Brain Structure and Function (2019) 224:1599–1607
https://doi.org/10.1007/s00429-019-01857-1

ORIGINAL ARTICLE

When does conscious memory become dependent on the hippocampus? The role of memory load and the differential relevance of left hippocampal integrity for short- and long-term aspects of verbal memory performance

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Received: 13 July 2018 / Accepted: 6 March 2019 / Published online: 13 March 2019

Abstract

Supraspan list learning tests are sensitive measures used to assess temporal lobe dysfunction. Most frequently employed is the Rey Auditory Verbal Learning and Memory Test (RAVLT). The test's structure is determined by a short- and long-term memory component. During the first of five learning trials, the short-term memory component is the highest and steadily decreases over the following trials, while the long-term memory component concurrently increases and reaches its maximum at the delayed recall after a retention interval of 30 min. The study aimed to test the hypothesis that the functional relevance of left hippocampal integrity for conscious memory rises along with the increasing degree of the long-term memory component. Moreover, we investigated whether classical measures of short-term and working memory are also dependent on the hippocampus. The analysis was based on 37 adult patients who had undergone surgery for left mesial temporal lobe epilepsy. Neuronal cell densities of the resected left hippocampus were correlated with the presurgical memory performance across trials of the VLMT (the German RAVLT) and with digit span and working memory capacity (WMS-R). Whereas digit span and working memory capacity were not related to hippocampal cell counts, there was a significant correlation between left hippocampal integrity and VLMT memory performance, already regarding the first supraspan learning trial. Correlations steadily increased during the learning course. The highest correlation was seen regarding the delayed free recall. The results indicate an increasing correspondence between the integrity of the left hippocampus and verbal memory with an increasing long-term memory component. Immediate recall of verbal material became already dependent on left hippocampal integrity when the verbal memory load exceeded the memory span (supraspan list learning), while classical span measures that assess verbal short-term and working memory were not affected by left hippocampal pathology.

Keywords Hippocampus · Neuronal cell counts · Cell densities · Cornu ammonis · Dentate gyrus · Memory · Declarative memory · Working memory · Learning

Introduction

In memory research, there is a long-standing differentiation between short- and long-term memory (Baddeley and Patterson 1971). Short-term memory provides the maintenance of information for brief periods of time (seconds to minutes) with a limited capacity of usually about 7 ± 2 information units (Miller 1956). The maintained information can be processed and manipulated by the central executive of the working memory system (Baddeley 1992). The long-term storage of information in turn depends on long-term memory systems, for which a largely unlimited capacity is assumed

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(Squire 1987–1988). Neuropsychological lesion studies have demonstrated a double dissociation[1] for short- and declarative long-term memory systems. The former depends on the integrity of (dorsolateral) prefrontal as well as parietal brain regions (Markowitsch et al. 1999; Barbey et al. 2013; Müller and Knight 2006), whereas the latter is primarily reliant on the (medial) temporal lobes and diencephalic structures (Squire 1982). The hippocampus represents the gate from short- to long-term memory and thus is an essential bottleneck structure (Brand and Markowitsch 2003).

Despite the clear dissociation between short- and long-term memory according to neuropsychological lesion studies, more and more functional imaging and electrophysiological studies reveal and underscore an involvement of the hippocampus already in working memory paradigms (Ranganath and D'Esposito 2001; Winston et al. 2013; Axmacher et al. 2007). Whether the hippocampus is just involved or whether it is really essential for the performance in these fMRI paradigms is an open question which cannot be addressed by imaging and electrophysiological studies.

Thus, the current study was set up to investigate (1) whether the hippocampus is essential for classical short-term and working memory tasks and (2) when the hippocampus does become relevant within a supraspan list learning paradigm that reflects varying degrees of short- and long-term memory aspects.

Supraspan list learning tests are sensitive measures used to assess temporal lobe dysfunction. The most frequently employed and recommended evidence-based test is the Rey Auditory Verbal Learning and Memory Test (RAVLT) and its derivates (Vogt et al. 2017; Witt and Helmstaedter 2009; Djordjevic and Jones-Gotman 2011; Helmstaedter and Witt 2017). Based on structural equation models of behavioral memory data, the structure of the RAVLT can be described by two latent factors: a short- and a long-term memory component (Müller et al. 1997). According to this structural equation model, the relevance of these two latent factors varies during the course of the memory test: during the first of five consecutive learning trials, the short-term memory component is the highest and steadily decreases over the following learning trials, while the long-term memory component concurrently increases and reaches its maximum at the delayed recall after a retention interval of 30 min.

Following this structural model, we hypothesize that the relevance of the hippocampal integrity, as assessed by neuronal cell densities, will rise along with the increasing degree of the long-term memory component. Furthermore, based on the classical lesion literature, we predict that classical measures of short-term and working memory will not be affected by the hippocampal integrity.

Temporal lobe epilepsy surgery with en bloc hippocampal resections offers the unique possibility to relate the neuropathological status of the hippocampus to neuropsychological performance assessed prior to surgery. The most frequent etiology of temporal lobe epilepsy is hippocampal sclerosis which is characterized by significant neuronal cell loss and reactive gliosis (Blümcke et al. 2002). The degree of hippocampal cell loss varies among patients (Wyler et al. 1992). The severity of the hippocampal pathology has been shown to be associated with episodic long-term memory deficits, especially in regard to verbal memory and the structural integrity of the left hippocampus (Baxendale et al. 1998; Zentner et al. 1999; Sass et al. 1995; Witt et al. 2014). Since hippocampal sclerosis is often associated with pharmacoresistance, it is the most frequent reason for elective epilepsy surgery (Berg 2008).

Methods

Patients

The retrospective study was based on a sample of 37 patients with left mesial temporal lobe epilepsy (mTLE) who had undergone epilepsy surgery at the Neurosurgery Department of the University of Bonn Medical Center. Comprehensive presurgical diagnostics (Kral et al. 2002) revealed seizure onset in the left mesial temporal lobe in all patients and resection of the hippocampus was clinically indicated in every case. All procedures were conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of the University of Bonn Medical Center. Informed written consent was obtained from all patients.

Inclusion criteria comprised a chronological age of at least 18 years, available data on neuropathologically assessed hippocampal neuronal cell densities and presurgical verbal memory parameters. An exclusion criterion was evidence of an atypical dominance for language- or material-specific memory functions. If available, results from the intracarotid amobarbital test (Wada) or the language fMRI (Fernández et al. 2001) were considered. In the remaining cases, atypical hand dominance or a neuropsychological suppression pattern (i.e., intraindividual profile with significantly better verbal than non-verbal memory performance despite left mesial temporal lobe epilepsy) served as markers for atypical dominance regarding language- or material-specific memory functions (Isaacs et al. 2006; Loring et al. 1999; Strauss et al. 1990; Gleissner et al. 2002; Wood et al. 1999).

[1] The strongest proof in neuropsychological research is the so-called double dissociation, i.e., function A but not function B is disrupted by lesion C, while function B is affected by lesion D which in turn does not interfere with function A.

All patients showed a preference of the right hand as determined by the Edinburgh Handedness Inventory (EHI) (Oldfield 1971). One of them, however, showed a tendency to ambidexterity, but subsequent fMRI revealed a typical left hemispheric language dominance and therefore the patient remained in the final dataset.

Demographic and clinical data of the investigated sample are presented in Table 1.

Memory assessment

Prior to epilepsy surgery, all patients underwent neuropsychological assessment of memory functions.

Verbal learning and memory performance was assessed via the Verbaler Lern- und Merkfähigkeitstest (VLMT) (Helmstaedter et al. 2001). The VLMT represents a modified German version of the RAVLT (Rey 1964). At first, the VLMT requires learning and immediate recall of 15 unrelated words (list A) in 5 consecutive learning trials (trials 1–5). After this learning phase, a new list of 15 words (list B) is presented with a subsequent immediate recall (interference trial). Directly after this interference trial and without anew presentation, the patient is requested to freely recall list A (trial 6). After a retention interval of 30 min, an unannounced free recall of list A is requested (trial 7). In a final recognition trial the patient has to recognize the words of list A among 35 distractors. During the retention interval, all patients performed a non-verbal design learning test, the revised version of the Diagnosticum für Cerebralschädigung, DCS-R (Helmstaedter et al. 1991).

Analyses were based on the number of correctly recalled words in each trial of the VLMT (trials 1–7 and the interference trial).

An unsteady/irregular learning curve was defined as a drop of memory performance of at least one word in two consecutive learning trials.

It has been shown, that the VLMT is sensitive to left temporal lobe dysfunction, left mesiotemporal pathology and left-sided temporal lobe surgery (Gleissner et al. 2004; Zentner et al. 1999; Helmstaedter et al. 1996, 1997; Witt et al. 2014).

Digit span and verbal working memory capacity were assessed via the digits forward and backward subtest of the revised German version of the Wechsler Memory Scale—revised edition (WMS-R) (Härting et al. 2000).

In the digits forward task, a sequence of digits is read aloud by the neuropsychologist and the patient has to repeat them in the same order immediately after presentation. The assessment starts with three digits. If at least one of two sequences has been correctly reproduced, a new longer sequence of digits is presented. The number of digits increases until the patient fails to reproduce two sequences

Table 1 Presurgical demographic and clinical characteristics

	N = 37
Sex	
Female	18 (49%)
Male	19 (51%)
Age (years)	
M (SD)	39.5 (12.9)
Range	18–67
Onset of epilepsy (age in years)	
M (SD)	15.5 (14.4)
Range	0–58
Duration of epilepsy (years)	
M (SD)	24.1 (12.7)
Range	2–57
Seizure types	
Simple partial	14 (38%)
Complex partial	36 (97%)
Secondary generalized	27 (73%)
Seizure frequency[a] (seizures per month)	(*N* = 34)
M (SD)	9.6 (12.6)
Range	1–60
Neuronal cell densities	
CA1 (neurons/mm^2)	
M (SD)	100.0 (105.3)
Range	0–416
CA2 (neurons/mm^2)	
M (SD)	240.0 (95.4)
Range	0–424
CA3 (neurons/mm^2)	
M (SD)	134.9 (95.7)
Range	0–408
CA4 (neurons/mm^2)	
M (SD)	87.1 (79.5)
Range	0–252
DGint (neurons/mm^2)	
M (SD)	1516.8 (861.9)
Range	300–3420
DGext (neurons/mm^2)	
M (SD)	1665.9 (835.2)
Range	170–3300
Hippocampal integrity index (standard values)	
M (SD)	61.6 (17.1)
Range	37.5–108.2
Number of AEDs	
M (SD)	2.2 (0.7)
Range	1–3

M mean, *SD* standard deviation, *CA* cornu ammonis, *DG* dentate gyrus, *int* internus, *ext* externus, *AEDs* antiepileptic drugs

[a]Monthly seizure frequency includes all seizure types

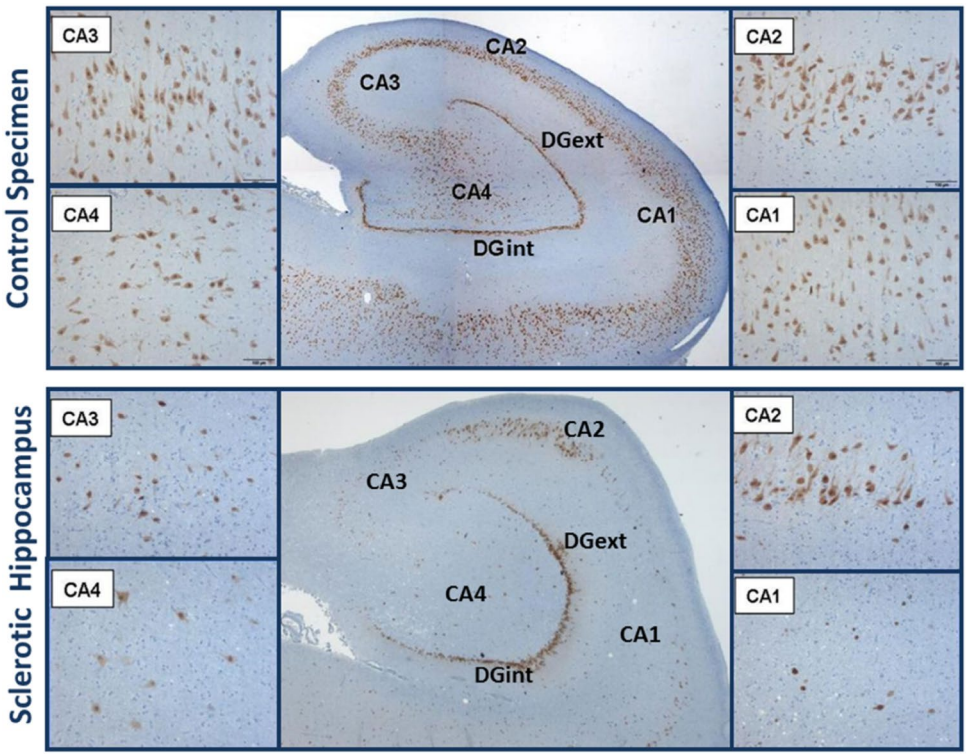

Fig. 1 Surgical specimen of a non-pathological human hippocampus (control specimen) as compared with a sclerotic hippocampus. The depiction shows the different anatomic subregions of the hippocampus including cornu ammonis (CA) sectors CA1–CA4 as well as the internal (DGint) and external limb (DGext) of the dentate gyrus

of the same length. The score of interest is the length of the longest correctly reproduced sequence.

The digits backward task is performed in the same manner. The decisive difference is that the patient is asked to repeat the digits in reversed order, beginning with the last presented digit (e.g. 4-2-9 should be 9-2-4). The digits backward task starts with two-digit sequences.

Quantification of the structural integrity of the hippocampus

The resected hippocampal specimens were microscopically examined at the Department of Neuropathology, University Hospital of Erlangen. En bloc specimens of the hippocampus were dissected into 5-mm-thick slices along the anterior–posterior axis. Solely tissue from the mid-hippocampal body was selected for this study to warrant unequivocal recognition of all subregions of the hippocampal pyramidal cell layer as well as the granule cell layer. The tissue was fixed overnight in 4% formalin and routinely processed into liquid paraffin. Four-micrometer sections were stained with hematoxylin and eosin (HE) for histopathological inspection. Pyramidal neurons of the cornu ammonis and granule cells of the dentate gyrus were specifically detected using immunohistochemistry for the neuronal core antigen NeuN (A60, Chemicon, Temecula, USA, dilution 1:1000, pre-treated with microwave) and an automated staining apparatus using the streptavidin–biotin method (Ventana; Strasbourg, France) and 3,3′-diaminobenzidine as chromogen as well as hematoxylin counterstaining. One representative hippocampal specimen was chosen from each subject for semi-quantitative neuronal cell counts (Fig. 1). Semi-quantitative measurements of neuronal cell numbers were performed with a microcomputer imaging system (ColorView II CCD camera, AnalySIS imaging software, Stuttgart, Germany) equipped to a BX51 microscope (Olympus, Japan). Only NeuN-immunoreactive neuronal cell bodies were tagged on the computer screen and counted separately within the Stratum pyramidale of the hippocampal sectors CA1, CA2, CA3 and CA4 in four randomly placed visual fields at 20× objective magnification. Examination of granule cells was separately performed for the external (DGext) and internal (DGint) limb at 40× objective magnification in ten randomly placed visual fields. The hippocampal subfield-specific quantification method was previously described to match data obtained from stereological cell counts and to be suitable for clinico-pathological correlations when using formalin-fixed and paraffin-embedded surgical human tissue specimens (Blümcke et al. 2007, 2009). Differentiation of human hippocampal subfields followed the first international classification system for hippocampal sclerosis (Blümcke et al. 2013).

To limit the number of relevant variables that will enter the statistical analysis and since a previous principal component analysis of segmental neuronal cell loss within the hippocampus had revealed a single factor structure (Witt

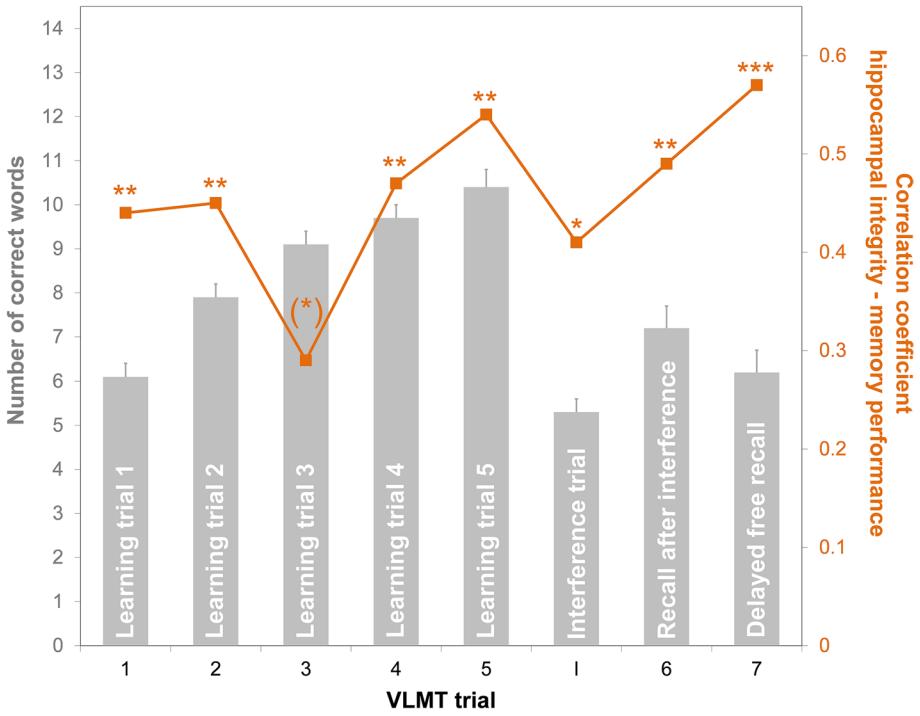

Fig. 2 Parallel illustration of the average memory performance in the different trials of the VLMT (gray bars) and the magnitude of the respective correlations with the structural integrity of the hippocampus (black squares). Error bars represent the standard error of the memory performance. Trials 1–5 represent the consecutive learning trials with immediate recall of list A. The interference trial (I) requests immediate recall of a new list (list B). In trial 6, list A needs to be retrieved again without anew presentation. Trial 7 assesses an unannounced delayed free recall after a retention interval of 30 min. (*)$p < 0.10$; *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$

et al. 2014), we determined the overall structural integrity of the hippocampus in the following way: neuronal cell counts (neurons/mm^2) were in the first instance transformed into standard scores (M 100, SD 10) according to control values obtained from autopsy brains from patients without a lifetime history of neurological diseases ($n = 8$; age: 49.0 ± 6.8 years) (Blümcke et al. 2007). This standardization procedure was necessary to integrate the data from the six different hippocampal subregions (CA1–CA4, DGext. DGint) because of the (natural) discrepancies of absolute cell densities across these subregions. It was not intended and not possible to provide an age correction. Finally, the mean standardized neuronal cell density across all hippocampal subfields was calculated. Thus, each of the subfields contributed equally to the total score without any weighting which is in concordance with the previous principal component analysis (Witt et al. 2014). The mean standardized neuronal cell density across all hippocampal subfields was termed "hippocampal integrity index" (HCI). Previous analyses have shown that the HCI reflected memory performance better than any of the hippocampal subfields alone (Witt et al. 2014).

The neuropathological investigator was blinded to the neuropsychological results.

Statistical analyses

Statistical analyses were performed using SPSS 24. Descriptive statistics comprised calculation of means as well as standard deviations and standard errors of the mean. The relationship between memory performance and hippocampal integrity was analyzed by Pearson correlations. According to Cohen (1998) coefficients $0.1 \le r < 0.3$ were rated as small, coefficients $0.3 \le r < 0.5$ as moderate, and coefficients $r \ge 0.5$ as large correlations. The level of significance was set to $\alpha = 0.05$.

Results

Descriptive data on segmental cell densities of the left hippocampus and the HCI are presented in Table 1.

Figure 2 illustrates both the mean memory performance within the different trials of the VLMT (gray bars), and the correlation of the memory performance with the left hippocampal integrity: A steady increase of the mean number of correctly recalled words from list A (gray bars) is apparent from learning trial 1 (6.1 words) to 5 (10.4 of a maximum of 15 words). After presentation of the interference list, a mean of 5.3 correct words from list B could be immediately recalled. After the interference trial, list A is requested again without anew presentation and the patients remembered 7.2 words on average. After a retention interval of 30 min, the memory performance with regard to the first word list (list A) dropped to a mean of 6.2 words (VLMT trial 7).

Figure 2 also depicts major findings of our analysis, i.e., the magnitude of correlation coefficients between memory performance and the different trials of the VLMT (orange squares). Analogous to the behavioral learning curve, correlation coefficients steadily increased during the learning course (trial 1: $r = 0.44$, $p < 0.01$—trial 5: $r = 0.54$,

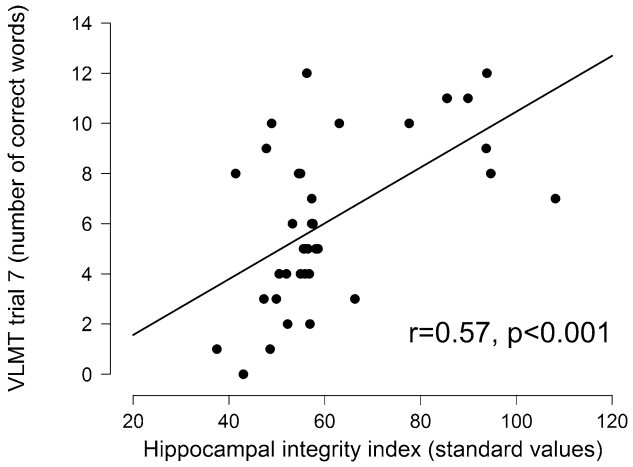

Fig. 3 Scatter plot showing the correlation between the hippocampal integrity index and the memory performance during the delayed free recall (VLMT trial 7)

Table 2 Correlation between the hippocampal integrity index and memory performance in supraspan and span measures ($N = 37$)

	Supraspan measures		Span measures	
	VLMT trial 1	VLMT interference trial	WMS-R forward digit span	WMS-R backward digit span
Hippocampal integrity index	0.44**	0.42*	−0.13	−0.02

VLMT Verbaler Lern- und Merkfähigkeitstest, *WMS-R* Wechsler Memory Scale—revised version

*$p < 0.05$; **$p < 0.01$

$p < 0.01$) except for the third trial (which is most likely due to unsteady/irregular learning curves in 19% of the patients which may have been caused by deficits in concentration and executive monitoring). The correlation coefficients for the interference trial (list B; $r = 0.42$, $p < 0.05$) and the first learning trial (list A; $r = 0.44$, $p < 0.01$) are comparable, both reflecting supraspan memory performance after the very first presentation of a word list. The correlation coefficient for the recall of list A after the interference trial was lower than for the final learning trial (trial 5: $r = 0.54$, $p < 0.01$). Finally, the largest correlation was seen regarding the delayed free recall after a retention interval of 30 min (trial 7: $r = 0.57$, $p < 0.001$; Fig. 3).

With regard to short-term and working memory, there were no significant correlations between the neuropathological status of the hippocampus and the WMS-R forward (average span: 5.7 ± 1.1 digits; $r = -0.13$, n.s.) as well as backward digit span (average span: 4.4 ± 1.2 digits; $r = -0.02$, n.s.). Table 2 compares the correlation coefficients between the hippocampal structural integrity and span measures versus the first immediate recall performance of the supraspan word lists of the VLMT (trial 1, list A, and interference trial, list B). There was no significant difference between the correlation coefficients for the first learning trial and the interference trial of the VLMT ($z = 0.13$, n.s.). The correlation coefficients for both VLMT parameters were significantly higher than the non-significant correlations regarding the span measures of the WMS-R ($z = 1.97$–2.71, $p = 0.025$–0.003).

Discussion

The present study was set up to clarify when conscious memory does become dependent on the hippocampus. To answer this neuroscientific question, we made use of the unique opportunity in the context of epilepsy surgery to relate the neuropathological status of resected hippocampal specimens to presurgical neuropsychological memory performance. The current analysis focused on the structural integrity of the left hippocampus and neuropsychological measures assessing verbal short- and long-term memory aspects.

The main findings indicate that (1) verbal short-term and working memory performance using classical span measures are not dependent on the structural integrity of the hippocampus, (2) the hippocampal integrity becomes already relevant when the information load which should be immediately recalled exceeds the working memory capacity, (3) the relevance of hippocampal integrity increases along with the increasing degree of the long-term memory involvement.

Classical neuropsychological lesion studies have provided evidence that structural lesions in the prefrontal or parietal cortex can compromise short-term and working memory (Markowitsch et al. 1999; Barbey et al. 2013; Müller and Knight 2006). Functional neuroimaging and electrophysiological studies confirmed networks comprising these structures (D'Esposito 2007; Wager and Smith 2003), but in addition also suggest a relevance of the hippocampus for working memory (Ranganath and D'Esposito 2001; Winston et al. 2013; Axmacher et al. 2007). However, functional imaging such as fMRI or PET—as an indirect measure of brain activation—as well as electrophysiology can only identify brain structures and networks that are involved in a task, but cannot discern whether a specific area is essential. In this regard, deactivating methods such as electrocorticostimulation or lesion-based studies such as the present study are required. Taken together, the left hippocampus may indeed be involved in classical verbal short-term and working memory tasks, but the present findings suggest that it has neither a necessary nor critical function. This is in line with studies reporting preserved working or short-term memory in patients with hippocampal sclerosis or severe bilateral

hippocampal volume loss (Cowey and Green 1996; Baddeley et al. 2011) and in amnestic patients due to bilateral hippocampal lesions (Jeneson et al. 2010; Eichenbaum 2013) and it is also supported by the observation that unilateral hippocampal or temporal resections are not associated with decline in short-term or working memory (Corsi 1972).

The role of the hippocampus in imaging and electrophysiological studies may be explained by the specific cognitive requirements of the paradigms employed to assess working memory, and by the fact that the hippocampus is involved in other functions apart from (declarative) long-term memory consolidation. The human hippocampus is also engaged in novelty detection (Grunwald et al. 1998; Nyberg 2005) as well as in spatial cognition and navigation (Burgess 2008). For example, Winston et al. used a visual–spatial n-back task to assess working memory (Winston et al. 2013), and the spatial demands may be sufficient to explain hippocampal activation. The working memory paradigm used by Ranganath and D'Esposito led to sustained bilateral hippocampal activation during maintenance of novel faces across a short delay period but not during face encoding or recognition (Ranganath and D'Esposito 2001). Moreover, that paradigm and the one employed by Axmacher et al. (2007) used human faces as stimuli. A face consists of many different parts in a spatial composition (eyes, nose, mouth, eye brows, hair etc.) and thus has per se a spatial component and a higher memory load than a digit. Therefore, another feasible explanation may be that faces that should be remembered already exceed the working memory capacity. Axmacher et al. indeed found an increased hippocampal involvement with an increasing memory load (1–4 faces).

According to the presented results, the hippocampus becomes relevant when the amount of information that needs to be remembered exceeds the working memory capacity. An early classical work by Corsi (1972) indicated that this appears already to be the case when the individual memory span is exceeded by one additional item (i.e., in case of a supraspan task). Accordantly, in the current study, the dependency on the hippocampal system is already seen for the immediate recall of a long list of memory items (in this case 15 words) which is presented for the very first time. Given that the hippocampal long-term memory system is already engaged, the number of correctly remembered items is also higher than the working memory capacity (6.1 words versus 4.4 digits). However, at this initial stage of the learning paradigm, the short-term memory component is still of greater magnitude than the long-term memory component (Müller et al. 1997).

Over the five consecutive learning trials, memory performance steadily increased. This was accompanied by an almost parallel increase of correlations with the pathological status of the hippocampus, reflecting the test structure of descending short-term and increasing long-term memory aspects (Müller et al. 1997). The otherwise steady increase of the correlation coefficients is only disrupted by a drop regarding the third trial. The drop can be due to individual irregular learning curves that were observed in nearly one-fifth of the patients. Most likely, this may have been caused by deficits in concentration and executive monitoring.

The highest linear relationship between hippocampal integrity and memory performance was observed at the delayed free recall after a retention interval of 30 min. Thus, the trial with the highest long-term memory component shows the highest association with the neuropathological status of the hippocampus.

In conclusion, the presented results confirm the a priori hypotheses that (1) the relevance of the hippocampal integrity rises with the increasing degree of long-term memory involvement, and (2) that classical measures of short-term and working memory are not dependent on the hippocampus.

The major limitation of the study is its retrospective nature and associated disadvantages compared to prospective approaches. Moreover, given the limited statistical power due to the relatively small sample size ($N = 37$), the correlation analyses were performed without correction for multiple comparisons, thereby increasing the risk of false positive results. However, the overall pattern of the reported correlations appears consistent and is in line with the a priori hypotheses.

Larger studies would be appreciated that employ experimental memory paradigms with a systematic manipulation of the memory load in relation to the individual working memory capacity. The neuropsychological–neuropathological study design could further be enhanced by the parallel use of presurgical functional brain imaging methods.

Compliance with ethical standards

Conflict of interest The authors state that they have no conflicts of interest regarding the manuscript.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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