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Cognitive Disorders, Depression and Anxiety in Temporal Lobe Epilepsy: An Overview

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Abstract

Partial epilepsies, originating in a specific brain region, affect about 60% of adults with epilepsy. Temporal lobe epilepsy (TLE) is the most prevalent subtype within this category, often necessitating surgical intervention due to its refractoriness to antiepileptic drugs (AEDs). Hippocampal sclerosis, a common underlying pathology, often exacerbates the severity by introducing cognitive and emotional challenges. This review delves deeper into the cognitive profile of TLE, along with the risk factors for cognitive disorders, depression, and anxiety in this population.

Keywords

Temporal Lobe Epilepsy, Cognitive Disorders, Anxiety, Depression

1. Introduction

The majority of adult epilepsy (60%) is due to seizures starting in a specific brain area, with temporal lobe epilepsy (TLE) being the most frequent type requiring surgery and often resistant to standard medication [1]. Hippocampal sclerosis (HS) is the most common histopathological abnormality found in patients with drug-resistant TLE [2].

Beyond physical manifestations, TLE is associated with multiple neuropsychological deficits encompassing cognitive and emotional [3]. Studies report impairments in memory, language, executive function, and attention [4]. Furthermore, 40% - 60% of patients are experiencing mood disorders. Notably, the risk of suicide attempts is markedly higher in TLE, with a 5- to 25-fold increase compared to the general population [5]. These comorbidities can significantly impact social interaction and communication, leading to challenges in daily life [3] [6].

This article aims to provide a comprehensive overview of the cognitive profile in TLE, encompassing key areas like memory, language, executive function, and visuospatial function. We will then delve into the various factors contributing to cognitive impairment in TLE, including: hippocampal sclerosis (HS), head injuries, other brain abnormalities, impact of seizures, antiepileptic drugs (AEDs), genetics factors and postoperative cognitive changes. Finally, we will explore the co-occurrence of depression and anxiety in TLE, highlighting their impact on both cognitive function and overall well-being. Understanding the multifaceted nature of TLE is crucial for developing effective treatment strategies and improving the quality of life for individuals affected by TLE.

2. Cognitive Profile in TLE

Cognitive Disorders (CD) are common in TLE and can manifest before diagnosis [7]. Therefore, neuropsychological assessment plays a crucial role in both diagnosing TLE and monitoring patients over time. This assessment helps quantify the nature and severity of CD. Epileptogenic location significantly influences the specific cognitive profile; as epileptic activity disrupts cognitive processes related to the affected brain structures. Consequently, the most common CD in TLE involves episodic memory and language furthermore. However, these disorders may involve other areas such as executive functions, visual recognition [4]. Multiple factors contribute to CD in TLE, including the neural, physical and psychological impact of seizures, comorbidities, head injuries and medical treatments [8].

2.1. Memory Impairments in TLE

Memory problems are a significant concern in TLE, with up to 70% of patients experiencing difficulties with declarative memory [8]. This is unsurprising, considering the crucial role temporal lobe structures, often affected by epilepsy, play in memory consolidation. Research suggests lesions in the Mesial Temporal Lobe Epilepsy (MTLE), particularly HS, are major contributors to memory impairments. These difficulties often manifest as: working memory deficits and episodic memory impairments [9] [10].

Scientific evidence confirms these issues through various studies. For example, Zhao *et al.* (2014) highlight the importance of working memory, noting its impact on long-term memory consolidation. If working memory is impaired in TLE, long-term memory suffers as well. Interestingly, differences in verbal memory deficits arise between left and right TLE [4]. Studies show a significantly higher prevalence of verbal memory problems in left TLE (70%) compared to right TLE (50%). However, both groups exhibit a similar rate of non-verbal memory issues (around 50%) [11]. While these population-level trends exist, it's crucial to remember that memory profiles can vary at the individual level. Therefore, reliable lateralization of temporal epilepsy requires comprehensive evaluation including neuropsychological assessments, Electroencephalogram (EEG), and

imaging data.

Neuropsychological tests typically reveal these memory impairments through performance difficulties in tasks assessing: short-term (working) memory, verbal episodic memory and non-verbal episodic memory. Further research also confirms accelerated forgetting over time (often after 24 hours) and documented issues with learning, storing, and retrieving information [12] [13] [14] [15].

It is worth highlighting the findings of studies investigating the memory impairment mechanisms in MTLE by analyzing functional connectivity (FC) using resting-state functional magnetic resonance imaging (rs-fMRI). In Chen *et al.*'s (2017) study, analysis of the results showed that the memory function of MTLE patients was impaired. Left-MTLE patients had lower scores on the pure verbal memory test, and Right-MTLE patients had lower performance on the pure visual memory test. MTLE patients exhibited widespread abnormal FC between the hippocampus and specific brain regions [16]. This is consistent with a study on the relationship between left hippocampal resting-state functional connectivity (RSFC) and verbal memory, which suggested that increased connectivity within the functional pathways of the contralateral hippocampus within the episodic verbal memory network represents a strengthening of alternative pathways in Left TLE patients with high verbal memory retention abilities [6].

A recent study showed that the epileptic hippocampus exhibits reduced connectivity with the medial prefrontal cortex (mPFC) and the posterior cingulate cortex (PCC), two key regions of the default mode network (DMN). This reduced connectivity was weakly associated with material-specific memory abilities. Specifically, in patients with left TLE, the connectivity of the anterior hippocampus was related to verbal memory, while in patients with right TLE, the connectivity of the posterior hippocampus was related to visual memory [17]. Future research could help to understand whether variations in connectivity between the anterior and posterior parts of the hippocampus are related to specific memory impairments in people with TLE.

2.2. Language Disorders in TLE

Language problems are very commonly reported in TLE patients. Studies have reported word-finding difficulties in almost half of TLE participants, who showed deficits in naming tests, particularly those with seizures originating in the language-dominant hemisphere [18] [19]. A study investigating language abnormalities in TLE patients found that nearly a third of patients had significant language impairments during spontaneous speech, reporting frequent and severe word-finding difficulties. Picture naming tasks confirmed these observations, revealing longer word retrieval times in patients. Despite identification and semantic activation of the target word, a lexical access difficulty persisted. This difficulty was partially improved with the provision of a phonetic cue. Left TLE patients showed less benefit from these cues, even when the word was known and semantically recognized [20].

In another study, L-TLE patients showed a consistent and almost systematic

impairment compared to matched controls in naming objects and famous people. This impairment was characterized not only by lower accuracy but also by more qualitative errors, tip-of-the-tongue phenomena, and slowed reaction time. In contrast, Right-TLE patients showed less cognitive impairment, which was limited to object naming [19]. When auditory and visual naming tests were administered to TLE patients, the results revealed a deeper impairment with significantly more errors in auditory naming than in visual naming. Additionally, the left TLE group performed significantly worse than the right TLE and healthy groups on auditory naming. In contrast, the visual naming performance of the left TLE group was virtually identical to that of the right TLE and healthy groups [18].

Research also implicates the hippocampus in naming function. The study by Oddo *et al.* (2003) reported visual naming and word-finding difficulties in 100% of their patients with hippocampal sclerosis, regardless of the lateralization of the epileptogenic zone [21]. Studies have also explored language laterality and its implications in temporal lobe epilepsy (TLE). A study on word recognition found that left TLE patients performed worse on low-frequency words, suggesting impaired orthographic processing in this region [22].

Another study using fMRI examined the efficiency of lexical and semantic processing and the associated brain activation in TLE patients. The results revealed significant differences between TLE patients and control subjects. Unlike the control group, both TLE groups showed more significant activation for non-word stimuli than for word stimuli. This increased activation involved the inferior frontal language areas, bilaterally in the HS (hippocampal sclerosis) group and left-lateralized in the NL (nonlesional) group. Differences were also observed in the processing of abstract and concrete words. The HS group showed activation of frontal areas associated with executive functions for abstract words, while the NL group activated more posterior semantic processing regions. These results suggest that left TLE is associated with impaired functional organization of the cortical networks involved in lexical and semantic processing. Additionally, the observed organization varies depending on the presence or absence of hippocampal sclerosis [23].

The results of the studies suggest that TLE patients, particularly those with Left TLE, have a general impairment in lexical access. Additionally, subtle difficulties (increased reaction times) have been observed in TLE patients. Despite the promising research, the understanding of language in TLE remains incomplete. Indeed, current studies on the subject are still limited and the results obtained, although suggestive, do not allow for definitive conclusions to be drawn. Further in-depth investigations are needed to explore this fascinating area in more depth.

2.3. Executive Function Impairments in TLE

Executive function (EF) deficits are a common feature of temporal lobe epilepsy (TLE), affecting 44% - 95% of patients (Strauss E., 2007; Oyegbile, 2004) [24].

Studies by Hermann *et al.* (2007) and Wang *et al.* (2007) provide compelling evidence of this widespread impairment [25] [26]. These deficits encompass various EF domains, including attention, inhibition, fluency, working memory, and planning. Commonly used assessment tools include the Wisconsin Card Sorting Test (WCST), along with other measures of cognitive flexibility and problem-solving [27]. However, it's important to acknowledge that divergent findings exist. While the majority of studies point towards EF impairments in TLE, some research like Cahn-Weiner *et al.* (2009) and Campo *et al.* (2012) present contradictory results [28] [29].

What is striking about TLE research is the great diversity of proposed explanations for EF deficits, despite their widely documented presence. Many interpretations have been put forward in studies on the specific role of the temporal lobe (TL) in relation to executive functions. Among the justifications put forward, these impairments can be due to extensive or multifocal interictal and critical spreading, post-critical dysfunction, or long-range network disruption [30]. In other study, the performance of TLE patients with left HS was significantly impaired. There was also a tendency for left TLE patients without HS to have poor outcomes. The authors argued that HS patients were compromised in their ability to form associations and register new information, two processes essential to the successful completion of this task [31].

In addition, results may vary depending on the type and sensitivity of the neurocognitive tests used. According to the results of the study by Rzezak *et al.* (2009), the assessment performed only with the WCST not only underestimated the number of patients suffering from executive dysfunction, but also missed relevant information regarding the executive dysfunction [4] [27]. Another study shows that a higher number of AEDs was associated with poorer outcomes, particularly in the area of executive functions [32]. In addition, the earlier the onset of epilepsy, the greater the impact on executive functions [33]. Also, Thompson and Duncan suggest that executive function declines with the duration of epilepsy and the number of complex partial seizures (CPS) [34].

2.4. Visuospatial Function in TLE

Visuospatial function in TLE remains a complex and somewhat controversial area of research. Some studies, like Grant *et al.* (2008), found no significant differences between TLE patients and healthy controls on luminance and frequency discrimination tasks [35]. However, several studies have demonstrated visual discrimination deficits in TL damage, with hippocampal lesions impairing complex spatial discrimination and perirhinal cortex damage causing complex object discrimination deficits. However, the interpretation and implications of these findings have been debated due to replication issues, potential confounding variables in testing methods, and a lack of detailed brain scans in relevant patient groups [36] [37] [38] [39].

Other research suggests a potential role for the temporal lobe in certain as-

pects of visuospatial processing [40]. Notably, Lee & Rudebeck (2010) provided compelling evidence that object processing deficits could occur in a TL patient even without comparing multiple stimuli, supporting the notion that the MTL goes beyond long-term declarative memory. As suggested by Barense *et al.* (2010), these structures play a critical role in integrating complex features of faces, objects, and scenes into view-invariant, abstract representations [40] [41] [42].

Recently, Tallarita *et al.* (2019) conducted a comprehensive study assessing various visuospatial functions in 198 patients with temporal lobe epilepsy (TLE) and 90 healthy subjects. Utilizing diverse cognitive tests like the Raven Colored Progressive Matrices (RCPM), Attentive Matrices (AM), Trail Making Test A (TMTA), Street Completion Test (SCT), Rey Complex Figure Copying (RCFC) and Delayed Reproduction (RCFDR), and Corsi Blocks Span (CBS) and Supraspan Learning (CBSSL), the researchers found that although both groups performed similarly on tasks involving non-memory visuospatial processing (RCPM, AM, TMTA, SCT, RCFC), TLE patients exhibited significantly lower scores on tests assessing visuospatial memory and learning (CBS, CBSSL, RCFDR).

Notably, patients with MTL sclerosis, a specific type of TLE involving damage to the medial temporal lobe, displayed even greater impairments compared to both controls and TLE patients without MTL damage. Interestingly, only those with other lesions outside the MTL showed deficits on the CBSSL test, suggesting a unique role for the MTL in visuospatial memory and learning processes [43]. This conflicting evidence suggests that visuospatial function in TLE might be domain-specific: Different aspects of visuospatial processing, like perception versus memory, could be differentially affected. Also, the impact of TLE on visuospatial function might vary considerably across patients, depending on factors like seizure location and severity. More comprehensive and targeted studies are necessary to fully understand the complex relationship between TLE and visuospatial function.

3. Factors Contributing to Cognitive Impairment in TLE

While TLE is often associated with cognitive decline, the precise mechanisms remain complex and multifactorial [44] [45]. Indeed, several factors can contribute to cognitive impairment, including genes, AEDs, recurrent seizures, and TL damage.

3.1. Hippocampal Sclerosis (HS)

Extensive research establishes a link between hippocampal sclerosis, a common pathology in TLE, and accelerated cognitive decline, particularly episodic memory impairment affecting both verbal and nonverbal episodic memory, also impacting language, visuospatial processing [46] [47]. Indeed, the hippocampus plays a key role in memory formation. During epileptic seizures, it exhibits the lowest threshold of abnormal excitability of all brain structures [48]. Surviving

pyramidal cells in the hippocampus form an abnormal hippocampal circuit, leading to long-term, short-term, and spatial memory impairments [49].

3.2. Other Epileptogenic Lesions and Head Injuries

Focal cortical dysplasia, tumors such as dysembryoplastic neuroepithelial tumors (DNETs), and other underlying structural abnormalities in the temporal lobe can also contribute to cognitive difficulties [45] [50] [51]. Also, frequent falls triggered by seizures can lead to head injuries, further contributing to cognitive decline [52]. The "indirect relationship hypothesis" suggests that seizures and other complications, like cognitive decline, might stem from disrupted neural networks due to the underlying cause of epilepsy, such as monogenic disorders, cortical developmental malformations, or traumatic brain injury [53].

3.3. Impact of Seizures

A common pathophysiological argument for the mechanisms of the relationship between epilepsy and cognition is that seizures and epileptiform discharges on EEG directly damage the neural networks that constitute the normal substrate of cognitive function [53].

Seizure Frequency and Seizure Duration: Higher seizure frequency is often associated with poorer cognitive performance, likely due to the repetitive neuronal disruptions caused by seizures. Recurrent seizures impair long-term memory by harming long-term potentiation (LTP), spatial memory by disrupting place cell timing, and overall cognition by affecting theta oscillations and network communication [6].

Individuals experiencing prolonged seizures lasting 30 minutes or more, known as status epilepticus (SE), or frequent recurrent seizures, are particularly at risk of brain damage that can lead to cognitive impairments. While the cause of the seizure clearly contributes to the cognitive outcome, there is ample evidence, both in humans and animal models, that seizures independent of the etiology worsen cognitive outcome [54]. Additionally, patients suffering from frequent and severe seizures are often prescribed higher doses of antiepileptic drugs and polytherapy. All of these factors can further exacerbate cognitive impairments [55].

Early Onset of Seizures: In a recent study of pre-pubertal children with epilepsy, those with an early onset (before age 5) had a tenfold increased risk of intellectual disability compared to age-matched controls. This risk was inversely correlated with the age of epilepsy onset [56]. The onset of epilepsy in childhood can hinder normal cognitive development compared to healthy individuals. Children and adolescents, whose brains are still developing, are particularly susceptible to cognitive impairments. This may be due to the combined effects of epileptogenic pathology, seizure frequency, and disruption of brain development [57] [58].

3.4. Antiepileptic Drugs

Antiepileptic drugs can have adverse effects on cognitive function. The most com-

mon cognitive effects of AEDs include: impaired attention, decreased vigilance and slowed psychomotor speed. Other cognitive functions can also be affected. The extent of AED-related cognitive dysfunction is generally modest with monotherapy and when the AED is present at therapeutic serum concentrations. Additionally, older AEDs tend to have more negative effects on cognition than newer AEDs. Older AEDs may be prescribed due to their lower cost, wider availability, and long-term experience, but they can be more toxic than newer AEDs. While newer AEDs are generally better tolerated than older AEDs, they can all have adverse effects on cognitive function [59] [60].

In terms of adverse cognitive effects, the vulnerabilities of individuals being treated must be carefully considered. Different metabolic profiles in children, the elderly, or those who are seriously ill can lead to an increased risk of toxicity. It is important to minimize the cognitive effects of AEDs in children, as their developing nervous system is more vulnerable. It is also important to consider interactions with other medications that the patient may be taking. Patients with existing cognitive problems may be a population more at risk of being influenced by agents with adverse cognitive effects [61] [62].

The cognitive side effects of AEDs are well known, but the underlying neurophysiological and anatomical mechanisms are not yet fully understood. The most common explanation is that AEDs reduce neuronal excitability, which is effective in preventing seizures but can also have a negative impact on cognitive function [60]. Many studies have used neuropsychological tests to assess the effects of AEDs on cognition. These studies have shown that people taking AEDs tend to score slightly lower in various cognitive domains, with some AEDs having a greater impact on certain domains than others. These findings suggest that the effects of AEDs on the brain are more complex than a simple reduction in neuronal excitability [63].

Advances in functional brain imaging have opened up fascinating new avenues for exploring the impact of pharmacological treatments on specific brain systems. The study by Xiao *et al.* (2018) is an excellent example. It revealed changes in the functional neuroanatomy of language in patients on AEDs, which could explain subtle language deficits in patients taking otherwise well-tolerated sodium channel blockers [64].

3.5. Genetics Factors

Genetic studies have shown that mutations can cause ion channel dysfunction or abnormal cortical development [65] [66] [67]. Multiple mutations can lead to hyperexcitability by engaging different mechanistic pathways (alterations in synaptic function, alterations in connectivity, impaired metabolism and homeostasis, etc.). Regardless of the underlying causal mechanisms, hyperexcitability leads to defective neuronal computation and impaired cognition [68] [69].

A study on cognitive function in unaffected siblings of TLE patients demonstrated that patients had significant cognitive deficits in multiple domains, in-

cluding long-term and short-term memory, attention, working memory, executive functions, and visuospatial functions. Unaffected siblings, who had never experienced seizures, taken any medication, or exhibited any symptoms, nevertheless showed impaired visuospatial function similar to that of the patients. These findings suggest that the visuospatial deficits observed in TLE may have a genetic component and are not dependent on seizures or AEDs use [70]. The role of genetic factors in cognitive dysfunction needs further investigation.

3.6. Postoperative Cognitive Changes

Continued decline: Studies suggest potential for ongoing cognitive decline following TLE surgery in some patients. This may be related to altered neuronal maturity, reduced regenerative capacity, and disrupted brain connectivity [71] [45]. Other research indicates potential for cognitive improvement or stabilization after successful TLE surgery, highlighting the complex and variable nature of these outcomes.

4. Depression: A Frequent Comorbidity in TLE

Depression stands as the most frequent psychiatric comorbidity in TLE, affecting an estimated 30% to 70% of patients [72]. This is significantly higher than the general population rate, highlighting the strong link between epilepsy and mood disorders. It has also been suggested that the presence of depression suffers an even more significant negative impact on quality of life than seizure frequency. Depression in TLE can manifest in various forms, including: a) Major depressive episodes: Characterized by intense sadness, loss of interest or pleasure in activities, changes in appetite and sleep, and suicidal thoughts; b) Dysthymic disorder: Chronic, low-grade depressive symptoms, c) Bipolar disorder: Cycles of depression and mania or hypomania and d) Minor depression: Milder depressive symptoms not meeting the full criteria for major depression [73] [74] [75].

In 2005, Kanner proposed a model suggesting epilepsy and depression may share a common root cause. Furthermore, several factors within TLE contribute to this increased risk, younger age at seizure onset is associated with an increased risk of depression, TLE, particularly with HS, is more likely to co-occur with depression, higher seizure frequency may exacerbate depressive symptoms, Some medications can have mood-altering side effects, the stress and stigma associated with epilepsy can contribute to depression [76] [77].

The hippocampus and amygdala, key structures in the limbic system involved in emotion regulation, play a crucial role. In TLE with HS, hippocampal damage might alter emotional processing, making individuals more susceptible to depression. Additionally, a relatively unaffected amygdala in the opposite hemisphere might further contribute to difficulties managing negative emotions, leading to chronic depressive symptoms [72]. Given its high prevalence and negative impact, early detection and treatment of depression are crucial in TLE manage-

ment. Addressing depression can significantly improve quality of life, reduce suicide risk, and decrease healthcare costs associated with persistent symptoms [78].

5. Anxiety Disorders: A Frequent Comorbidity in TLE

Individuals with epilepsy experience 2 - 3 times higher lifetime rates of anxiety disorders and suicidal thoughts compared to the general population [79]. Anxiety symptoms in TLE can be categorized based on their timing in relation to seizures: a) peri-ictal: occurring around seizures, including pre-ictal (before), ictal (during), and post-ictal (after) types, and interictal: independent of seizures, occurring between episodes. Ictal anxiety can manifest as part of the seizure itself, while post-ictal anxiety often involves fear and distress following a seizure. Interictal anxiety symptoms can worsen during this period [80]. Additionally, iatrogenic anxiety due to certain medications or surgical treatments can sometimes occur. Notably, anxiety can not only be a consequence of epilepsy, but may also precede its onset [81].

Studies show that TLE patients with HS have a 25% - 52% prevalence of anxiety disorders, significantly impacting their quality of life [82] [83] [84]. Research also suggests a link between critical anxiety (during seizures) and interictal psychopathology. Structural imaging reveals associations between anxiety symptoms and abnormalities in mesial temporal structures, particularly the amygdala [85]. Notably, individuals with HS have a higher risk of seizure anticipation anxiety [86]. Interestingly, a bidirectional relationship exists between anxiety and epilepsy. Seizures can trigger anxiety symptoms, and conversely, anxiety, with its associated stress and arousal, can potentially trigger seizures (especially in TLE). This highlights the complex interplay between anxiety and epilepsy at both the etiological (seizure development) and symptomatic (seizures and psychological distress) levels [87].

6. Conclusion

While TLE was traditionally viewed as a solely seizure-generating disorder, research has increasingly revealed its broader impact on brain function. The well-documented relationships between TLE and various cognitive, and psychiatric comorbidities paint a complex picture with far-reaching implications for future patient management and research directions.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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