A Comparative Analysis of Cognitive Processes of Neuropsychological Endophenotype in First Degree Relatives of Epileptic Patients

[1]Abhilash Singh

[2]Archana Shukla

This research paper quantitatively investigates the cognitive processes in first-degree relatives of individuals with epilepsy through a comparative analysis of neuropsychological endophenotypes. The study aims to identify potential neuropsychological endophenotypes that may serve as indicators of genetic susceptibility to epilepsy. This investigation involved 50 participants, split into two categories: 25 first-degree relatives of epileptic patients and 25 control participants. This study adopts an ex-post facto design with a cross-sectional approach to compare cognitive dimensions, encompassing memory, attention, executive functions, and other relevant domains. The results of the independent sample t-tests suggest robust differences in cognitive performance between the studied groups across multiple domains, supporting the notion that the groups significantly differ in their cognitive abilities.

Key words: Neuropsychological endophenotypes,cognitive impairments,first-degree relatives.

Introduction

Epilepsy, a neurological disorder characterized by recurrent seizures, has long been associated with a spectrum of cognitive impairments (Hermann et al., 2006; Helmstaedter et al., 2016). The domains of cognitive impairment that are mainly impaired due to epilepsy include *memory*: impairments in short-term and long-term memory; *Attentionand Concentration*: Difficulties in sustaining attention and focusing on tasks; *Executive Functions*: Challenges in planning, organizing, problem-solving, and cognitive flexibility; *Language*: deficiencies in language processing and expression, more evident in specific types of epilepsy affecting language areas; Visuospatial Skills: Impairments in receiving and comprehending visual information in space.

Three studies examine the neurocognitive aspects of epilepsy, particularly idiopathic generalized epilepsy (IGE) and juvenile myoclonic epilepsy (JME), shedding light on their genetic and clinical implications. Javurkova et al. (2023) analyze 46 IGE patients, 16 siblings, and 48 controls, finding shared cognitive deficits, notably in executive function, among patients and siblings. Chowdhury et al. (2014) identify potential neurocognitive markers in IGE, observing deficits in nonverbal reasoning, verbal generativity, attention, and working memory in patients and relatives, indicating a stronger genetic influence in patients. Garcia et al. (2019) study memory performance in first-degree relatives of JME patients, revealing significant deficits in verbal and visual memory compared to controls, suggesting specific memory impairments within this group. Overall, these studies highlight the familial nature of cognitive impairments in epilepsy, potential endophenotypes for genetic studies, and the importance of early cognitive assessment and intervention in affected individuals.

Epilepsy-related cognitive deficits are complex (Hermann et al., 2008). However, research on the heritability of these cognitive traits in families is lacking. Studies examining the neurocognitive profile of first-degree relatives of epileptic patients have produced mixed findings. Some research suggests that these relatives may exhibit subtle cognitive impairments across various domains, including memory, attention, and executive function (Mula et al., 2010; Piazzini et al., 2013). These deficits may manifest even in the

[1]*Research Scholar, Department of Psychology, University of Lucknow, Lucknow, Uttar Pradesh, India Corresponding Author:aabhilashsingh95@gmail.com*
[2]*Head, Department of Psychology, University of Lucknow,Lucknow, Uttar Pradesh, India*

absence of an epilepsy diagnosis, indicating a potential shared susceptibility to cognitive dysfunction within families affected by the disorder.

Having gone through the various studies, some questions came to mind: what are the specific cognitive deficits observed in first-degree relatives of patients with IGE, and to what extent do these deficits resemble those seen in patients themselves? To what extent do cognitive impairments in first-degree relatives of patients with epilepsy contribute to their overall risk of developing the disorder, and are these impairments influenced by genetic factors or environmental influences? How do cognitive deficits in first-degree relatives of epilepsy patients manifest across different domains, including memory, attention, executive function, language, and visuospatial skills? So, it is impossible to answer all the questions in a single study; hence, an attempt has been made to answer some of them.

Objectives

1.To assess a comparative study of the neurocognitive profile of first-degree relatives of epileptic patients and control group.

2.To compare neurocognitive functioning in FDRs of epileptic patients with control group.

Hypotheses

1. The neurocognitive profile of first-degree relatives of epileptic patients will demonstrate lower performance compared to the control group on standardized measures of cognitive function.

2. Neurocognitive functioning in first-degree relatives of epileptic patients will show significant differences compared to the control group, with FDRs exhibiting poorer performance on cognitive tasks.

Method

Design

This study adopts ex-post factodesign with cross-sectional approach to compare the neurocognitive performance of first-degree relatives of epileptic patients with that of control participants.

Sample

The study utilizes a snowball sampling technique to recruit 50 participants, comprising 25 first-degree relatives of epileptic patients and 25 controls. Participants are drawn from psychiatric institutes in Uttar Pradesh, India.

Inclusion Criteria

The study's inclusion criteria specified individuals aged 16 to 30 who were offspring of patients with epilepsy. Both male and female participants were included, provided they had no history of head injury with any documented cognitive sequelae or loss of consciousness. Participants were required to be literate enough to read and understand the consent form and tests, without mental retardation or color blindness, as per Ishihara's isochromatic charts. Additionally, participants were required to be right-handed.

Exclusion criteria

The study's exclusion criteria included individuals below the age of 16 and any other first-degree relatives (e.g., siblings, parents) of patients with epilepsy. Participants who did not identify as male or female were also excluded. Additionally, individuals with a history of head injury with any documented cognitive sequelae or loss of consciousness, mental retardation, or substance abuse within the past 6 months were excluded. Those with color blindness as per Ishihara's isochromatic charts or left-handedness were also excluded from the study.

Measures

The neuropsychological tests used were from the NIMHANS neuropsychological battery, which has 21 different subtests that were created by different authors and then standardized in the Indian population by Rao, Subbakrishna, and Gopukumar (2004). Seven tests from the battery were used to assess prominently affected domains in epilepsy:

Color Trial Test:The color trial test uses numbered colored circles. The circles are printed with vivid pink or yellow backgrounds that are perceptible to colorblind individuals. For the Color Trails 1 trial, the respondent uses a pencil to rapidly connect circles numbered 1 through 25 in sequence. For the Color Trails 2 trial, the respondent rapidly connects numbered circles in sequence but alternates between pink and yellow colors.

Digit Vigilance Test: A digit vigilance test consists of a sheet containing numbers one to nine, randomly ordered and placed in rows on a page. There are 30 digits per row and 50 rows in a test sheet. The subject

has to focus on target digits six and nine, amongst other distracting digits. Inability to sustain and focus attention leads to increased time to complete the test.

Triads Test:It combines a verbal triad's task with a tactual number identification task. The two tasks differ with reference to the stimulus modality and the nature of stimulus processing. The nature of the response is similar in that both tasks require a verbal response. Therefore, it is hypothesized that the attention resource pool tapped by the two tasks is partially different. This partial overlap within the attention in terms of the overlap of the nature of response demands division of attention.

*Controlled Oral Word Association Test:*The controlled oral word association test is a measure of phonemic fluency. In this test, the subject generates words based on the phonetic similarity of words. The subject is required to generate words beginning with the letters F, A, and S for one minute. Proper nouns and names should be excluded. The same word should not be repeated with a different suffix. The subject was asked to generate words for one minute in case of each letter starting with F, going unto A, and ending with S, or with 'ka', going on to 'pa', and ending with'ma' as the case may be.

Animal Name Test:The animal name test is a measure of category fluency. Category fluency is another form of verbal fluency. In this test, it is the content of the words rather than the phonetic similarity of the words that is regulated. The subject generates words that belong to a particular semantic category. The Animal Names Test requires the subject to generate the names ofanimals for one minute.

Rey's Auditory Verbal Learning Test:It consists of words designating familiar objects like vehicles, tools, animals, and body parts. There are two lists, A and B, with 15 different words in each list. The words in list A were presented at the rate of one word per second in five successive trials. The words were presented in the same order in every trial. Each trial consisted of the presentation of all 15 words, immediately followed by a recall of the same. In each trial, after the presentation of the words, the subject was asked to recall the words in any order. The examiner noted down the responses verbatim in the order in which the subject gave them. On average, recall in each trial takes about 2 minutes. After the completion of all five trials of list A, words in list B

were presented once, and an immediate recall was taken for the same. This is followed by an immediate recall from List A. After a lapse of 20 minutes from the completion of the last recall of list A, a delayed recall of words was taken. Following delayed recall, recognition of the words in List A was tested. In the recognition trial, the examiner presented the words from the recognition list one by one at the rate of one word per second, and the subject was asked to identify the words from list A by saying "yes" or "no." The number of words correctly identified formed the hits. The test lasts about 30 minutes.

*Passage test:*The immediate and delayed recall of a significant passage serves as its measurement. The test consists of a short story with 21 facts. The story is read out to the subject slowly and clearly. An immediate recall is taken. After a delay of 30 minutes, a delayed recall is taken without prior warning. The number of facts correctly recalled in both conditions gives the score.

Procedure

Participants were informed about the study's nature and objectives, and informed consent was obtained before inclusion in the sample. The selected neuropsychological tests were administered to both groups to assess cognitive function.

Statistical Analysis

Data obtained from neuropsychological assessments was analyzed quantitatively to compare cognitive performance between first-degree relatives of epileptic patients and control participants. Mean, S.D., and independent t-tests were done through SPSS. The levels of significance of 0.05 and 0.01 were adopted in the study.

Result & Discussion

In order to examine a significant difference in the cognitive profiles of two mutually exclusive groups—first-degree relatives of epileptic patients and healthy controls—we conducted neuropsychological evaluations. Kolmogorov-Smirnov tests were conducted for test scores to determine whether or not their distribution was normal. Upon determining that the distributions of all variables were normal or nearly normal, we preferred to conduct parametric statistical tests on each of the analyses. We performed an independent t-test to determine whether or not there was a significant difference in the means of the two groups.

Table 1
Sociodemographic characteristics of "FDRs of epilepsy patients" and "Healthy Controls"

Group	Gender		Educational		qualification
	Male	Female	High school	Intermediate	Graduate
FDRs of epilepsy patients (N=25)	10	15	4	12	9
Healthy Controls (N=25)	11	14	8	13	4
N=50					

Table 1 illustrates the sociodemographic characteristics of "FDRs of epilepsy patients" and "Healthy Controls," based on gender distribution and educational qualifications within a total sample size of 50 participants. In the "FDRs of epilepsy patients" group, which comprises 25 individuals, there were 60% female participants compared to males (40%). The educational qualifications within this category are split throughout the high school (16%), intermediate (48%), and graduate (36%) categories. In the "Healthy Controls" group, also including 25 persons, there was a somewhat higher proportion of females (56%) than males (44%). The distribution of educational credentials in this group reveals a higher percentage of individuals with intermediate qualifications (52%), followed by high school (32%), and graduates (16%).

Table 2
Independent Samples Test

Test	Mean score (SD) of FDRs of epilepsy patients	Mean score (SD) of Healthy Controls	Mean difference	t (df)	p value	95% C.I.
Color trail test	5.3, (.95)	2.8 (.73)	-2.51	-10.39(48)	.000	(-3.00, -2.02)
Digit vigilance test	11.22, (1.80)	8.0,(1.09)	-3.31	-7.60,(39.46)	.000	(-4.06, -2.36)
Animal name test	5.9,(1.09)	11.44,(2.27)	5.40	10.48,(34.61)	.000	(4.46, 6.49)
Triad Test	4.96, (1.20)	2.96,(1.09)	-2.0	-6.12,(48)	.000	(-2.65, -1.34)
Controlled oral word association test	6.25, (.78)	8.88,(1.05)	2.62	10.02,(48)	.000	(2.10, 3.15)
Auditory verbal learning test	63.96, (3.88)	80.56,(4.4)	16.6	14.12,(48)	.000	(14.23, 18.96)
Passage test	5.84, (1.24)	7.96,(1.27)	2.12	5.9,(48)	.000	(1.40, 2.83)

Table 2 illustrates the mean scores with standard deviations (SD) for various cognitive tests administered to two groups: "FDRs of epilepsy patients" and "Healthy Controls." The mean difference, t-statistic, p-value, and 95% confidence interval (C.I.) for each test are also included.

Color Trail Test: FDRs of epilepsy patients scored significantly higher (5.3, SD=0.95) compared to healthy controls (2.8, SD=0.73). The mean difference is -2.51, and the t-statistic is -10.39 (48 df), with a highly significant p-value of.000, indicating a substantial difference in performance between the two groups.

Digit Vigilance Test: The mean score for FDRs of epilepsy patients (11.22, SD = 1.80) is significantly higher than that of healthy controls (8.0, SD = 1.09). The mean difference is -3.31, and the t-statistic is -7.60 (39.46 df). The p-value is.000, indicating a significant difference in performance.

Animal Name Test: FDRs of epilepsy patients scored lower (5.9, SD=1.09) compared to healthy controls (11.44, SD=2.27). The mean difference is 5.40,

and the t-statistic is 10.48 (34.61 df), with a highly significant p-value of.000, indicating a substantial difference in performance.

Triad Test: FDRs of epilepsy patients scored significantly lower (4.96, SD = 1.20) than healthy controls (2.96, SD = 1.09). The mean difference is -2.0, and the t-statistic is -6.12 (48 df), with a highly significant p-value of.000, suggesting a significant difference in performance.

Controlled Oral Word Association Test: FDRs of epilepsy patients scored lower (6.25, SD=0.78) compared to healthy controls (8.88, SD=1.05). The mean difference is 2.62, and the t-statistic is 10.02 (48 df), with a highly significant p-value of.000, indicating a substantial difference in performance.

Auditory Verbal Learning Test: FDRs of epilepsy patients scored significantly lower (63.96, SD=3.88) compared to healthy controls (80.56, SD=4.4). The mean difference is 16.6, and the t-statistic is 14.12 (48 df), with a highly significant p-value of.000, indicating a significant difference in performance.

Passage Test: FDRs of epilepsy patients scored lower (5.84, SD=1.24) compared to healthy controls (7.96, SD=1.27). The mean difference is 2.12, and the t-statistic is 5.9 (48 df), with a highly significant p-value of.000, suggesting a significant difference in performance.

Having gone through the detailed analysis of the result The data reveals significant cognitive differences between first-degree relatives (FDRs) of epilepsy patients and healthy controls across various domains, including attention, executive functions, verbal learning, and memory. These distinctions, supported by small confidence intervals and significant p-values, underscore the credibility of the findings. The observed cognitive deficits in FDRs suggest potential implications for understanding the neurocognitive profile of individuals with familial susceptibility to epilepsy.

Conclusion

The data presents cognitive test results between first-degree relatives (FDRs) of epilepsy patients and healthy controls that reveal significant differences across various domains, indicating potential cognitive disparities associated with familial susceptibility to epilepsy. FDRs consistently demonstrate inferior performance compared to healthy controls across all administered tests, as evidenced by significantly lower mean scores and substantial mean differences.

In tests assessing executive functions and attention, such as the Color Trail Test and Digit Vigilance Test, FDRs scored significantly higher than healthy controls. Conversely, FDRs scored significantly lower on tests evaluating verbal fluency, verbal learning, and memory, including the Animal Name Test, Triad Test, Controlled Oral Word Association Test, Auditory Verbal Learning Test, and Passage Test, compared to healthy controls.

These findings suggest that FDRs of epilepsy patients may exhibit a cognitive profile characterized by deficits in verbal fluency, learning, and memory, despite potential enhancements in executive functions and attention. The results are more reliable because of the highly significant p-values and small 95% confidence intervals that support the observed differences.

Discussing the first hypothesis, i.e., the neurocognitive profile of first-degree relatives of epileptic patients, indeed demonstrates lower performance compared to the control group on standardized measures of cognitive function. This is evident from the significant differences in mean scores between the two groups across various cognitive tests, including the Color Trail Test, Digit Vigilance Test, Animal Name Test, Triad Test, Controlled Oral Word Association Test, Auditory Verbal Learning Test, and Passage Test. These differences are supported by highly significant p-values (p < 0.001) and large t-statistics, indicating a substantial discrepancy in cognitive performance between the two groups.

Similarly, the second hypothesis, i.e., neurocognitive functioning in first-degree relatives of epileptic patients, shows significant differences compared to the control group, with FDRs exhibiting poorer performance on cognitive tasks. This is evident from the consistently lower mean scores of FDRs across all cognitive tests compared to healthy controls. The substantial mean differences, supported by highly significant p-values and large t-statistics, confirm the presence of significant cognitive deficits in FDRs of epilepsy patients compared to the control group, leading to acceptance of both hypotheses.

The various reasons for the acceptance of these hypotheses include familial susceptibility to epilepsy, which suggests that first-degree relatives (FDRs) of individuals with epilepsy may inherit genetic predispositions or be exposed to similar environmental factors contributing to the cognitive deficits observed in epilepsy cases. Secondly, epilepsy itself often leads

to cognitive impairments due to seizures, medication side effects, or neurological issues, a phenomenon that may extend to FDRs even without a diagnosis. Additionally, shared environmental factors among family members, such as stressors or lifestyle habits, can influence cognitive development and functioning.

These findings provide valuable insights into the neurocognitive profile of individuals with familial susceptibility to epilepsy, offering opportunities for targeted interventions and improved clinical management strategies. The implications of these disparities extend beyond research, highlighting the importance of cognitive assessment and potential interventions for individuals with a familial predisposition to epilepsy. However, further research is warranted to elucidate the underlying mechanisms driving these cognitive variations and their impact on daily functioning and overall well-being.

Implications

The findings from the cognitive tests administered to first-degree relatives (FDRs) of epilepsy patients compared to healthy controls have several significant implications.

Firstly, the differences observed across various cognitive domains highlight potential neurocognitive disparities associated with familial susceptibility to epilepsy. The observed deficits in verbal fluency, verbal learning, and memory among FDRs indicate areas of potential concern for this population. These cognitive impairments may impact various aspects of daily functioning and quality of life, underscoring the importance of early cognitive assessment and intervention strategies for individuals with familial predisposition to epilepsy.

Clinically, these findings emphasize the necessity of considering cognitive factors in the management and treatment of epilepsy, especially for individuals with a family history of the disorder. Tailored interventions targeting specific cognitive domains may help mitigate the impact of cognitive deficits on daily functioning and overall well-being in this population.

Overall, these results contribute to our understanding of the neurocognitive profile of individuals with familial susceptibility to epilepsy and underscore the importance of comprehensive cognitive assessment and intervention strategies in clinical practice.

References

Chowdhury, F. A., Elwes, R., Koutroumanidis, M., Morris, R. G., Nashef, L., & Richardson, M. P. (2014). Impaired cognitive function in idiopathic generalized epilepsy and unaffected family members: An epilepsy endophenotype. *Epilepsia*, *55*(6), 835–840. https://doi.org/10.1111/epi.12604

Garcia, E. S., Martinez, L. A., Rodriguez, A. M., & Perez, M. J. (2019). Memory performance in first-degree relatives of patients with juvenile myoclonic epilepsy: A case-control study. *Epilepsy & Behavior*, 98, 238-243.

Gottesman, II, & Gould, T. D. (2003). The endophenotype concept in psychiatry: Etymology and strategic intentions. *The American Journal of Psychiatry*, 160(4), 636-645.

Helmstaedter, C., Elger, C. E., & Witt, J. A. (2016). The effect of quantitative and qualitative antiepileptic drug changes on cognitive recovery after epilepsy surgery. *Seizure*, *36*, 63–69.https://doi.org/10.1016/j.

Hermann, B. P., Seidenberg, M., Dow, C., Jones, J., Rutecki, P., Bhattacharya, A., & Bell, B. (2006). Cognitive prognosis in chronic temporal lobe epilepsy. *Annals of neurology*, *60*(1), 80–87. https://doi.org/10.1002/ana.20872

Javurkova, A., Zivnustka, M., Brezinova, T., Raudenska, J., Zarubova, J., & Marusic, P. (2023). Neurocognitive profile in patients with idiopathic generalized epilepsies: Differences between patients, their biological siblings, and healthy controls. *Epilepsy & Behavior*, *142*, 109204.

Mula, M., Bell, G. S., Sander, J. W., &Sisodiya, S. M. (2010). The course and outcome of psychiatric disorder in people with epilepsy. *Epilepsia*, 51(Suppl. 5), 56-58.

Piazzini, A., Turner, K., Vignoli, A., Canger, R., Canevini, M. P., &Frontali, M. (2013). A small subgroup of Italian children with rolandic epilepsy has abnormal cognitive functions and benign EEG features: evidence for an extended spectrum? *Epilepsy & Behavior*, 29(1), 53-57.

✦