Mechanisms of memory deficit in temporal lobe epilepsy

Rohit S Aiyer
Fifth Year Medical Student
University of Birmingham
United Kingdom

Jaidev R Nath
Fifth Year Medical Student
University of Birmingham
United Kingdom

Rohit S Aiyer is a final year medical student at the University of Birmingham (UK) who will be graduating next May. He has an interest in oncology. He is looking forward to commencing post-graduate education in either London, England or Canada next year. He completed his BScH in Canada in Life Sciences, at Queen's University.

ABSTRACT

Epilepsy is a condition that is caused by disruption in the normal electrophysiological functioning of the brain and therefore there are numerous types that can affect an individual. Temporal lobe epilepsy (TLE) can cause severe life changing deficits in a patient, particularly from a memory perspective, which can then impact on their functional abilities. Several research articles have demonstrated the negative effects that TLE has on patients, and this paper intends to investigate and review studies that illustrate the neurological impact of TLE on patients.

Analysis of models, studies and graphs give strong evidence that there are certain mechanisms involved that play a role in neurological deficits, especially since it is apparent that neuropathology is a major cause for this. As a result, TLE patients are unable to perform cognitive and memory tasks to their best ability.

INTRODUCTION

Epilepsy is a neurological disorder that is based on the recurrence of seizures in an individual. These seizures tend to create a disturbance in brain activity which can lead to eccentricities in behaviour, emotions and convulsions. There are two main types of seizures: focal (partial) and generalised.

In 1985, the International League Against Epilepsy described temporal lobe epilepsy (TLE) as a condition which involves recurrent unprovoked seizures that originate within the lateral or medial areas of the temporal lobe. Seizures classified as focal can be simple (involving no loss of consciousness) or complex (involving loss of consciousness).[1]

In 60% of TLE patients the medial area of the temporal lobe is the epileptogenic zone, which is primarily due to pathology of the hippocampus. Other causes of TLE include tumours, viruses, infectious diseases and trauma.[2]

This paper will investigate temporal lobe epilepsy and analyse the mechanisms for memory deficits in patients with this type of epilepsy.

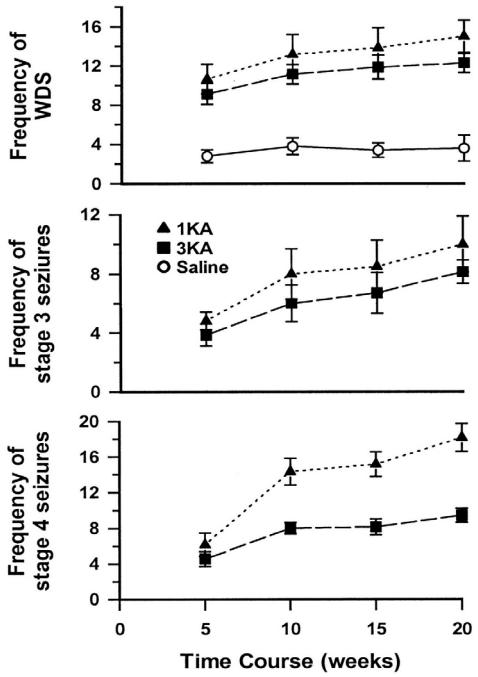

Figure 1: Illustrates the increase in frequency of seizures in 1KA and 3KA rats as well as increase in severity over a 20 week period.

Source: Zhang X, Cui S, Wallace AE, Hannesson DK, Schmued LC, Saucier DM et al. Relations between brain pathology and temporal lobe epilepsy. *The Journal of Neuroscience. 2002, 22*(14):6052–6061.

NEUROPATHOLOGY OF TEMPORAL LOBE EPILEPSY

An area that will be investigated in this paper is the neuropathology involved in TLE, which will help provide background information behind why memory deficits occur in these epilepsy patients. As discussed earlier, the region most commonly affected in TLE is the hippocampus, and pathology is often broadly referred to as hippocampal sclerosis or atrophy. The hippocampus is important since it plays a role in memory. This memory loss can be attributed to a loss of neurones in the CA3 and CA1 regions of the hippocampus.[3]

A hypothesis that has been quite popular amongst researchers is that the pathology and degeneration of the hippocampus is due to neuronal loss and mossy fibre sprouting, leading to chronic progression of TLE. A study conducted by researchers at the University of Saskatchewan in Canada helped give evidence for this. The scientists induced epileptic like symptoms in rats with kainic acid (KA) and compared them with saline injected control rats over several weeks. The occurrence of seizures was then compared with neuronal loss and mossy fibre sprouting to see if there was any correlation. Results indicated that there was in fact a relationship,

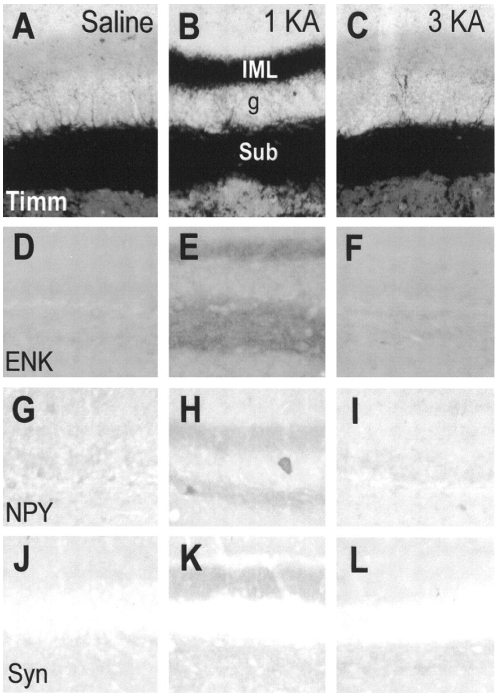

Figure 2: Shows a presence of mossy fibre growth and neuronal cell loss in the 1KA rats (particularly inner molecular layer of hippocampus), but an absence in the saline and 3KA rat groups.

Source: Zhang X, Cui S, Wallace AE, Hannesson DK, Schmued LC, Saucier DM et al. Relations between brain pathology and temporal lobe epilepsy. *The Journal of Neuroscience. 2002, 22*(14):6052–6061.

particularly in the severity and frequency of chronic seizures later on in the epilepsy.[4]

This correlates with the immuno-histochemistry findings that demonstrate the mossy fibre sprouting in the inner molecular layer of the dentate gyrus in both ventral and dorsal areas of the hippocampus (Figure 2).

However, it is important to note that this correlation is only true for the 1KA rats compared to the controls, as the 3KA (three times the quantity of kainic acid) rats do not display any mossy fibre sprouting or neuronal loss.[4]

Pathologically, there are two types of damage that should be highlighted in TLE. The first, as mentioned before, is hippocampal sclerosis or atrophy, and the other is corpora amylacea. Sclerosis of the hippocampus involves gliosis, loss of pyramidal neurons and granule cell dispersion. Corpora amylacea on the other hand involves the presence of hyaline masses which are derived from degeneration of neural cells. A group of neuropathology researchers in South India conducted an extensive study on over 100 temporal lobectomies from TLE patients that took place over a 3 year period. The results showed that over 58% and 54% of patients had Ammon's horn sclerosis and corpora amylacea, respectively.[5]

The study also demonstrated that other forms of pathology can be present in the temporal lobe, particularly neoplastic and non-neoplastic lesions. The sample group of 16 surgical specimens from TLE patients illustrated that 35% had tumours and 23% had non-neoplastic lesions such as vascular malformations and heterotopias.[5]

MEMORY DEFICIT

Another experiment analysed 25 patients with TLE, 14 with seizures originating from the left temporal lobe and 11 who had seizures originating from the right side. To assess memory, the Autobiographical Memory Interview (AMI) was utilised, as this test helps to obtain an objective measure of the patient's semantic and episodic memories. Furthermore, this study wanted to see which theory would be supported in their research: the consolidation theory or multiple trace theory (MTT). The consolidation theory states that any damage to the hippocampus should result in equal levels of decline in episodic and semantic memories. However, the MTT

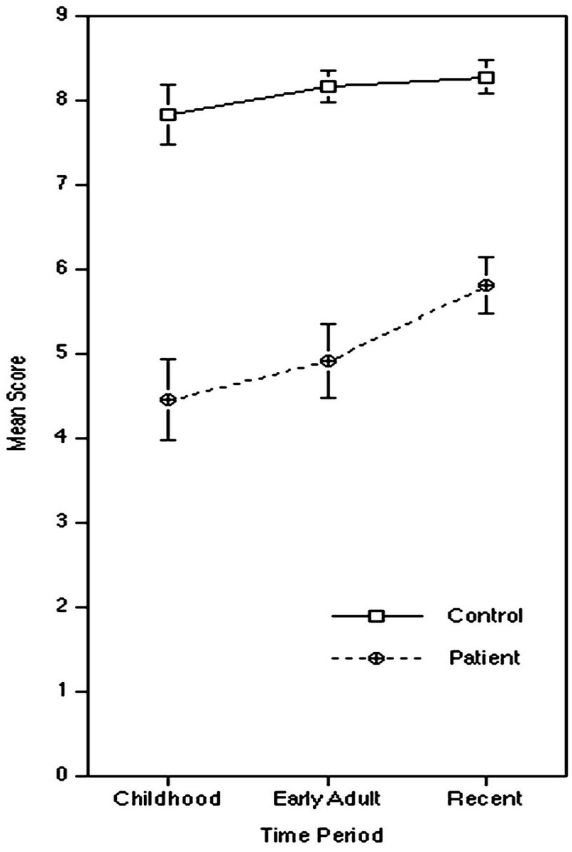

Figure 3: Lower mean score in TLE patients with regards to episodic memory recall.

Source: Viskontas IV, McAndrews MP, Moscovitch M. Remote episodic memory deficits in patients with unilateral temporal lobe epilepsy and excisions. *The Journal of Neuroscience. 2000;20*(15):5853-5857.

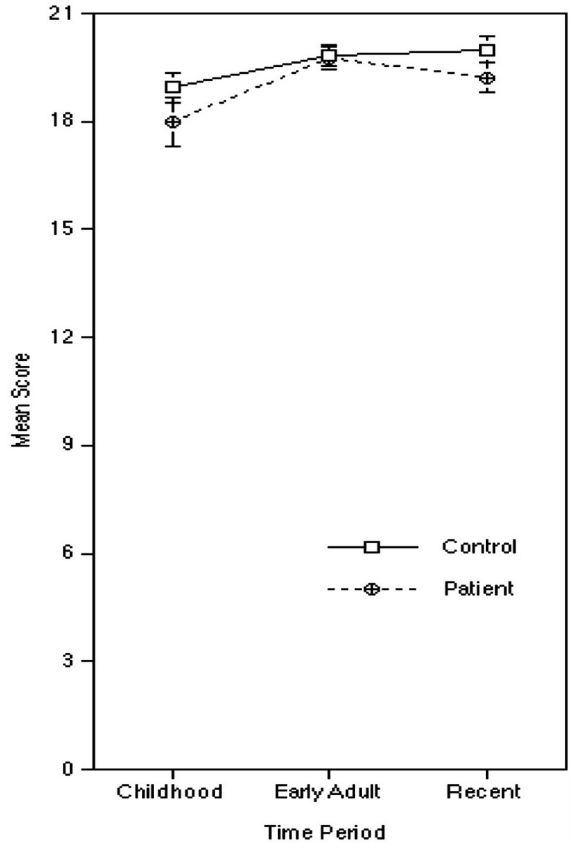

Figure 4: No difference in mean score between TLE and control patients with regards to semantic memory.

Source: Viskontas IV, McAndrews MP, Moscovitch M. Remote episodic memory deficits in patients with unilateral temporal lobe epilepsy and excisions. *The Journal of Neuroscience. 2000;20*(15):5853-5857.

proposes that the hippocampus puts together pieces of information and encodes memories with the help of extra-hippocampal neocortical neurons, meaning that the hippocampus is not responsible for both types of memory, only episodic.[6]

According to Figures 3 and 4, episodic memories suffered a decline in TLE patients whereas there did not seem to be any significant difference between the control and TLE patients with regards to semantic memories.[6]

A neuropsychological study conducted by a group in London helped to illustrate the differences between short term and long term memory deficits seen in TLE patients. That study showed a significant difference in TLE patients with regards to delayed recall. The research looked at TLE patients who had either left or right hippocampal pathology and their success on memory tests including: logical memory stories, and word list learning, subtests taken from the Wechsler Memory Scale. When performing these memory tests, the research results showed no differences in immediate recall when both left and right TLE patient groups and the control group were compared. However, when analysing the delayed recall results, the left TLE patients performed significantly worse than the other two groups.[7,8]

It is clear that TLE patients do in fact suffer from memory decline and that there are diverse approaches to explore the deficits experienced by the epilepsy patients.

MEMORY

A group of researchers carried out analysis on TLE and the effect it has on memory, particularly the learning processes. Effects of TLE on learning and recall of newly learned information were demonstrated by carrying out experiments with rats in a water maze. One particular experiment had control and TLE induced rats that had learned where to swim to in order to find a platform among four quadrants in a water chamber. The platform allowed the rats to get out of the water and into a more hospitable environment. After 4 days of training, the rats were timed to see how long it would take them to use their newly learned ability to find the platform. Figure 5. illustrates the results and shows that it took much longer for the TLE rats to find the platform when compared to the control rats.

It should also be noted that even within the training days, the rats with induced temporal lobe epilepsy performed relatively poorly in response times when compared to the control group.[9]

Other studies also helped illustrate the presence of intellectual decline in TLE patients. Research conducted by two German scientists involved a series of tests on 209 TLE patients to see if they were affected with regards to the Full Scale Intelligence Quotient (FSIQ), measured by using the Wechsler Adult Intelligence Scale (WAIS-III). The patients were divided into three groups based on how long they had had TLE for: <15 years, 15-30 years and >30 years. The patients all completed psychometric testing that determined the FSIQ. Statistical analysis took into consideration confounding variables such as educational background, and the results demonstrated that there was a statistically significant decrease in FSIQ in individuals with TLE for over 30 years in the higher socio-economic group.

These outcomes were obtained using ANOVA statistical analysis, since there were several variables to consider, namely: duration of epilepsy, side of seizure origin and presence of temporal lesions.[10]

CONCLUSION

Looking at the research on this subject, it is evident that there are neuropathological changes that occur in temporal lobe epilepsy patients which impact on those diagnosed with the disorder.

This article has surveyed some of the research into the pathology that underlies and causes TLE, as well as some of the research that has investigated the memory deficits and general intellectual decline that is experienced by some people in this clinical population. There is evidence that both memory and intellectual functions generally can be negatively affected, and this can cause significant functional difficulties for some people with TLE, which thereby impacts adversely on their overall quality of life. Different areas of knowledge were considered in this paper, ranging from neuropsychology to neurophysiology. This was done to show that TLE is a disorder that affects the individual in many different aspects, and thus needs to be researched by a multi-disciplinary team to achieve better results.

It has been shown that research on this issue dates back to the 1950s, but even today scientists continue to inquire and make inroads into understanding the role of pathology and the outcomes it creates for TLE patients. As medical technology improves in the relevant fields, researchers will continue to understand the disorder better, thereby making the medical and surgical treatments of the epilepsy much more feasible and realistic.

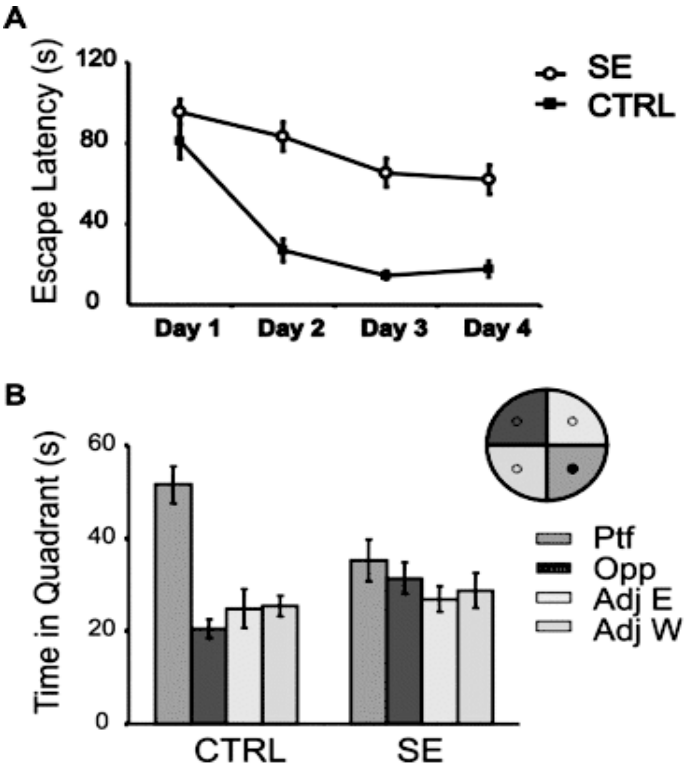

Figure 5: TLE rats performing worse on returning to platform quadrant, much slower time in seconds both on the final day and during training days (Days 1-4).

Source: Lenck-Santini PP, Holmes GL. Altered phase precession and compression of temporal sequences by place cells in epileptic rats. *The Journal of Neuroscience. 2008;28*(19):5053-5062.

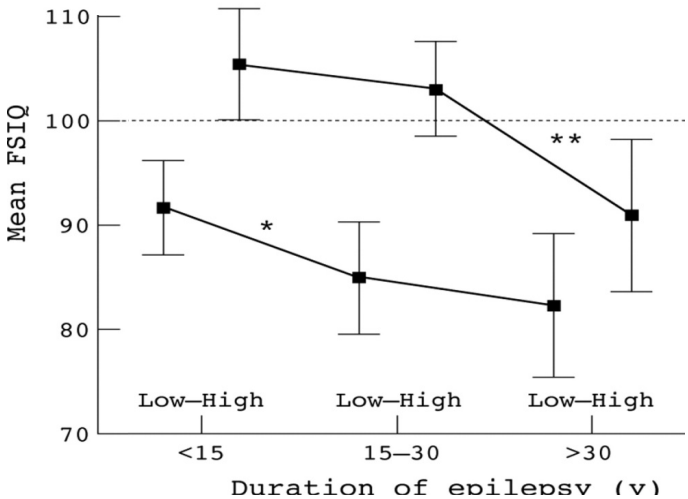

Figure 6: TLE patients, divided according to Low-High socio-economic levels, showing a statistically significant difference in the reduction of FSIQ in the High socio-economic group of patients, compared to the Low socio-economic group when duration of epilepsy is 30 years or more

Source: Jokeit H, Ebner A. Long term effects of refractory temporal lobe epilepsy on cognitive abilities: a cross sectional study. *Journal of Neurology, Neurosurgery & Psychiatry. 1999; 67*: 44-50.