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MRI-assessed volume of left and right hippocampi in females correlates with the relative length of the second and fourth fingers (the 2D:4D ratio)

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Abstract

Atrophy of the left or right side of the hippocampus has been related to cognitive deficits and psychiatric disease. In this study, we examined the correlation between the hippocampal volume laterality index and the relative lengths of the second (index finger) and fourth (ring finger) digits (2D:4D) in healthy female subjects. The 2D:4D ratio is fixed in utero, and the ratio is higher in women than in men. There is evidence that this ratio is an indicator of the intrauterine concentration of testosterone, which influences the development of different regions of the brain. Assessing the volume of different parts of the brain of 40 healthy adult female students by magnetic resonance imaging (MRI), we found that the 2D:4D ratio was associated with an asymmetry in the hippocampal sub-regions. Smaller volume on the left side was found in the posterior part of the hippocampus in females with a low (masculine type) 2D:4D ratio. On the other hand, smaller volume on the left side was found in the middle part of the hippocampus in females with a high (female type) 2D:4D ratio. Thus, the development of the middle and posterior regions of the hippocampal formation may respond in opposite ways to prenatal levels of testosterone. Other brain regions such as the amygdala, the cerebral cortex, the total volume hippocampus, and the head of the hippocampus did not show such a difference.

Keywords: Brain laterality; 2D:4D ratio; Testosterone; Hippocampus volume

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1. Introduction

Recent studies support the presence of significant gender differences in several psychiatric disorders that may reflect the interplay of sex hormones as well as neurodevelopmental and psychosocial sex differences (Leung and Chue, 2000). Gonadal hormones, such as androgen, act in an organizational role before birth and influence the development of different brain areas, brain and body asymmetry, handedness, sexual orientation and cognitive skills in humans (Kimura, 1999). In addition to brain laterality differences, other types of sex-dependent traits have been found, such as the relative lengths of the second (index finger) and fourth (ring finger) digits (2D:4D ratio) in the right and left hands in females and males (Manning et al., 1998).

The ratio between the length of the second and fourth digits in the right and left hands has a sexually dimorphic pattern. In comparison to females, males tend to have longer fourth digits in relationship to their second digits.

It is thought that low 2D:4D ratios are associated with high levels of prenatal testosterone and low oestrogen, and that high 2D:4D ratios are associated with low levels of testosterone and high levels of oestrogen in utero because (a) the sex difference in the 2D:4D ratio appears as early as 2 years of age and does not change at puberty (Manning et al., 1998); (b) relative digit lengths are determined by week 14 of pregnancy (Garn et al., 1975); (c) the waist/hip ratio of mothers is negatively related to the 2D:4D ratio of their children (Manning et al., 1999); (d) children with congenital adrenal hyperplasia have lower 2D:4D ratios than population controls (Brown et al., 2001); and (e) mothers with low 2D:4D ratios tend to have high levels of testosterone in the amniotic fluid of their foetuses (Manning, 2002). This correlation between the 2D:4D ratio and hormonal levels in adults may originate from an association between the 2D:4D ratio and prenatal hormonal level, with the 2D:4D ratio in adults reflecting prenatal hormonal conditions (Manning et al., 1998; Manning and Taylor, 2001). The ability of androgenic steroids to influence the 2D:4D ratio is indicated by a study of homosexual men and women. The right-hand 2D:4D ratio of homosexual women is significantly more masculine (i.e. smaller 2D:4D ratio) than that of heterosexual women and does not differ from that of heterosexual men (Williams et al., 2000).

The differentiation of the genital system and the appendicular skeleton in vertebrates is controlled by Homeobox (*Hox*) genes. Hox-d genes play a major role in the formation of an anatomical and physiological subdivision of the gut, the ileocaecal sphincter, and the proper digits, and therefore are important for the development of the lumbosacral area as well as for proper limb and urogenital development (Zákány and Duboule, 1999). The distal limbs and the genital eminence are regions of apical growth and involve epithelial–mesenchymal interactions; they represent morphogenetic ends of the body, digits at the distal end of the limbs (Kondo et al., 1997). Manning et al. (1998) have pointed out that the common control of digit and gonad differentiation raises the possibility that the length pattern of digit formation may relate to spermatogenesis, the intrauterine hormonal concentration and sexually dimorphic differentiation of the central nervous system (Zhao et al., 1999). However, the exact nature of these influences on the developing brain remains unclear.

The prenatal testosterone concentration is critical for the differentiation of the laterality of several parts of the nervous system, and the development of visual–spatial judgment, speed, endurance and physical strength (Geschwind and Galaburda, 1985; Hugdahl, 1996; Kimura, 1999). According to the testosterone hypothesis of the development of brain laterality formulated by Geschwind and Galaburda (1985), testosterone in utero inhibits the normal development of the left hemisphere, thus setting the stage for symmetry rather than asymmetry as a working principle between the cerebral hemispheres.

Significant brain asymmetries in normal subjects are seen in both of the cerebral hemispheres (Galaburda, 1995), as well as in the hippocampus (Pruessner et al., 2001). The hippocampal formation (HF) contains both oestrogen and androgen receptors, and the structure, size, and migration of cells in the hippocampus may partly be determined by these steroids (O'Keefe et al., 1993).

Volumetric differences are frequently found between the two sides of the hippocampus in magnetic resonance imaging (MRI). Unilateral volume decreases or atrophy of the hippocampal formation

has been reported in many chronic neurological (Babb and Brown, 1987; Juhász et al., 1999) and psychiatric diseases (Driessen et al., 2000). MRI studies of hippocampal volume in posttraumatic stress disorder have found that subjects who underwent physical or sexual abuse in childhood show smaller left hippocampal volume relative to matched controls without showing a corresponding decrease in the volumes of the amygdala, the caudate, and the temporal lobe (Bremner et al., 1997). Chronic schizophrenic patients show a bilateral reduction in the volume of the hippocampal formation compared with matched healthy controls. The extent of the reduction has been related to the severity of functional disorganization (inappropriate affect, positive formal thought disorder, and bizarre behavior) but not to psychomotor poverty (apathy, asociality, alogia) or reality distortion (hallucinations, delusions). However, no significant correlation has been reported between the clinical symptoms on psychiatric rating scales and the rate of hippocampus asymmetry (Fukuzako et al., 1997). Shenton et al. (2002) have observed amygdala–hippocampal shape differences in schizophrenia.

Elevated levels of cortisol during depressive episodes and posttraumatic stress could cause hippocampal damage, leading to a reduction in volume (Driessen et al., 2000). Even though the effects of epilepsy (Juhász et al., 1999), traumatic stress disorder, depression and schizophrenia have been examined with MRI (Bremner et al., 2000), very few studies have examined the development of volume differences in healthy subjects.

There are some experimental results on the correlation between intrauterine hormonal concentration, currently circulating hormonal level, verbal recall performance, chronic stress, several psychiatric illnesses, individual brain development, and volume of the hippocampal formation (Bremner et al., 1995; Starkman et al., 1992). However the exact nature of lateral volume differences in the hippocampal formation remains unclear (Sullivan et al., 1995).

In the present study, the 2D:4D ratio was considered as an indicator of intrauterine testosterone concentration. We examined the 2D:4D ratio and circulating endogenous testosterone concentrations in relation to volumetric findings in subregions of the hippocampus in healthy adult women.

2. Methods

2.1. Subjects

Forty female subjects from the general population of the University of Pécs were recruited through advertisements. All volunteers were interviewed to ensure that they had no history of psychiatric or neurological illness. The revised Symptoms Checklist-90 (SCL-90-R, Derogatis, 1977) was used to screen for psychiatric symptoms. All subjects scored in the normal range on the SCL-90-R, were free of chronic medical conditions, and were not taking any medications that could influence the radioimmunoassay results. A full-scale Wechsler IQ (Kun and Szegedi, 2000) score below 100 was a criterion for exclusion from the study. Subjects ranged in age from 19 to 26 years (mean = 21.28, S.D. = 1.58; mean height = 166.3 cm, S.D. = 6.5, Max.: 180, Min.: 152; mean weight = 59.6 kg, S.D. = 6.3, Max.: 84, Min.: 45.2; mean Wechsler IQ = 116.7, S.D. = 5.6, Max.: 126, Min.: 104. All subjects were right-handed as indicated by the Chapman and Chapman (1987) Handedness Scale with right-handed scores from 11 to the upper quartile of the Handedness scores. Subjects were reimbursed for their participation. Permission for the protocol was given by the Regional Research Ethics Committee of the Pécs Medical Center, and participants gave informed consent.

2.2. Procedure

2.2.1. Measurement of second to fourth digit ratio

The method of assessment of the right and left hand fingers was followed as described by Manning (1995). The length of the second and fourth digits was measured on the ventral surface of the hand from the basal crease of the digit proximal to the palm to the tip of the digit (Fig. 1). Vernier calipers were used throughout this study. The measurement was performed three times by the same operator. The digit ratio was calculated by dividing the length of the second digit by that of the fourth digit (2D:4D). The repeatability of similar measurements made directly on digits has been high in previous studies (e.g. Manning et al., 2001; Csathó et al., 2003). Individuals who reported injuries to their second and/or fourth digits were not recruited. The results of the three measures were averaged and con-

sidered as the 2D:4D score. Next, the respective right 2D:4D and left 2D:4D ratios were calculated, and a mean 2D:4D score was derived (right 2D:4D + left 2D:4D / 2D.

2.2.2. MR investigation

MRI-based volumetry was performed in all cases using a previously described method (Watson et al., 1997). All scans were performed on a 1.0 Tesla Siemens Magnetom Impact unit (Siemens Medical, Erlangen, Germany). Volumetric imaging was obtained with a Fast Imaging with Steady State Free Precession (FISP) 3D sequence, with contiguous T1-weighted 1-mm slices, with no interslice gap (repetition time = 30 ms, echo time = 10 ms, slip angle = 40°, matrix = 160 × 256, pixel size = 1.05 × 1.05 mm). Standard head position was used during the measurements, and all data were saved in 8-bit grayscale DICOM format for further analysis.

2.2.3. Image analysis

Images were transferred to a Suse Linux 7.0 based workstation and analyzed using Mass 4.0 and Mass 4.1 MRI analytic software (Medis, Netherlands). The data were obtained in a DICOM 8-bit grayscale format. Six regions of interest (ROI) were measured: hippocampus, amygdala and a 3 mm thickness of hemisphere on both sides in accordance with the anatomic boundaries described below. CSF spaces were excluded from all parenchymal measurements, except the hemisphere. All ROIs were measured sequentially, slice-by-slice (1 mm), using a mouse-driven cursor, for manual tracing. Absolute volumes of right, left, and total hippocampus and amygdala were defined independently by two observers. The volumetric procedure was carried out manually. The interrater reliability index for measuring the volume of the affected structures was: hippocampus $\alpha = 0.96$ and amygdala $\alpha = 0.77$. The averaged volumes were used for further analysis. To assess volume differences in MR images of hemisphere, amygdala, entire hippocampus, and anterior (head), middle (body) and posterior (tail) portions of hippocampus (see Fig. 2. and http://spacelab.btk.pte.hu), we used the volume difference index (VDI), which was calculated as follows: $VDI = (R/L) \times 100) - 100$. R = right side; L = left side volume of the assessed structures. VDI indicates the percentage of the right to left volume ratio (see Table 1). A positive score indicates that the right side is larger than the left side, and a negative score indicates the left side is larger than the right.

Special sub-regions of brain volume were measured to carry out relative volume calculations. Small, well-defined brain regions were drawn from the level of foramen interventrivulare Monroi in the direction of the occipital lobe. The volumes of these 3-mm-thick slices were treated as brain volume (BV). The relative

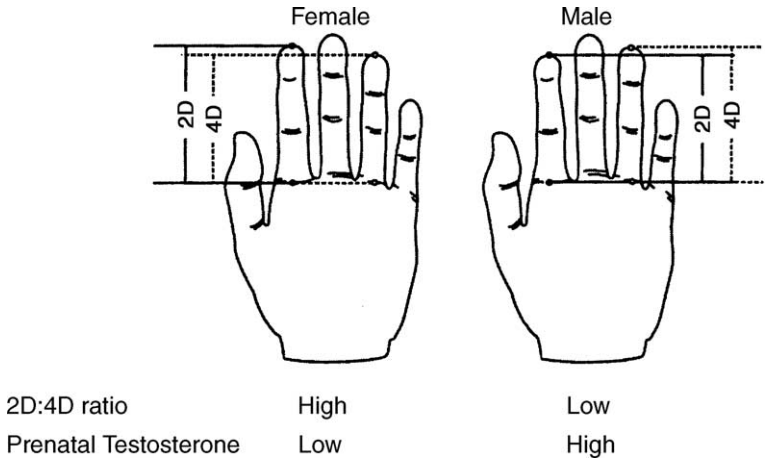

Fig. 1. A schematic representation of a female and a male type left hand. The length of the second digit (2D) and the fourth digit (4D) was measured from the basal crease of the digit to the tip. The 2D:4D ratio was calculated by dividing the length of the second digit by that of the fourth. The 2D:4D ratio was found to be negatively related to prenatal testosterone level.

Table 1
Absolute volumes and volume differences of the compared brain structures (cm^3) in 40 healthy females

Brain regions	Mean ± S.D.	Minimum	Maximum
Right hippocampus	2.128 ± 0.32	1.68	2.91
Left hippocampus	2.078 ± 0.31	1.65	2.91
Total hippocampus	4.206 ± 0.63	3.33	5.82
Hippocampus right–left difference index	3.374 ± 2.08	0	8.26
Right hippocampus head	0.648 ± 0.10	0.475	0.9
Left hippocampus head	0.628 ± 0.10	0.43	0.895
Total hippocampus head	1.276 ± 0.20	0.905	1.795
Head right–left difference index	6.612 ± 4.71	0	17.14
Right hippocampus body	0.72 ± 0.11	0.55	1.025
Left hippocampus body	0.711 ± 0.11	0.55	1.065
Total hippocampus body	1.43 ± 0.22	1.13	2.09
Body right–left difference index	4.207 ± 2.92	0	9.231
Right hippocampus tail	0.758 ± 0.144	0.56	1.14
Left hippocampus tail	0.741 ± 0.143	0.53	1.095
Total hippocampus tail	1.499 ± 0.282	1.1	2.235
Tail lateraity index	5.921 ± 4.11	0	17.004
Right amygdala	1.167 ± 0.194	0.9	1.2585
Left amygdala	1.172 ± 0.207	0.89	1.7
Total amygdala	2.339 ± 0.397	1.81	3.255
Amygdala right–left difference index	3.655 ± 2.907	0	11.21
Right hemisphere	15.27 ± 0.94	13.50	17.52
Left hemisphere	14.97 ± 0.92	13.34	16.77
Total hemisphere	30.24 ± 1.81	26.84	33.99
Hemisphere right–left difference index	2.01 ± 2.6	0	11.3

volumes (RV) were calculated as follows: RV = Absolute volume × (actual BV / average BV).

2.2.4. Anatomic boundaries of the regions of interest

A standard anatomic protocol was used to define the borders of the hippocampus and amygdala published by Watson et al. (1997). The measurements included hippocampus proper, dentate gyrus, subicular complex from subiculum to entorhinal cortex, alveus and fimbria. It is difficult to define the boundaries of the hippocampus from its most anterior portion, the hippocampal head. The most reliable structure separating the head of the hippocampus from the amygdala in this region is the inferior horn of the lateral ventricle. Hence to standardize the measurement, the hippocampus drawing began anteriorly from the first slice where the inferior horn of the lateral ventricle appeared. To outline the boundary, the drawing progressed along the hippocampal sulcus, medially to the inferior horn of the lateral ventricle and turned up laterally along the choroidal fissure. The most posterior section of the hippocampus was measured in the sections with the crus of fornix clearly separated from the hippocampus and its fimbria. The average length measured was 30 mm (for portions of hippocampus, see Fig. 2). Anatomical boundaries of the hippocampus were drawn on the coronal slices. When a contour of the ROI was accepted, the projection area immediately appeared on the sagittal and axial images as well, allowing us to make the appropriate corrections if they were necessary. Separating different subregions on the hippocampal models seems to be promising (Watson et al., 1997; Juhász et al., 1999). Instead of visual subregional separation of the hippocampus, a mechanical partition was used. The distance between the most anterior and the most posterior points of the calculated hippocampus model was divided into three equal parts. The space between the two points of intersection was labeled as the middle part of the hippocampus. Respectively, the first compartment was anterior and the third was considered as a posterior subregion of the hippocampus. However, the anterior part corresponds mostly to the head, the middle part to the body, and the posterior part to the tail of the hippocampus.

2.2.5. Salivary testosterone assay

Subjects provided two samples of saliva for radioimmunoassay of testosterone using a method described previously by Walker (1984) and Johnson et al. (1987). The first sample was collected at the start of a test session assessing cognitive abilities, at 8.00 h a.m. ± 10 min, and the second at the end of the examination at 11 h ± 20 min. In order to avoid saliva impurities, subjects were asked to refrain from eating, drinking (alcohol, coffee or tea), and smoking for at least 5 h prior to saliva collection. Each saliva sample consisted of 8–9 ml of saliva collected in a glass tube pre-treated with sodium acid as a bacterostatic agent. Saliva specimens were stored at −20 °C until the completion of the study, then assayed in a single lot. The radioimmunoassay (RIA) was performed by an experienced RIA technician who was blind to the nature of the study. The procedure employed a single MAIA (BioChem ImmunoSystem) kit for testoster-

Table 2
Rate of volume differences of right and left hemispheres, amygdala, and several portions of hippocampus

	Right	Left	t	$P<$	Diff %
Hippocampus total	2.128 ± 0.32	2.078 ± 0.32	4.792	0.0001	2.4
Hippocampus head	0.648 ± 0.11	0.628 ± 0.10	2.771	0.009	3.1
Hippocampus body	0.72 ± 0.11	0.711 ± 0.12	1.559	ns	1.3
Hippocampus tail	0.75 ± 0.14	0.741 ± 0.14	2.167	0.036	2.3
Hemisphere	15.27 ± 0.94	14.97 ± 0.92	4.127	0.001	1.7
Amygdala	1.167 ± 0.194	1.172 ± 0.208	0.360	ns	0.43

one. The intra-assay coefficient of variation averaged 4.6% and the sensitivity of the assay was 0.69 pmol/l. Each of the saliva samples was assayed in duplicate. The intraclass correlation between duplicates for testosterone was 0.899. For each subject, the mean values from the two saliva samples were used to indicate the endogenous concentration of testosterone. The mean of the sample was 51.23 ± 18.5 pmol/l.

3. Results

The 2D:4D ratio between the right and left hands showed a powerful intersubject consistency (Pearson's $r=0.604$ $P<0.001$). On the other hand, the left and right 2D:4D ratio did not correlate with the current level of circulating testosterone (left $r=-0.022$, NS; right $r=-0.157$, NS).

The right 2D:4D and the left 2D:4D ratios were not related to the weight (right $r=-0.046$, NS; left $r=0.099$, NS) or height (right $r=-0.156$, NS; left $r=0.001$, NS) of the subjects and were not associated (right 2D:4D $r=0.155$, NS; left 2D:4D $r=0.120$, NS) with overall psychiatric symptom factor scores on the SCL-90-R. The right–left difference score of the total hippocampal volume (HV) (weight $r=0.017$, NS; height $r=-0.066$, NS; SCL-90-R, $r=0.101$, NS), anterior HV (weight $r=-0.019$, NS; height $r=-0.155$, NS; SCL-90-R, $r=0.007$, NS), middle HV (weight $r=-0.016$, NS; height $r=-0.023$, NS; SCL-90-R, $r=0.093$, NS), and posterior HV (weight $r=0.084$, NS; height $r=0.123$, NS; SCL-90-R, $r=0.091$, NS) did not relate to these variables.

Table 1 presents the right–left volumes and volume differences of the assessed brain regions. The results indicate that volumes are larger on the right side except for the middle hippocampus portion and the amygdala. Volume significantly differed in the case of the total, anterior and posterior regions of the hippocampus but not for the middle region. In addition, volumes of the right hemisphere were larger than volumes of the left (Table 2).

Univariate regression parameters between each of the right, left and right and left 2D:4D ratio and all assessed brain variables were estimated to determine the predictive power of each brain variable independently. Univariate regression analysis (Table 3) revealed that the rate of the volume difference of the posterior part of the hippocampus was negatively correlated with the right hand (Fig. 3), left hand (Fig. 4) and overall (right+left hand) (Fig. 5) 2D:4D ratios. Furthermore, the volume difference rate of the middle hippocampus correlated with the left hand (Fig. 6) and overall (right+left hand) (Fig. 7) 2D:4D ratios.

Table 3
Regression parameters of the ratio of the second to fourth digit length and the rate of volume differences of several brain regions

	Right 2D/4D ratio		Left 2D/4D ratio		Overall 2D/4D ratio		Testosterone	
	R^2	β	R^2	β	R^2	β	R^2	β
VDI hemisphere	0.001	0.009	0.015	0.124	0.014	0.120	0.014	−0.118
VDI amygdala	0.022	−0.147	0.019	−0.123	0.020	−0.143	0.001	−0.018
VDI hippocampus (H)	0.025	−0.159	0.018	−0.136	0.021	−0.144	0.038	0.196
VDI H Anterior (head)	0.014	−0.116	0.002	−0.048	0.003	−0.053	0.041	0.203
VDI H middle (body)	0.056	0.237	0.120*	0.346	0.110*	0.332	0.004	−0.066
VDI H posterior (tail)	0.139*	−0.336	0.181**	−0.426	0.188**	−0.433	0.004	0.060

* $P<0.05$.
** $P<0.01$, Pearson's correlation.

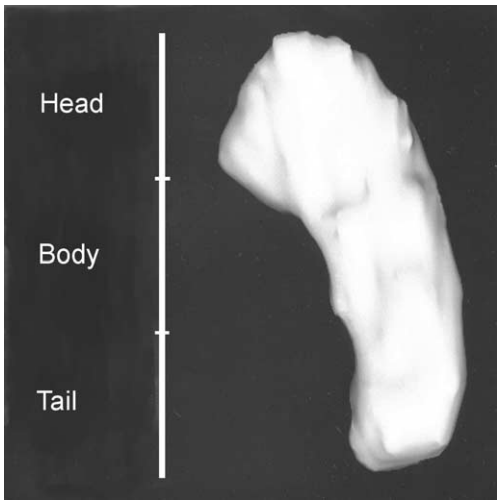

Fig. 2. Three-dimensional illustration of the hippocampus.

At the same time, we did not find volume differences in other assessed symmetrical anatomical structures associating with 2D:4D ratios. The circulating endogenous testosterone concentration was not associated with the analyzed right–left brain volume differences.

These results suggest that different parts of the hippocampus, especially the medial and the posterior regions, develop differently in response to the effects of intrauterine concentration of testosterone. The rate of rightward laterality of the posterior hippocampus is smaller and the middle HV larger in feminine type (2D:4D) female subjects. In contrast, the rate of rightward laterality in masculine type 2D:4D ratios is larger in the posterior hippocampus and smaller in the middle regions in females.

4. Discussion

The results of the present study show that healthy female subjects whose scores on a psychiatric symptoms rating scale are in a normal range, who are in the above average IQ range, and who are without medical illness showed powerful volumetric differences between the left and right sides of several portions of the brain. Except for the middle part of the hippocampus and amygdala, the volumes of the right side of each assessed hippocampal portion and the right hemisphere were larger than the left ones. The difference of the posterior (tail) and middle (body) portions of hippocampus was correlated with the 2D:4D ratios but in an opposite manner. The ratio of the right and left second to fourth digit length (2D:4D) was correlated negatively with the rate of volume difference of the posterior hippocampus, suggesting that intrauterine testosterone level played an essential role in the development of the laterality rate of this formation. Low intrauterine testosterone (feminine type 2D:4D)

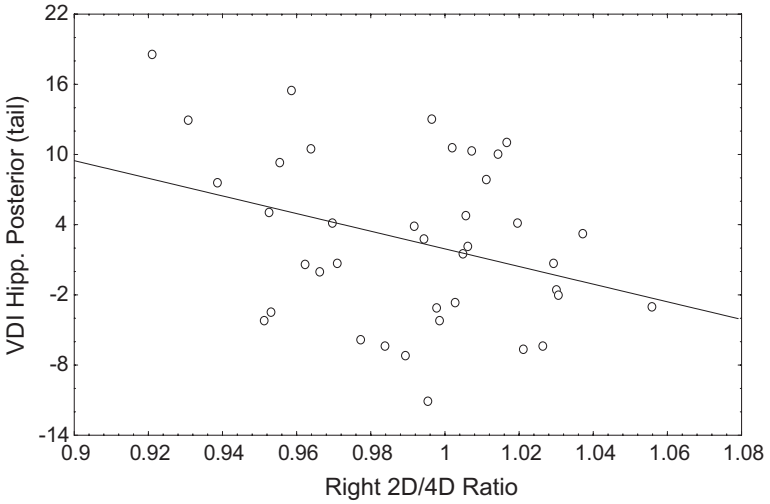

Fig. 3. Regression line for the association between the right 2D:4D ratios and the posterior hippocampus.

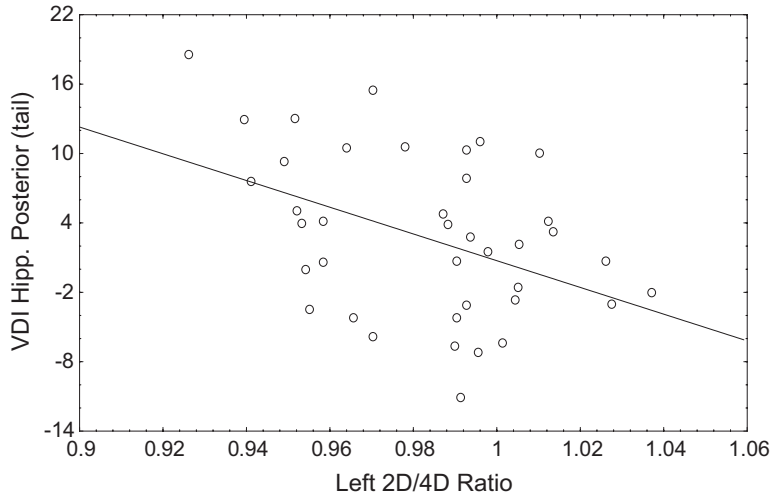

Fig. 4. Regression line for the association between the left 2D:4D ratios and the posterior hippocampus.

was associated with smaller right posterior hippocampus volume. At the same time low intrauterine testosterone was associated with a larger right middle hippocampus volume. In contrast high intrauterine testosterone (masculine type 2D:4D) was associated with larger right posterior and smaller right middle hippocampus volume. Other assessed asymmetric brain structures, amygdalas, hemispheres, and the total HF and anterior region of HF did not relate to 2D:4D ratios. On the other hand circulating testosterone did not correlate with 2D:4D and the analyzed brain asymmetries.

Three theories have been advanced that link prenatal testosterone exposure to individual differences in rate of cerebral lateralization, but most of these have focused on cortical hemispheric differences (Annett, 1985; Geschwind and Galaburda, 1987; Bryden, 1982), pruning of the collosal axons during neonatal

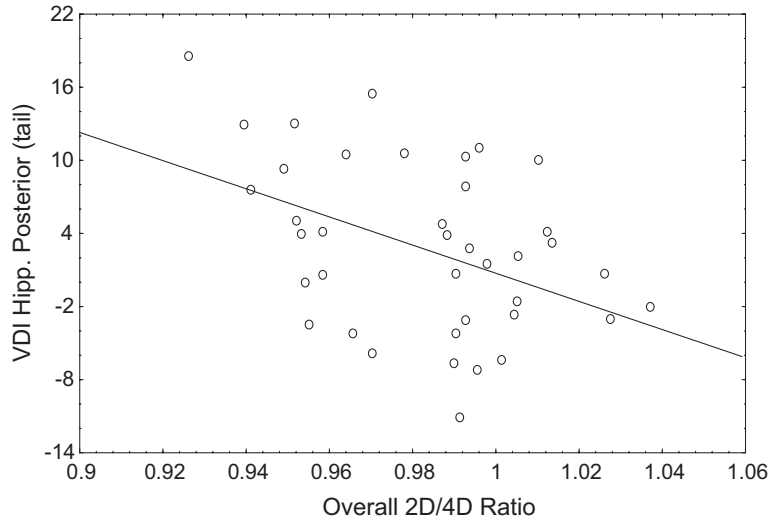

Fig. 5. Regression line for the association between the overall 2D:4D ratios and the posterior hippocampus.

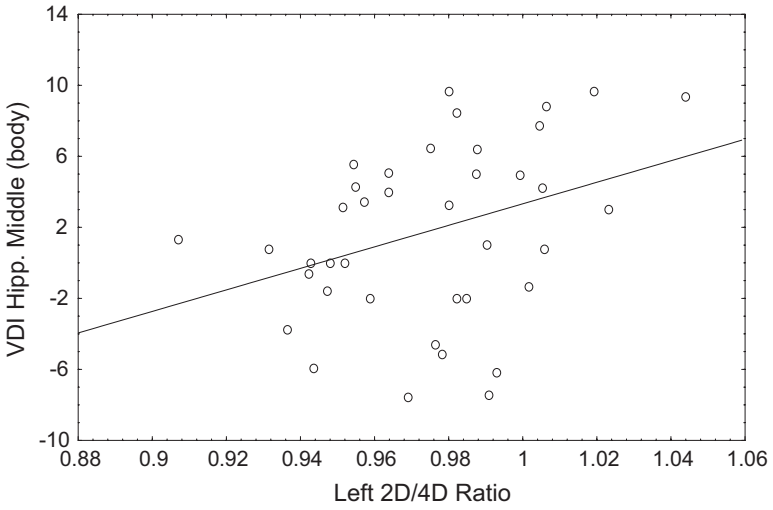

Fig. 6. Regression line for the association between the left 2D:4D ratios and the middle portion of the hippocampus.

development, or callosal size (Witelson, 1991) and do not explain anatomical differences in the sub-cortical areas. According to Geschwind and Galaburda (1985), a high prenatal testosterone level slows the growth of certain areas of the left hemisphere and facilitates the growth of the homologous area of the right one. A higher circulating level of testosterone in utero causes masculine type anatomical, physiological, behavioral and cognitive changes in females. According to our present results, these changes involve sub-cortical asymmetries as well.

The intrauterine hormonal environment is associated with the etiology of a number of diseases such as autism, dyslexia, and immune system disorder that may depend on levels of testosterone (Geschwind and Galaburda, 1987).

In vivo hippocampal volumetric data are not supported by postmortem studies of hippocampal size and cells number (Dwork, 1997). Nevertheless, there are reliable, although contradictory, in vivo data on the role of the hippocampal volume differences in psychiatric and cognitive disorders. The degree of

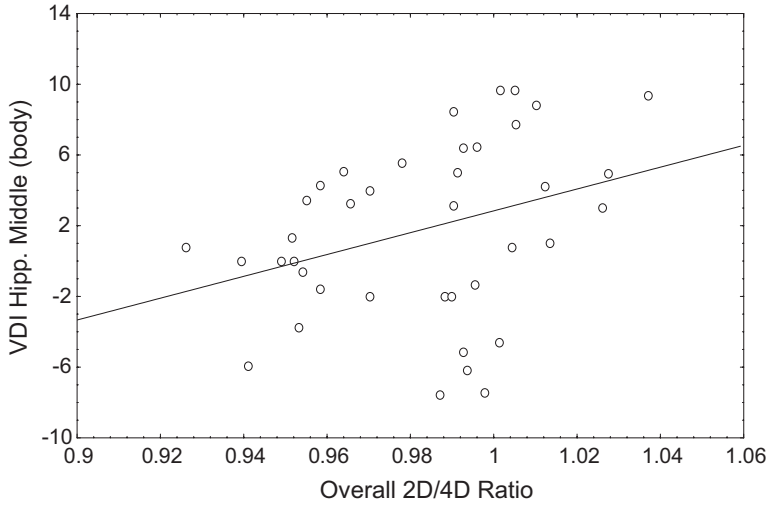

Fig. 7. Regression line for the association between the overall 2D:4D ratios and the middle portion of the hippocampus.

decreased hippocampal volume provides reliable information about the cognitive capacity of the subjects, but we do not know if the differentiation of the hippocampus along the longitudinal axis is a graded or discontinuous process (Jack et al., 1992). Considerable experimental evidence shows that a smaller hippocampus can be found in patients with early psychological traumatization (Driessen et al., 2000), a smaller left hippocampus in patients with drug-resistant depression (Mervaala et al., 2000), and a left-sided volume reduction in schizophrenic patients (Maier et al., 2000). It has been found that the decreases in left-sided posterior hippocampus volume are sensitive to cognitive dysfunctions and subjects at risk for Alzheimer's disease in the elderly population (Wolf et al., 2001). At the same time left hippocampal atrophy was found in traumatically brain-injured patients with episodic memory disorder (Bigler et al., 1995). Smaller size of the left hippocampus was found in patients with combat exposure dissociative symptoms and episodic memory disorders (Gurvits et al., 1996; Stein et al., 1997; Bremner et al., 1997). Furthermore verbal memory positively correlated with both the left and right MRI-determined hippocampal volumes, and the volume of the right hippocampus, relative to the left HF, is positively correlated with visual memory in women with temporal lobe epilepsy (Trenerry et al., 1995).

The psychiatric and neurological literature on the presence of hippocampal sexual dimorphisms that might influence behavior and sex-type-dependent cognition provides only limited evidence to interpret the relations between brain volume, behavior and cognitive function. Studies with animals have demonstrated the sexual dimorphism of cellular morphology of the hippocampus. Female rats had more primary dendrites in the hippocampus, and the mossy fiber system volume was smaller in females compared to males, while the total synapses between CA3 pyramidal cell apical excrescences and mossy fibers was the same (Madeira et al., 1991). The size of this region negatively correlates with performance in the Morris water maze. The exogen enhancement of neonatal testosterone results in a male-like dentate granulate cell layer and improves water maze performance (Roof and Havens, 1992).

The morphological development of the human hippocampal formation can be correlated with cognitive development (Seress, 2001). High levels of prenatal testosterone act on the undifferentiated brain tissue resulting in more masculine behavior, and lower levels of prenatal testosterone may lead to more feminine postnatal behavior (Goy and McEwen, 1980).

A prior study had found that the ratio between the length of the second and fourth digits (2D:4D) is influenced by the concentration of intrauterine testosterone, as well as luteinizing hormone and estrogen level in utero (Manning et al., 1998).

The growth of left hemisphere structures, especially the volume of the left posterior temporal cortex, may be influenced by prenatal testosterone exposure. But after puberty this hormonally driven structural change in the architecture of the brain is finished. That may be the explanation for our finding that circulating testosterone levels are not associated with the hippocampal volume difference in adult females.

It has been suggested that in the early stage of development, a high concentration of testosterone slows the rate of growth of the left hemisphere and disrupts cortical architecture in temporal areas (Geschwind and Galaburda, 1987). However, there are no reliable data on the influence of intrauterine testosterone concentrations on subcortical regions, especially on the growth of the hippocampal formation in humans. The results of studies by Manning (2002) have revealed that the 2D:4D ratio is likely to be correlated with intrauterine testosterone concentrations, and it may well be an indirect indicator of the intrauterine level of testosterone. In the present study we have examined how 2D:4D relates to the growth of subcortical regions in the female brain. We hypothesized that prenatal testosterone would enhance the rate of volume difference of the entire hippocampus. In contrast, it was found that 2D:4D indicates testosterone affects the development of the middle and posterior parts of the hippocampus in opposite ways.

In summary, we can note for certain that there are some cognitive and behavioral experiences that are associated with the volume of the posterior hippocampus (Maguire et al., 2000). Further, the adult hippocampus has a neuronal production capacity but might lose neurons under stress during adulthood (Bremner et al., 1995; Eriksson et al., 1998). Taking into account the volume changes, these differences in the anatomical structure of the brain provide possibilities

to interpret the functions of the affected regions and define their roles in the induction of several psychiatric diseases. The present findings strengthen Shenton et al.'s (2002) results that the volume and shape difference of the hippocampus provides important information toward the analysis of the brain abnormalities in different psychiatric illnesses. Volume difference between the middle and posterior portions of the hippocampus may aid in the understanding of the biological basis of sexually dimorphic cognitive and psychiatric disease related functions in different groups of subjects.

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