LETTER TO THE EDITOR

Is there evidence of a subordinate role of the hippocampal CA1 field for declarative memory formation?

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Sir,

Neuropsychological investigations in patients with temporal lobe epilepsy (TLE) substantially contributed to our understanding of the neural underpinnings of human memory (Saling, 2009). Given the essential role of the hippocampus for episodic memory, epilepsy surgery for the treatment of pharmaco-resistant mesial TLE offers the unique possibility of relating the neuropathological status of the resected hippocampus to presurgical memory performance. With one exception (Zaidel et al., 1998), almost all respective studies found significant correlations between segmental neuronal cell loss within the left hippocampus and preoperative verbal memory functions (Sass et al., 1990, 1992, 1995; Baxendale et al., 1998; Zentner et al., 1999; Witt et al., 2014). One of these studies also reported significant correlations between cell counts of the right hippocampus and non-verbal memory (Zentner et al., 1999). Three additional studies found significant relationships between hippocampal cell loss and global memory performance of the isolated ipsilateral hemisphere during the Intracarotid Amobarbital Test (Sass et al., 1991; O'Rourke et al., 1993; Pauli et al., 2006).

However, no clear picture emerged regarding the eventual superior role of specific subfields of the cornu ammonis (CA) or the dentate gyrus for episodic memory processes. Six of 10 relevant studies (60%) found significant correlations between presurgical memory performance and cell densities within the subfields CA3 and CA4, followed by CA1 (50%), dentate gyrus (40%) and CA2 (30%). Sample characteristics (often small, heterogeneous, and in some cases including both mesial and lateral TLE) and the use of different memory tests may well have contributed to this heterogeneity.

In a recent study of 104 patients with mesial TLE only, we analysed the role of segmental hippocampal cell loss and its underlying factor structure with regard to presurgical memory performance (Witt et al., 2014). In line with the medium-to-high intercorrelations between cell losses across hippocampal subfields (CA1–4 and internal and external limb of the dentate gyrus), principal component analysis indicated one single factor only which appeared to reflect the overall pathological status of the hippocampus. In-depth analyses revealed that the overall pathological status of the left hippocampus, rather than any specific subfield pathology, was relevant for verbal memory. Thus, the overall cell loss rather than cell loss within a specific subfield represents a marker for the structural and functional integrity of the hippocampus in mesial TLE.

In their recent study published in Brain, Coras and colleagues (2014) took a different approach compared to the cited correlational studies; they investigated different cell loss patterns across hippocampal subfields and their impact on memory. The authors provided a comparison of the presurgical memory performance of patients with different subtypes of hippocampal sclerosis as differentiated by the first international consensus classification system of the International League Against Epilepsy (ILAE) (Blümcke et al., 2013). The sample was comprised of 63 patients with hippocampal sclerosis ILAE Type 1 (which represents the most common type of hippocampal sclerosis with significant neuronal cell loss across all subfields, but with emphasis on CA1); 13 patients with hippocampal sclerosis ILAE Type 2 (CA1 predominant neuronal cell loss and gliosis whereas other sectors only show mild cell loss); six patients with hippocampal sclerosis ILAE Type 3 (CA4 predominant neuronal cell loss and gliosis...
whereas other subfields are only moderately affected); and 18 patients with no hippocampal sclerosis.

The main result revealed that ‘patients with CA1 predominant cell loss (hippocampal sclerosis ILAE Type 2; n = 13) did not show declarative memory impairment and were indistinguishable from those patients without any hippocampal cell loss (n = 19)’. In this study, global memory performance during the Intracarotid Amobarbital Test and a verbal memory score from the Berliner Amnesie Test were the neuropsychological measures of interest. Focusing on the Intracarotid Amobarbital Test memory performance, ‘[r]egression and correlation analysis confirmed that decreased neuronal cell densities in CA1 did not contribute to the extent of memory impairment’. The authors conclude that ‘CA1 pyramidal cells are less critically involved in declarative human memory acquisition compared to dentate gyrus granule cells or CA4/CA3 pyramidal cells’. Referring to a study by Bartsch et al. (2011), it is argued that CA1 neurons are less related to anterograde memory than autobiographical or remote memory which, however, had not been assessed.

Looking into the existing literature, such a subordinate or even negligible role of CA1 for anterograde declarative memory function is an unexpected and striking finding. This is because (i) there are case reports indicating that bilateral lesions limited to CA1 in humans lead to moderate-to-severe, predominantly anterograde amnesia, i.e. an impairment of declarative episodic memory formation (Zola-Morgan et al., 1986; Rempel-Clower et al., 1996); (ii) CA1 is known to be a relevant part of two major hippocampal circuits/pathways, the ‘tri-synaptic circuit’ and the temporo-ammonic pathway, both associated with memory functions (Remondes and Schuman, 2004); and (iii) several studies have demonstrated significant correlations between neuronal cell densities of CA1 (and other subfields) and preoperative anterograde memory functions in patients with TLE (Sass et al., 1995; Baxendale et al., 1998; Zentner et al., 1999; Pauli et al., 2006; Witt et al., 2014). For example, Baxendale et al. (1998) found significant correlations between pre- and post-surgical verbal memory and neuronal cell densities of CA1 in patients with left TLE, while granule cell densities of the dentate gyrus were unrelated to memory function. Moreover, regarding the subfields of the cornu ammonis (CA1–4), another study from the Erlangen group (Pauli et al., 2006) reported the highest correlations between Intracarotid Amobarbital Test memory performance and neuronal cell densities within CA1 (r = 0.736, P < 0.001). Finally, Rausch and Babb (1993) identified cell densities within CA1 as most representative for total cell loss across all subfields in a sample of patients who underwent epilepsy surgery for TLE. In that study, a higher CA1 cell loss was again associated with worse verbal memory performance in patients with left TLE.

Apart from these more general considerations, a closer look into the presented data by Coras et al. (2014) additionally raises the question of whether the results might have been biased by the evaluation method. (i) The main findings and conclusions of this study are based on the neuropathological and neuropsychological results of a subgroup comprised solely of 13 patients with hippocampal sclerosis ILAE Type 2. Given the small sample size, the question of the degree of representativity and statistical power arises. Moreover, only 5 of these 13 patients (38%) were resected on the language-dominant, presumably left side, and only these five were compared regarding verbal memory performance as assessed by the Berliner Amnesie Test:

‘Patients with left CA1 predominant sclerosis (HS ILAE Type 2) and left no hippocampal sclerosis had better preoperative verbal memory than patients with left HS ILAE Type 1 or left hippocampal sclerosis Type 3’.

In the majority of those patients with hippocampal sclerosis ILAE Type 2 the side of focus was in the non-dominant hemisphere [8/13 patients (62%)], therefore, one would not necessarily expect a presurgical deficit in verbal memory. As the authors used a total verbal memory score as the only measure of the Berliner Amnesie Test, the question remains as to whether non-verbal visuospatial memory deficits have been missed. (ii) Regarding the neuropsychological findings, only group data are reported and not the frequencies of individually impaired patients per subgroup. However, the authors present a figure in which 2 of 13 patients (15%) with hippocampal sclerosis ILAE Type 2 show below average/impaired Intracarotid Amobarbital Test memory performance, and two additional patients (15%) with hippocampal sclerosis ILAE Type 2 show borderline performance. At least some patients with hippocampal sclerosis ILAE Type 2 did indeed show mild memory deficits.

Searching our own database, we identified six patients who underwent epilepsy surgery in Bonn for mesial TLE (three within the left, three within the right hemisphere) and whose hippocampal specimens had been classified as hippocampal sclerosis ILAE Type 2 at the Department of Neuropathology at the University Hospital of Erlangen. Using measures with proven sensitivity to mesiotemporal pathology (Helmstaedter et al., 1997; Gleissner et al., 1998; Zentner et al., 1999), the presurgical assessment of verbal and figural learning and memory (VLMT + DCS-R) indicated impaired performance in all six patients in at least one of the key memory parameters (Table 1). A higher sensitivity/clinical validity of these measures regarding temporomesial (dys)function might explain this divergent finding. Different verbal memory tests may have different sensitivities to left hippocampal function depending on the specific cognitive architecture of the employed test as pointed out by Saling (2009). In this regard, we are not aware of studies on the validity of the Berliner Amnesie Test and its total verbal memory score, which was used in the study by Coras et al. (2014) as a verbal memory measure.

In light of our raised concerns and our own data presented, we suggest a more cautious interpretation and generalization of the findings by Coras et al. (2014). Nonetheless, it is important to highlight that the clinical and neuropsychological characterization of neuropathological subtypes is an important and necessary approach in establishing the validity and relevance of newly proposed classification systems. In the case of hippocampal sclerosis, the low number of ‘atypical’ subtypes (such as hippocampal sclerosis ILAE Types 2 or 3) calls for multicentric studies supervised by investigators with excellent neuropathological expertise, such as Roland Coras and Ingmar Blümcke from the University of Erlangen.
### References


### Table 1

**Age-corrected presurgical memory performance of patients with hippocampal sclerosis ILAE Type 2 (standard values)**

<table>
<thead>
<tr>
<th>Patients with HS ILAE Type 2</th>
<th>Side of surgery</th>
<th>Presurgical verbal memory (VLMT)</th>
<th>Presurgical figural memory (DCS-R)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Learning</td>
<td>Delayed free recall</td>
</tr>
<tr>
<td>1</td>
<td>Left</td>
<td>107</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>Left</td>
<td>97</td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td>Left</td>
<td>81</td>
<td>66</td>
</tr>
<tr>
<td>4</td>
<td>Right</td>
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<td>80</td>
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</tr>
<tr>
<td>6</td>
<td>Right</td>
<td>95</td>
<td>99</td>
</tr>
</tbody>
</table>

Impairments (i.e. performance of >1 standard deviation below the mean of the normative sample) are highlighted in bold.

HS = hippocampal sclerosis; VLMT = Verbaler Lern- und Merkfähigkeits test; DCS-R = Diagnostik für Cerebralschädigung – revised.