

# Temporal Lobectomy Versus Multiple Hippocampal Transections for the Management of Temporal Lobe Epilepsy



**Amelia Simmons, Thomas Nilles Melchert and Arun Angelo Patil\***

*Department of Surgery, Creighton University School of Medicine, Omaha, NE USA*

**Submission:** March 15, 2021; **Published:** April 14, 2021

**\*Corresponding author:** Arun Angelo Patil, Department of Surgery, Creighton University School of medicine, 7710 Mercy Road, Suite 501, Omaha, NE 68124, USA

## Abstract

Temporal lobectomy has been the most common procedure for temporal lobe epilepsy for many decades when medical therapy fails. This procedure involves resection the anterior part of the temporal lobe, the hippocampus, and the amygdala. Though temporal lobectomy has produced good results in terms of seizure control, resection of the temporal lobe neocortex, the amygdala and the hippocampus always have adverse effect on speech, memory, cognition, and behavior. However, it is still the procedure of choice because lack of seizure control has greater ill effects. A combination of multiple hippocampal transections with multiple cortical transections is an alternate approach to temporal lobectomy. In this approach, circuits transmitting or generating seizure activity are transected, while the function fibers and cells are left intact. This newer approach is free of the side effects associated with temporal lobectomy. In this paper the authors report the status of this approach.

**Keywords:** Temporal lobe epilepsy; Multiple hippocampal transections; Anterior temporal lobectomy; Intractable epilepsy

**Abbreviations:** ILAE: International League Against Epilepsy, EEG: Electro Encephalography,

PFC: Prefrontal Cortex, fMRI: Functional Magnetic Resonance Imaging; MHT: Multiple Hippocampal Transections, mTLE: Mesial Temporal Lobe Epilepsy

## Introduction

Epilepsy is a neurological disorder defined by the International League Against Epilepsy (ILAE) as a condition characterized by two or more recurrent epileptic seizures over a period longer than 24 hours, unprovoked by any immediate identified cause [1]. It is a disorder which affects individuals of all ages and races. Epilepsy impacts the lives of more than one-percent of the population residing in the United States; ranking as the seventh most prevalent neurological disorder in the United States according to a systematic analysis of the Global Burden of Disease from 1990 to 2017 [2,3]. Even with advances in its treatment, the burdens of this neurological disease reduce an individual's quality of life. The authors will discuss two surgical techniques for managing temporal lobe epilepsy and address their impact for patient outcomes.

Temporal lobe seizures tend to represent the majority of intractable seizures which require surgical management [4]. The ILAE defines drug-resistant epilepsy as the failure to achieve sustained seizure-free outcomes using two antiepileptic drugs

either as monotherapies or in combination [5]. With failure to respond to medical therapies, surgical intervention offers an alternative therapy with the goal of becoming seizure-free without causing further neurocognitive dysfunctions. These procedures are more effective when an epileptogenic zone is identified, often with assistance of neuroimaging and EEG. Operations available include resection of the medial temporal lobe such as entorhinal cortex, amygdala and/or hippocampus with possible involvement of temporal neocortex [6]. The two surgical techniques that this review will discuss are temporal lobectomy versus multiple hippocampal transections for the management of temporal lobe epilepsy.

## Discussion

In the modern era, the practice of temporal lobectomy refers to a standard anterior temporal lobectomy or cortico-amygdalohippocampectomy in order to avoid confusion with complete resection of temporal lobe structures [7]. The standard

anterior temporal lobectomy procedure resects the lateral temporal structures which assists in identifying the mesial structures followed by the en bloc removal of the hippocampus. The following is a summary of the standard anterior temporal lobectomy approach. Patient is placed in a supine position and tilted at an approximately 10-degree angle in relation to the floor. Techniques for opening skin and temporalis muscle are variable, however the goal is to avoid unnecessary injury to the frontalis branch of facial nerve and attempt to preserve superficial temporal artery. Muscle is removed from bone via subperiosteal dissection followed by a craniotomy through the frontal bone. A posterior cortical incision is made along the lateral temporal gyri and subpial dissection allows for elevation of T1 region of temporal lobe from the Sylvian fissure. Exposure of insula allows for dissection to the lateral incus and posterior resection is extended from T1 to T3. Access to the temporal horn is made through the white matter located superior to fusiform gyrus. An anterior incision into the ventricle exposes the head of the hippocampus. Excision of temporal neocortex is performed, and further resection of mesial structures can occur if en-bloc temporal resection is desired. Caution is used during mesial structure removal to avoid injury to arachnoid mater due to close proximity to midbrain, third cranial nerve, posterior cerebral artery, and basal vein of Rosenthal. Variability of this procedure exists due to lack of clear demarcations for anatomic landmarks of the mesial structures [8].

Randomized studies examining surgery techniques for surgical management of epilepsy is limited. A study by Wiebe et al. assessed the effectiveness of surgical management of epilepsy compared to use of antiepileptic drugs of eighty patients over a one-year period. Following the one-year period, 58 percent of patients in the surgical group were free of seizures with impaired awareness compared to 8 percent receiving drug therapies; the determined number needed to treat was two patients. The trial found 38 percent of patients in the surgery group were free of all seizures compared to 3 percent in the drug therapy group; the determined number needed to treat was three patients. Within the surgery group, four patients sustained adverse effects including sensory deficits from a thalamic infarct, wound infection and impaired verbal memory. Additionally, 22 patients had asymptomatic visual field defects involving the superior quadrants. Adverse events in both groups included depression and transient psychosis (one per group). Outcomes from this study supported surgical intervention with anterior temporal lobectomy to provide seizure-free outcomes and improvement to patient's quality of life [9].

In a literature review by Jobst and Cascino, ideal surgical candidates were determined based on outcomes reported following resective surgical interventions. The surgical outcomes were less beneficial when extratemporal lesions present, epilepsy not associated with a specific structural abnormality or a mixture of both. Surgical outcomes were better in individuals

with benign tumors or hippocampal sclerosis. Subtle differences were reported in seizure and neuropsychological outcomes between standard temporal lobectomy compared to selective amygdalohippocampectomy. This review identified the benefits of surgical management for epilepsy with regards to seizure-free periods, however limited data is available on the long-term neuropsychological sequelae [10]. Understanding the functional neural reorganizations following a standard anterior temporal lobectomy is poorly understood. In the study by Liao et al., they used resting-state functional connectivity with fMRI and graph-based theoretical analyses to examine the pathophysiology associated with different surgical outcomes for mesial temporal lobe epilepsy. Findings of preoperative neural network resilience were associated with seizure-free outcomes following the operation; suggests there are stronger neural connections to maintain network integrity in patients who achieve freedom of seizures. This study also identified increased functional reorganization between the ventromedial Prefrontal Cortex (PFC) and temporoparietal junction in patients with seizure-free outcomes; studies previously identified ventral PFC as a crucial component in the epileptogenic network. Findings suggest postoperative neural reorganizations may serve as a biomarker to assist in determining surgical outcome and assist in identifying optimal surgery candidates [11].

The anterior temporal lobectomy remains a commonly used procedure that is safe and effective for the management of intractable epilepsy, however it is important to be aware of its possible adverse outcomes. Complications more frequently associated with this procedure include psychiatric disorders (eg, depression, psychosis, anxiety and/or obsessive-compulsive disorders), visual field defects (eg, hemianopsia, quadrantanopsia) and cognitive disorders. Less often are reports of language disorders, infections (eg, meningitis, wound infection, empyema), hemorrhage, cranial nerve injuries, hemiparesis, mortality and other [12]. Several long-term follow-up studies have determined surgery as the superior method for achieving seizure-free outcomes in adults with intractable temporal lobe epilepsy when compared to prolonged antiepileptic drug therapy. More than two-thirds of study participants in surgery group achieved seizure-free outcomes by one year [13,14]. In these studies, prognostic factors for postoperative outcomes following the standard anterior temporal lobectomy procedures were identified. The nature of the underlying epileptogenic zone was investigated using MR imaging to examine hippocampal volume and histopathology to detect hippocampal sclerosis. Findings suggestive of better surgical outcomes included hippocampal atrophy with or without temporal cortical atrophy/other lesions [13,15]. Onset of seizures after five years of age and predominant seizure-types consisting of focal seizures with ictal impairment of consciousness were additional favorable prognostic factors. Seizure relapses were noted to predominantly occur within two years of the operation. In a review by Jutila et al., no mortality was associated with the

surgery, rather deaths were related to their recurrent epilepsy [13]. Psychosocial outcomes were noted to vary among individuals [14,15]. Surgical management with anterior temporal lobectomy approach for intractable temporal epilepsy has improved their quality of life, offered seizure-free outcomes and been identified as a relatively safe procedure compared to the detrimental effects of uncontrolled epilepsy.

Another common treatment of intractable temporal lobe epilepsy is multiple hippocampal transections (MHT). This alternative technique has been used since the mid-2000's and has shown to have similar success rates compared to the temporal lobectomy [16]. One distinct advantage of MHT over temporal lobectomy is the preservation of memory post-operatively, particularly when the dominant hemisphere undergoes the temporal lobectomy and there is no hippocampal sclerosis seen on MRI before the procedure. However, the MHT procedure has shown early success and has been applied to more patient populations.

The original target patient population for MHT are patients with intractable temporal lobe epilepsy in the dominant hemisphere without hippocampal atrophy. Temporal lobectomies have shown to be less effective in curing seizure and result in greater memory deficits when there is no atrophy or sclerosis of the hippocampus [16,17]. A study by Helmstaeder, et al., shows that lesioned tissue hinders memory. Prior to a temporal lobectomy, patients with lesioned hippocampus tissue had significantly lower memory function, specifically verbal memory, and removing this tissue may perhaps be beneficial to the patient. The same study also demonstrated that removing non-lesioned hippocampus tissue resulted in greater memory deficits [18,19]. Other studies observe that regardless of the presence of hippocampal sclerosis, a dominant-sided temporal lobectomy is associated with post-operative verbal memory deficits. These findings suggest that other structures removed by a temporal lobectomy are important for post-surgical memory plasticity, not just the hippocampus [20-24]. Avoiding damage to these key structures is the distinct advantage of the MHT procedure. Common side effects of this procedure were temporary postoperative deficits in memory, however, these symptoms resolved within 6 months [16,25-28].

There is minimal damage to surrounding structures in the mesial temporal lobe and the hippocampus itself is lesioned in a way which preserves memory function. Other factors implicated in successful outcomes include extra-hippocampal subpial transections or elective amygdectomy depending on location of epileptogenic foci. The MHT procedure may be indicated over the temporal lobectomy in cases of mesial temporal lobe epilepsy (mTLE) without hippocampal sclerosis or atrophy as well as mTLE of the dominant lobe. However, the indication of one procedure over the other is still a gray area as there is not enough longitudinal data of MHT procedures to make a clear decision. There have been substantially fewer MHT procedures done due

to the effectiveness of temporal lobectomies and the relative newness of the procedure.

Another indication for the MHT procedure over a temporal lobectomy is a failed Wada test. The Wada test involves unilateral injection of amobarbital. This test can help determine hemisphere dominance and memory function. It can also aid prediction of lateralization of memory after a temporal lobectomy.<sup>30,31</sup> Due to the risks associated with this procedure, use of an fMRI is preferred to evaluate hemisphere dominance. Regardless, a failed Wada test does correlate with an increase in verbal memory after a temporal lobectomy. Therefore, in the event of a failed Wada test, the MHT procedure could be considered instead of a temporal lobectomy [29,30].

A case report by Sunaga et al. demonstrated these memory preserving qualities of the MHT procedure. The patient had marked decline in Rey Auditory Verbal learning test after the procedure, but the score returned to normal 6 months after the operation [17]. Transient memory deficit with full recovery were seen again in a prospective study involving 24 patients by Usami, et al. [19] This is an important distinction as verbal memory deficits following a dominant-hemisphere temporal lobectomy. A study done by Rausch et al., showed that verbal memory does not improve at the 1-year mark following a temporal lobectomy. In addition, there was no improvement in verbal memory long term (9+ years) so verbal memory impairment from a temporal lobectomy is assumed to be permanent [20]. These findings highlight the plasticity of the hippocampus and the memory preserving qualities of the MHT procedure. In brief, the multiple hippocampal transection surgery involves multiple vertical transections of the hippocampus and other epileptogenic tissue. There are 2 orthogonal planes of hippocampal circuitry: longitudinal and transverse (vertical). The longitudinal circuits run through the hippocampus. Epileptic propagation in the hippocampus occurs along the longitudinal axis in an anterior-posterior direction [16, 24]. The transverse circuits run along the long axis and is part of the synaptic loop ending in the entorhinal cortex [23]. The vertical transections disrupt the longitudinal circuitry and prevent seizure propagation while the transverse circuits remain intact. The transections are made using a steel ring and are done in 4-5mm intervals. For successful outcomes, transections must be parallel to hippocampal digitations and should completely transect the pyramid cell layer. CA1, CA2, CA3, CA4, and the dentate gyrus all are targets for transection during the procedure. However, it is important to preserve the fimbria as it is a major outflow tract. Electrodes may be placed along the hippocampus to observe a decrease in electrical conductance after the transection of tissue [23-25,29]. MHT can be combined with selective amygdectomy or multiple subpial transections. These additional procedures are tailored if other foci of epileptogenesis are identified. Adding procedures when appropriate have shown good results in controlling seizures. In addition, the amygdala

resection or additional subpial transections have been shown to not impact memory postoperatively [16,19,25,29]. Postoperative findings include decreased glucose metabolism of the affected temporal lobe and hippocampal atrophy. Despite these findings, memory remains intact [19]. MHT is a relatively safe procedure and there are many promising studies which show the efficacy of this procedure. However, a systematic review by Warsi et al., emphasizes that this procedure is still in its infancy. There have been no randomized trials studying MHT but there are for temporal lobectomy. Data from multiple studies show that MHT can lead to 64-94% Engel Class I outcome at 1 year. In addition, 86.8% of patients demonstrated complete preservation of memory postoperatively.<sup>23</sup> However, there are studies examining the long term effects of this surgery. The few studies that had patient follow-ups over 2 years showed 67-94% Engel Class I outcomes and 17-54% of patients had Engel class Ia results. Unfortunately, these studies only include a total of 52 patients [19,25,26]. Troubling data from a 10 year follow-up study of 24 patients that underwent MHT showed a large increase in the return of seizures, 50% to 17% Engel Class Ia outcome, from 1 to 5 years. Despite the return of seizures, most patients (88%) seizures were well controlled (Engel class I & IIa) at the 5+ year follow-up in this study.<sup>19</sup> Other studies have presented results that contradict this return of seizures but these reports were inconsistent with long-term follow up [25,26]. Multiple smaller reports have also shown this procedure's specific effectiveness in the pediatric population [25-28]. These reports emphasized a lack of neurologic symptoms from the procedure. In a detailed report of 3 pediatric cases, the author stated there was good control over seizure after the procedure but only 1 patient became seizure free. As a whole, there is promising evidence that multiple hippocampal transections can (1) control drug-resistant seizures caused by mesial temporal epilepsy and

(2) preserve memory function. It should be considered as an alternative to a temporal lobectomy in patients who meet surgical criteria in addition to one of the following: no hippocampal sclerosis, epileptic foci in the dominant hemisphere, or a failed Wada test. Until further data shows otherwise, the procedure should be avoided in patients with hippocampal sclerosis as MHT has reduced effectiveness and the temporal lobectomy procedure is proven to be successful in this population [14,19,29-33].

## Conclusion

Due to the limited number of MHT procedures, it is difficult to directly compare the efficacy of MHT versus temporal lobectomy. MHT is a promising alternative to a temporal lobectomy in treating drug-resistant mesial temporal epilepsy due to its reduction in memory-related side effects. Long-term follow up (greater than 1 year) of patients who received MHT and volume of cases represent key pieces of data that would prove beneficial in determining one procedure over the other [20]. The exact rates of freedom from seizure after MHT is highly variable from study to

study as reported by the meta-analysis (Warsi, et al.). Engel Class I outcomes after 1 year or more following the MHT procedure range from 67.4 to 94.7% for patients receiving the MHT [23]. Studies examining the effectiveness of the temporal lobectomy procedure are comparable to MHT. In a cohort consisting of 288 patients who underwent standard anterior temporal lobectomy with amygdalohippocampectomy and lesionectomy-guided by electrocorticography for drug-resistant temporal lobe epilepsy, approximately 73% of patients were seizure free at the last follow-up and 82% were Engel's favorable outcome (Engel's class I and IIa) at the end of one-year postoperative follow-up.<sup>32</sup> Mansouri et al. compared anterior temporal lobectomy and amygdalohippocampectomy for mesial temporal lobe epilepsy in 96 patients, which identified seizure outcomes as statistically insignificant. The use of surgical management for medically-refractory temporal epilepsy is to achieve seizure-freedom without extensive morbidity (eg, neurocognitive dysfunction). The appeal of MHT is to spare non-epileptogenic areas in order to maintain language and cognition, however, temporal lobectomy allows for potentially more effective disruption of epileptogenic circuits and further prevention of neocortical epileptogenesis [33, 34].

## References

1. Guidelines for Epidemiologic Studies on Epilepsy (1993) Commission on epidemiology and prognosis, international league against epilepsy *Epilepsia* 34(4): 592-596.
2. Zack MM, Kobau R (2017) National and state estimates of the numbers of adults and children with active epilepsy - United States, 2015. *MMWR* 66(31): 821-825.
3. GBD 2017 US Neurological Disorders Collaborators (2021) Burden of Neurological Disorders Across the US From 1990-2017: A Global Burden of Disease Study. *JAMA Neurol* 78(2): 165-176.
4. Téllez-Zenteno JF, Hernández-Ronquillo L (2012) A review of the epidemiology of temporal lobe epilepsy. *Epilepsy Res Treat.* 630853.
5. Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, et al. (2010) Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia* 51(6):1069-1077.
6. Jobst BC, Cascino GD (2015) Resective epilepsy surgery for drug-resistant focal epilepsy: a review. *JAMA.* 313(3): 285-293.
7. Boling WW (2018) Surgical Considerations of Intractable Mesial Temporal Lobe Epilepsy. *Brain Sci* 8(2): 35.
8. Al-Otaibi F, Baeesa SS, Parrent AG, Girvin JP, Steven D (2012) Surgical techniques for the treatment of temporal lobe epilepsy. *Epilepsy Res Treat:* 374848.
9. Wiebe S, Blume WT, Girvin JP, Eliasziw M (2001) Effectiveness and Efficiency of Surgery for Temporal Lobe Epilepsy Study Group. A randomized, controlled trial of surgery for temporal-lobe epilepsy. *N Engl J Med* 345(5): 311-318.
10. Jobst BC, Cascino GD (2015) Resective epilepsy surgery for drug-resistant focal epilepsy: a review. *JAMA.* 313(3): 285-293.
11. Liao W, Ji GJ, Xu Q, et al. (2016) Functional Connectome before and following Temporal Lobectomy in Mesial Temporal Lobe Epilepsy. *Sci Rep* 6: 23153.

12. Brotis AG, Giannis T, Kapsalaki E, Dardiotis E, Fountas KN (2019) Complications after Anterior Temporal Lobectomy for Medically Intractable Epilepsy: A Systematic Review and Meta-Analysis. *Stereotact Funct Neurosurg* 97(2): 69-82.
13. Jutila L, Immonen A, Mervaala E, Partanen J, Partanen K, et al. (2002) Long term outcome of temporal lobe epilepsy surgery: analyses of 140 consecutive patients. *J Neurol Neurosurg Psychiatry* 73(5): 486-494.
14. Jones JE, Blocher JB, Jackson DC (2013) Life outcomes of anterior temporal lobectomy: serial long-term follow-up evaluations. *Neurosurgery* 73(6): 1018-1025.
15. de Tisi J, Bell GS, Peacock JL, et al. (2011) The long-term outcome of adult epilepsy surgery, patterns of seizure remission, and relapse: a cohort study. *Lancet (London, England)* 378(9800): 1388-1395.
16. Shimizu H, Kawai K, Sunaga S, Sugano H, Yamada T (2006) Hippocampal transection for treatment of left temporal lobe epilepsy with preservation of verbal memory. *Journal of Clinical Neuroscience* 13(3): 322-328.
17. Sunaga S, Morino M, Kusakabe T, Sugano H, Shimizu H (2011) Efficacy of hippocampal transection for left temporal lobe epilepsy without hippocampal atrophy. *Epilepsy & Behavior* 21(1): 94-99.
18. Helmstaedter C, Petzold I, Bien CG (2011) The cognitive consequence of resecting nonlesional tissues in epilepsy surgery-Results from MRI- and histopathology-negative patients with temporal lobe epilepsy. *Epilepsia* 52(8): 1402-1408.
19. Usami K, Kubota M, Kawai K, Kunii N, Matsuo T, et al. (2016) Long-term outcome and neuroradiologic changes after multiple hippocampal transection combined with multiple subpial transection or lesionectomy for temporal lobe epilepsy. *Epilepsia* 57(6): 931-940.
20. Rausch R, Kraemer S, Pietras CJ, Le M, Vickrey BG, et al. (2003) Early and late cognitive changes following temporal lobe surgery for epilepsy. *Neurology* 60(6): 951-959.
21. LoGalbo A, Sawrie S, Roth DL, Kuzniecky R, Knowlton R, et al. (2005) Verbal memory outcome in patients with normal preoperative verbal memory and left mesial temporal sclerosis. *Epilepsy & Behavior* 6(3): 337-341.
22. Martin RC, Kretzmer T, Palmer C, Sawrie S, Knowlton R (2002) Risk to Verbal Memory Following Anterior Temporal Lobectomy in Patients With Severe Left-Sided Hippocampal Sclerosis. *Archives of Neurology* 59(12): 1895-1901.
23. Warsi N, Thiong'o GM, Zuccato J, Ibrahim GM (2019) Multiple hippocampal transections: Post-operative Memory Outcomes and Seizure Control. *Epilepsy & Behavior* 100, 106496.
24. Umeoka SC, Lüders HO, Turnbull JP, Koubeissi MZ, Maciunas RJ (2012) Requirement of longitudinal synchrony of epileptiform discharges in the hippocampus for seizure generation: a pilot study. *Journal of Neurosurgery* 116(3): 513-524.
25. Patil AA, Andrews R (2013) Long term follow-up after multiple hippocampal transection (MHT). *Seizure* 22(9): 731-734.
26. Koubeissi MZ, Kahrman E, Fastenau P, Bailey C, Syed T, et al. (2016) Multiple hippocampal transections for intractable hippocampal epilepsy: Seizure outcome. *Epilepsy & Behavior* 58: 86-90.
27. Park JT, Fernandez Baca Vaca G, Tangen R, Miller J (2018) Hippocampal transection for stereo-electroencephalography-proven dominant mesial temporal lobe epilepsy in a child: a detailed case report and critical review. *Journal of Neurosurgery: Pediatrics* 22(5): 497-503.
28. Marashly A, Koop J, Loman M, Kim I, Maheshwari M, et al. (2020) Multiple hippocampal transections for refractory pediatric mesial temporal lobe epilepsy: seizure and neuropsychological outcomes. *Journal of Neurosurgery: Pediatrics* 26(4): 379-388.
29. Giris F, Greil ME, Fastenau PS, Sweet J, Lüders H, et al. (2017) Resection of Temporal Neocortex During Multiple Hippocampal Transections for Mesial Temporal Lobe Epilepsy Does not Affect Seizure or Memory Outcome. *Operative Neurosurgery* 13(6): 711-717.
30. Lacruz ME (2004) Neuropsychological effects associated with temporal lobectomy and amygdalohippocampectomy depending on Wada test failure. *Journal of Neurology, Neurosurgery & Psychiatry* 75(4): 600-607.
31. Kemp S, Wilkinson K, Caswell H, Reynders H, Baker G (2008) The base rate of Wada test failure. *Epilepsy & Behavior* 13(4): 630-633.
32. Jayalakshmi S, Vooturi S, Vadapalli R, Somayajula S, Madigubba S, et al. (2016) Outcome of surgery for temporal lobe epilepsy in adults - A cohort study. *Int J Surg* 36(Pt B): 443-447.
33. Mansouri A, Fallah A, McAndrews MP, Cohn M, Mayor D, et al. (2014) Neurocognitive and Seizure Outcomes of Selective Amygdalohippocampectomy versus Anterior Temporal Lobectomy for Mesial Temporal Lobe Epilepsy. *Epilepsy Res Treat* :306382.
34. Mohan M, Keller S, Nicolson A, Biswas S, Smith D, et al. (2018) The long-term outcomes of epilepsy surgery. *PLoS One* 13(5): e0196274.



This work is licensed under Creative Commons Attribution 4.0 License  
DOI: 10.19080/OAJNN.2021.15.555902

**Your next submission with Juniper Publishers  
will reach you the below assets**

- Quality Editorial service
- Swift Peer Review
- Reprints availability
- E-prints Service
- Manuscript Podcast for convenient understanding
- Global attainment for your research
- Manuscript accessibility in different formats  
( Pdf, E-pub, Full Text, Audio)
- Unceasing customer service

**Track the below URL for one-step submission**

<https://juniperpublishers.com/online-submission.php>