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Cognitive impairment in older adults with epilepsy: Characterization and risk factor analysis

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ABSTRACT

Objective: Cognitive deficits are common in epilepsy, though the impact of epilepsy on cognition in older adults is understudied. This study aimed to characterize cognition in older adults with epilepsy compared with healthy older adults and identify potential risk factors for impairment.
Methods: Thirty-eight older adults with epilepsy and 29 healthy controls completed a comprehensive neuropsychological battery, as well as measures of depression and anxiety. Chart review for current medications, seizure history, and neuroimaging was also completed. To compare cognitive performance between groups, ANOVA was used, and linear regression identified predictors of impairment among the group with epilepsy.
Results: Patients with epilepsy performed worse across nearly all cognitive domains, and were clinically impaired (i.e., ≥1.5 SD below mean) on more individual tests when compared with controls, including a subset of patients with epilepsy with normal MRIs. For all patients with epilepsy, taking a greater number of antiepileptic drugs was associated with poorer language and visuospatial abilities, and higher anxiety was associated with poorer visual memory.
Conclusions: Older adults with epilepsy demonstrated greater cognitive deficits than matched controls. Polytherapy and anxiety heightened the risk for cognitive impairment in some cognitive domains, but not in others. Understanding the nature of cognitive decline in this population, as well as associated risk factors, may assist in the differential diagnosis of cognitive complaints and improve the design of treatment studies for older patients with epilepsy. Replication in larger, longitudinal studies is warranted to generalize these findings.

1. Introduction

The incidence of epilepsy in adults increases significantly with advancing age, particularly in those over the age of 60 years [1]. Compared with healthy controls, older adults with epilepsy demonstrate deficits across numerous cognitive domains [2–4]. Older adults with epilepsy also demonstrate deficits when compared with individuals with known cognitive impairment. For example, Griffith et al. [4] found that older adults with epilepsy demonstrated worse performance on aspects of the Dementia Rating Scale (DRS), a measure of global cognitive functioning, and letter fluency when compared with individuals with amnestic mild cognitive impairment (MCI). Moreover, they performed similarly to those with amnestic MCI on all other measures [4].

The relationship between cognitive decline and epilepsy characteristics is complex and still incompletely understood. The available literature has demonstrated that the duration of seizure disorder and age of onset correlated with memory performance, with longer seizure duration associated with worse performance, and a later age of onset associated with better performance [2]. Individuals with refractory temporal lobe epilepsy for more than 30 years also demonstrated lower full scale IQ scores compared with those with shorter duration of illness [5]. The negative impact of antiepileptic drugs (AEDs), particularly AED polytherapy, on cognition has been cited consistently. Individuals on AED monotherapy have performed worse than controls on measures of conceptualization and verbal learning. Moreover, when compared with AED monotherapy and healthy controls, polytherapy was associated with worse overall performance on the DRS as well as poorer performance on the DRS subtests of attention, initiation/perseveration, and memory, and delayed recall on a story memory task [2]. Antiepileptic drug polytherapy has also surfaced as a significant predictor of poorer performance on additional tasks of attention,

Abbreviations: DRS, Dementia Rating Scale; MCI, mild cognitive impairment; AEDs, antiepileptic drugs; BDI-II, Beck Depression Inventory—II; BAI, Beck Anxiety Inventory; MMSE, Mini-Mental State Examination.

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executive function, and memory [3]. In addition, patients taking AED polytherapy had worse cognitive performance compared with those with MCI taking a cholinesterase inhibitor [4].

Previous work has also found that older adults with epilepsy endorsed higher levels of depression than controls, and that depression was negatively correlated with performance on tasks of memory, fluency, and global cognition [2]. To our knowledge, the relationship between anxiety and cognitive function has not been systematically examined in the older adult population with epilepsy.

Through a comprehensive neuropsychological battery, the current study aimed to expand on previous work by more precisely characterizing the nature and prevalence of cognitive deficits in older adults with epilepsy. We also sought to identify specific risk factors for cognitive impairment within this population by examining the impact of epilepsy-related factors (i.e., age of onset, seizure frequency in past month, total AEDs, AEDs with well-established cognitive side effects), as well as psychiatric factors (i.e., depression and anxiety) on cognitive performance. Our study extends previous work through the inclusion of anxiety as a potential risk factor for cognitive impairment and by examination of the impact of specific AEDs on cognition, particularly those with known cognitive side effects. A greater understanding of the nature of cognitive deficits among older adults with epilepsy, as well as the associated risk factors, would help guide treatment selection in this population.

2. Methods

2.1. Participants

This research was approved by the Rhode Island Hospital Institutional Review Board, and all study participants provided written informed consent prior to initiating study procedures. Thirty-eight adults with epilepsy and twenty-nine cognitively intact adults, 55 years of age or older, participated in the current study. Patients with epilepsy were recruited through a hospital-based neurology practice, and controls were recruited through community advertising. Individuals in the group with epilepsy had documented epilepsy as diagnosed by a neurologist. Healthy controls had no history of seizures or epilepsy and no current cognitive complaints. Exclusion criteria for both groups included a history of intellectual disability or other serious developmental disorder; progressive CNS disorders (e.g., dementia, demyelinating conditions, Parkinson's disease); significant hepatic, renal, or cardiopulmonary condition; brain injury beyond concussion; severe psychiatric conditions (e.g., schizophrenia, bipolar disorder); and substance abuse disorders within the past 6 months.

2.2. Measures

2.2.1. Emotional functioning

All participants completed the Beck Depression Inventory—II (BDI-II) [6] and the State-Trait Anxiety Inventory (STAI) [7]. A higher score on the BDI-II is indicative of greater levels of depressive symptomatology. Total score on the trait component of the STAI was computed to determine levels of chronic anxiety, with higher scores reflective of greater levels of anxiety.

2.2.2. Epilepsy characteristics

A comprehensive history was taken for each older adult with epilepsy. Specific characteristics examined in the current study included: age of first seizure, patient's reported seizure frequency over the past month, and total number of currently prescribed AEDs. Antiepileptic drugs were further categorized based on the presence/absence of known cognitive side effects. Medications with the most clinical evidence for cognitive side effects included: topiramate, zonisamide, phenobarbital, primidone, phenytoin, carbamazepine, divalproex, clonazepam, and lorazepam. Medications considered lacking robust clinical evidence for adverse cognitive side effects included: levetiracetam, lamotrigine, oxcarbazepine, pregabalin, gabapentin, and lacosamide [8–10].

Additional medications among patients with epilepsy included those for managing typical medical conditions among older adults (e.g., hypertension, acid reflux), as well as a small number of antidepressant and anxiolytic medications. The control group had a similar medication profile. We would expect the burden of these medications on cognition to be minimal.

2.2.3. Neuropsychological tests

All study participants completed a comprehensive battery of well-established neuropsychological tests including:

Global cognition

Mini-Mental State Examination (MMSE) [11]. This is brief screening measure of cognition that assesses orientation, basic attention, working memory, learning, naming, construction, comprehension, and repetition. The maximum score is 30, with scores below 24 suggesting cognitive impairment.

Mattis Dementia Rating Scale—2 (DRS) [12]. The DRS is a screening test designed to assess cognition in older adults. It consists of five subscales—Attention, Initiation/Perseveration, Construction, Conceptualization, and Memory. The maximum score is 144, with lower scores indicating greater cognitive impairment, and scores less than or equal to 124 suggesting dementia.

Verbal memory

Hopkins Verbal List Learning Test—Revised [13]. Participants are asked to learn and remember a list of 12 words over the course of three trials. After a 20-minute delay during which other tasks are completed, participants are asked to recall as many words from the list as possible. Total learning and delayed recall are recorded.

Verbal Paired Associates [14]. Participants are asked to learn 14 word pairs over the course of 4 trials. Some pairs are congruent (e.g., sky–cloud), while others are incongruent (e.g., tree–luck). They are given the first word of the pair and are asked to provide the other word. After a 30-minute delay, they are again asked to provide the second word of the pairing. Total learning and delayed recall are recorded.

Visual memory

Brief Visuospatial Memory Test—Revised [15]. Participants are shown a 2 × 3 array of 6 simple geometric designs. They are given 10 s to study the display and are then asked to draw what they can recall as accurately as possible and in the correct location. Learning over 3 trials and free recall after a 20-minute delay are recorded.

Attention/psychomotor speed

Trail Making Test—A [16]. Participants are asked to connect a series of 25 numbered dots in ascending order as quickly as they can (e.g., 1–2–3, etc.). Time to completion is recorded.

Digit Symbol Coding [17]. Participants are asked to transpose a coded sequence. They are provided with a key at the top of the page (e.g., a "1" means "+") and an array of numbers below, and are asked to draw the corresponding symbol. Total number of correct responses in 120 s is recorded.

Executive function

Trail Making Test—B [16]. This test adds a set-shifting component to Trail Making Test—A and requires participants to alternate between numbers and letters in ascending order (e.g., 1–A–2–B, etc.). Time to completion is recorded.

Controlled Oral Word Association [18]. Participants are asked to generate as many words as they can that begin with a given letter. A total of three letters are given. Participants have 60 s for each letter