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Observations on the relationship between verbal explicit and implicit memory and density of neurons in the hippocampus

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Abstract—The relationship between neuronal density and verbal memory in left and right hippocampal subfields was investigated in patients who underwent surgery for alleviation of temporal lobe epilepsy. The surgery consisted of unilateral partial removal of the hippocampus along with the anterior temporal lobe and amygdala. Study 1 looked at post-surgical explicit vs implicit verbal memory for lists of words while Study 2 looked at pre- and post-surgical explicit memory for word pairs. Left subfield CA1 appeared to be the most consistently involved in explicit and implicit memory. The results of the two studies confirm presence of hemispheric asymmetry in verbal memory. The notion that hippocampal control of memory is most apparent in post-surgical performance is discussed. © 1998 Elsevier Science Ltd. All rights reserved

Key Words: epilepsy; CA1; human; plasticity; mind-brain; hemispheric specialization.

Introduction

Sperry and Cajal

Around the turn of the 20th century, the eminent neuroanatomist Santiago Ramon y Cajal (Nobel Laureate, 1906) proposed the notion of regularity in neuronal connectivity in the brain. Axons connect with each other according to a predetermined specific plan and this through chemical signals emanating from the tips of the axons themselves. Much later, in the 1940's, Roger W. Sperry proposed the notion of chemoaffinity to explain how developing axons in one part of the nervous system "know" where their final target is located. He conducted a series of elegant, by now classic, critical animal experiments which illustrated the notion of specificity in neuronal connectivity. Sperry admired Cajal greatly; he remarked that "he was the greatest neuroscientist of this century". Despite his prodigious output, Cajal did not pay much attention to left–right differences in the brain nor to a huge bundle of fibers, the corpus callosum, that connected the two halves of the cerebrum. The left and right sides were the main focus of Sperry's work with cats, monkeys, and neurosurgical patients [47, 48]; his findings on functional brain asymmetries in commissurotomy patients ("split-brain") won him a Nobel Prize in 1981. A world-wide scientific interest in brain asymmetry was sparked by the work that he began and the observations on hippocampal asymmetries described here reflect one of the outcomes of this interest.

Ramon y Cajal conducted many anatomical investigations of the hippocampus and provided some of the most detailed descriptions of this structure to date [37]. His specimens were mostly (though not exclusively) from the mouse and rabbit which are now known to have somewhat different anatomical arrangements in the hippocampus than humans, especially with regards to commissural connection between the hippocampi in the two sides [3, 4, 13, 36]. The hippocampal commissure appears to have grown relatively smaller in evolution as one moves from rats, to cats, to monkeys, to humans [40, 58, 59]. From a phylogenetic perspective alone, as hemispheric specialization evolved the size of the corpus callosum grew; there may have also been a progression toward somewhat less direct communication between the left and right hippocampi but with increased ipsilateral structural/functional connections between hippocampus

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and neocortex [40]. Such an evolutionary trend would support the notion that human memory systems in the two sides are wired up differently to support separate but complementary functional specialization in the hemispheres [61].

Sperry

Anyone who has ever worked with Roger Sperry at Caltech, Pasadena (first author of this article, DWZ) sensed his love and commitment to science, especially to the biological basis of behavior. He was an original and creative thinker who had a deep understanding for current problems and issues in brain research, who always interpreted scientific findings within a global context and who always supported and encouraged innovative research. Setting an example, he worked continuously and involved himself in the nitty gritty aspects of research. His scientific approach was data driven; truths are to be found in observations themselves and in the data, not in elaborate theories or in artificial models, he said. Books or journal articles alone do not untangle the mysteries of the brain and mind. Ideas in themselves are not "proofs". If one persists in looking and exploring through direct experimentation and investigation, one could find the answer, or an important part of it. But, then, one must be committed and enjoy the scientific search. These were some of the lessons this important scientist of the 20th century imparted to those who worked closely with him.

Asymmetries in memory

The hippocampus has been considered a major anatomical structure for memory and learning functions, for both verbal and non-verbal material as well as for spatial orientation. The bulk of the evidence for selective unilateral hippocampal contribution to memory comes from cases with unilateral hippocampal damage. Left-sided anterior temporal lobectomy (LTL) due to epilepsy, which includes the hippocampus in resected tissue, may lead to worse memory for verbal material [31, 67], whereas right-sided resection (RTL) may lead to impairments in non-verbal memory such as faces, routes, or musical melodies [7, 23–26, 68, 69]. Support for right hippocampus activation in topographical knowledge has been shown in an fMRI study [28]. These findings on memory functions are consistent with left hemisphere specialization for language and right hemisphere specialization for non-verbal, visuo–spatial, or some musical abilities.

Hippocampus anatomy

There is a complete hippocampal formation in either side of the brain, each consisting of distinct cytoarchitectonic regions (the Amonic subfields) which are said to be linked to each other in a single, unidirectional synaptic circuit. Anatomical comparisons between the human left and right hippocampal formations have largely been neglected in contrast to the attention given to anatomical asymmetries in the human neocortex [17]. However, recently, we have reported asymmetries in regional interconnectivity in the presence of mostly symmetrical neuronal density [62, 65, 66]. Our findings imply that memory and learning have asymmetrical computational machinery. The present study examines the relationship between neurons in the hippocampus in the left and right sides and verbal memory.

Memory and hippocampal subfield specificity

Despite the fact that the hippocampal subfields are linked in a single synaptic circuitry, they have selective sensitivity to damage. For example, in humans, the most "vulnerable" subfield to hypoxia is CA1, and the least sensitive are CA2 and CA3 (see classifications in [14]). Given differential susceptibilities, it is reasonable to suppose that the hippocampal subfields play differential roles in memory and learning. A few recent studies correlated pre-surgical scores with neuronal density and found evidence for subfield specificity although not all focused on left–right differences [33, 44, 45]. Taken together, the left hippocampus was consistently implicated in cell loss and verbal memory, and the CA3 and hilar regions were significantly more involved than CA1 or CA2 in a study by Sass *et al.* [44]. However, these previous studies were somewhat limited in that they tested only explicit memory or measured only pre-surgical memory. Thus, they were narrowly focused.

The present article describes the results of two experiments in which verbal memory was tested in patients with unilateral hippocampal damage, that is, in LTL and RTL. In both experiments, memory scores were compared to hippocampal neuronal density. The first measured post-surgical memory for explicit vs implicit memory for lists of words, and the second measured pre- and post-surgical explicit immediate and delayed memory for unrelated paired-words. Together, the two studies provide convergent evidence for the importance of post-surgical testing in inferring hippocampal function and for the selective role of left hippocampal neurons in verbal memory.

Study 1: Explicit vs Implicit Memory and Neuronal Density

Introduction

It is important to distinguish between explicit and implicit memory in patients with suspected memory defi-