

## The case for a relationship between human memory, hippocampus and corpus callosum

DAHLIA W ZAIDEL

Behavioral Neuroscience Group, Department of Psychology,  
University of California, Los Angeles, California, USA

*Unilateral brain damage which includes the hippocampus leads to memory impairments consistent with hemispheric specialization on the same side. Damage to the corpus callosum, the major connecting pathway between the left and right hemispheres, also leads to memory impairments. This suggests both hemispheric specialization on the hippocampal level and a critical role for the corpus callosum in memory functions. A complete hippocampal formation is present on either side of the brain but traditionally only one is studied. However, a comparison between the neuronal populations in the hippocampus on both sides revealed asymmetry in connectivity among hippocampal subfields. The profile of memory impairments of commissurotomy ('split-brain') patients is described. The results are discussed in terms of a relationship between hippocampus and corpus callosum in humans. As hemispheric specialization evolved, inter-hippocampal connections became less important and the corpus callosum became prominent in memory functions.*

**Key words:** *asymmetries, CA fields, corpus callosum, hippocampus, memory, sex differences.*

### INTRODUCTION

The hippocampal formation is considered to be the predominant anatomical structure in the brain that subserves memory functions. While much attention has been given to the relationship between the mechanisms that operate in this structure and memory, the interaction between the corpus callosum, the largest structure of the interhemispheric commissures, and memory functions has been largely overlooked. In the present paper, the focus is on (1) evidence for hippocampal asymmetries and (2) the relationship between the corpus callosum and hemispheric memory.

human brain. Left-right anatomical asymmetries in neocortical regions are present in humans and –to some extent– in non-human primates (reviewed by Galaburda, 1994). Structural asymmetries parallel the functional asymmetries of the hemispheres, although the relationship between specific forms of anatomical and functional asymmetries is not yet understood. And while much is known about neocortical regions, the anatomical or morphological status of asymmetries between the left and right hippocampi has rarely been studied, despite ample evidence for hemispheric differences in memory functions.

### HEMISPHERIC SPECIALIZATION

Hemispheric specialization for cognition and memory is a well established fact for the

### ASYMMETRIES IN SOME KINDS OF MEMORY

The critical role of the hippocampus in newly learned human memory has received much attention ever since neurosurgeons

resected the adult hippocampus, bilaterally, in case H.M. (Scoville and Milner, 1957). Following surgery, the patient suffered from profound anterograde amnesia while leaving relatively intact previously stored memory. There were no changes in general intelligence or mannerisms, suggesting a dissociation between memory for newly learned material in adulthood and general intelligence. There has been some evidence that certain newly presented material such as a motor skill, was learned to a limited extent. On the other hand, unilateral anterior temporal lobectomy, which includes removal of most of the hippocampus, does not result in severe amnesia but rather in memory impairments that are consistent with hemispheric specialization in perception, motor control, or problem solving on the same side (Beardsworth and Zaidel, 1994; Jones-Gotman, 1987; Milner, 1958). Left-sided surgery may result in worse memory for verbal material such as word-lists or paired-associates (pairs of words) than in normal or than right-sided cases. Conversely, right-side surgery may result in worse memory for non-verbal material such as faces or nonsense figures than in normal subjects or left-sided cases. These impairments are particularly noticeable in delayed-testing conditions and imply that the anterior temporal lobe/hippocampal formation regions are important in long-term memory consolidation processes rather than in short-term memory; some would consider the impairments to be that of immediate memory (the delays are typically within the 30 min range) as distinguished from short-term memory which is typically tested immediately after stimulus presentation. Although the surgery includes the anterior temporal lobe along with hippocampal and amygdala resection, the cause of the memory impairments is attributed to the hippocampus.

Moreover, studies on normal subjects and complete commissurotomy patients ('split-brain') all point to asymmetries in storage/retrieval between the hemispheres. In typical behavioral tests it is difficult to distinguish between storage and retrieval. Accuracy is taken as indication of competence, of storage. Reaction time measures (time taken to respond) are taken to reflect retrieval strategies. Of course, retrieval may be dictated

by the nature of the memory store itself, and encoding may have determined the nature of the store in the first place. Using the available dependent measures, the findings to date suggest similar stores in both hemispheres but with different retrieval strategies (Sperry *et al*, 1979; D Zaidel, 1990a; D Zaidel and Sperry, 1974).

#### *Evolutionary trends*

In contrast to the unilateral involvement of the hippocampus in human memory, animal research shows that bilateral resections are essential in order to elicit some kind of memory deficit. The fact that unilateral removal does not lead to deficit, suggests an evolutionary change from animals (*e.g.*, rats, cats, monkeys) to humans in the way the hippocampus supports memory functions. The critical change may be the development of hemispheric specialization in humans. To support this notion, there is some evidence to suggest a structural and physiological ipsilateral coupling between the neocortex and hippocampus on the same side. Specifically, (1) Physiologically, Wilson and associates (1990) have provided physiological evidence for reduced hippocampal functional commissural connections (via the hippocampal commissure) in humans. (2) Anatomically, the monkey amygdala (Pandya and Rosene, 1985) and hippocampus (Amaral *et al*, 1984) have reduced inter-hemispheric commissural connections in the amygdala and hippocampus compared to rats and cats. (3) Comparative anatomy studies (see Rosene and Van Hoesen, 1987) built a case for a progressive phylogenetic reduction in hippocampal commissural connections from rats, to cats, to monkeys, to humans. Taken together, this suggests that instead of the two hippocampi "communicating" with each other via the hippocampal commissure, ipsilateral (functional) linkage developed between the hippocampal formation and neocortex instead, as hemispheric specialization evolved. And hemispheric specialization is most developed in humans.

#### *Explicit versus implicit memory*

To complicate matters, not all kinds of memory functions are subserved by the

hippocampus (Mishkin *et al*, 1984; Squire and Zola-Morgan, 1991). Explicit memory and implicit memory may have different anatomical substrates. The view of explicit memory is that it reflects cognitive processes available to conscious awareness while implicit memory consists of cognitive processes unavailable to conscious awareness. According to one line of evidence, for example, the hippocampal formation appears to be critical in explicit memory but not in implicit memory (Squire and Zola-Morgan, 1991). This evidence is based largely on studies of amnesic patients with extensive bilateral cortical damage, which includes the hippocampal formation, due to alcoholism, Alzheimer's disease, or stroke. These patients typically have impairments in recall or recognition, explicit memory, but not on word-completion or skill learning, implicit memory, as compared to control subjects (Graf *et al*, 1982, 1984; Shimamura *et al*, 1987). Because the brain damage is bilateral in such patients, it is difficult to know the separate hemispheric contributions of the neocortex or of the hippocampal formation on one side to either kind of memory.

#### ASYMMETRIES IN HIPPOCAMPUS

The most readily available hippocampal specimens in humans come from surgical removals in unilateral anterior temporal lobectomy, a surgery that is performed in order to alleviate drug-resistant temporal lobe epilepsy. Typically, the anterior two-thirds of the hippocampus is removed. Neuropathological investigation of neuronal cells have revealed abnormally low number of pyramidal cells in hippocampal subfields CA1, CA3, CA4, and the granule cells in the dentate gyrus (DG) (see Duvernoy, 1988, for hippocampal diagrams). However, such investigations normally do not distinguish between neuronal counts in the left and right sides (Babb *et al*, 1984a, b; Dam, 1979; Margerison and Corsellis, 1966; Sagar and Oxbury, 1987). Equal total cell loss due to abnormal discharges of the epilepsy may mask asymmetries of cell loss within each of the hippocampal subfields, for example. If the two sides had unequal subfield differen-

tiation so that neuronal loss in one hippocampal subfield is coupled with loss in another subfield, as function of neuronal connectivity only on that side, this would go unnoticed given lack of interest in comparisons between the two sides.

However, I and my colleagues (MM Esiri and JM Oxbury) have compared the hippocampus on both sides to each other, for the first time (D Zaidel *et al*, 1993). We studied neuronal density of pyramidal cells in subfields CA1 and CA4 and of the granule cells in DG in 27 (14 left; 13 right) temporal lobe epilepsy patients who have undergone unilateral anterior temporal lobectomy. Most cases –except for two– were right handed, and the majority –but for two– were left hemisphere dominant for language (determined by the sodium amobarbital procedure); they all had a Full Scale IQ of 80 and above. Left and right patients presumably did not differ in the severity of the epilepsy nor in the post-operative drug management.

A light-microscope fitted with a grid (10 x 10) in the eyepiece was used to count nucleolated neurons in 27 cases (14 right, 13 left). The thickness of each slice which was examined was 20  $\mu\text{m}$ ; it was taken from the body of the hippocampus. The clinical identity of the patients was not known at the time when the counts were done. Sampling was accomplished in five different regions within each hippocampal subfield. Neurons were counted if they fell within the grid area and cells which fell on the upper or left boundaries of the grid. As is normally done in studies of volumetric cell counts, Abercrombie's formula was used to correct any overestimation of counts due to section thickness (Abercrombie, 1946).

The findings indicated that mean density was not statistically significant between the left and right sides in CA1 and the DG. However, mean density was significantly lower in the right CA4 than in the left CA4. This may be attributed to hitherto unsuspected susceptibility to epilepsy in the right CA4. The reasons and origin for the susceptibility could not be determined with the methods and data available in that study. Future studies might profit from an investigation into the synaptic, neurochemical and structural features of the right CA4.

Importantly, we found statistical evidence for asymmetry in hippocampal interconnectivity: There were high positive significant correlations among subfields only in the left hippocampus. On the right, correlations were low and not significant. These findings were interpreted as reflecting high interdependence among subfields on the left versus independence on the right. These findings have important clinical implications. Epilepsy on the left may have stronger effects than right epilepsy because the subfields may work in unison whereas they may work as independent units on the right. On the left, damage to one subfield may affect other subfields, while damage to one subfield on the right may not have consequences to the other subfields. Taken together, the results suggest left-right asymmetries in the vulnerability of the hippocampi to epilepsy-associated damage and/or higher neuronal connectivity or interdependence on the left than on the right.

What creates neuronal interconnectivity or lack of it, is difficult to say. It is likely that synaptic factors such as higher levels of certain critical neurotransmitters are involved, and this might be under genetic control. Other factors such as asymmetric blood supply may play a critical role in degrees of interconnectivity as well.

There are implications to memory functions from these findings. Left-sided connectivity may be necessary for supporting verbal and language-related memory while the independent right connectivity may be a necessary anatomical basis for spatial memory. The hippocampus may indeed prove to be a model for neocortical left versus right connectivity.

#### *Sex-related hippocampal asymmetries*

When we examined a large ( $n = 52$ ) series of these patients (with unilateral anterior temporal lobectomy), we were able to analyze the data for neuronal density with respect to sex of patient (D Zaidel *et al*, 1994). We have used the same methods described above. On the left, there were 15 males and 15 females; on the right, there were 13 males and 9 females. The findings indicated that males had significantly more neurons in the left hippocampus than on the right for all 3

subfields sampled (CA1, CA4 and DG). In the females, this asymmetry was not present. Moreover, statistical correlation among subfields on the left was consistently positive only in males, while it was positive in only 2 of 3 possible comparisons in females (Fig 1). In the right, the correlation between subfield densities was consistently low and nonsignificant in males, while it was positive and significant in 1 of 3 possible comparisons in females (Fig 1). The similarities and differences between the sexes fit existing notions on functional lateralization in the brain. Males are considered to be more functionally lateralized than females (Kimura, 1992; Weekes, 1994). Our findings for the pattern of neuronal density in the hippocampus may be yet another line of evidence to support this notion.

#### *Sex differences in the hippocampus in animals*

There are scant data on laterality differences in the non-human hippocampus. However, Marian Diamond and her colleagues have investigated left-right differences in the

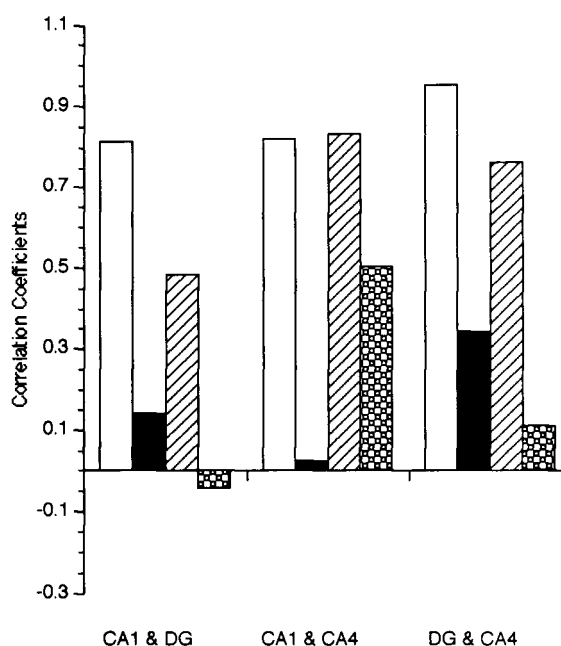


Fig 1. Correlation coefficients between neuronal density in hippocampal subfields, on the left and right sides. The left and right hippocampi were resected unilaterally in patients who underwent anterior temporal lobectomy. Open bars, left males; black bars, right males; hatched bars, left females; cross-striped bars, right females.

hippocampus in the rat (reviewed in Diamond, 1985). They found that in male rats (Long-Evans) the right hippocampus was maximally thicker than the left during the period from 6 days up to 41 days of age; this difference disappeared by 900 days of age. In female rats, the left hippocampus was significantly thicker than the right between 21 and 90 days of age, although the left was thicker than the right at other ages of development as well (*e.g.*, 7, 14, 180 and 390 days of age). That is, the trend was present from 7 through 390 days of age. Based on an experimental manipulation in which female rats were ovariectomized early on (age 1 day), Diamond (1985) suggests that this pattern in female rats may be influenced by ovarian hormones. In male rats, early removal of the testes led to a reduction and reversal of the asymmetry, at least at 90 days of age. The important conclusion advanced by these investigators is that for the female rat asymmetry was not as pronounced as in the male rat and furthermore that it was not as consistent. However, the results clearly suggest a sex difference in one anatomical parameter, namely hippocampal thickness.

Further studies on volumetric hippocampal asymmetry in rats were conducted and reviewed by Sherman and Galaburda (1985). They found that environmental enrichment (handling) was a major factor in determining hippocampal asymmetry, in the absence of effects of handling on the neocortex of the same rats!. The handling favored the right hippocampus in most cases, although these differences did not interact with sex.

#### *Additional considerations*

There are many questions to be answered regarding hippocampal asymmetries. First, only sections from the body of the hippocampus were sampled. The nature of the asymmetry might be different in the head and tail. This comparison remains to be studied. Second, our cases represent a population with pathology, a condition which might interfere with normal development of hippocampal circuits. Third, age is known to be associated with decreased neuronal density in the hippocampus and our cases were all in

the "young" range; this may be an important consideration (in our favor) in explaining our results.

#### FURTHER WORK ON HIPPOCAMPAL ASYMMETRIES

We (D Zaidel, Eastwood, Esiri and Harrison) have continued to investigate the nature of hippocampal asymmetries by counting nucleolated neurons in normal brains (post-mortem). The left and right sides for each case were available for examination. Our preliminary results indicate left-right symmetry in density with left-right asymmetry in intra-hippocampal correlations. The latter pattern is consistent with the pattern obtained for the epileptic cases described above, namely high interconnectivity on the left and independence on the right. No sex difference analysis was performed at this initial stage.

The question of ontogenesis in hippocampal asymmetries is also currently being investigated by us. We have begun to count neurons in left-right matched hippocampi in very young infants with relatively normal brains (*e.g.*, sudden infant death etiology). This work is in its initial stages.

In the future, pathological populations such as schizophrenic patients and Alzheimer Disease patients, should be studied as well. It is critical to determine if there is a predilection for disease as function of hippocampal asymmetrical circuitry.

#### THE CORPUS CALLOSUM AND MEMORY

There is ample evidence that the two hemispheres of the human brain are specialized for different yet complementary functions (*e.g.*, Sperry, 1974), including different storage/retrieval processes in long-term semantic memory (D Zaidel, 1986, 1987). The major question is the role of the inter-hemispheric commissures in memory functions. The first systematic investigation with the largest group of patients was reported in 1974 (D Zaidel, 1990b; D Zaidel and Sperry, 1974). Since then, several studies of other patients, in whom the same or different regions of the forebrain commissures have been sectioned, were reported some with

conflicting results while others consistent with the original 1974 findings.

Following surgery, previously known events, faces, names, skills, mannerisms and so on, remain unchanged. Since there is no change and since memory for new events is impaired, the interhemispheric commissures may be seen as important for the acquisition and storage of new information.

In the 1974 study, 10 patients were studied; two underwent a partial section of the corpus callosum (CC) and 8 had a complete section of the CC. In the partial commissurotomy patients, the anterior two-thirds of the CC was severed along with the hippocampal and anterior commissures. In the complete commissurotomy cases, the CC, hippocampal and anterior commissures were all sectioned. Whenever the massa intermedia was visualized it, too, was sectioned. The surgery was performed in a single stage. In addition, because of the surgical approach it is assumed that fornix fibers have been partially interrupted on one side (only) in a few cases. Damage other than callosal damage in the cortex due to the surgery or to the epilepsy is assumed in all cases but it is not thought to be extensive nor concentrated in hippocampal structures.

Unfortunately, no pre-operative testing on memory tests was performed. A variety of standardized memory tests were administered; the Wechsler Memory Scale (WMS) and the Benton's Revised Visual Retention Test (BVRT), are some of the tests which were used. The results indicated that all patients, regardless of surgery, had memory performance substantially below their IQ's (WAIS Intelligence Quotient), as determined by the IQ-MQ (Wechsler Memory Quotient) difference. Complete commissurotomy patients were especially poor in remembering the non-verbal, visual tasks. Both partial and complete commissurotomy patients obtained particularly low scores on the "hard" versus "easy" word associations subtest in the WMS. The hard associations consist of pairs such as school-grocery, while the easy associations consist of pairs such as apple-pear. The latter can be "remembered" by pure guessing whereas the former require active memory processes. A subsequent study by Huppert (1981) on three of these complete

commissurotomy patients compared their performance to that of amnesic patients (due to alcoholism) confirmed presence of memory deficits. One patient, LB, had normal scores on 4 of the tests administered in the 1974 study, and yet the difference between IQ and MQ was substantially higher than normal. In sum, events experienced and learned before the surgery appear intact after the surgery. Newly learned material is poorly retained after surgery.

#### CONCLUSION: THE CORPUS CALLOSUM AND THE HIPPOCAMPUS

If the comparatively small hippocampal commissure in humans reflects an evolutionary trend occurring together with the development of hemispheric specialization, we may infer logically that what has become essential in human memory is interhemispheric communication. The hypothesized ipsilateral connection between hippocampus and neocortex on the same side, as well as the morphological findings for asymmetry in intra-hippocampal connectivity, would seem to fit such an evolutionary trend. In commissurotomy patients, retrieval of old memory, encoded and stored prior to surgery appears intact. Presumably the status of the hippocampus facilitated adequate storage of events. When communication between the hemispheres is severed on a cortical level, in the commissurotomy patients, it is new memory that suffers. Since we assume that what has changed after such surgery is not the status of the hippocampus, on either side, the natural conclusion is that the interhemispheric connections are critical for new memory.

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