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Review

Functional heterogeneity of the limbic thalamus: From hippocampal to cortical functions

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ABSTRACT

Today, the idea that the integrity of the limbic thalamus is necessary for normal memory functions is well established. However, if the study of thalamic patients emphasized the anterior and the mediodorsal thalamus as the critical thalamic loci supporting cognitive functions, clinical studies have so far failed to attribute a specific role to each of these regions. In view of these difficulties, we review here the experimental data conducted in rodents harboring specific lesions of each thalamic region. These data clearly indicate a major functional dissociation within the limbic thalamus. The anterior thalamus provides critical support for hippocampal functions due to its cardinal location in the Papez circuit, while the mediodorsal thalamus may signal relevant information in a circuit encompassing the basolateral amygdala and the prefrontal cortex. Interestingly, while clinical studies have suggested that diencephalic pathologies may disconnect the medial temporal lobe from the cortex, experimental studies conducted in rodent show how this may differently affect distinct temporo-thalamo-cortical circuits, sharing the same general organization but supporting dissociable functions.

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1. Introduction

The observation that discrete damage to restricted parts of the diencephalon can produce an amnesic syndrome similar, in many aspects, to that observed in patients with hippocampal damage is not new. As early as the end of the 19th century, Sergueï Korsakoff reported severe impairments of current and recent memory in several patients with or without chronic alcohol abuse (Kopelman et al., 2009). Later on, it was confirmed that these patients typically exhibit diffuse damage at the level of the diencephalon, encroaching on the mammillary bodies (Delay and Brion, 1969) and the thalamus (Victor et al., 1971), which was assumed to be responsible for the memory deficits. Today, it is generally well accepted that the distinction between temporal lobe and diencephalic amnesia has limited, if any value (Carlesimo et al., 2011; Caulo et al., 2005; Gold and Squire, 2006) so that the use of the single term "amnesia" may be sufficient to characterize symptoms that essentially overlap. However, while the neuropathology of temporal lobe amnesia has been identified early due to the availability of several famous clinical cases including Henry Molaison (Annese et al., 2014; Scoville and Milner, 2000), determining specific loci within the diencephalon that invariably produce amnesia when damaged has proven to be a much more difficult task. Damage to either the mammillary bodies (Delay and Brion, 1969), the mediodorsal (Victor et al., 1971) or the anterior thalamus (Harding et al., 2000) have been thought to be primarily responsible for the memory deficits associated with diencephalic amnesia. The use of unbiased stereological techniques has provided convincing support for the view that damage to the anterior thalamus is consistently associated with memory deficits in patients suffering from Korsakoff's syndrome (Harding et al., 2000). However, the diffuse nature of the diencephalic damage in these patients still leaves room for alternate views and it is possible that concurrent damage at both the level of the mammillary bodies and of the anterior and mediodorsal thalamus may best account for the severe memory impairments (Kril and Harper, 2012). In view of these difficulties, an effort has been made to consider another pathological condition of the thalamus resulting in more defined damage, lacunar infarcts targeting the anteromedial portion of the thalamus. A meta-analysis run on 83 patients recently supported the notion that vascular thalamic amnesia may primarily result from damage to the anterior thalamus (Carlesimo et al., 2011). However, the authors still recognized that the anterior and mediodorsal thalamic regions may mediate different aspects of the declarative memory system and that deficits originating from damage to the anterior thalamus may be more easily detectable with neuropsychological tests than deficits resulting from direct damage to the mediodorsal thalamus (Carlesimo et al., 2011). Furthermore, clinical studies continue to provide conflicting information and the case of a patient sustaining bilateral thalamic infarctions with relatively selective mediodorsal, but not anterior thalamic damage was recently documented with the rather surprising description of a typical amnesic syndrome, which included anterograde and retrograde memory impairments while implicit memory was spared (Hampstead and Koffler, 2009).

The major conclusion that can be derived from these clinical studies is that although they invariably demonstrate a crucial contribution of the diencephalon to learning and memory, they do not provide solid ground to establish the specific contribution of the limbic thalamus beyond the observation that the anterior and the mediodorsal thalamus appear as critical loci. Experimental studies conducted in non-human primates and even more in rodents have however led to considerable progress on the identification of the specific functional contributions of these thalamic regions. We will focus here on the experimental evidence derived from rodent studies supporting the existence of dissociable functions within the thalamus. The scope of the present review is therefore to show that the contribution of the limbic thalamus to cognitive functions can be better understood by considering the specific functional connectivity of each of these thalamic regions with the temporal lobe and the cortex.

2. The anterior thalamus and hippocampal functions

The earliest significant experimental attempt to identify the functions of the anterior thalamus in cognition was probably the work conducted by Michael Gabriel, with a series of experiments in the intact rabbit showing a correlation between neuronal activity in the anteroventral nucleus and discriminative avoidance behavior (Gabriel et al., 1977, 1980; Orona et al., 1982). Subsequently, it was confirmed that anterior thalamic lesions not only impaired this type of behavior but also reduced neuronal activity in a network of connected structures, namely the anterior cingulate and the retrosplenial cortices (Gabriel et al., 1983). This discovery was later supported by extensive experimental evidence indicating a specific role of the anterior thalamic nuclei in an integrated "extended" system encompassing the hippocampus, the mammillary bodies as well as the cingulate region (Freeman et al., 1996a,b; Gabriel et al., 1983; Gabriel and Sparenborg, 1986; Gabriel et al., 1987). Therefore, Gabriel's pioneer work prefigured much of the data subsequently reported in rodents and successfully captured one of the core aspect of the functional connectivity of the anterior thalamus, its integration in a specific temporo-cortical circuit. In the following sections, we will first review the main behavioral data showing an involvement of the anterior thalamus in spatial and nonspatial cognition and then confront these data with those from the hippocampal literature to highlight general and specific functional roles of this region.

2.1. The anterior thalamus and spatial memory: reference versus working memory

Ironically, the early studies from Michael Gabriel relied on an instrumental procedure devoid of any relevant spatial information (rabbits were required to run in a wheel in response to conditioned auditory stimuli), which greatly contrasts with the overwhelming dominance of spatial paradigms in the next generation of studies conducted in the rat. It is likely that this prevalence of spatial studies was initiated by the discovery of the head-direction cells (HD cells, see Section 2.3.2) in a network of structures including the anterior thalamus (Taube, 1995).

Behavioral tests taxing spatial reference memory abilities focus on the use of permanent information. They have been mostly conducted using water maze or radial arm maze procedures, the water maze probably being best suited to study spatial behaviors governed by distal, extramaze cues and allocentric spatial processing. Due to the inherently relational nature of integrated representations of multiple distal cues, such processing is expected to be supported by hippocampal functions (Bird and Burgess, 2008). Early studies conducted with this paradigm indicated a major deficit in rats with anterior thalamic damage, not only after large, moderately specific, electrolytic lesions (Sutherland and Rodriguez, 1989) but also following more refined excitotoxic lesions (Warburton and Aggleton, 1999). In fact, even extensive pretraining does not prevent the occurrence of these deficits after anterior thalamic damage (Warburton et al., 1999). This critical impairment produced by ATN lesions has been confirmed numerous times (Lopez et al., 2009; van Groen et al., 2002a) and it is also clear that damage to the anterior but not the adjacent intralaminar group is responsible for these deficits (Lopez et al., 2009; Moreau et al., 2013; Wolff et al., 2008a). There is also evidence that damage restricted to the laterodorsal nucleus, a region considered

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