Mammillothalamic and Mammillotegmental Tracts as New Targets for Dementia and Epilepsy Treatment

Naci Balak[1], Ece Balkuv[2], Ali Karadag[3], Recep Basaran[4], Huseyin Biceroglu[5], Buruç Erkan[6], Necmettin Tanriover[7]

Key words
- Amnesia
- Brain
- Epilepsy
- Mammillary body efferents
- Memory
- Neuroanatomy

Abbreviations and Acronyms
DBS: Deep brain stimulation
MTgT: Mammillotegmental tract
MThT: Mammillothalamic tract

From the Departments of [1]Neurosurgery and [2]Neurology, Üsküdar State Hospital, Istanbul; [3]Department of Neurosurgery, Saglik Bilimleri University, Tepecik Research and Training Hospital, Izmir; [4]Department of Neurosurgery, Sancaktepe Education and Research Hospital, Istanbul; [5]Department of Neurosurgery, Ege University, Faculty of Medicine, Izmir; [6]Department of Neurosurgery, Bakirkoy Research and Training Hospital for Neurology, Neurosurgery, and Psychiatry, Istanbul; [7]Department of Neurosurgery, Istanbul University, Cerrahpasa Faculty of Medicine, Istanbul, Turkey

To whom correspondence should be addressed: Naci Balak, M.D. [E-mail: naci.balak@gmail.com; drnacibalak@yahoo.com]

Citation: World Neurosurg. (2018) 110:133-144. https://doi.org/10.1016/j.wneu.2017.10.168

Journal homepage: www.WORLDNEUROSURGERY.org

Available online: www.sciencedirect.com

BACKGROUND: **Recently, neuromodulation through deep brain stimulation (DBS) has appeared as a new surgical procedure in the treatment of some types of dementia and epilepsy. The mammillothalamic and mammillotegmental tracts are involved among the new targets. To our knowledge, a review article focused specifically on these mammillary body efferents is lacking in the medical literature. Their contribution to memory is, regrettably, often overlooked.**

METHODS: **A review of the relevant literature was conducted.**

RESULTS: **There is evidence that mammillary bodies can contribute to memory independently from hippocampal formation, but the mechanism is not yet known. Recent studies in animals have provided evidence for the specific roles of these mammillary body efferents in regulating memory independently. In animal studies, it has been shown that the disruption of the mammillothalamic tract inhibits seizures and that electrical stimulation of the mammillary body or mammillothalamic tract raises the seizure threshold. In humans, DBS targeting the mammillary body through the mammillothalamic tract or the stimulation of the anterior thalamic nucleus, especially in the areas closely related to the mammillothalamic tract, has been found effective in patients with medically refractory epilepsy. Nonetheless, little knowledge exists on the functional anatomy of the mammillary body efferents, and their role in the exact mechanism of epileptogenic activity and in the memory function of the human brain.**

CONCLUSIONS: **A comprehensive knowledge of the white matter anatomy of the mammillothalamic and mammillotegmental tracts is crucial since they have emerged as new DBS targets in the treatment of various disorders including dementia and epilepsy.**

INTRODUCTION

Recently, neuromodulation through deep brain stimulation (DBS) has appeared as a new surgical procedure in the treatment of some types of dementia and epilepsy.[1-12] The mammillothalamic tract (MThT) and mammillotegmental tract (MTgT) are the efferents of the mammillary body. The mammillary bodies have been recognized as being involved in some human functions like memory and emotion. Because of their connections with the hippocampus, they are also thought to contribute to the generation of epileptic discharges in the occurrence of mesial temporal lobe epilepsy, which is the most common form of medically refractory epilepsy.[6]

There is a long-lasting and unresolved issue regarding the neuroanatomic basis of memory impairments.[13,14] The role of the hippocampus in the function of memory is well established. Yet to accurately apprehend the neural roots of memory, it is necessary to look beyond the hippocampus and focus on other interconnected structures, whose contribution to memory is, regrettably, often overlooked.[13] In routine clinical practice, besides meticulous evaluation of radiologic scans of the brain, a comprehensive knowledge of the white matter anatomy of these structures is crucial for the understanding of memory function and treatment of memory deficiencies in various central nervous system pathologies.

There is evidence that mammillary bodies can contribute to memory independently from hippocampal formation, but the mechanism is not yet known. The main mammillary tract, containing the efferents of the mammillary nuclei, constitutes a large compact bundle that splits into 2 components, the large MThT and the smaller MTgT[15,16] (Figure 1). Recent studies in animals have provided evidence for the specific roles of these mammillary body efferents in regulating memory independently.[13] Although the functional anatomy of MThT and MTgT have been reported in animal experiments, the importance of these individual components in human brain functional anatomy associated with memory remains uncertain.

The MThT, which projects from the mammillary body to the anterior thalamic nucleus, and the MTgT, which projects to the brainstem tegmental nuclei, seem to

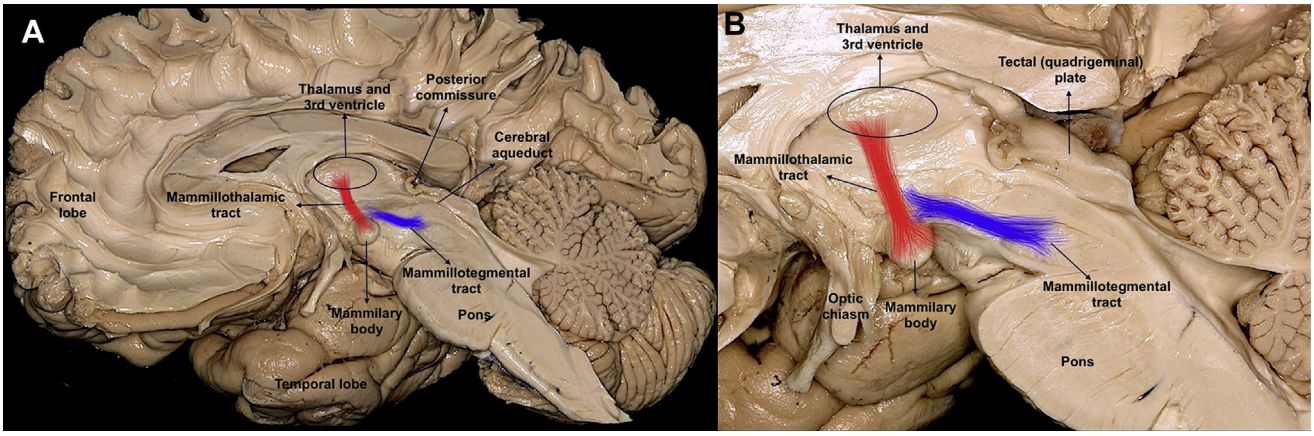

Figure 1. (**A**) Photograph of cadaveric brain obtained during dissection of cerebral hemisphere. The red-colored brush stroke represents the mamillothalamic tract. It interconnects the mammillary bodies with the anterior nucleus of the thalamus. The blue-colored brush stroke shows the mammillotegmental tract. It is a small efferent white matter fiber bundle between the dorsal end of the main mammillary tract of the mammillary body and the mesencephalic tegmentum's dorsal and ventral tegmental nuclei and caudal gray matter areas. (**B**) Enlarged view of the same picture.

play a role in the mediation of seizure activity according to the animal studies.[17] In these animal studies, it has been shown that the disruption of the MThT inhibits seizures and that electrical stimulation of the mammillary body or MThT raises the seizure threshold.[17,18] In humans, DBS targeting the mammillary body through the MThT or the stimulation of the anterior thalamic nucleus, especially in the areas closely related with the MThT, has been found effective in patients with medically refractory epilepsy.[3,6,19] Identification of the MThT in magnetic resonance images is crucial for visual delineation and augmented targeting of the anterior thalamic nucleus during DBS.[10,20] Nonetheless, little knowledge exists on the functional anatomy of the mammillary body efferents and their role in the exact mechanism of epileptogenic activity.

For the previously mentioned reasons, in this article historical, phylogenetic, anatomic, and functional aspects of the MThT and the MTgT are revisited, and their pathologic conditions, primarily related to memory dysfunction, are recalled. To our knowledge, an article focused specifically on the mammillary body efferents is lacking in the medical literature.

METHODS

For our review article, the relevant literature was retrieved by electronic search from the databases of PubMed, Scopus, EBSCO, Web of Science, and Google Scholar. This review was restricted to the published data only. All potentially suitable studies were read in full. Papers written in English, French, German, Turkish, or Swedish were considered and, whenever available, English abstracts of articles in other languages were also inspected. The search was not limited by date of publication, and whenever possible, the relevant parts of rare books were also read. Special attention was given to obtaining related information from selected main textbooks, historical journal articles, and currently published or in-press journal articles. The references of retrieved articles were also screened.

HISTORICAL REMARKS AND NOMENCLATURE OF THE MAMMILLARY BODY EFFERENTS

Some historical aspects and nomenclature of the mammillary body efferents are summarized in Tables 1 and 2.

Table 1. Summary of Historical Aspects of Mammillary Body Efferents

Author	Year	Feature
Thomas Willis[21-24]	1621—1675	Performed probably the first dissection of the MThT but misinterpreted it
Francois Pourfour du Petit and Giovanni Domenico Santorini[21,23,24]	1664—1741 1681—1737	First discovery of the MThT
Félix Vicq d'Azyr[21,24-26]	1748—1794	First detailed description of the MThT
Herbert Mayo[27]	1827	Published a book that included several of the best illustrations of dissected brains available at that time and depicted the MThT
Johann Bernhard Aloys von Gudden[28-31]	1824—1886	First definition of the MTgT described the dorsal and ventral tegmental nuclei in 1884[29]
Ramón y Cajal[32]	1895	Demonstrated the mammillary body and its projections, the MThT and the MTgT, in Golgi specimens
Josef Klingler[33]	1935	First illustration of the MThT by using the fiber-dissection technique
James W. Papez[34]	1937	Included the MThT as an element of Papez circuit
Mahmut Gazi Yaşargil and Uğur Türe[35]	2005	Revitalized the fiber-dissection technique and illustrated the MThT