



## Temporal Lobectomy: Is Hippocampectomy Necessary for an Optimal Outcome

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### Abstract

Hippocampectomy is a standard part of temporal lobectomy; because, hippocampus play an important role in epileptogenesis and seizure propagation. However, hippocampus is responsible for creating and retrieving memories and organizing auditory and visual information. Therefore, standard temporal lobectomy can result in memory loss and social, emotional, vocational, linguistic and psychiatric complications. In addition, hippocampus, is the main source of stem cells; which are essential for the ongoing repair process of the brain. In light of these facts, an alternative option should be considered. One such technique is known as Multiple Hippocampal Transection (MHT). This procedure involves transection of the horizontal fibers in the hippocampus, which play an important part in synchronizing seizure activity within the hippocampus. The stem cells and fimbria are however preserved. This overcomes some of the drawbacks of hippocampectomy. Recently publications have two papers that have long term follow up of patients who had MHT, Multiple Subpial Transections (MST) over the neo cortex and minimal cortical resection at the temporal tip; if the intra-operative EEG recording showed persistence of epileptogenic activity after MST. Both of them reported seizure outcome better than standard temporal lobectomy. In addition, verbal memory was either preserved or got better. Further studies therefore are therefore required to definitively determine the value of MHT; and to determine if hippocampectomy is really required.

**Keywords:** Temporal lobe epilepsy; Multiple subpial transection; Multiple hippocampal transection; Hippocampectomy

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### Introduction

Hippocampectomy is a standard part of temporal lobectomies because of the role of the hippocampus in epileptogenesis and propagation. Temporal lobectomies are a common surgical treatment option involving the resection of the hippocampus and fimbria, amygdala, parahippocampal gyrus, and a small anterior portion of the temporal lobe ranging in size from 3.5 cm - 5 cm. While this option includes extensive resection of the temporal lobe, it remains common practice due to desirable results [1,2]. Despite this common practice, there is evidence showing that resection of the hippocampus proves to be less than optimal. As a vital part of the limbic system, the hippocampus receives signals from the entorhinal cortex and is responsible for creating and retrieving memories and organizing auditory and visual information [3,4]. The disruption of these functions following hippocampectomy is manifested in certain postoperative complications. Most evaluations for temporal lobectomies include WADA testing to lateralize language and memory to a dominant hemisphere. While this testing helps localize these functions, unexpected asymmetry is a problem. This asymmetry arises when the hemisphere exhibiting seizure activity is the same hemisphere that possesses the best memory capacity. During WADA testing, when an injection ipsilateral to the hemisphere planned for resection results in better memory, we refer to this as expected asymmetry. However, when an injection made contralateral to the hemisphere planned for resection results in better memory, this indicates memory dominance in the diseased hemisphere and we refer to this as unexpected asymmetry [7,8]. Therefore, evidence shows decreased memory function when the dominant hemisphere is involved in the temporal lobectomy [9,10]. Furthermore, social, emotional, vocational, linguistic and psychiatric complications can also result from temporal lobectomy. Furthermore, hippocampus is the major source of stem cells, that are essential for ongoing repair process in the brain. Therefore, alternative options should be considered. On such technique is known as Multiple Hippocampal Transection (MHT) [5-14]. This procedure allows for transverse lines to be made in the hippocampus following the localization of seizure propagation

to specific hippocampal fibers thereby allowing for the resection of the responsible fibers along with the preservation of parts of the hippocampus not involved in the seizure activity. This would allow for optimal benefits while minimizing damage caused by extraneous resection of vital neural tissue [15-17].

## Pathophysiology of Seizure

The cellular pathophysiology of seizure is explained by electrophysiologic dysfunction of neurons in the brain. This dysfunction is characterized by an imbalance between excitatory and inhibitory signals which are governed by electrical potentials originating from ions rushing through neuronal membrane channels [18-21].

While there are obvious inciting events that can change the conductance of ions across the membranes of neurons, the exact etiology for epilepsy is still not completely understood. One current hypothesis is based on the significant role that glial cells play in epileptogenesis. Astrocytes monitor the composition of the extracellular space by regulating both the flow of water and potassium ions. Neuronal excitability relies on both the volume and potassium ion level of the extracellular matrix [22]. Various factors can cause damage to these astrocytes thereby influencing the stability of neuronal membrane potentials. This process can lead to a change in membrane ion channel composition of astrocytes thereby affecting the membrane potential of surrounding neurons [23]. Astrocytes are further thought to induce neuronal damage by releasing autocrine and paracrine cytokines leading to their own dysfunction and causing inflammatory damage. As vital immune regulators of the nervous system, microglia and astrocytes activate each other, fueling the inflammatory process [24]. Various factors can damage glial cells leading to dysregulation of neuronal excitability. Seizures can increase the chance of developing epilepsy through the promotion of inflammation by activation of both astrocytes and microglia. In less than an hour after a seizure-induced insult, microglia production of proinflammatory cytokines begins. This quick response is understood by the principle that microglia do not require adjuvant production of cytokines to remain activated [25-29]. Other events that activate microglia are components of gram-negative bacterial walls, such as lipopolysaccharides and traumatic brain injuries [30]. With these findings, it is evident that glial cells can indeed play a role in epileptogenesis [31].

## Temporal Lobectomy Indications/CI's

In general, Temporal Lobectomies (TLs) are performed in individuals with seizures proven to be refractory to pharmacological therapy and whose epileptogenic zones can be identified and precisely localized to the temporal lobe. Patients with seizures emanating from the amygdala and hippocampus are the most common candidates for effective surgical therapy.

In order to evaluate individuals for surgery, a number of tests are used to localize the epileptogenic zone, which is defined as "the minimal amount of cortical tissue that must be resected to achieve seizure freedom [32]."

Neuropsychological testing for cognitive deficits and clinical evaluation are paramount to rule out diffuse pathology and multiple epileptogenic zones respectively, since both are considered relative contraindications for TL [33]. Furthermore, EEGs, MRI and FDG-PET scans are used to precisely localize the epileptogenic focus,

while speech and language localization testing using intraoperative Electrical Cortical Stimulation (iECOS) is utilized to determine the regions to avoid during resection [34-35].

When compared to adults, it is less common for children to manifest a localized TLE. However, TL is still indicated in children who are refractory to medical management; even those younger than 3 years of age, provided they meet the same indications as adults [36-37].

## Temporal Lobe Anatomy

Performing TL requires a comprehensive understanding of both the underlying regional anatomy and of the functional role of each structure. The temporal lobe contains cortical, subcortical and vascular structures that are vital to sensation and cognition. The neural features can be split into four regions based on their location within the temporal lobe: inferior, lateral, superior and medial [38].

The inferior surface contains the fusiform gyrus and parts of the parahippocampal and inferior temporal gyrus. Together these structures are involved in the ventral stream of visual processing; notably consisting of the fusiform face area, which is involved in facial recognition, and the parahippocampal place area, which is involved in distinguishing objects from scenes [39]. The lateral surface of the temporal lobe contains the superior, middle and inferior temporal gyrus. The superior and middle temporal gyrus contain Wernicke's area and are important for language processing and social cognition [40]. The inferior temporal gyrus contains neurons which take part in the ventral stream of visual processing where image form and color are processed to allow for object recognition [39].

The superior surface contains the planum polare, Heschl's gyrus and the planum temporale, all of which, along with the superior temporal gyrus form the auditory cortex and are involved in language lateralization. Variations in these areas have been observed in individuals suffering from dyslexia as well those possessing perfect pitch [41]. The medial surface of the temporal lobe is the most complicated of the cortical surfaces and contains the uncus, amygdala, hippocampus, parahippocampal gyrus. The uncus contains part of the olfactory cortex and is involved in olfaction. Uncinate fits are focal temporal lobe epilepsies that uniquely occur with olfactory and gustatory hallucinations and inappropriate chewing movements. The amygdala, hippocampus and parahippocampal gyrus together make up part of the limbic system and are crucial for the processes of learning, spatial memory, emotional awareness, social cognition and emotional autobiographical memory [42].

From this basic anatomy, we can conclude that the temporal lobe acts as a center for convergence of visual, olfactory and acoustic information as well as mediating the processes of memory and emotion. Therefore when performing TL, great precautions must be taken to spare the maximum amount of cortical tissue while resecting enough to provide long term seizure-free outcomes. In particular, the main forms of functional decline, which are related to the operative route and type of TL, include visual deficits due to damage of optic radiations and neurocognitive decline due to hippocampal resection [38].

## TL Types

TL is a general term that corresponds to a range of resective techniques performed with a variety of surgical exposures. The main techniques include: standard Anterior Temporal Lobectomy

(ATL), electrocorticography tailored temporal lobectomy, anteromedial temporal lobectomy, transcortical selective amygdalohippocampectomy (transcortical SAH), transsylvian SAH, subtemporal SAH, temporal lobe disconnection and hippocampal transection. Although there are a variety of techniques, they share in common the fact that they all involve transection or resection of the hippocampus, a region proven to be vital to learning and memory formation [43].

### Cognitive Outcomes after TL

It has been shown that TL can have either positive or negative cognitive outcomes depending on the age at resection, the side that is resected as well as the resective technique. For example, children younger than 12 years old seemed to have less probability of significant cognitive decline after TL when compared to those older than 12 [44]. Children also showed higher rates of cognitive improvement following TL [45].

In addition, right TL tends to result in improved cognitive function whereas left TL can impair verbal or semantic memory and thus lead to a cognitive deficit. This can be explained by the fact that in left dominant individuals, language lateralizes to the left temporal cortex, which undergoes considerable trauma and scarring post TL [46-49]. Furthermore, it has been shown in some studies that the resective technique, ATL vs. transsylvian SAH for example, can have an effect on cognitive outcome as measured by verbal IQ. A transsylvian SAH, which tends to spare the lateral temporal cortex has been shown to result in better postoperative verbal IQs, presumably due to the role of the lateral temporal cortex in the ventral stream of visual processing. [46,50]. Although the cognitive and visual outcomes following TL have been researched in detail, there is a great need for studies that also evaluate psychiatric outcomes.

### TL and Hippocampectomy

The connection between TLE and the hippocampus goes back to surgeries conducted by Wilder Penfield. Research shows that the hippocampus is responsible for the generation and propagation of TLE and there is a close relationship between hippocampal sclerosis and seizures [51].

Therefore, it is believed that hippocampectomy is necessary for seizure freedom. Some studies that attempt to prove the latter include a randomized control trial conducted by Wyler et al. [52] where the authors compared a total vs. partial hippocampectomy on a total of 70 patients and found a significantly superior seizure outcome in the total hippocampectomy group (69 versus 38% seizure-free. Other studies which looked at the length of hippocampal resection and seizure free outcome have concluded the same [53,54].

### Objections to Hippocampectomy

In addition to the cognitive problems described in the introduction section of this paper, there are other objections to resecting the hippocampus. For one, the subgranular and subventricular zones of the hippocampus are important sources of neural progenitor cells [55-59] which allow for tissue repair following trauma or ischemia [60-64]. In addition, it is thought that impaired neurogenesis at the hippocampus could play a role in depression and Alzheimer's disease [65-67]. Therefore, resection of the hippocampus will deprive the patient of these much-needed stem cells [2]. Furthermore, when a study looked at the surgical outcome of matched groups where one group of epilepsy patients had only a temporal lobectomy with

amygdalectomy and the other group had an amygdalectomy along with hippocampectomy, it showed there was no benefit to adding hippocampectomy to the procedure [68,69]. Although a link has been established between TLE and hippocampal sclerosis [70,71] and some animal studies identify CA3 as an epileptogenic site, [72] some still dispute that a sclerotic hippocampus could generate epileptiform discharges [73] and point to other limbic areas and extrahippocampal structures as more likely epileptogenic foci [74-76]. In addition, it is known that seizures which are generated within the hippocampus never become generalized. Some authors propose that the interictal spike in the hippocampus could actually serve to inhibit seizure onset and stopping seizure generalization. Seigel et al. [77] show that when performing a selective amygdalohippocampectomy, seizure control was correlated with both the extent of hippocampal resection, as well as the amount of mediobasal temporal lobe structures that were removed [78]. This could mean that the hippocampus is actually more involved in seizure propagation than generation, [79] which would then make MHT with MST an ideal procedure for TLE.

### Multiple Hippocampal Transections (MHT)

While the hippocampus is responsible for both the functions discussed above and seizure propagation, each function seems to be limited to very specific types of fibers. The fibers that are responsible for seizure activity run longitudinally within in the hippocampus, while those responsible for common hippocampal functioning run vertically within the hippocampus. The longitudinal pathways include the longitudinal fibers of the following projections following: CA3 pyramidal cell axis projections, molecular axonal ramifications from both the inner and outer layer, and dentate gyrus fibers. On the other hand, the perpendicularly arranged fibers responsible more in part for hippocampal function include the circuit of CA3 to CA1 via the Schaffer collateral pathway and from CA1 to the entorhinal cortex after passing through the subiculum [80,81].

With this organization in mind, the technique of multiple hippocampal transections was designed by Shimizu et al. Different from the technique involving multiple subpial transections (MSTs), MHTs allow for transections to made destroying the synchronization between certain hippocampal regions and the ipsilateral anterior parahippocampal gyrus. This method of destruction, different from the abruption of localized synchrony achieved by MSTs can be achieved with a maximum of two transections made from the head to the body of the hippocampus [80].

The vertical cuts made to destroy the longitudinal fibers thought to be responsible for seizure activity and synchronization are optimal in their ability to maximize the destruction of longitudinal fibers while minimizing damage to the fibers responsible for hippocampal function. This success is specifically achieved by transecting the entire thickness of the hippocampus in the manner above throughout the hippocampus excluding the fimbria due to its role in hippocampal outflow.

The procedure, involving stereotactic opening into the temporal horn, has been found to be fairly safe. First a sharp knife is used to break through the alveus, the tough lining of the hippocampus. A blunt loop, optimal for its inability to penetrate the alveus on the medial side of the hippocampus and damage local structures is used to both enter the gray matter and make the vertical transections [82]. While an MHT is optimal for localizing destruction of seizure generating fibers, MSTs are used as a primary procedure to prevent



extensive resection of brain tissue. It is important to maintain intraoperative electrocorticography (ECoG) in order to quickly assess the success of the MST. Secondary MSTs may be performed if seizure activity persists, but these resections are usually much smaller than the initial resection. MSTs are advantageous in that larger transections are better tolerated and that they can significantly decrease the area responsible for epileptic electrical activity. However, the common need for secondary resection necessitates intraoperative ECoG [82]. Paving the way for MHT, Shimizu et al. studied 21 patients who received MHT as a treatment for epilepsy. On the basis of seizure reduction, the 17 who persisted for follow-up longer than year showed an 82% rate of seizure elimination, 12% rate of infrequent seizure occurrence, and 6% with noticeable seizure reduction. On the basis of memory assessment, 7 out of 8 patients showed no change in memory, with only 1 experiencing short-term progression of worsening memory. 16 In the series of 15 patients previously studied by Patil et al., [82] 94.7% of patients experienced cessation of seizures and only 1 patient experienced seizures that were rare post-operatively. Specifically, verbal memory was assessed to be improved in 7 out of the 9 tested patients and static in the remaining 2. Some theories for the explanation for the good outcomes of the study of Patil et al. are the increased localization of resection made during MHTs compared to MSTs. MSTs involve large areas of brain that include both parts responsible for seizure activity and those not. The presence of secondary MST following refractory activity on ECoG may also explain the extensive resections made. It is for this reason why MHTs are advantageous when compared to MSTs and standard temporal lobectomies [1].

## Conclusion

At present, the standard of care for refractory temporal lobe epilepsy is a temporal lobectomy. Although many precautions are taken to try and preserve non-epileptogenic tissue, nonetheless healthy neural tissue is still resected. One important structure that is often resected in TL is the hippocampus, an area of spiraled cortex on the medial temporal lobes which is responsible, among other things, for short term memory, organized thought and tissue repair following neural injury. It is an area of contention amongst authors in the field whether a hippocampal resection is necessary to provide seizure freedom, with some claiming that the hippocampus is a potent epileptogenic focus, and others maintaining that the hippocampus is more often a propagator of epileptic discharges that are actually generated in nearby structures. In light of the importance of sparing non-diseased neural tissue in temporal lobe epilepsy surgery, various alternative techniques are being studied, including; stereotactic radio ablation, neuromodulation using a combination of stimulation, drug delivery, tissue transplant and gene therapy, temporal disconnection, deep brain stimulation, vagal nerve stimulation and multiple hippocampal transection.

We conclude that multiple hippocampal transection, which targets only those fibers in the hippocampus that are responsible for the propagation of epileptiform discharges could be a safer and effective alternative to conventional temporal lobectomy while critically reducing the amount of healthy neural tissue that is resected. Although the current strategy of performing TL in refractory temporal lobe epilepsy is effective when only looking at reducing seizure number, there are many cognitive deficits that can occur in these patients that can go unnoticed and underreported. For example, multiple studies exist that show cognitive outcomes following TL,

however there is a clear dearth of information regarding psychiatric outcomes following TL. Considering the fact that the temporal lobe is widely known to be the neural correlate of emotion and many psychiatric disorders including schizophrenia and depression have pathognomonic findings in the temporal region, it stands to reason that resection of temporal tissue can have significant impact on the psychiatric well-being of TL patients. Therefore, future studies should aim to quantify psychiatric outcomes of TL in comparison to alternative methods and these studies should not be ignored when reporting surgical outcomes.

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