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Review

How do mammillary body inputs contribute to anterior thalamic function?

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ABSTRACT

It has long been assumed that the main function of the mammillary bodies is to provide a relay for indirect hippocampal inputs to the anterior thalamic nuclei. Such models afford the mammillary bodies no independent role in memory and overlook the importance of their other, non-hippocampal, inputs. This review focuses on recent advances that herald a new understanding of the importance of the mammillary bodies, and their inputs from the limbic midbrain, for anterior thalamic function. It has become apparent that the mammillary bodies' contribution to memory is not dependent on afferents from the subicular complex. Rather, the ventral tegmental nucleus of Gudden is a vital source of inputs that support memory processes within the medial mammillary bodies. In parallel, the lateral mammillary bodies, via their connections with the dorsal tegmental nucleus of Gudden, are critical for generating head-direction signals. These two parallel, but distinct, information streams converge on the anterior thalamic nuclei and support different aspects of spatial memory.

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1. Introduction

The anterior thalamic nuclei, a core component of Papez' circuit, are assumed to form a vital node within a network of related structures that support memory and cognition. Evidence for this assertion comes from the finding that damage or disconnection of the anterior thalamic nuclei is consistently associated with anterograde amnesia in humans and profound learning and memory impairments in rodents (e.g. Aggleton and Sahgal, 1993; Aggleton and Brown, 1999; Carlesimo et al., 2011; Harding et al., 2000; Jankowski et al., 2013). The anterior thalamic nuclei receive inputs (often reciprocal) from a complex array of cortical and subcortical

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structures; as such, understanding the importance of this circuitry represents a vital step towards uncovering anterior thalamic nuclei functions. Given the extensive direct and indirect hippocampal-anterior thalamic interconnections, as well as the undeniable importance of the hippocampus itself for memory, it is perhaps no surprise that there has been particular focus on the significance of the projections from the hippocampus, via the fornix, for anterior thalamic function (e.g. Aggleton and Brown, 1999). Dense inputs to the anterior thalamic nuclei also arise from the mammillary bodies, reaching the anterior thalamus via the mammillothalamic tract (Cruce, 1975; Seki and Zyo, 1984; Vann et al., 2007) (Fig. 1). These mammillary body efferents are particularly striking, as it appears that almost every neuron within the mammillary bodies projects to the anterior thalamic nuclei (Guillery, 1955; Vann et al., 2007; Aggleton et al., 2010). Yet, the separate functional significance of these mammillary body inputs to the anterior thalamic nuclei has often been overlooked (Vann, 2010).

Indeed, most accounts of mammillary body function, and by inference the mammillary body-anterior thalamic axis, again highlight the importance of hippocampal connections to this region, such that the mammillary bodies are often referred to as a constituent of an 'extended hippocampal system' that simply relay hippocampal inputs to the anterior thalamus (e.g. Aggleton and Brown, 1999; Delay and Brion, 1969; Gaffan, 1992). Apparent support for this position comes from evidence that, like the hippocampus and anterior thalamus, damage to the mammillary bodies and their thalamic projections can result in memory impairments in both humans and rodents (e.g. Gudden, 1896; Carlesimo et al., 2007; Van der Werf et al., 2003a,b; Vann and Aggleton, 2003; Yoneoka et al., 2004). The unidirectional nature of subicular complex inputs to the mammillary bodies, and thence to the anterior thalamic nuclei, might also appear to be consistent with the notion of an 'extended hippocampal system' (Aggleton et al., 2005). This account has two major shortcomings. First, it ascribes no independent role to the mammillary body-anterior thalamic axis, thereby effectively rendering it redundant and second, it completely overlooks the non-hippocampal inputs to the mammillary bodies that originate predominately in the limbic midbrain.

Recent advances in our understanding of the mammillary bodies and their thalamic projections challenge hippocampal-centric models of memory. By revealing a role for the mammillary bodies in mnemonic processes that is independent of its inputs from the subicular complex, this work heralds the need to look beyond the hippocampus and consider a wider network of structures that may contribute to mammillary body, and in turn anterior thalamic nuclei, function. These advances in our understanding of both the anatomical and functional properties of the mammillary bodies and the implications for diencephalic, and in particular anterior thalamic contributions to cognition, will be the focus of this review.

2. Anatomy

The mammillary bodies comprise two main subregions: the medial and lateral nuclei. In turn, the medial mammillary bodies

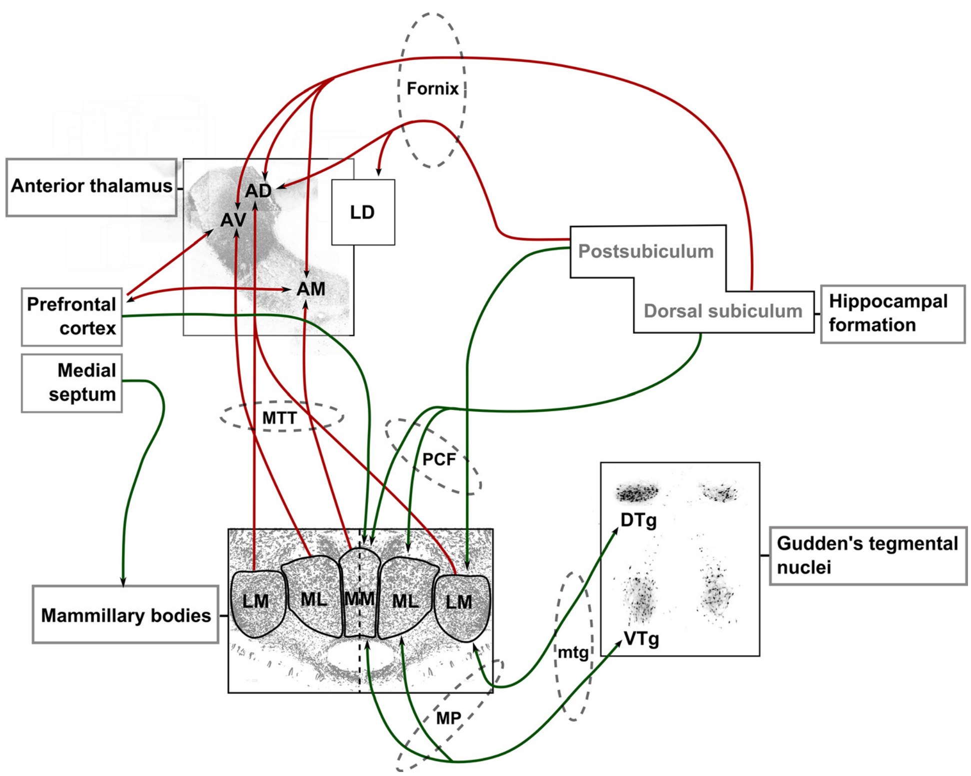

Fig. 1. A Semi-schematic diagram showing the major afferent and efferent connections of the mammillary bodies. Mammillary body inputs are represented by green arrows: The medial mammillary nuclei, comprising pars medialis (MM) and pars lateralis (ML) subdivisions, receive input from the dorsal subiculum (via the descending postcommisural fornix (dPCF)) and prefrontal cortex, and have reciprocal connections with the ventral tegmental nuclei of Gudden (VTG), via the mammillary peduncle (mp; VTg/DTG → mammillary bodies) and the mammillotegmental tract (mtg; mammillary bodies → VTG/DTG). The lateral mammillary nuclei are innervated by the postsubiculum and the dorsal tegmental nuclei of Gudden (DTG) via the same respective pathways. In addition, both medial and lateral mammillary body nuclei receive inputs from the medial septum; Anterior thalamic nuclei inputs are represented by red arrows: The major efferent projection of the mammillary bodies is to the anterior thalamic nuclei, via the mammillothalamic tract (MTT). Anterodorsal (AD) and laterodorsal (LD) thalamic nuclei both receive postsubicular inputs while the dorsal subiculum projects to the anteroventral (AV) and anteromedial (AM) thalamic nuclei, all of which are largely via the fornix. In turn, AM has reciprocal connections with the prefrontal cortex. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)