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Contributions of volumetrics of the hippocampus and thalamus to verbal memory in temporal lobe epilepsy patients ☆

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ABSTRACT

Recent theories have posited that the hippocampus and thalamus serve distinct, yet related, roles in episodic memory. Whereas the hippocampus has been implicated in long-term memory encoding and storage, the thalamus, as a whole, has been implicated in the selection of items for subsequent encoding and the use of retrieval strategies. However, dissociating the memory impairment that occurs following thalamic injury as distinguished from that following hippocampal injury has proven difficult. This study examined relationships between MRI volumetric measures of the hippocampus and thalamus and their contributions to prose and rote verbal memory functioning in 18 patients with intractable temporal lobe epilepsy (TLE). Results revealed that bilateral hippocampal and thalamic volume independently predicted delayed prose verbal memory functioning. However, bilateral hippocampal, but not thalamic, volume predicted delayed rote verbal memory functioning. Follow-up analyses indicated that bilateral thalamic volume independently predicted immediate prose, but not immediate rote, verbal recall, whereas bilateral hippocampal volume was not associated with any of these immediate memory measures. These findings underscore the cognitive significance of thalamic atrophy in chronic TLE, demonstrating that hippocampal and thalamic volume make quantitatively, and perhaps qualitatively, distinct contributions to episodic memory functioning in TLE patients. They are also consistent with theories proposing that the hippocampus supports long-term memory encoding and storage, whereas the thalamus is implicated in the executive aspects of episodic memory.

1. Introduction

It is widely recognized that both the hippocampus and thalamus play a critical role in episodic memory functioning (Kopelman, 1995; Kopelman & Stanhope, 2002; Squire, 1982; Van der Werf, Witter, Uylings, & Jolles, 2000). However, the extent to which the hippocampus and thalamus make unique contributions to episodic memory functioning and the nature of their respective contributions remains somewhat unclear. Recent theories have proposed that the hippocampus and thalamus serve distinct, yet related roles, in episodic memory. Whereas the hippocampus supports long-term memory encoding and storage of the associations among the constituent elements of an experience (i.e., relational material) (Eichenbaum, 2004; Eichenbaum & Cohen, 2001; Morris et al., 2003; O'Reilly & Rudy, 2001; Rolls, 1990; Ryan & Cohen, 2003; Squire & Zola-Morgan, 1991), the thalamus has been implicated in the executive aspects of episodic memory. Specifically, it has been hypothesized that the anterior thalamic nuclei play a role in the selection of items for subsequent memory storage and are thus involved in encoding strategies (Aggleton & Brown, 1999; Van der Werf, Jolles, Witter, & Uylings, 2003), that the mediodorsal nucleus of the thalamus is involved in the coordination and selection of suitable, active retrieval strategies in conjunction with the prefrontal cortex (Van der Werf, Jolles, et al., 2003), and that the intralaminar and midline nuclei of the thalamus are implicated in the allocation of cortical activation necessary for the execution of encoding and retrieval processes (Van der Werf, Jolles, et al., 2003).

Although the hippocampus and thalamus are believed to support different episodic memory processes, dissociating the contributions of these brain structures to episodic memory has proven difficult. The hippocampus and thalamus share extensive

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reciprocal connections (Dolleman-van der Weel & Witter, 1996; Herkenham, 1978; Oikawa, Sasaki, Tamakawa, & Kamei, 2001; Su & Bentivoglio, 1990; van Groen & Wyss, 1990; Wouterlood, Saldana, & Witter, 1990), and injury to either structure may alter neuronal functioning in the other structure (Bertram & Zhang, 1999; Dolleman-Van der Weel, Lopes da Silva, & Witter, 1997; Meyer, Obara, & Muramatsu, 1993). Moreover, injury to either the hippocampus or thalamus can result in comparably dense amnesic syndromes (Kopelman & Stanhope, 2002), a finding that led Aggleton and Brown (1999) to state that "the traditional distinction between temporal lobe and diencephalic amnesics is misleading; both groups have damage to the same functional system" (p. 426).

However, other research has illustrated subtle differences in the memory impairments exhibited by temporal lobe and diencephalic amnesics. It has been demonstrated that Korsakoff's patients, who have sustained injury to the thalamus, exhibit heightened susceptibility to proactive interference, in addition to deficits in judging the temporal order of events, compared to temporal lobe amnesics (Squire, 1982). Additionally, lesions to the mediodorsal, midline nuclei, or intralaminar nuclei of the thalamus have been associated with executive dysfunction (e.g., impaired set-switching and inhibition), in addition to memory deficits (Van der Werf, Scheltens, et al., 2003), whereas hippocampal lesions have been shown to result in highly selective memory deficits (Eichenbaum & Cohen, 2001). These findings appear to suggest that thalamic injury results in deficits in the executive aspects of episodic memory (i.e., the selection of to-be-encoded information and retrieval strategies). However, it remains unclear whether the thalamus proper directly subserves some of these mnemonic processes or whether the observed deficits arise secondarily from a disconnection of the medial temporal lobe from the prefrontal cortex following diencephalic injury, a theory that was put forth by Warrington and Weiskrantz (1982).

The current study aims to quantify the relative contributions of magnetic resonance imaging (MRI) volumetric measures of the hippocampus and whole thalamus to episodic memory functioning in patients with temporal lobe epilepsy (TLE). Patients with TLE present a suitable population for such an investigation because episodic memory impairments are prevalent in these patients when compared to healthy controls (Leritz, Grande, & Bauer, 2006) and when compared with patients with extra-temporal or generalized seizures (Bergin, Thompson, Baxendale, Fish, & Shorvon, 2000). Moreover, both the hippocampus and thalamus are involved in the propagation of seizure activity and exhibit pathologic changes in TLE. Electrophysiological studies in animal models of TLE and in human clinical TLE patients have implicated the hippocampus and other temporal limbic structures in seizure initiation (Spencer & Spencer, 1996), whereas the thalamus is believed to play a role in seizure modulation (Bertram, Mangan, Zhang, Scott, & Williamson, 2001; Guye et al., 2006). MRI and positron emission tomography (PET) studies have also revealed structural and metabolic abnormalities of the temporal lobe (Hermann, Seidenberg, & Bell, 2002; Rubin et al., 1995), hippocampus (Henry, Mazziotta, & Engel, 1993; Seidenberg et al., 2005), and thalamus (Juhasz et al., 1999; Keller, Wilke, Wieshmann, Sluming, & Roberts, 2004) in TLE patients. Concerning the latter, a recent study concluded that thalamic atrophy in TLE patients was most prominent in those thalamic subnuclei having strong connections with the hippocampus, such as the anterior portion of the thalamus (Bonilha, Rorden, Castellano, Cendes, & Li, 2005).

Whereas several TLE studies have demonstrated relationships between structural volumetric measures of hippocampal integrity and performance on measures of episodic memory (Griffith et al., 2003), far fewer have examined atrophy of extra-hippocampal structures in relation to memory functioning in TLE patients (e.g., Bonilha et al., 2007; Martin et al., 1999). Regarding thalamic-memory relationships, Seidenberg et al. (2008) reported that smaller whole thalamic volume was associated with poorer performance in episodic memory, as well as in several other cognitive domains (e.g., confrontation naming, IQ, executive functioning), in TLE patients. Additionally, Rausch, Henry, Ary, Engel, and Mazziotta (1994) reported that asymmetric resting PET glucose metabolism of the whole thalamus and lateral temporal lobe, but not mesial temporal lobe, independently predicted verbal memory functioning in TLE patients. Also of relevance, Kopelman et al. (2001) found significant correlations of hippocampal and thalamic volume with measures of recall and recognition in memory disordered patients with diencephalon, temporal lobe, or frontal lobe injury. Although noteworthy, these studies do not indicate whether measures of hippocampal and thalamic integrity make independent quantitative contributions to episodic memory functioning in TLE patients. They also provide limited information regarding the qualitative nature of the contributions of the hippocampus and thalamus to episodic memory.

Our study investigated these issues by directly examining the relative contributions of volumetric measures of the hippocampus and whole thalamus to verbal episodic memory in TLE patients. To this end, we employed statistical models in which hippocampal and whole thalamic MRI volume served as potential predictors of performance on one measure of delayed prose verbal memory and two measures of delayed rote verbal memory. Measures of delayed prose and rote verbal memory were specifically chosen because prose verbal memory ostensibly relies on the encoding and storage of relational material in long-term episodic memory, in addition to the executive aspects of episodic memory (e.g., the organization of propositionally- or logically-related material at encoding and the retrieval of this material at recall), whereas rote verbal memory (e.g., paired associates) predominately relies on encoding and storage processes in long-term episodic memory (Lillywhite et al., 2007; Rausch et al., 1994; Saling et al., 1993). Based on contemporary neurobiological theories of episodic memory (Aggleton & Brown, 1999; Van der Werf, Jolles, et al., 2003), we hypothesized that hippocampal and whole thalamic volume would independently predict delayed prose verbal memory functioning in the TLE sample, whereas hippocampal, but not thalamic, volume would predict delayed rote verbal memory functioning.

2. Method

2.1. Participants

Data for the current study were derived from 18 participants with TLE who participated from July 1988 to November 1999 in a larger study of the neuro-developmental impact of epilepsy (Hermann et al., 2002, 2003) conducted at the University of Wisconsin Hospital Department of Neurology (UW). Initial selection criteria included: (1) chronological age from 14 to 60 years, (2) complex partial seizures of *definite* or *probable* temporal lobe origin (see details below), (3) absence of MRI abnormalities other than atrophy on clinical reading, and (4) no other neurological disorder. A board-certified neurologist with special expertise in epileptology reviewed patients' medical records. This review, blinded to all MRI volumetric and neuropsychological data, included seizure semiology, previous EEGs, clinical neuroimaging reports, and all available medical records. On the basis of this review, each patient was classified as having seizures of *definite*, *probable*, or *possible* temporal lobe origin. *Definite* temporal lobe epilepsy was defined by continuous video/EEG monitoring of spontaneous seizures demonstrating temporal lobe seizure onset; *probable* temporal lobe epilepsy was determined by review of clinical semiology with features reported to reliably identify complex partial seizures of temporal lobe origin versus onset in other regions (e.g., the frontal