

Facilitation of memory by contextual cues in patients with diencephalic or medial temporal lobe dysfunction

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ABSTRACT

Item-context binding is crucial for successful episodic memory formation, and binding deficits have been suggested to underlie episodic-memory deficits. Here, our research investigated the facilitation of cued recall and recognition memory by contextual cues in 20 patients with Korsakoff's amnesia, 20 unilateral medial-temporal lobectomy (MTL) patients and 36 healthy controls. In a computerized task participants had to learn 40 nouns that were randomly combined with a photograph of an everyday scene. Korsakoff patients showed a general memory deficit in both the cued recall and the recognition condition. A less severe memory impairment was found in the patients with medial-temporal lobectomy. Contextual cues facilitated cued recall to an equal extent in unilateral temporal lobectomy patients and healthy controls. However, no facilitation was observed in Korsakoff patients, suggesting an impairment in item-context binding during cued recall tasks. In contrast to the presumed exclusive dependency of recognition memory on item information, all groups equally profited from the contextual cues in recognition tasks. Our findings show that unilateral lesions as with MTL result in normal binding of context and item information, while bilateral dysfunction of the hippocampal-diencephalic system results in impaired context and item binding.

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1. Introduction

Structures in the medial temporal lobe (MTL) and diencephalon are essential for episodic memory formation. Damage to these regions can result in episodic memory disorders, leaving semantic memory intact (Aggleton & Brown, 2006; Rosenbaum et al., 2008; Vargha-Khadem et al., 1997). One function of this circuitry has been suggested to be the linking of various components of an episode, such as context and target information, into an integrated unit of information (Eldridge, Knowlton, Furmanski, Bookheimer, & Engel, 2000; Jakson & Schacter, 2004).

A computational model suggested by Talamini, Meeter, Elvevåg, Murre, and Goldberg (2005) represents episodic memory formation as a two-stage process. Firstly, an integrated representation of the

co-occurrence of the item and context is formed in the entorhinal cortex, based on information provided by two interrelated streams of input. One stream covers object-related information and comprises the anterior and lateral entorhinal cortex and the perirhinal cortex, while the other stream contains information about spatial relations and other contextual factors, and comprises the posterior parts of the entorhinal cortex and the parahippocampal cortex. Subsequently, representations are stored through an ensemble code in the hippocampus. Although it was not part of the original model, this second function would probably rely on diencephalic integrity, as the diencephalon and hippocampus have been suggested to function as one integrated system (Aggleton & Brown, 2006; Brown & Aggleton, 2001).

A study in patients with first-episode schizophrenia offered support for this model. As predicted in simulations, these patients performed normally on a cued recall task when no contextual support was given but recalled less than healthy controls when contextual cues were added (Talamini, De Haan, Nieman, Linszen, & Meeter, 2010). The study also contained a challenge to the model, however. Contrary to predictions, contextual cues facilitate

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Table 1

Characteristics for the medial temporal lobectomy (MTL) patient group, the younger control group, the Korsakoff patient group (KS), and the older control group.

	MTL patients (n = 20)	Younger controls (n = 16)	KS patients (n = 20)	Older controls (n = 20)
Age (years) (mean (SD))	37.3 (14.9)	38.1 (12.5)	56.5 (6.5)	55.7 (6)
Sex (m:f)	13:7	10:6	18:2	18:2
Educational level (mode (range))	5 (4–7)	5 (5–7)	5 (2–6)	5 (3–6)
IQ	92.4 (12.3) (n = 17)	101.8 (4.8)	97.9 (10.2)	104.5 (7.9)
	WAIS-III (n = 3)			

recognition memory in neither first-episodic schizophrenia patients nor healthy controls. Talamini et al. (2010) explained this by suggesting that recognition memory depends only on item information.

The Source of Activation (SAC) model, as proposed by Reder, Park, and Kieffaber (2009), analyzes the role of context in recognition in more detail. This model conceptualizes recognition of an episodic memory as summed activation in a network of nodes. This network contains several types of nodes: general context nodes are activated by general contextual characteristics of the experiment, specific context nodes are activated by unique contextual characteristics of a stimulus, concept nodes are activated by conceptual information of an item, and episodic nodes are activated by the sum of activation. For example, when someone remembers a car accident he experienced in the past, the conceptual node could comprise the fact that he had an accident. An example of information from the general context could be the presence of his wife during the accident. The specific contextual information could be the fear of the accident, the weather and the song playing on the radio. According to this model, recognition can result both from activation of a concept node only (I have had an accident) and from activation of the episodic node (remembering the accident in its context). The first process is equivalent to familiarity, the second to recollection. Contextual information can aid recognition only through recollection, as the context nodes play no role in familiarity.

In this study, we further examined the importance of binding in episodic memory. We assumed that item-context binding is an important aspect of episodic memory and that impairments in this binding are a factor in episodic memory deficits. To study this, Korsakoff patients and unilateral temporal lobectomy patients were compared with healthy controls. Patients with Korsakoff's syndrome have an amnesic disorder with severely impaired episodic memory due to lesions in the mammillary bodies and thalamus that receive their input from the hippocampus via the fornix (Aggleton & Brown, 2006; Kopelman, Thomson, Guerrini, & Marshall, 2009). Temporal lobectomy patients are characterized by clear-cut damage in one hemisphere as a resulting from surgery to treat intractable epilepsy. Decreases in cognitive functioning are usually reported only after a temporal lobectomy in the left hemisphere, in the form of declines in verbal memory (Hamberger & Drake, 2006). Based on the results of Talamini et al. (2010) and findings discussed by Aggleton and Brown (2006), it was expected that none of the groups would profit from contextual cues in recognition but that healthy controls would profit from contextual cues in cued recall. Temporal lobectomy patients were also expected to profit from contextual cues in the recall condition, as the MTL memory system is assumed to be intact in one hemisphere. Damage to the other hemisphere may result in a lower memory capacity, but was not expected to change qualitative aspects of MTL function. However, patients with Korsakoff's syndrome can be expected to have a problem with episodic binding, as the diencephalic part of the hippocampal-diencephalic memory circuitry is assumed to be bilaterally affected in these patients.

2. Method

2.1. Participants

Twenty outpatient medial temporal lobectomy patients (nine with a left-hemisphere temporal lobectomy and eleven with a right-hemisphere temporal lobectomy) from the Epilepsy Centre Kempenhaeghe at Heeze (The Netherlands) were selected for this study. Inclusion criteria were (1) had undergone a temporal lobectomy, (2) aged between 18 and 65 years, (3) nonimpaired intellectual abilities represented by an education-matching total, verbal and performance IQ on the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) of at least 70 (Wechsler, 1997), or by the NLV (Schmand, Lindeboom, & Van Harskamp, 1992) the Dutch version of the National Adult Reading Test (Nelson & Willison, 1991) (4) having the ability to memorize verbal information represented by a verbal memory index on the Wechsler Memory Scale-Revised (WMS-R) of at least 60 (Wechsler, 1987), and (5) sufficient command of the Dutch language based on clinical judgement. All patients underwent a standard medial temporal lobectomy. Surgically, the neo-cortex is removed 4–6 cm from the temporal pole, including the mesial temporal structures (i.e., hippocampus, parahippocampal gyrus and the amygdale).

In addition, twenty inpatient Korsakoff patients of the Korsakoff Clinic of the Vincent van Gogh Institute for Psychiatry in Venray (The Netherlands) were recruited for this study. Inclusion criteria for these patients were (1) meeting the criteria of the diagnosis Alcohol-Induced Persisting Amnesic Disorders from the DSM-IV (American Psychiatric Association, 1994) and (2) impaired performance on the Rivermead Behavioural Memory Test (RBMT) (Van Balen & Groot Zwaafink, 1987) and/or the Dutch version of the California Verbal Learning Test (VLGT) (Mulder, Dekker, & Dekker, 1996). All patients were in the chronic, amnesic stage of the syndrome; none of the patients was in the confusional Wernicke phase at the moment of testing. All patients were diagnosed by experienced neuropsychologists and psychiatrists on the basis of clinical, psychiatric and neuropsychological examinations (including signs such as confabulation behavior and anterograde amnesia). All patients were alcohol-abstinent since their admittance to the clinic (>2 months before testing). None of the patients fulfilled the clinical criteria for alcohol dementia (Oslin et al., 1998). Neuroradiological examination (CT or MRI) showed signs of brain atrophy and non-specific white-matter lesions in most patients, which are often found in KS but not a necessary criterion for the diagnosis (Kopelman, 2002).

Furthermore, 36 healthy controls were recruited and assigned to either an older control group, which was matched in terms of age, gender and educational level with the Korsakoff patient group, or the younger control group, which was matched in terms of age, gender and educational level with the temporal lobectomy patient group.

Table 1 provides an overview of the characteristics of the four groups. In three patients with a temporal lobectomy intelligence was assessed with the Wechsler Adult Intelligence Scale-III, because of an invalid measure of the NLV. Educational level was categorized according to the Verhage system (Duits & Kessels, 2006). The temporal lobectomy patients were matched with their healthy controls in terms of age, $t(34) = -.177, p = .860$, sex, Mann-Whitney $U = 156, Z = -.153, p = .912$, and educational level, Mann-Whitney $U = 114, Z = -1.567, p = .149$. Similarly, Korsakoff patients did not differ from their control group in terms of age, $t(38) = .401, p = .691$, sex, Mann-Whitney $U = 189.0, Z = -.053, p = .957$, or educational level, Mann-Whitney $U = 152.0, Z = -1.405, p = .160$.

2.2. Procedure

The paradigm was adjusted from Talamini et al. (2010). All participants had to study 40 concrete nouns of five to ten characters, which were presented in a small gray rectangle in the centre of a computer screen (6.5×2.1 visual degrees). The 40 nouns were randomly selected from a set of 80 for each participant (the other 40 were used as lures in the recognition phase – see below). On the background of each word a unique color photograph of an everyday scene or place was presented. Which photograph was combined with which word was randomly determined for each participant in the learning phase. All words were presented twice in the same order, each for four seconds, with the same picture being used on each occasion for the temporal lobectomy patients and their matched younger controls. To avoid floor effects, the words were presented three times (also for four seconds) to the patients



Fig. 1. Example of the employed paradigm in this study. Participants had to learn forty nouns, which were presented on a unique colour photograph of an everyday scene or place. During the subsequent, two memory tasks (not depicted), the photograph on the background was the same for one half of the words, while for the other half it was a random other photograph. During the a cued recall phase the beginning of the learned words are presented and the participants had to complete them. During the recognition phase the recognition of the learned words was measured.

with Korsakoff's syndrome and their matched older controls. In Fig. 1, an example of the employed paradigm in this study is shown.

The experimenter started the memory task on the computer. Instructions appeared on the computer screen, and were read aloud by the experimenter. Participants were instructed to study words, while the pictures were described as just a background to provoke incidental learning. They were thus contextual in that they were not important for the task. After two examples of stimuli, the experimenter started the *learning phase*. Between each word a gray screen with a fixation cross was presented for 500 ms. All words were presented once, after which they were presented again in the same ordering with the same photograph in the background.

Immediately after the learning phase, a *cued recall* phase followed. During this phase a cue consisting of the first two characters of studied words were presented one by one on the same gray box as during learning, and the subject had to complete the word. If the participant had no idea how to complete the word he or she was allowed to type 'XX'. A photograph was again presented in the background of each cue. For one half of the words, the photograph was the same as during the learning phase, while for the other half it was a random other photograph (photographs were permuted, so that each photograph was presented only once during cued recall). By pressing the ENTER button the next cue appeared until all cued had shown. The order of the cues was randomized, with the provision that words presented in the first half of the learning phase were also tested in the first half of the cued recall phase.

The task ended with a *recognition* phase. In this phase eighty words were sequentially presented gray screen with, again, a photograph: forty of these were from the learning phase and forty were lures. For each word the subject had to indicate whether the word was presented in the learning phase or not. When subjects recognized the word as coming from the learning phase they had to press the Z-button on the keyboard and in case they thought that the word was new, they had to press the N-button (this instruction was shown below each word during the recognition phase). Studied words were presented with the same background as in the cued recall task (although not always the same as the original pairings). Therefore, some of the words had the same background picture as in the learning phase and some had a different picture. For lures, it was a random photograph from the study phase.

Each photograph was thus presented twice during the recognition phase: once with a studied word, and once with a lure. The total task lasted between thirty and forty minutes.

2.3. Analyses

Two separate Repeated Measures ANOVAs were performed, one for the temporal lobectomy patients vs. younger controls and one for the Korsakoff patient group vs. older controls for as well the cued recall condition and recognition condition. Memory performance was the dependent variable, Context (same context vs. different context, depending on whether the photographs were the same during study and test, or not) a within-subject factor, and Group (patients vs. controls) a between-subject factor. Alpha was set at .05 for all analyses.

3. Results

The upper panels of Fig. 2 shows the results of the Korsakoff patients and the older controls, while the results of the temporal lobectomy patients and the younger controls are presented in the lower panels of Fig. 2. We will first discuss results from the first two groups, and then the last two groups.

Korsakoff patients performed significantly worse on cued recall than their age-matched controls, $F(1,38) = 37.2$, $p < .001$. Moreover, cued recall was better in the same context condition than in the different context condition, $F(1,38) = 25.5$, $p < .001$, suggesting that context aided recall. Importantly, there was a significant interaction between group and context condition, $F(1,38) = 10.1$, $p = .003$. Paired samples *t*-tests revealed cued recall of the Korsakoff patients was no different in the same context than in the different context condition, $t(19) = 1.4$, $p = .175$, whereas it was better in the same context condition compared to the different context condition for the older controls, $t(19) = 5.5$, $p < .001$.

In recognition, healthy controls again performed better than the Korsakoff patients, $F(1,38) = 458.2$, $p < .001$. Moreover, recognition was better in the same context condition than the different context condition, $F(1,38) = 19.4$, $p < .001$. In contrast to cued recall, there was no group $\times$ context interaction effect, $F(1,38) = 1.12$, $p = .297$. Controls and patients thus profited to the same extent from the contextual cues in the recognition task. Paired *t*-tests revealed that this same-different context difference also holds within the patient and control groups (Korsakoff's syndrome $t(19) = 2.428$; $p = .025$; Controls $t(19) = 3.759$; $p = .001$).

As was the case for patients with Korsakoff's syndrome, cued recall was worse for the temporal lobectomy patients than for their matched controls, $F(1,34) = 9.499$, $p = .004$. Moreover, cued recall was better in the same context condition than in the different context condition, $F(1,34) = 15.364$, $p < .001$, again as before. However, there was no group $\times$ context interaction effect, $F(1,34) = .659$, $p = .422$, suggesting that temporal lobectomy patients profited from the contextual cues to the same degree as controls.¹ Paired *t*-tests revealed that this same-different context difference also holds within the patient and control groups (temporal lobectomy patients $t(19) = 3.272$, $p = .004$; Controls $t(19) = 2.366$; $p = .032$).

Recognition was better in the same context condition than in the different context condition, $F(1,34) = 39.299$, $p < .001$. The temporal lobectomy patients did not perform worse than their controls on recognition, $F(1,34) = .100$, $p = .754$, and there was no significant group $\times$ context interaction effect, $F(1,34) = .529$; $p = .472$. Patients thus profited from the contextual cues to the same degree as controls did in the recognition task. Paired *t*-tests revealed that this same-different context difference also holds within the patient and

¹ The patient sample consisted of 9 patients with left temporal lobectomy and 11 with right temporal lobectomy. As is typically the case, patients with left temporal lobectomy performed worse (e.g., average recall performance of .25) than patients with right temporal lobectomy (av. recall of .33). Since there was no interaction between this variable and the effect of context, it will not be further reported on.

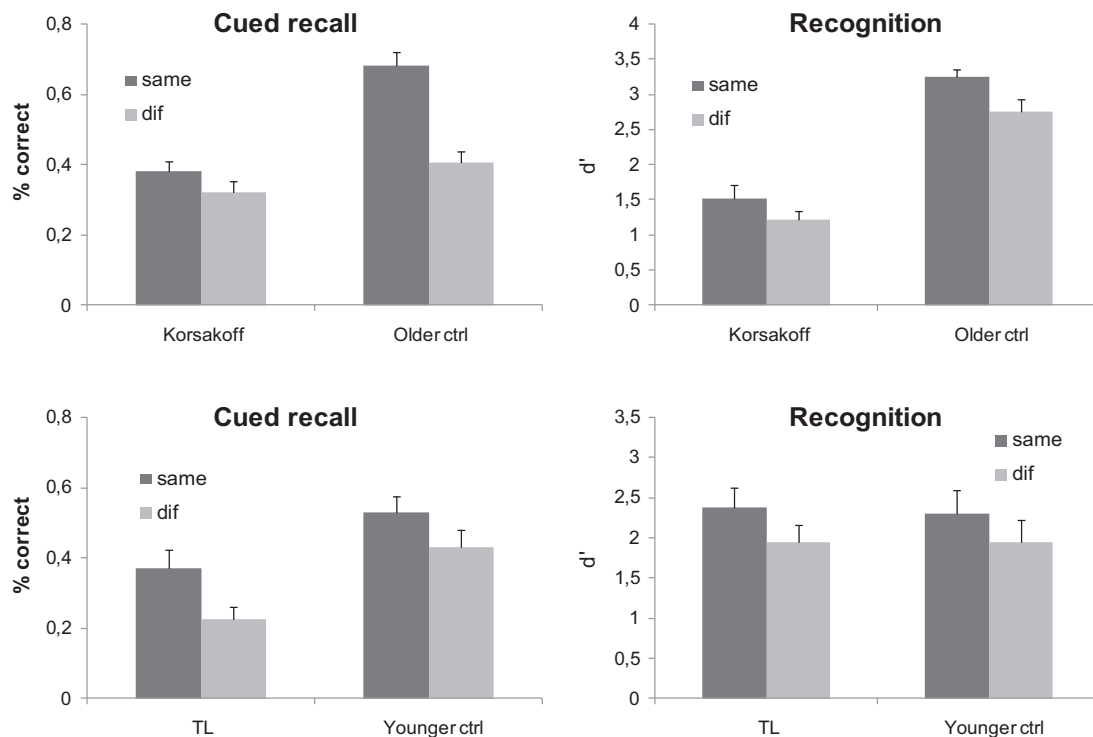


Fig. 2. Cued recall and recognition performance (the latter measured as d') for the Korsakoff Group and their age-matched controls (upper panels) and for the Temporal Lobectomy Group and their age-matched controls (lower panels). The error bars reflect standard errors of the mean.

control groups (temporal lobectomy patients $t(19) = 4.940$, $p < .001$; Controls $t(15) = 4.062$, $p = .001$).

4. Discussion

This study examined the importance of binding in episodic memory. Based on a previous study in first-episode schizophrenia patients and healthy controls, we expected memory facilitation by contextual cues to only take place in cued recall because of the exclusive dependence of recognition memory on item information (Talamini et al., 2010). To investigate this, facilitation of cued recall and recognition by contextual cues was compared in Korsakoff patients, patients with a well defined temporal lobectomy, and healthy controls.

The expected general memory deficit in Korsakoff patients and, although less severe, in temporal lobectomy patients was found. Facilitation of cued recall by context was absent in Korsakoff patients but did take place in patients with a unilateral temporal lobectomy. This suggests that the integrity of at least one MTL is necessary for context to aid in recall – possibly because the MTL underlies binding of item and context information (e.g., Talamini et al., 2010). This assumption is in accordance with earlier studies showing various types of context memory impairment in patients with bilateral temporal lobe pathology as well as Korsakoff (Kopelman, Stanhope, & Kingsley, 1997; Shqeirat & Mayes, 1991).

In contrast to the presumed exclusive dependence of recognition memory on item information, contextual information facilitated recognition in Korsakoff patients as well as in temporal lobectomy patients and healthy controls. All groups equally profited from the contextual cues in recognition tasks. Despite the overall lower memory performance of Korsakoff patients and temporal lobe patients, both groups thus seem to have at least some ability to integrate contextual information. In temporal lobectomy patients less severe memory impairments were reported. The fact that for these patients the contralesional hemisphere is intact might mean that their episodic memory works in a qualitatively similar

way as that of controls. This is supported by our results in that only a quantitative difference was found in the form of lower overall cued recall performance for patients.

Both controls and patients in this study did profit from contextual cues during the recognition task, which is in contrast to the results of the study of Talamini et al. (2010). The SAC model would suggest that participants in the Talamini et al. study relied solely on familiarity (seen as insensitive to context) while our participants additionally relied on recollection (seen as context-sensitive). Indeed, Meeter et al. (unpublished data) recently found that if instructions emphasized recollection, recognition performance became sensitive to context change. This was accompanied by a large increase in reaction times. For all groups reported on here, reaction times in the recognition task were around 1700 ms for old items and 2400 ms for lures, while these values were around 1400 ms and 1650 ms for the groups in Talamini et al. (2010). These values are in the range that in the experiments of Meeter et al. (unpublished data) were found for responses based on recollection or familiarity, respectively. It is not immediately clear why participants in the Talamini et al. (2010) study would base their recognition responses on familiarity while participants in our study did so on recollection. Instructions were the same in both studies. One difference between these studies concerns the mean age of the participants. For example, Talamini et al.'s control group has a mean age of while in this study the youngest control group has a mean age of 38 years. An age-related difference in the ability to use source memory has been proposed due to the development of the frontal lobe into late adolescence and early twenties (Cycowicz, Friedman, Snodgrass, & Duff 2001). The control group of Talamini et al. might not have profited from contextual cues because of a less developed ability to use contextual information during retrieval of memories.

In our opinion these results cannot be explained in terms of utilization because unitization of item and context seems to take place only in intentional unitizing conditions (Diana, Yonelinas, & Ranganath, 2008). In this study participants received an instruction

that is as far away from intentional unitizing as possible, namely to only study the word. Therefore, our results are proposed to reflect a recollection process instead of a familiarity process resulting from a unitization process.

Moreover, the large context effect in older controls during cued recall is assumed not to explain the absence of a context effect in Korsakoff patients. Given that context in other papers has been found to aid older adults less than younger adults, we surmise that the cause is more likely to be the longer exposure of the older adults and Korsakoff patients to the words and their background photograph (3 instead of 2 study trials) than a true difference between the populations (Kessels, Hobbel, & Postma, 2007; Spaniol & Grady, 2012).

A critical note for this study concerns the difference in amount of learning trials: the temporal lobectomy patients and their controls saw all the words two times, while the Korsakoff patients and their controls saw all the words three times during the learning phase. It has been proposed that repetition of material results in an enhancement of recollection and familiarity in healthy controls but in the case of amnesia only in an enhancement of familiarity (Verfaellie, Rajaram, Fossum, & William, 2008). It is thus possible that Korsakoff patients relied more strongly on familiarity than other groups. However, this would explain little in our data since the context effects in recognition were as strong in these patients as in their controls.

Another restriction of this study is the possibility that performances in the recognition task might be enhanced by performances in the earlier cued recall task. Such a testing effect can be expected when lures are so similar to the studied items that detection of lures cannot be based on familiarity and recollection is required (Chan & McDermott, 2007). As mentioned before, recollection seems to play a role in recognition in this study. Therefore, a testing effect might have occurred.

A further limitation is that while we included Korsakoff and MTL patients to study the MTL–diencephalic memory circuitry, fundamental differences exist between these two patient groups. That is, in patients with Korsakoff's syndrome, brain damage is typically not limited to the diencephalon but functional and structural changes have also been reported in the MTL itself, as well as the neocortex (Reed et al., 2003; Visser et al., 1999), which may also result in nonmemory deficits (e.g., in attention or executive function). However, we believe that our findings can be explained by the profound amnesia due to the bilateral diencephalic lesions rather than other cognitive deficits that may be present in these patients. With respect to the MTL patients, although (or because of that) they have had a unilateral temporal lobectomy, none of these patients could be classified as amnesic in the clinical sense. Furthermore, epilepsy patients with foci in the left temporal lobe have an increased risk for verbal memory impairments, while epileptogenic abnormalities in the right temporal lobe may lead to non-verbal memory impairments (Hendriks et al., 2004). The task used in this study cannot be classified as either verbal or non-verbal, which may have affected the severity of the memory deficits. Moreover, also in this patient group, we cannot rule out that structural or functional changes may have taken place in the unaffected hemisphere presurgically due to the history of epileptic seizures in these patients. Although in both groups the clinical diagnosis was supported by neuroimaging findings – we only had access to clinical neuroimaging reports – making it not impossible to relate structural brain lesions to task performance in more detail.

This study provides further insights in binding in episodic memory. Specifically, it seems that unilateral lesions in the MTL results in normal binding of context and item information, while dysfunction in the hippocampal–diencephalic system bilaterally (as in Korsakoff's syndrome or schizophrenia, see Talamini et al., 2010) results in impaired context and item binding. Our findings

also support the idea of a threshold value in the SAC model (Reder et al., 2009).

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