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Multiple thalamo-cortical disconnections in anterior thalamic infarction: Implications for thalamic mechanisms of memory and language

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ABSTRACT

Amnesia and linguistic deficits that are associated with thalamic damage have attracted the attention of researchers interested in identifying the neural networks involved in memory and language. The Papez circuit, which is composed of the hippocampus, mammillary body and anterior thalamic nuclei, was first proposed to be critical for memory. However, subsequently, the roles of the neural circuit consisting of the rhinal/parahippocampal cortices and the mediodorsal thalamic nuclei became evident. The ventral lateral nuclei or its adjacent structures have been found to be involved in semantic processing, but the specific neural circuits dedicated to language functions have not been identified.

Anterior thalamic infarcts, which affect very circumscribed regions of the ventral anterior portion of the thalamus, often cause paradoxically prominent memory and language deficits. We conducted tractography analyses in 6 patients with left anterior thalamic infarcts to identify neural connections or circuits in which disruptions are associated with memory and language deficits in this condition. The current study demonstrated that the mammillothalamic tract, which connects the mammillary body with the anterior thalamic nuclei, and the anterior and inferior thalamic peduncles, which contain neural fibers that extend from several thalamic nuclei to the anterior temporal, medial temporal and frontal cortices, are disrupted in anterior thalamic infarction. These extensive thalamo-cortical disconnections appear to be due to the dissection of the neural fibers that penetrate the ventral anterior nucleus of the thalamus. Our results suggest the following: (1) amnesia that is associated with anterior thalamic infarction is best interpreted in the context of dual/multiple-system theories of memory/amnesia that posit that multiple neural circuits connecting the anterior and mediodorsal thalamic nuclei with the hippocampus and rhinal/parahippocampal cortices work in concert to support memory function; and (2) the semantic deficits observed in this syndrome may be associated with thalamo-anterior temporal and thalamo-lateral frontal disconnections.

1. Introduction

1.1. A historical overview of diencephalic amnesia

The role of thalamic damage in the amnesia observed in alcoholics (i.e., Wernicke–Korsakoff syndrome) was uncovered in the 1930s (Aggleton, 2008; Bender & Schilder, 1933; Kopelman, 1995). This modest discovery preceded Scoville and Milner's landmark discovery of medial temporal amnesia by 20 years (Scoville & Milner, 2000). Subsequent studies demonstrated striking similarities between the neuropsychological features of thalamic and medial temporal amnesias and led to the idea that memory functions are supported by a network that consists of these neural structures. Various theories have been proposed to synthesize the empirical findings on medial temporal lobe mechanisms of memory (Eichenbaum, Yonelinas, & Ranganath, 2007; Saksida & Bussey, 2010; Wixted & Squire, 2011), whereas fewer attempts have been made to do the same for the counterpart of this structure; i.e., the thalamus (Aggleton & Brown, 2006). Empirical evidence concerning thalamic amnesia has originated from several different lines of research that include studies of Wernicke–Korsakoff syndrome, thalamic infarcts and animal

Abbreviations: AN, anterior thalamic nuclei; IML, internal medullary lamina; MD, mediodorsal nuclei; MTT, mammillothalamic tract; VA, ventral anterior nucleus; VAmc, magnocellular ventral anterior nucleus; Vim, ventral intermediate nucleus; VLa, ventral lateral anterior nucleus; VLp, ventral lateral posterior nucleus

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neuropsychological studies. Integration of the findings from these research fields is essential for further understanding of the neural mechanisms of memory.

Although a series of neuropathological studies have revealed that the mammillary body, anterior thalamic nuclei (AN) and mediodorsal nuclei (MD) are the primary loci of neurodegeneration in Wernicke–Korsakoff syndrome (Kopelman, 1995; Malamud & Skillicorn, 1956), the roles of each of these diencephalic structures in memory functions have been matters of debate. In a study that is probably one of the most systematic investigations currently available, Harding, Halliday, Caine, and Kril (2000) demonstrated that significant degeneration of the AN is found only in patients with Wernicke–Korsakoff syndrome and not in patients with Wernicke's encephalopathy in the absence of profound amnesia. On the basis of these findings, the role of the AN in memory has been emphasized (Aggleton, 2008; Harding et al., 2000). However, the study by Harding and colleagues demonstrated that the mammillary body and MD were consistently affected in Wernicke's encephalopathy and Wernicke–Korsakoff syndrome irrespective of the presence or absence of profound amnesia. These findings allow alternative interpretations in which simultaneous damage to these structures or the amount and severity of diencephalic pathology contribute to the development of profound amnesia.

One of the earliest, but still influential, hypotheses concerning the neural network of memory was proposed by Delay and Brion (Gaffan & Wilson, 2008; Mayes, 2000). Their theory assigns a central role to the Papez circuit, which arises from the hippocampus, travels through the fornix, mammillary body, mammillothalamic tract (MTT), AN and posterior cingulate cortex, and then returns to the hippocampus. Although the importance of the AN and hippocampus is stressed in this theory, subsequent neuropsychological studies in monkeys have demonstrated that neither isolated damage to the AN nor damage to the hippocampus results in dense amnesia, and additional lesions in the MD or the rhinal cortices are necessary for the development of severe memory impairments (Gaffan & Parker, 2000; Gaffan, Parker, & Easton, 2001; Mishkin, 1978; Murray & Mishkin, 1998; Parker & Gaffan, 1997). These discoveries promoted the development of new theories that embrace both the contributions of structures outside the Papez circuit and the neural network views of memory; these dual- or multi-system theories propose that distinct diencephalic and medial temporal structures form parallel, but partially interconnected, neural circuits (i.e., the hippocampal-AN (Papez) and rhinal-MD circuits), and that these two neural circuits work in concert to support memory functions (Aggleton & Brown, 1999, 2006; Mishkin, 1982). Specifically, some authors hypothesize that the hippocampal-AN circuit supports the process of recollection, which may be involved in the retrieval of detailed information associated with previous experiences, whereas the rhinal-MD circuit may play a pivotal role in the process of familiarity, which is a fundamental process in recognition memory (Aggleton & Brown, 1999; Yonelinas, Aly, Wang, & Koen, 2010). However, there has been considerable controversy regarding both the familiarity/recollection distinction of memory and their neural substrates (Wixted & Squire, 2011). As the theories for neural networks of memory have been developed, there have been attempts to understand amnesia associated with Wernicke–Korsakoff syndrome in relation to neural network disruption. Previous PET studies consistently demonstrated decreased glucose metabolism in extensive cortical regions, including the frontal, temporal and parietal cortices, in Wernicke–Korsakoff syndrome, suggesting that thalamo-cortical network disruptions are not restricted to the AN-hippocampal circuit but may be more widespread in this disorder (Paller et al., 1997; Reed et al., 2003).

Memory research actively focused on the amnesia associated with isolated thalamic infarction with the advent of CT and MRI in the 1980s and 1990s, respectively. Thalamic infarcts are classified into 4 subtypes on the basis of arterial territories: anterior, paramedian, inferolateral and posterior thalamic (Carrera & Bogousslavsky, 2006; Schmahmann, 2003). Among these subtypes, anterior and paramedian thalamic infarcts have received particular attention because their primary clinical manifestations are amnesia and other cognitive deficits. Another remarkable aspect of these thalamic vascular syndromes is that very small and circumscribed lesions often produce profound memory sequelae, which allows researchers to examine the roles of single or limited thalamic structures that are critical for memory. Because the AN, which is considered to be one of the most important diencephalic structures in Wernicke–Korsakoff syndrome and the Delay–Brion hypothesis, is spared in most cases of anterior and paramedian thalamic infarcts, the following 3 hypothetical mechanisms of thalamic infarct-associated amnesia have been proposed: (1) disruption of the Papez circuit due to damage to the MTT; (2) damage to the MD; and (3) disruption of the MD-rhinal cortical circuit due to dissection of the neural fibers that pass through the internal medullary lamina (IML) (Graff-Radford, Tranel, Van Hoesen, & Brandt, 1990; Mori, Yamadori, & Mitani, 1986; von Cramon, Hebel, & Schuri, 1985). Most of these studies are based on single or small numbers of cases because isolated thalamic infarcts are relatively rare. Therefore, several authors have attempted to integrate the findings from the relevant case studies in literature reviews. Van der Werf, Witter, Uylings, and Jolles (2000) analyzed the locations of lesions in 60 published cases of isolated thalamic infarcts and concluded that damage to the MTT is crucial for the development of amnesia. Additionally, in a review of 83 cases, Carlesimo, Lombardi, and Caltagirone (2011) demonstrated that 95% of patients with MTT damage and 46% of those without MTT damage had amnesia (chi-square 25.3; $p < 0.01$), whereas the involvement of neither the MD nor the IML (referred to as the 'intralaminar nuclei' by these authors) predicts the development of amnesia . In the discussions of these review papers, the roles of the MTT and the Papez circuit was emphasized and less attention was given to the contributions of other thalamic structures and related neural circuits. However, the review by Carlesimo et al. (2011) reported that half of the patients without MTT damage developed amnesia, suggesting mechanisms other than the disruption of the Papez circuit in the thalamic infarct associated-amnesia.

1.2. Theoretical and methodological issues in studies of memory impairment associated with thalamic infarcts

Here, we review inconsistencies between the current interpretations of the empirical findings from animal and human studies of thalamic amnesia and between the theories derived from those studies. Neuropsychological studies in animals have demonstrated that disruptions of two or more of the neural circuits that consist of distinct thalamic and medial temporal structures are necessary for profound memory impairment; thus, these studies have led to proposals that these multiple neural circuits work in concert to support memory function (Aggleton & Brown, 1999, 2006; Mishkin, 1982; Zola-Morgan & Squire, 1993). Conversely, the studies of Wernicke–Korsakoff syndrome and thalamic infarcts have been interpreted to indicate that profound amnesia can be ascribed to lesions that are restricted to the AN or the MTT (for a counter view, see Paller et al., 1997). The supposition that lesions to the MTT alone are capable of producing profound amnesia is consistent with the idea that the integrity of the Papez circuit is most critical for the maintenance of normal memory function (Aggleton, 2008; Carlesimo et al., 2011; Harding et al., 2000; Van der Werf et al., 2000). These differences in interpretation may partially originate from the complicated nature of lesions in human patients. In animal studies, targeted thalamic nuclei, such