produced by GSK Co. Ltd.) only and 2 patients used both VPA and LTG. The group without IEDs contained a total of 15 patients (8 males and 7 females); 8 of those patients used VPA only and 7 patients used LTG only. The group with IEDs contained a total of 23 patients (11 males and 12 females); 12 of those patients used VPA only, 9 patients used LTG only and 2 patients used both VPA and LTG. The healthy control group (HC) included 24 participants (11 males and 13 females).

The number of male and female participants was equal across the three groups. We found no significant differences in age, education, MoCA scores, BDI scores and HAMA scores between the three groups. There was also no significant difference in the age at seizure onset, disease duration, seizure-free time and the average daily dose of LTG between the two IGE groups. The IGE group with IEDs had a higher average daily dose of VPA compared to the group of IGE patients without IEDs. The details are shown in Table 1.

the Verbal Fluency Test (words) and the subscales of WCST (Preservative Responses). In addition, the daily dosage of VPA did not effect the differences in executive function observed between the three groups. Considering the wide age range and ongoing brain development in all participants, age were also included as a covariate in the analyses and found that age effect the differences in Verbal Fluency Test observed between the three groups. The details are shown in Table 2 and the results of the post-hoc tests are shown in Figure 1.

	With IEDs	Without IEDs	HC	P-Value
N	23	15	24	
Gender(Male/Female)	11-Dec	08-Jul	Nov-13	X^2=0.213, p=0.899
Age(years)	17.87 ± 5.27	20.53 ± 6.05	18.46 ± 6.44	X^2=2.595, df=2, p=0.273
Education(years)	9.26 ± 2.85	11.00 ± 3.32	10.13 ± 3.25	X^2=2.893, df=2, p=0.235
MoCA	27.39 ± 1.07	27.20 ± 1.52	28.25 ± 1.42	X^2=5.841, df=2, p=0.054
BDI	6.14 ± 5.83	5.46 ± 4.68	2.74 ± 3.49	X^2=4.680, df=2, p=0.096
HAMA	4.36 ± 4.66	3.21 ± 3.40	2.21 ± 2.99	X^2=3.877, df=2, p=0.144
Age at seizure onset	12.10 ± 4.82	15.38 ± 7.20	-	Z=1.436, p=0.153
Disease duration(years)	5.78 ± 4.33	5.15 ± 4.07	-	Z=0.329, p=0.746
Seizure Free(years)	2.46 ± 2.03	3.40 ± 2.83	-	Z=1.389, p=0.172
Dose of VPA (g/day)	0.982 ± 0.229	0.718 ± 0.282	-	Z=2.134, p=0.033*
Dose of LTG (g/day)	0.118 ± 0.040	0.100 ± 0.029	-	Z=0.986, p=0.324

Table 1: Demographic variables and performance on the background tests (*P<0.05).

Performance on the executive function tests

The IGE patients with IEDs performed worse on executive function tests compared with patients without IEDs. Furthermore, the IGE patients without IEDs performed worse compared with the healthy controls. There were significant differences between the three groups in performance on the Stroop Test, the Digit Span Test (forward and backward), Verbal Fluency Test (animals, fruits) and the subscales of WCST (Categories Completed, Correct Response and Preservative Errors). There were no significant differences between the groups on

	With IEDs	Without IEDs	HC	P-Value	VPA dose effect
Strop	17.02 ± 12.61	10.54 ± 8.36	6.39 ± 4.82	F=3.555, df=2, p=0.036*	F=0.055, df=1, p=0.815
DS(Forward)	7.48 ± 1.08	7.93 ± 0.62	9.29 ± 1.16	F=5.417, df=2, p=0.007**	F=1.122, df=1, p=0.294
DS(Backward)	5.57 ± 1.41	6.00 ± 1.41	7.18 ± 1.63	F=6.249, df=2, p=0.004**	F=0.884, df=1, p=0.351
VFT(Animals)	11.00 ± 2.71	13.00 ± 6.13	22.24 ± 6.38	F=15.788, df=2, p=0.000**	F=0.827, df=1, p=0.367
VFT(Fruits)	9.91 ± 0.90	11.29 ± 3.58	14.35 ± 3.77	F=5.693, df=2, p=0.006**	F=1.663, df=1, p=0.203
VFT(words)	5.00 ± 2.34	6.29 ± 2.81	7.71 ± 4.88	F=1.448, df=2, p=0.245	F=0.436, df=1, p=0.512
WCST					
Categories Completed	5.15 ± 2.52	6.64 ± 1.65	8.06 ± 1.44	F=8.377, df=2, p=0.001**	F=0.757, df=1, p=0.388
Correct Response	86.6 ± 15.10	95.86 ± 8.76	98.94 ± 5.60	F=8.776, df=2, p=0.000**	F=3.603, df=1, p=0.063
Total Errors	40.57 ± 15.76	30.57 ± 9.74	23.53 ± 7.73	F=12.260, df=2, p=0.000**	F=3.035, df=1, p=0.087
Perseverative Responses	45.39 ± 16.29	39.43 ± 6.79	41.82 ± 6.13	F=1.879, df=2, p=0.162	F=2.077, df=1, p=0.155
Perseverative Errors	23.43 ± 12.06	15.36 ± 5.72	15.71 ± 5.03	F=4.425, df=2, p=0.017**	F=0.854, df=1, p=0.359

Table 2: Performance on the executive function tests (Mean ± SD), DS: Digital Span; VFT: Verbal Fluency Test; WCST: Wisconsin Card-Sorting Test; *P<0.05; **P<0.01.

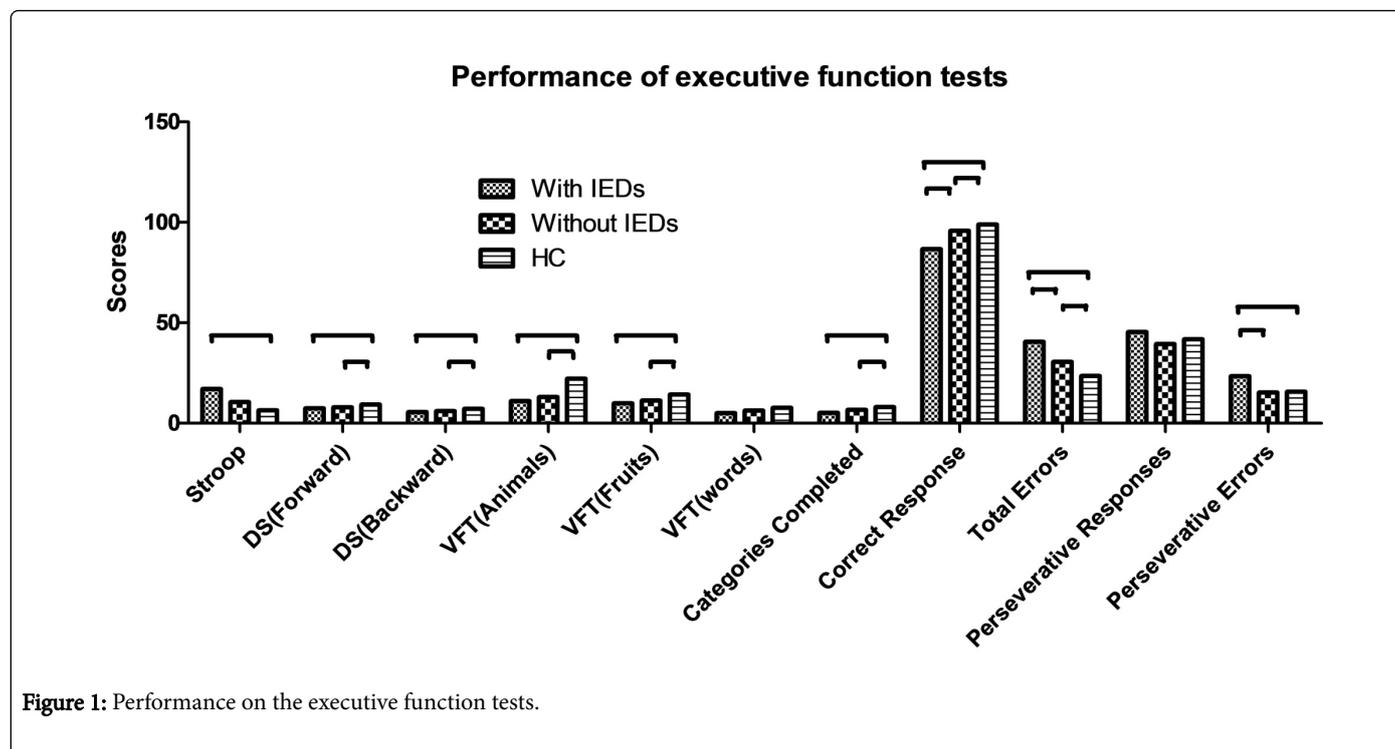**Figure 1:** Performance on the executive function tests.

Discussion

In the present study, we found impaired executive function in patients with IGE, which is consistent with previous findings [24,28]. IGE Patients with IEDs performed worse in executive function than patients without IEDs. Given that the patients were well-controlled such that the two groups did not significantly differ with respect to the other variables, this difference is likely attributed to the IEDs.

IGE is characterized by bilateral synchronous epileptiform discharges on EEG and recurrent generalized seizures. Evidence from previous studies suggests that epileptiform activity is the dominant factor that inhibits specific brain areas. A higher spike-wave index during NREM (non-rapid eye movement) sleep is associated with impaired performance in the nonverbal task in patients with idiopathic epilepsies [29]. Tassinari and Rubboli suggested that focal spikes could disrupt cortical functions and produce TCI. The authors speculate that prolonged focal epileptic activity impairs neural processes and possibly the local plastic changes associated with learning and other cognitive functions [30]. Nicolai et al. reported that cognitive and behavioural problems are related to epileptiform discharges in children with BECTs (benign childhood epilepsy with centrotemporal spikes) [31]. In humans, IEDs recorded using depth electrodes implanted into the hippocampus showed a disruption in memory maintenance and retrieval, but not encoding [32]. These studies strengthen the argument that IEDs may contribute to cognitive impairment in epilepsy depending upon when and where they occur.

However, not all studies have found a relationship between epileptiform discharges or short seizures and cognitive impairment [33]. Studies have shown that simple motor tasks and other tasks with low information processing demand (i.e., tasks that do not require information processing of complex sets of information) are slightly or not affected by epileptiform discharges, whereas tasks with high information processing demand are considered to be more sensitive

[10,34]. In our study, executive function was assessed using the Stroop Test, the Verbal Fluency Test, the Digit Span Tests and the WCST, which have been used in several studies and have been demonstrated to be suitable to investigate executive function [15,24,35].

Based on the causal relationship between epileptiform discharges and cognitive impairment, several studies have investigated whether treatment of IEDs can improve the cognitive and behavioural problems associated with IEDs. Treatment of subclinical epileptiform discharges in cerebral palsy patients without clinical epilepsy has been shown to improve their prognosis and quality of life [36-38]. Furthermore, suppression of IEDs has been found to improve behaviour only in patients who showed a significant decrease in either the frequency or duration of the discharges [39]. Children who showed a significant reduction in subclinical seizures after initiation of LTG also showed significant improvement in behaviour [40]. Uncontrolled reports and many preliminary randomized controlled trials of antiepileptic treatment for IEDs have suggested that suppression of discharges is associated with significant improvement in psychosocial function [41].

All commonly used AEDs have some effect on cognitive function, which may be substantial when crucial functions are involved [42]. For example, phenytoin may affect mental speed and phenobarbital may affect attention and memory. Evidence has shown that LTG has a cognitive-enhancing effect on attention [42]. A recent study demonstrated that the cognitive side effect profile of lacosamide is comparable to that of LTG and superior to that of topiramate, which was indicated by both subjective and objective measures [43]. VPA does not appear to impair cognition if sufficiently controlled for hyperammonemia [42]; however, studies have shown VPA can reduce spatial working memory and cell proliferation in the hippocampus [44]. These results support the idea that VPA may cause cognitive impairment by reducing neurogenesis within the hippocampus [44]. In this study, the average daily dose of LTG was similar between the two IGE groups, but the patients with IEDs had a higher average daily dose

of VPA compared with the patients without IEDs; however, the daily dose of VPA was used as covariant in our analysis, and we found this difference did not affect our results. Therefore, the differences in executive function between the two groups (the patients with IEDs and the patients without IEDs) may be caused by the IEDs themselves.

Decisions on treatment in daily clinical practice partly depend on the question of whether the IEDs diminish cognitive function; however, official guidelines on the treatment of TCI in the presence of focal or generalized IEDs have not been established. A recent study found that the IED index of 10% (a measurement that indicates if a spike or spike-wave complex occurs within 1 s of one page or 10 s) is the minimum threshold for the negative effects of IEDs on cognitive performance in adult patients with epilepsy [45], which suggests that treatment of IEDs to improve cognition should be further examined. Although there is increasing evidence for an impact of IEDs on cognition, a consensus has not been reached for different populations (child or adult patients) or on different IED indexes (distribution or location). Therefore, future studies should include a large number of patients and placebo-controlled randomized trials to address these crucial questions.

Also this study has some limitations. Brain development is potential mediator to affect the cognitive function in patients with epilepsy [46]. Considering the wide age range and ongoing brain development in all participants, age were included as a covariate in the analyses and found that age affect the differences in Verbal Fluency Test observed between the three groups. The cognitive effect of brain development in patients with epilepsy should be discussed in our future studies.

Conflict of Interest

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Acknowledgements

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