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RESEARCH****Research Report****Spatial and non-spatial contextual working memory in patients with diencephalic or hippocampal dysfunction**

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## ABSTRACT

Damage to the medial temporal lobe (MTL) and diencephalon results in impaired long-term memory, which relies on the binding of multiple, mostly contextual, features. Recent neuroimaging and patient studies have suggested that impairments may also be present in working memory after MTL or diencephalic damage. To examine whether patients with damage to these brain structures have impairments in working memory for contextual information, 15 patients with damage to the diencephalon due to Korsakoff's syndrome and 12 patients with unilateral MTL lesions, and 30 age-matched healthy controls performed a delayed match-to-sample (DMS) task in which they had to maintain either object-location associations, color-number associations, single colors or single locations. Compared to their age-matched controls, performance on the DMS task was generally impaired in both patient groups, whereas no deficits were found on standard neuropsychological span tasks that do not rely on maintenance aspects of working memory. The patients did not show disproportionate impairments on the binding condition. In all, the results clearly show that impairments in working memory maintenance are present in patients with MTL or diencephalic lesions. However, we did not find a disproportionate inability in maintaining spatial or non-spatial associations within working memory as previously demonstrated in long-term memory.

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**1. Introduction**

It has been well established that the diencephalon and the medial temporal lobe (MTL) are important for human declara-

tive memory, specifically for the formation of new memories (Aggleton and Brown, 1999; Aggleton and Saunders, 1997; Squire, 1982). Furthermore, it has been shown extensively that these structures play a crucial role in the encoding of associations (e.g.,

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Mayes et al., 1985; Chalfonte and Johnson, 1996; Burgess et al., 2005). Earlier studies have suggested that memory for single items, such as a color or a location, does not depend on structures within the MTL. However, associative or contextual memory, in which multiple features have to be bound together, has been proven to be dependent on the MTL (Eichenbaum et al., 1994; Henke et al., 1997, 1999; Brasted et al., 2003; for a review see Kessels et al., 2001). With respect to the types of binding within memory, a distinction can be made between intrinsic feature binding (e.g., non-spatial binding, such as object-to-color) and extrinsic feature binding (e.g., spatial binding, such as object-to-location).

Neuropsychological studies have identified a number of specific cognitive impairments associated with lesions of the diencephalon and medial temporal lobe, mainly focusing on spatial contextual memory. For instance, spatial probability learning (Oscar-Berman et al., 1976), spatial reversal learning (Oscar-Berman and Zola-Morgan, 1980), maze learning (Nissen et al., 1989), spatial delayed response performance (Oscar-Berman et al., 1992) and priming of spatial configurations (Verfaellie et al., 1992) have been found to be impaired in these patient groups. More recently, Van Asselen and colleagues (2005) have shown that patients with damage to the diencephalon due to Korsakoff's syndrome (KS) do not benefit from contextual cueing on spatial memory retention. Additionally, it has been suggested that these patients display a clear deficit in contextual long-term memory, in which spatial or temporal relations between stimuli are relevant (Mayes, 1988; Mayes et al., 1985). A long-term memory study carried out by Chalfonte and Johnson (1996) has shown that patients with diencephalic or MTL lesions were disproportionately impaired on those tasks in which an object had to be bound to its location.

The aforementioned studies have investigated contextual spatial memory in diencephalic and MTL patients using long-term memory paradigms. Short-term memory function, specifically working memory, is assumed to be unimpaired in these patient groups (Baddeley et al., 2002). However, most investigations on working memory function in amnesia have used single words, letters or digits as stimuli (e.g., Scoville and Milner, 1957; Cave and Squire, 1992; Aggleton et al., 2000; Spiers et al., 2001; Ryan and Cohen, 2004). Conversely, studies using working memory paradigms that rely on contextual processing have demonstrated impaired working memory performance in patients with MTL or diencephalic lesions. For instance, Van Asselen and colleagues (2005) found deficits in the maintenance of spatial information in working memory in patients with KS. Furthermore, short-term memory deficits for topographic information have been shown in patients with hippocampal lesions (Hartley et al., 2007). In a recent fMRI study, we have also found MTL involvement in a working memory paradigm in which associations had to be made between objects and their spatial locations (Piekema et al., 2006). These findings are in agreement with the notion that long-term and short-term memory interact and may not be fully independent memory systems, as demonstrated in patient studies (e.g., Olson et al., 2006) and in neuroimaging studies (e.g., Wagner, 1999; Davachi et al., 2001; Schon et al., 2004; for a review, see Ranganath and Blumenfeld, 2005).

In all, damage to both the MTL and the diencephalon result in profound deficits in episodic contextual memory. However,

contextual working memory has been scarcely studied in patients. Especially studies examining non-spatial contextual features, such as object-color binding, are lacking. Therefore, we set out to investigate whether previously observed findings in patients with diencephalic or MTL lesions concerning contextual long-term memory extend into the domain of short-term or working memory when contextual processing is required. We designed a delayed match-to-sample task (DMS) (Sternberg, 1966) in which participants had to maintain either spatial (item–location) or non-spatial (item–color) associations over a short period of time and that were compared to single-item condition (color only and location only). We compared patients with KS and patients with unilateral MTL lesions following a selective amygdalohippocampectomy with two healthy control groups.

KS is caused by chronic alcohol abuse together with malnutrition, which may result in a chronic thiamine deficiency causing damage in the diencephalon, notably the mammillary bodies and thalamus (Visser et al., 1999). KS is characterized by severe amnesia that has been linked to these diencephalic lesions (Caulo et al., 2005). Also, other cognitive impairments exist in KS that may be due to frontal lobe pathology that is also present in these patients, such as executive deficits (Joyce, 1994; Langlais and Savage, 1995; Mayes et al., 1988; Sziklas and Petrides, 1997). According to the general consensus, short-term memory is typically intact in Korsakoff's syndrome (Kopelman, 2002), but previous research has shown deficits in contextual short-term and working memory (Van Asselen et al., 2005). In contrast, patients with MTL following selective unilateral amygdalohippocampectomy as a treatment for epileptic seizures are generally only mildly impaired with respect to long-term memory function and do not show overt amnesia (Alpherts et al., 2006) or working memory deficits (Kessels et al., 2004). However, deficits in long-term spatial binding have been demonstrated (Kessels et al., 2004), but working memory binding has not been studied in these patients yet.

We hypothesized that overall performance on a delayed match-to-sample task with spatial and non-spatial single items and associations would be significantly impaired in both patient groups as compared to the performance of their age-matched control group. Due to the underlying diencephalic and frontal-lobe pathology in KS, we expected the overall performance of this group to be most impaired, with specific deficits in the binding conditions, in line with previous findings on long-term memory binding (Chalfonte and Johnson, 1996; Postma et al., 2006). For the MTL patients, we expected overall performance to be worse than their age-matched healthy controls, with a specific deficit in spatial working binding (cf. Kessels et al., 2004). However, in the absence of frontal-lobe damage, the MTL group is expected to be impaired to a lesser extent than the KS patients. With this study, we aim to gain more knowledge about working memory processes and binding of multiple features in patients with diencephalic or MTL lesions.

## 2. Results

Fig. 1A shows the results for the MTL and matched controls and Fig. 1B shows the results for the KS and matched controls. Participants in all groups performed significantly above chance

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