LETTER TO THE EDITOR

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

Roland Coras,1 Elisabeth Pauli2 and Ingmar Blumcke1

1 Department of Neuropathology, University Hospital Erlangen, Schwabachanlage 6, 91054 Erlangen, Germany
2 Epilepsy Centre, Department of Neurology, University Hospital Erlangen, Schwabachanlage 6, 91054 Erlangen, Germany

Correspondence to: Dr Ingmar Blumcke,
Department of Neuropathology,
University Hospital Erlangen,
Schwabachanlage 6, 91054 Erlangen, Germany
E-mail: bluemcke@uk-erlangen.de

Sir,

Witt and colleagues from the Bonn Epilepsy Centre in Germany reviewed a recent study about differential influence of hippocampal subfields on memory formation in a series of 100 patients with temporal lobe epilepsy (TLE) (Coras et al., 2014). A previous report from the Bonn group addressed a similar issue (Witt et al., 2014) but came to different conclusions. This controversy on impact of hippocampal subfields in the anatomical organization of human memory requires a comprehensive discussion, as raised by Witt et al. (2014) in their letter to Brain, but also reflect a long-standing debate resulting from lack of international consensus and diversity of applied neuropsychological memory test protocols in patients with TLE. Thus, any comparison of published results remains difficult.

Recent progress in histomorphological analysis of the epileptic human hippocampus identified different lesion patterns, which are now classified according to an international consensus classification for hippocampal sclerosis (Blumcke et al., 2012, 2013a, b). It suggests that hippocampal sclerosis in TLE result from different aetiologies (and clinical histories) rather than representing a single disease. Clinical features support this assumption, i.e. differences in age of epilepsy onset and post-surgical seizure control. Our working group also studied differences in memory performance related to hippocampal sclerosis subtypes using invasive intracarotid amobarbital injection (Wada and Rasmussen, 1960) with a standardized testing protocol (Intracarotid Amobarbital Test) and multiple regression and partial correlation analysis of subfield-specific hippocampal cell densities obtained from en bloc resected surgical specimens in the same patients. We identified 13 patients with an atypical CA1 predominant neuronal cell loss pattern, i.e. hippocampal sclerosis ILAE Type 2. Interestingly, most patients with CA1 predominant sclerosis had good memory performance, suggesting functional integrity of the hippocampus despite neuronal depletion of the CA1 region. Indeed, statistical analysis identified dentate gyrus granule cells rather than CA1 pyramidal neurons as predictor for memory acquisition and recall (Pauli et al., 2006; Coras et al., 2010). In other words, only patients with sufficient granule cell numbers had good memory performance during WADA testing, whereas CA1 cell densities did not show such a correlation. These results are supported by experimental findings in animal models (Deng et al., 2010; Nakashiba et al., 2012; Rangel et al., 2014) and human specimens (Coras et al., 2010).

Witt et al. (2014) reviewed their own database and could not approve our conclusion. They present a series of six patients with CA1-predominant hippocampal sclerosis and detected impaired memory performance in all six patients in at least one of their key memory parameters. In our reading and understanding of their table, however, five patients had good verbal learning and recall. We addressed only these parameters in our study, as linkage of figural-spatial memory with the (right) hippocampus represents another ongoing debate (see below). Anticipation of their different interpretation of neuropsychological data also requires an in-depth comparison of statistical methods and testing protocols. In our assessment and understanding of statistics, principal component analysis, as used by Witt et al. (2014), would not be chosen to explore differences between hippocampal subfields. Principal component analysis was developed to reduce complexity of factors/variables in a given observation by transforming the set of possibly correlated variables into a smaller set of linearly uncorrelated variables. Our scatter plot from individual patient data clearly
Tate gyrus cell densities showed poor memory performance (as shown by Witt et al., 2014), but not in patients with severe CA1 predominant sclerosis (as defined by Coras et al., 2014). Nevertheless, 3 of 19 patients with normal densities necessary for the competence in question. Our working hypothesis was thus based on the observation that good memory performance was observed in patients with severe CA1 predominant sclerosis (as shown by Witt et al., 2014), but not in patients with severe granule cell loss, suggesting a subordinate role of the hippocampal CA1 field in declarative memory formation.

Controversial interpretation of presented results also reflects different neuropsychological test batteries used to assess left and right hippocampal functionality. As mentioned above, there is as yet no international consensus to allow better comparison of published data. Our outcome measure was Intracarotid Amobarbital Test memory performance given as z-scores and normalized for dominant and non-dominant hemispheres (Coras et al., 2014), allowing a direct assessment from one isolated hippocampus. Non-invasive neuropsychological tests used by Witt et al. (2014) assess verbal memory performance from the left (speech dominant) and figural-spatial memory from the right temporal lobe. However, evidence linking spatial memory with the right temporal lobe is weaker than established knowledge connecting verbal memory with the dominant temporal lobe (Glikmann-Johnston et al., 2008; McConley et al., 2008). Still, linkage between the left hippocampus and verbal memory capacity may be uncertain when early precipitating injuries occurred in a patient’s history, such as febrile seizures or birth trauma. In about one-third of patients with left TLE, language is reorganized bilaterally or exclusively to the right hemisphere (Rasmussen and Milner, 1977; Loring et al., 1990). Verbal memory can be reorganized to the right hippocampus even in left language dominance, with a time-window for plasticity up to puberty (Jokeit et al., 1996). In our own database, 27% of left speech dominant patients demonstrated right-sided memory dominance. Interpretation of non-invasive memory test batteries would have been difficult in these patients.

Figure 1 Relationship between preoperative Intracarotid Amobarbital Test, CA1 pyramidal cell loss and granule cell loss. Relationship between preoperative ipsilateral Intracarotid Amobarbital Test memory scores (transformed into z-scores) and pyramidal cell loss in CA1 (A) or granule cell loss in the dentate gyrus (B). Memory function can be sustained even in the presence of most severe cell loss in CA1 (individuals on the upper left side) whereas it was significantly impaired in patients with granule cell loss (B). Normal memory performance (defined by $z > -1$) was seen only in patients with granule cell densities above $-3.5$ SD (left perpendicular dotted line). When granule cell densities decreased below this margin, none of our patients were able to reach normal memory performance (indexed upper left quadrant). Good memory performance ($z > 0$) was possible only in individuals with granule cell densities above $-2$ SD (B, right perpendicular dotted line). DG = dentate gyrus. Modified from Coras et al. (2014).
It will be of overt importance for future research to negotiate an international consensus regarding methodological shortcomings, pitfalls and used protocols to allow reliable comparisons, as study design and methodology will remain diverse. In addition, we cordially invite Witt et al. to share their neuropsychology database for statistical analysis with our protocols, as we offered them subfield-specific histomorphological analysis for their series of surgical hippocampus specimens.

References
Nakashiba T, Cushman JD, Pelkey KA, Renaudineau S, Buhl DL, McHugh TJ, et al. Young dentate granule cells mediate pattern separation, whereas old granule cells facilitate pattern completion. Cell 2012; 149; 188–201.