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# Regional differentiation of neuron morphology in human left and right hippocampus: comparing normal to schizophrenia

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**Abstract**

Regional differentiation based on size, form, and orientation angle of the soma of individual neurons in human post-mortem hippocampus was determined through correlations between pairs of hippocampal subfields in each side separately. The neurons were previously measured on a computer. In the normal cases, a left–right asymmetrical pattern of regional differentiation based on soma size emerged, while for form and orientation angle, the patterns appeared symmetrical. In schizophrenia, regional soma size, form, and orientation variability were expressed largely symmetrically. Regional correlations based on neuronal density revealed an asymmetrical hemispheric pattern in the normal cases versus a nearly symmetrical pattern in schizophrenia. Taken together, the inter-regional correlations favor a hippocampal landscape that deviates in each side from connectivity based on the canonical trisynaptic hippocampal circuitry. It is proposed that during morphogenesis, rudimentary inter-regional networks are formed through specific interactions between regional neurons; these networks are present in the adult hippocampus and may be vulnerable in brain diseases. 

*Keywords:* Morphogenesis; Brain hemispheres; Neuron size; Neuron form; Memory; Brain asymmetry

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## 1. Introduction

In the hippocampus, as in the rest of the brain, neurons populate regions differentiated according to their morphology, axonal targets, patterns of dendritic arborization, or synaptic and histochemical properties. Regional formation in the hippocampus (the Amonic subfields CA1–CA4, dentate gyrus, subiculum) in early brain development is most likely under genetic control and guidance, although regional integrity could be compromised by events both intrinsic and/or extrinsic to the hippocampus. The canonical view of the hippocampus is that its regions operate in a unidirectional, trisynaptic circuitry (henceforth referred to in this paper as the canonical circuitry), a view derived from anatomical and physiological observations mostly in non-humans (see Duvernoy, 1988; Amaral and Insausti, 1990). However, alternative regional networks may be active in the hippocampus and expressed in inter-regional correlations (Zaidel et al., 1992, 1993, 1994a). The alternative regional networks may have originated in morphogenesis, a time when neurons in spatially related regions signal and interact with each other (Tanabe and Jessell, 1996; Ikeya et al., 1997). This paper describes for the first time the patterns of regional differentiation (Amonic subfields) as can be inferred from statistical inter-regional correlations of neuronal soma size, form, and variability in orientation, within the left and right hippocampus separately.

The hemispheric issue in hippocampal regional differentiation was first reported for neuronal density in surgically resected hippocampal tissue from unilateral temporal lobectomy patients (Zaidel et al., 1992, 1993, 1994a). Differentiation was inferred from correlation values in permutations of all possible hippocampal subfield pairings. A pattern of high positive correlations, for example, suggests a lack of regional differentiation. Thus, 'fuzzy' regional differentiation within the left hippocampus (high positive rho values) versus regional 'distinctiveness' in the right hippocampus (low rho values) was revealed. Such asymmetry implies presence of anatomical underpinning for asymmetry in memory. A subsequent study of neuronal density in normal subjects was undertaken in postmortem tissue; it confirmed the epilepsy finding (Zaidel et al., 1995). Neuronal density in hippocampal subfield CA2 has since been determined in the postmortem tissue, and the larger picture of hippocampal regional relationships with respect to neuronal density is presented for the first time in the present paper.

It is widely accepted that the hippocampus is an important brain structure for human memory; there is by now ample evidence for asymmetry in memory functions from patients with unilateral brain surgery (Milner, 1958, 1978; Zaidel, 1990; Beardsworth and Zaidel, 1994; Zaidel et al., 1994b), in evidence from fMRI (Maguire et al., 1997), and in the relationship between neuronal density and memory (Sass et al., 1990; Trenerry et al., 1993).

In schizophrenia, the hippocampus is a sensitive anatomical site for abnormal patterns in neurochemistry (Joyce, 1993; Weinberger, 1995), neuronal density (Falkai and Bogerts, 1986; Zaidel et al., 1997a), neuronal soma size (Benes et al., 1991; Arnold et al., 1995; Zaidel et al., 1997b), neuronal soma form (Zaidel et al., 1997b), and other neuronal parameters (Kovelman and Scheibel, 1984). There may indeed be a strong relationship between schizophrenia and functions subserved by the hippocampus (Zaidel, 1998b), even if memory impairment, a function most easily associated with this structure, is not a salient feature of the disease. Nevertheless, the importance of hemispheric asymmetry in understanding schizophrenia has been emphasized by several investigators (e.g. Gruzelier and Flor-Henry, 1979; Gruzelier et al., 1988; Doty, 1989; Crow, 1990; DeLisi et al., 1997). In view of the foregoing, it seemed reasonable to search for hippocampal networks other than the canonical circuitry, based on regional differentiation and expressed in hippocampal inter-regional correlations.

## 2. Method

### *2.1. Subjects*

The post-mortem cases described here were 17 normal subjects (seven females and 10 males)

whose age ranged from 22 to 84 years, and 14 subjects with schizophrenia (five females and nine males) whose age ranged from 28 to 83 years. Brain tissue was examined and no neuropathological abnormalities were uncovered. DSM-III-R criteria were applied in the diagnosis in the schizophrenia group. There was no history of neurological disorders or of excessive substance abuse in the normal cases or in the subjects with schizophrenia. All the cases with schizophrenia had been on antipsychotic medication at the time of death, some having been on the medication periodically or for prolonged periods. Details about the cases including causes of death have been published previously (Zaidel et al., 1996, 1997a,b).

### 2.2. Procedures

#### 2.2.1. Histology

The brain tissue was fixed in formalin, the left and right hippocampi (from the same brain) were wax-embedded, coronally sectioned, and 10-μm specimens from the body of the hippocampus were stained with cresyl violet.

#### 2.2.2. Measurements

The neurons from hippocampal subfields CA1, CA2, CA3, CA4, and subiculum were digitized with a JVC KY-F30, 3CCD color video camera attached to an Olympus BH2 microscope (objective $\times 10$) connected to an IBM compatible computer. They were measured with NIH-Image, version 1.59 on a Macintosh computer. The computerized measurements determined neuronal size, form, and orientation angle. I have reported many additional details on the data collection previously (Zaidel et al., 1997b). Neuronal density was determined with a light microscope (Olympus BH2) on the same microscope slides; the identical hippocampal subfields were sampled plus the granule cells in the dentate gyrus (DG). A $10 \times 10$ grid in the microscope's eyepiece was used to count the neurons which fell within the boundaries of the grid. A detailed description of these procedures was published previously (Zaidel et al., 1993, 1997a)

## 3. Results

Regional differentiation was determined through inter-regional correlation values (Pearson Product Moment) in permutations of all possible pairings of the subfields, in each side separately. Those correlation values which were significantly different from zero are described below. Significance level was set to $P < 0.05$.

### 3.1. Normal cases

Fig. 1a summarizes the correlations between subfields based on neuron soma size and shows a pattern of hemispheric asymmetry in the direction (positive) and the significance level (above zero) of the rho values. Two rho values were significantly above zero on the left side (left CA1 and CA3, $P < 0.002$; left CA1 and CA4, $P < 0.04$), whereas on the right none was significant. The pattern of all 10 correlations produced on each side was asymmetrical (Wilcoxon Sign Test: left-side, $z = -1.89$, $P < 0.05$; right-side, $z = -0.35$, $P < 0.7$).

Fig. 1b shows correlation values between pairs of subfields based on neuronal variability in orientation angle. (Variability in orientation angle of the neurons is considered a measure of neuronal disarray.) One correlation value was significantly different from zero (left CA2 and left subiculum, $P < 0.01$). The Wilcoxon Sign Test applied to all 10 correlation values produced on each side revealed non-significant $z$-values ($P > 0.05$).

Fig. 1c shows correlation values based on neuron form. (Neuron form was derived from the following formula: length of the best fitting minor ellipse/length of the best fitting major ellipse; this formula corrects for neuron size.) The correlation patterns appear similar in both sides. None of the correlation values was significantly different from zero.

Fig. 2 illustrates the rho values based on neuronal density for all pairings of the six hippocampal subfields sampled. The findings for neuronal density revealed five significant rho values (positive) in the left side and none in the right side (CA1 and CA4, $P < 0.0004$; CA1 and DG, $P < 0.001$; CA4 and DG, $P < 0.03$; CA3 and DG, $P < 0.003$;

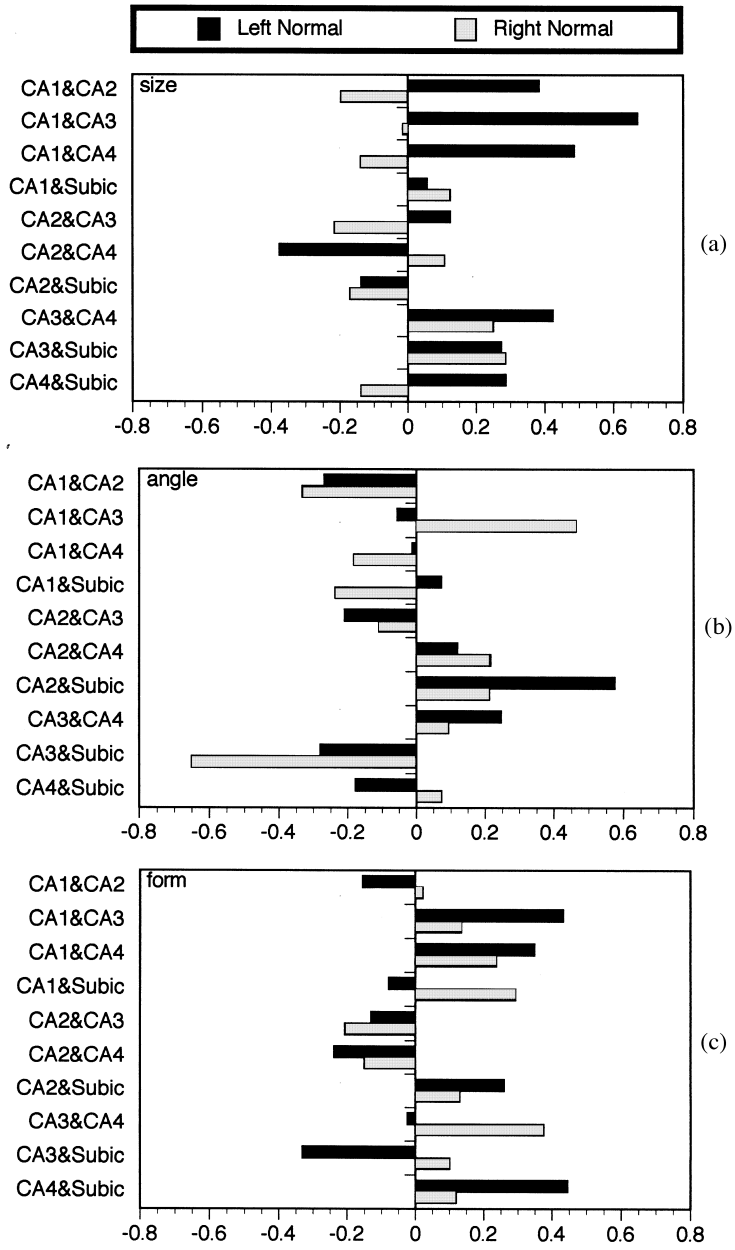


Fig. 1. Normal subjects. A bar graph illustrating correlation positive and negative (Pearson's rho) values between all possible pairings of hippocampal subfields, on each side of the brain separately. (a) Correlations based on the mean value of neuronal soma size in each subfield. Two correlations were significantly above zero (left CA1 and CA3, $P < 0.002$; left CA1 and CA4, $P < 0.04$). (b) Correlations based on the mean value of the variability in orientation angle of the neurons in each subfield (variability itself is a measure of neuronal disarray). One correlation was significant (left CA2 and subiculum, $P < 0.01$). (c) Correlations based on the mean value of neuronal form (calculated by dividing the length of the minor ellipse by the length of the major ellipse fitted around the neuron; this corrects for neuron size). None of the values was significantly different from zero.

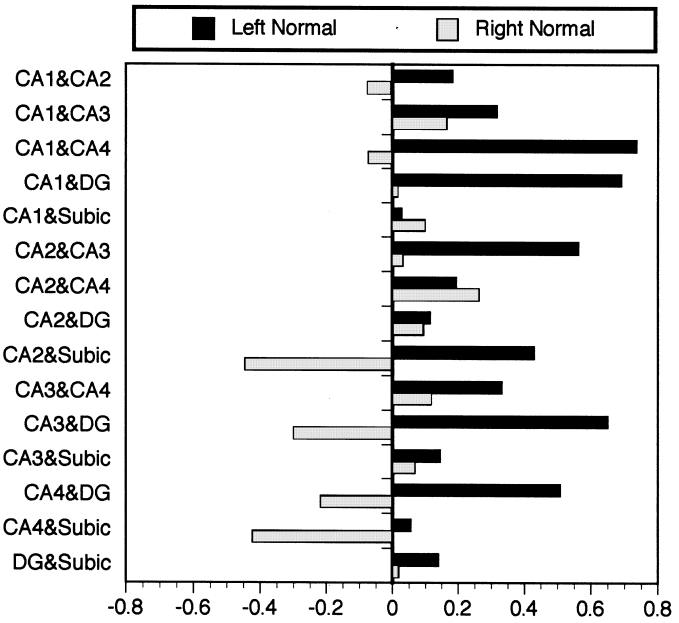


Fig. 2. Normal subjects. A bar graph illustrating correlation values based on mean neuronal density in all possible pairings of hippocampal subfields. In the left side, 5 values were significant (CA1 and CA4, $P < 0.0004$; CA1 and DG, $P < 0.001$; CA4 and DG, $P < 0.03$; CA3 and DG, $P < 0.003$; CA2 and CA3, $P < 0.01$) while in the right none of the values were significant. None of the 'negative' correlations was significant.

CA2 and CA3, $P < 0.01$). Fig. 2 reveals asymmetry in patterns of correlations, with greater fuzziness in regional differentiation in the left than in the right side. The Wilcoxon Sign Test applied to all 15 correlation values produced in each side confirmed asymmetrical correlation patterns (left-side, $z = -3.40$, $P < 0.0007$; right-side, $z = -0.21$, $P < 0.8$).

### 3.2. Schizophrenia

Fig. 3a summarizes the correlation values between pairs of subfields based on neuron size. Four correlations in the left side (none in the right) had values significantly above zero (left CA1 and left CA4, $P < 0.04$; left CA1 and left subiculum, $P < 0.002$; left CA2 and left CA3, $P < 0.03$; left CA2 and left CA4, $P < 0.005$; left CA3 and left CA4, $P < 0.006$). Significant correlations were consistently in the positive direction. The pattern of all 10 correlations produced on each side was symmetrical (Wilcoxon Sign Test: left-side, $z = -2.80$, $P < 0.005$; right-side, $z = -1.98$, $P < 0.04$).

Fig. 3b provides a summary of the correlation values for variability in neuronal orientation angle, and Fig. 3c illustrates the correlation values for form where one correlation value was significantly different from zero (right CA2 and right CA4, $p < 0.05$). The correlation patterns in Fig. 3b,c show largely left–right symmetry, as in the normal subjects.

Fig. 4 provides a summary of neuronal density for correlations between pairs of subfields on each side. Three (positive) correlations had values which were significantly different from zero in the left side (left CA1 and left CA2, $P < 0.04$; left CA1 and left CA3, $P < 0.009$; left CA3 and left CA4, $P < 0.01$), one (positive) value on the right was significant, and two (negative) values in the right were significant (right CA3 and right CA4, $P < 0.003$; right CA3 and right subiculum, $P < 0.01$; right DG and right subiculum, $P < 0.02$).

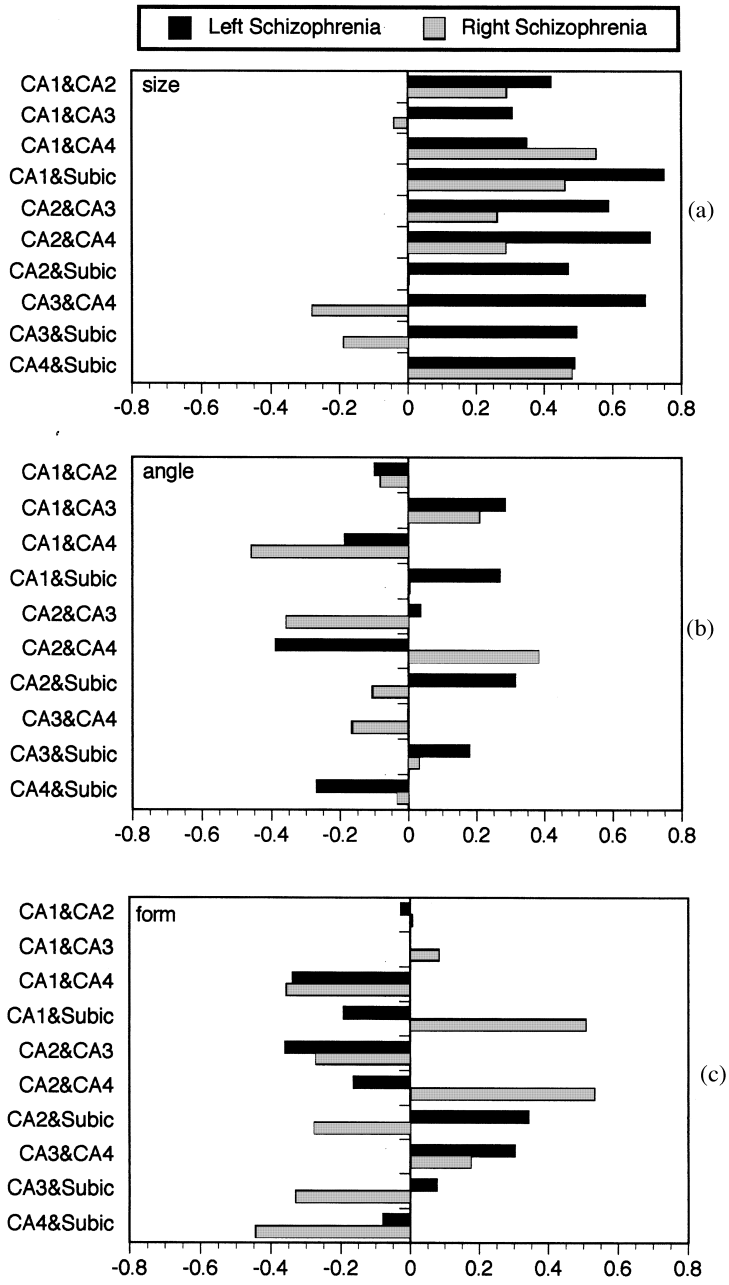


Fig. 3. Schizophrenia. A bar graph illustrating positive and negative correlation (Pearson's rho) values in permutations of all possible pairings of hippocampal subfields, in each side of the brain separately. (a) Correlations based on the mean value of neuronal soma size in each subfield. Four correlations were significantly above zero (left CA1 and CA4, $P < 0.4$; left CA1 and subiculum, $P < 0.002$; left CA2 and CA3, $P < 0.03$; left CA2 and CA4, $P < 0.005$; left CA3 and CA4, $P < 0.006$). Positive values dominated the inter-regional landscape. (b) Correlations based on the mean value of the variability in orientation angle of the neurons in each subfield (variability itself is a measure of neuronal disarray). None of the rho values was significant. (c) Correlations based on the mean value of neuronal form (calculated by dividing the length of the minor ellipse by the length of the major ellipse fitted around the neuron; this formula corrects for neuron size). One correlation value was significant (CA2 and CA4, $P < 0.05$).

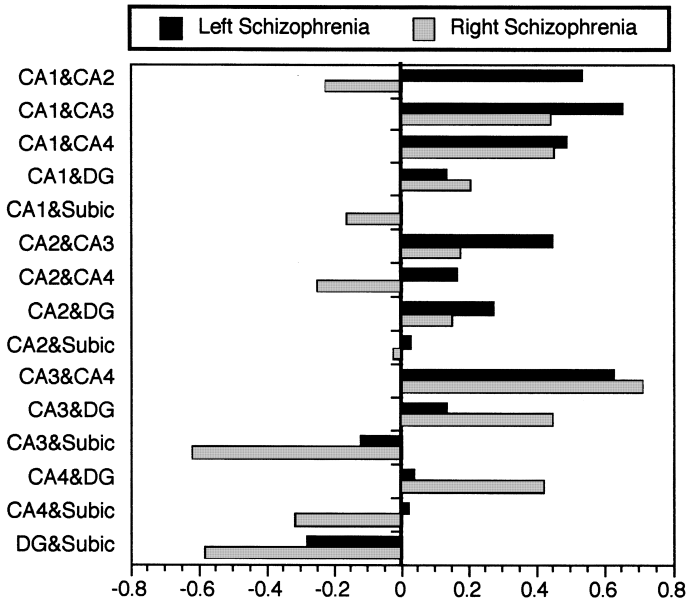


Fig. 4. Schizophrenia. A bar graph illustrating correlation values based on mean neuronal density in each subfield in permutations of all possible pairings of hippocampal subfields. In the left side, three values were significantly different from zero (CA1 and CA2, $P < 0.04$; CA1 and CA3, $P < 0.009$; CA3 and CA4, $P < 0.01$) and three were significant on the right (CA3 and CA4, $P < 0.003$; CA3 and subiculum, $P < 0.01$; DG and subiculum, $P < 0.02$). Two of the 'negative' correlations were significant.

Inspection of Fig. 4 reveals a pattern of regional fuzziness in both sides (Wilcoxon Sign Test: left-side, $z = -2.41$, $P < 0.01$; right-side, $z = -1.98$, $P < 0.04$).

## 4. Discussion

Regional differentiation based on the neuronal parameters of size, form, orientation angle, and density was examined in correlation values between pairs of hippocampal subfields in each side separately. The major interest was in the hemispheric correlation patterns and in patterns that reflect regional 'fuzziness' versus 'distinctiveness', where high positive correlation values imply the former and low correlation values imply the latter. I propose that the inter-regional correlations reflect the computational landscape for memory and cognitive functions. The differences between the computational landscapes observed in normal subjects and in schizophrenia then reflect different functional capacities of the hippocampus.

If the operations of the human hippocampus were represented solely by the canonical circuitry (i.e. synaptic directionality DG/ CA4/ CA3/ CA1/ subiculum), inter-regional correlations would mirror connectivity implied by the circuitry. The fact that this was not the case here suggests the presence in the hippocampus of alternative networks. Here, for example, several significant correlations emerged between the CA2 subfield and other hippocampal subfields, while in the canonical circuitry CA2 is typically left out, being lumped together with subfield CA3; this is despite anatomical evidence indicating the separate cyto-architectural identities of CA2 and CA3 (e.g. (Lorente de No, 1934; Duvernoy, 1988). Alternatively, one could argue that inter-regional correlations that do not reflect the canonical circuitry are spurious, or are not indications of hippocampal synaptic connectivity, but rather of extrinsic influences. However, given certain consistencies in the patterns of the correlations (i.e. hemi-

spheric) and their alteration in disease (e.g. schizophrenia), the inter-regional networks should be given serious consideration.

In fetal brain development, interactions and signals between regional neurons play a critical role in maintaining borders between regions, or, put differently, in regional specificity and identity (Tanabe and Jessell, 1996; Ikeya et al., 1997). Thus, events in early regional morphogenesis would suggest that inter-regional cross-talk establishes a rudimentary neuronal landscape. Such a network may be a source of regulatory effects on the canonical circuitry. It is not unreasonable to suggest that the adult hippocampal landscape reflects the early-sculpted landscape, modified in natural development and growth, from infancy to old age, and expressed in inter-regional correlation values. Experiential effects (e.g. personal, educational, environmental) are likely to have contributed to the modifications as could the operations of the canonical circuitry itself (Zaidel, 1998a) but the extent and scope of the modifications must be self-limiting.

The present findings based on inter-regional correlations contrast with the findings based on ANOVAs applied to each of the neuronal parameters (Zaidel et al., 1997a). Neuronal soma size was found to be smaller than normal in the disease and neuronal soma form in the normal cases was found to be different from cases with schizophrenia (tending to be 'circular' rather than 'triangular'). Mean neuronal density was not left–right asymmetrical within either the normal group or the group with schizophrenia, but the latter group had significantly higher density than normal in the right side (Zaidel et al., 1997a). The picture obtained in analyzing mean values alone (i.e. ANOVAs, *t*-tests) provided only a partial view of the hippocampus; it did not account well for regional relationships (Zaidel, 1995; Zaidel et al., 1993, 1994a)

In the best of circumstances, any direct comparison between the present findings and findings on the various developmental stages of the left and right hippocampus (Duvernoy, 1988; Zaidel et al., 1997c; Zaidel and Esiri, 1997; Zaidel, 1999) would suffer from interpretation difficulties. We would not know whether or not the subjects with schizophrenia did originally have normal hippocampal circuitry (Altman and Bayer, 1990a,b; Angevine and Sidman, 1965). Ruling out either possibility is not trivial given the present set of data.

The canonical circuitry of the hippocampus is based primarily on anatomical and physiological observations in rodents and non-human primates (see Rosene and Van Hoesen, 1987), an approach which ignores the issue of left–right asymmetries in the human brain (Geschwind and Levitsky, 1968; Witelson and Pallie, 1973; Wada and Davies, 1977; Turkewitz, 1988). For example, there is now some evidence for a genetic determination of left–right asymmetry in the mammalian central nervous system (Brueckner et al., 1989; Supp et al., 1997). Nor does it consider hippocampal regional relationships and networks formed by them. I propose that several rudimentary hippocampal circuits as revealed through inter-regional correlations operate in parallel with the canonical circuitry, and may be particularly sensitive to disease processes because of their early morphogenetic origin.

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