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ORIGINAL PAPER

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Hippocampal shape deformity analysis in obsessive–compulsive disorder

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Abstract Abnormalities of orbital prefrontal cortex and caudate nuclei have, thus far, been the main findings regarding the pathophysiology of obsessive–compulsive disorder (OCD). On the other hand, neuroimaging studies have failed to reach a consensus with regard to the issue of hippocampal abnormalities in OCD patients. Shape analysis may facilitate a resolution of the discordance among these former studies by detecting local structural changes, thus enhancing power to discriminate structural differences. It has been suggested that neural circuitry interconnecting brain areas may critically influence the shape of neuroanatomical structures, serving as a rationale for better sensitivity of shape analysis compared to volume analysis, especially in detecting abnormalities of neural circuitry. Shape analysis of the hippocampus was performed in 22 matched pairs of OCD patients and normal control subjects. As a result, we observed a bilateral hippocampal shape deformity including the most prominent characteristic of downward displacement of the head. The hippocampal structural alteration observed in this study indicates that this structure may play a role in the pathophysiology of OCD. Also, further considering the hippocampal neural connections specific to its surface topography, these surface deformities may reflect developmental alterations in these patients with regard to the neural circuitry involving hippocampus.

Key words obsessive–compulsive disorder · hippocampus · MRI · shape analysis

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Introduction

It has been suggested that OCD may involve functional abnormalities of the hippocampus. However, neuroimaging studies incorporating various methods have, thus far, failed to achieve a consensus with regard to this issue. Studies involving positron emission tomography (PET) [1, 2] or functional magnetic resonance imaging (fMRI) [3] have often indicated that hippocampal abnormalities may play a role in the pathophysiology of OCD, although this has occasionally been considered to be of little importance and neglected in the discussion [3]. Also, other functional imaging studies [4, 5] have yielded no evidence of this. In addition, MRI-based volumetric studies [6–8] again with their mixed results have failed to resolve this discordance among functional imaging studies.

The purpose of volumetrically measuring a structure is to eventually determine the functional significance of that structure from the volumetric data. Now, for the sake of communication, let us use the term "unit" to represent each separate hypothetical minimum of the functional or structural entity. Then, in extrapolating the functional significance of a structure from its volume, one structural unit of which the volume is measured may constitute a set of multiple functional units, and vice versa. Thus, the measurement of the overall volume of a structure that does not correspond to one individual functional unit may not reflect the functional alterations of the brain with

adequate sensitivity. Of course, the brain does not appear to be a structure that readily lends itself to the separate anatomical delineation of independent functional units, nor does it seem easy, if even possible, to define individual units of human brain function independently of one another in the first place. One strategy, however, which may be feasible for the moment with regard to approaching the functional secrets of the human brain via structural imaging techniques, is to employ a variety of mutually complementary structural viewpoints, thus augmenting our power to discriminate structural differences and thus unveil some of the brain's previously inscrutable secrets.

Shape analysis may prove to complement this shortcoming of volume analysis, by providing a far more fractionated set of three-dimensional information regarding a structure of interest. In terms of rationale for shape investigation, the hypothesis of tension-based morphogenesis of central nervous system has suggested that neural circuitry interconnecting brain areas may critically influence the shape of specific neuroanatomical structures [9]. On the ground of this theory, it has been suggested that shape analysis may exhibit better sensitivity than volume analysis, especially in detecting neuropsychiatric illnesses involving abnormalities of neural circuitry [10]. Of note is that the hippocampus, along with the olfactory bulb, has been introduced to be a structure of particular interest form the viewpoint of tension-based morphogenesis theory [9].

Shape analysis is a relatively new approach to the delineation of neuroanatomical structures. However, the methodology of this technique has not yet fully crystallized, and the concept is still in the process of being evaluated while being tentatively applied to studies of a variety of mental disorders, including schizophrenia [10–13], major depressive disorder [14], and Alzheimer's type dementia [15]. In a previous study [16], our research group also demonstrated a characteristic hippocampal shape deformity pattern in schizophrenia patients, heralding an original methodological modification of the shape analysis process. We have again applied this method to OCD in the present study.

The purpose of this study is to extend the applicability of the hippocampal shape analysis process, which was previously developed and applied to the study of schizophrenia by our group, to that of OCD. Also, we hoped that the results would provide us with new insights as to the inconsistencies among previous functional and structural imaging studies of the hippocampus in OCD patients.

Methods

Subjects

The two subject groups in the present study consisted of 22 OCD patients (15 men and 7 women, mean age of 26.7 ± 7.2 years), all of whom were right-handed, and an equal number of normal control subjects, all of whom were matched with the patient group for age (mean age of 26.2 ± 6.1 years), sex (15 men and 7 women), handedness (all right-handed), and mean parental socioeconomic status score (patients, 3.2 ± 0.7 and controls, 3.0 ± 0.7) [17]. The patient group was exclusively recruited from the Seoul National University Hospital, in Seoul, Korea, and all of the patients were interviewed and diagnosed with OCD, according to the criteria of the Structured Clinical Interview for DSM-IV [18]. The normal control group was made up of volunteers who had been recruited through newspaper advertisements, and none of the control subjects had ever exhibited a DSM-IV axis I disorder. Also, none of the subjects included in the present study had any history of significant medical or neurological illnesses, nor did they ever meet the DSM-IV criteria for substance abuse. Among the OCD patients, seven were drug-naïve and the other 15 had histories of psychotropic medications for the purpose of anti-obsessional treatment, including four who had a history of anti-psychotic medications. However, all of the patients were free of psychotropic drugs for at least 4 weeks prior to the beginning of the study. The severity of symptoms was measured in the patient group according to the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) [19, 20], and the scores are provided in Table 1 with a summary of the other characteristics of the subjects. Two other studies conducted by our group had been published with these subjects included [8, 21]. This study was approved by the Institutional Review Board for use of human subjects at Seoul National University Hospital. Written, informed consent was provided by all subjects.

Image acquisition and processing

MRI scanning of the entire brain was performed, and 3D T1-weighted spoiled gradient echo MR images were acquired using a 1.5-T General Electric SIGNA system (GE Medical Systems, Milwaukee, WI, USA) with imaging parameters of 1.5 mm sagittal slices, echo time = 5.5 ms, repetition time = 14.4 ms, number of excitation = 1, rotation angle = 20°, field of view = 21 × 21 cm, and matrix = 256 × 256. MRI data were then processed with the ANALYZE software package (version 4.0, Mayo Foundation, USA), as previously described [16].

Table 1 Demographic and clinical characteristics of the subjects

Variables	Control subjects (n = 22)	OCD patients (n = 22)	df	t	P
Age, years (range)	26.2 ± 6.1 (20–43)	26.7 ± 7.2 (18–42)	42	−0.248	0.804
Male/female	15/7	15/7			
Education, years	14.9 ± 1.5	14.2 ± 2.0	42	1.313	0.196
Duration of illness, years		8.2 ± 6.5			
IQ (range)	114.3 ± 9.4 (89–127)	107.9 ± 11.2 (78–126)	42	2.052	0.046
Y-BOCS					
Obsession		12.7 ± 2.8			
Compulsion		10.6 ± 4.5			
Total		22.2 ± 8.5			

Data are given as mean ± SD. SES indicates socioeconomic status; IQ, intelligence quotient; Y-BOCS, Yale-Brown Obsessive Compulsive Scale

Boundary definition and manual delineation

The neuroanatomical boundaries of the hippocampus were manually delineated first on the sagittal slices and then through all the coronal slices taking all three planes into account. The region of interest (ROI) tracing procedure was performed using the ANALYZE ROI module, applying a minor modification of the hippocampal boundary defining method, which was described in a previous report [22]. One rater who was blind to clinical data and diagnostic classification results traced the hippocampus [8]. Inter-rater reliability was evaluated with volumes of regions that two raters had manually traced on a set of 10 MR scans independently of each other. The intra-class correlation coefficients (ICC) were 0.89 and 0.90 for the left and the right hippocampus, respectively.

Preprocessing, parameterized shape model, and alignment process

The ROI data were extracted, then clipped and smoothed for subsequent processing. And then, a three-dimensional volume of hippocampus was rendered, which was corrected for its intra-cranial volume. Cortical surface parameterization was performed in order to determine the homologous surface points between two compared objects, using the deformation process originally developed and described in a previous report [23]. The optimal parameterized model of the surface of the hippocampus was then obtained, yielding 2,562 points constituting the surface of each object. In order to optimize the accuracy of our determinations of the homologous points, an alignment procedure was applied following the deformation process. Coarse and then fine alignment steps were performed, the evaluation of which, according to artificial data, indicated that all of the alignment errors were within 3° for each axis. Detailed descriptions and discussions of this method are available elsewhere [16].

Results

Volume analysis, which compared the amount of space enclosed within the parameterized hippocampal surface via *t*-tests, revealed bilaterally reduced hippocampal volumes in OCD patients as compared to the normal control subjects (Table 2). The exact data values are slightly different from those of our previous reports [8, 21], in which the traced ROIs were measured directly into volume without the preprocessing step included in this study. And between-group differences in shape were expressed numerically, after aligning each shape to a single template, with the mean square difference (MSD) between the corresponding surface points. No correlations were determined to exist between the volume and shape differences (Table 3). The significant differences in shapes between the groups were calculated with *t*-tests and subsequently mapped (Fig. 1).

The most prominent surface deformity, as determined both by the size of the colored area and by the depth of its color, was observed in the anterior portion of the right hippocampus, with its superior surface most profoundly deformed inward, and its inferior surface most prominently deformed outward. A similar surface deformity pattern was observed in the left anterior hippocampus; its superior surface exhibited a profound inward deformity, and its inferior surface exhibited a prominent outward deformity. The superior inward deformity of the head of the right hippocampus was determined with more detail, and was found to wind around mediolaterally and cephalocaudally, extending to the inferior inward deformity of lesser prominence in its body. The left hippocampus exhibited some islands of inward deformity in the inferior portion of its body, corresponding to the similar deformity pattern observed in the right. Bilateral superior outward deformities were observed around the border between the body and the tail, with a lateral outward deformity observed in the tail of the right hippocampus and a medial outward deformity observed in the tail of the left hippocampus.

Table 3 The correlation coefficients between the volume and the shape deformity

	Left	Right
Control subjects	−0.168 (P = 0.454)	−0.299 (P = 0.176)
OCD patients	0.271 (P = 0.223)	−0.166 (P = 0.461)

The variance's mean of distance from the center of object to the boundary vertices were used to represent the shape deformity measurement. Note that the numbers in the blankets are the P values

Discussion

In the present study, we observed a bilateral hippocampal shape deformity in OCD patients, with the most prominent characteristic being a marked downward displacement in its head. The shape deformity findings of this study will be discussed primarily in terms of two dimensions; hippocampal neural connections and hippocampal functions.

Reports regarding distinct neural connections specific to hippocampal topography have been reproduced in monkeys [24–27] with a relatively minor range of discordance in the detailed presentation of the connections. This suggests a comparable pattern of topographical specificity in humans. And apart from the general assumption that distinct connections reflect distinct functions, functional differences between hippocampal regions have actually

Table 2 Bilaterally reduced hippocampal volume in OCD patients compared to normal controls

	Control subjects (n = 22)	OCD patients (n = 22)	df	t	P
Left hippocampus	3.338 ± 0.489	3.030 ± 0.323	42	2.912	<0.01
Right hippocampus	3.192 ± 0.514	2.967 ± 0.384	42	2.631	<0.05

Data are given as mean ± SD. Using the *t*-tests, statistically significant differences were found in both the left and the right volume data

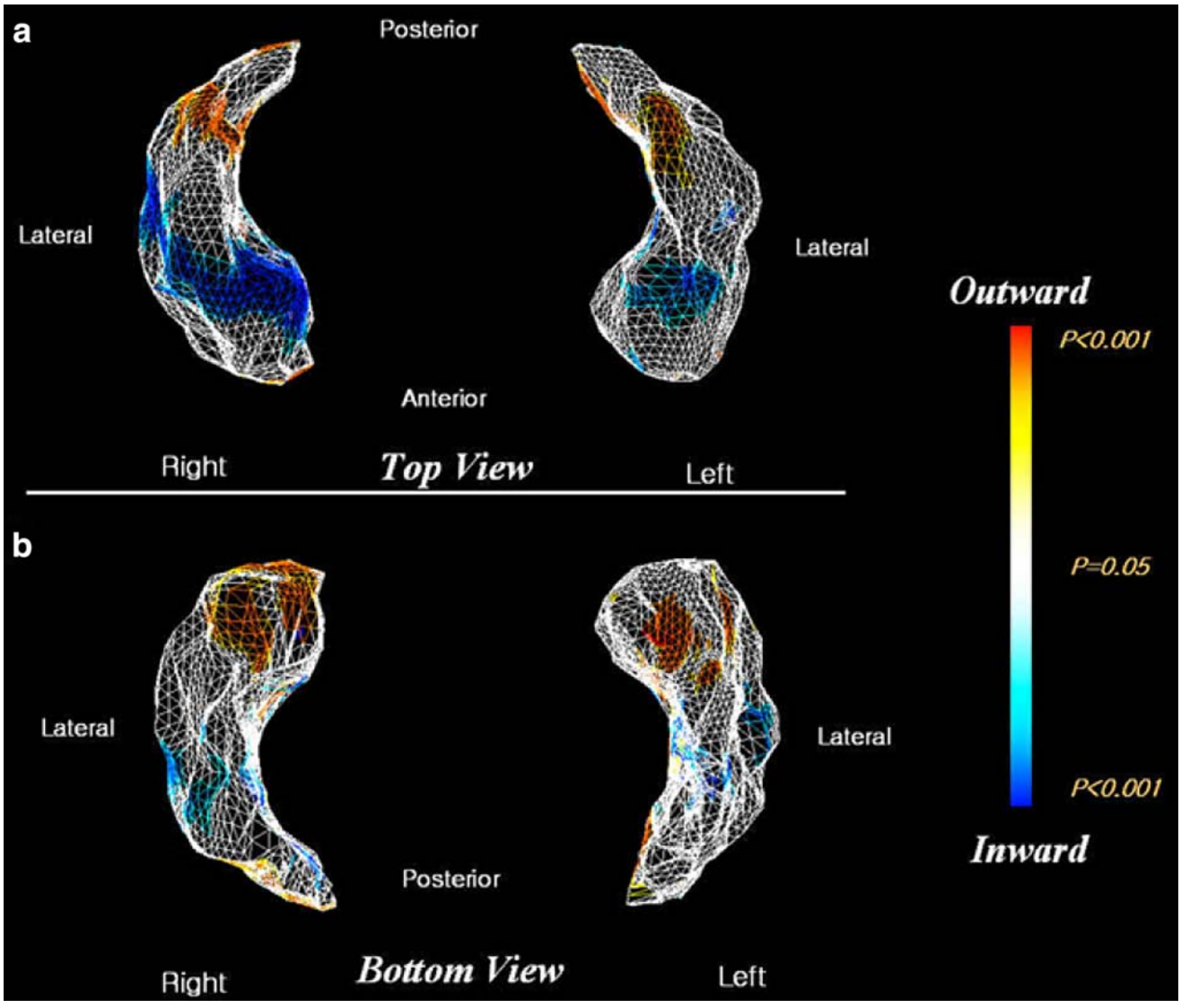

Fig. 1 Hippocampal surface deformity pattern in OCD patients visualized against the hippocampus of normal controls. Statistically significant differences ($P < 0.05$) of shape based on the *t*-tests are mapped. The top and the bottom views of the right and the left hippocampus are presented separately

been reported in humans. More precisely, the anterior and posterior portions of the hippocampus have been determined to be functionally different, especially in the function of memory [28, 29], although consistent reproduction of these findings appears to be lacking.

The main findings of recent studies that have assessed neuropsychological abnormalities in OCD patients can be classified, in general, into cognitive impairments of three distinct fields; memory, visuospatial abilities, and executive functions [30–32]. Of these three fields, memory is probably the most extensively investigated, and it has been consistently suggested that OCD patients exhibit impairments of visuospatial memory. However, memory impairments appear not to be assimilated completely into the most famous and powerful neurobiological hypothesis regarding the pathophysiology of OCD, the fronto-striatal circuitry model. This model has been repeatedly supported by findings from a host of neuroimaging studies, with the orbital prefrontal cortex and caudate nuclei suggested to be principally involved. It was later suggested that the memory impairments associated with OCD might constitute secondary phenomena attributable to the primarily impaired executive functions of organizing and planning [30, 33]; this is a way of interpreting the memory impairments associated with OCD in the context of frontostriatal dysfunction. One study [31], however, demonstrated that the memory impairments associated with OCD are, in part, mediated by impaired organization abilities, thus supporting the findings of former reports, but that OCD patients also exhibit independent nonverbal memory impairments as well.

Under these circumstances, evidence for hippocampal structural alterations in OCD patients, if properly demonstrated, may implicate an actual memory deficit in these patients. Thus, the hippocampal shape deformities observed in this study, together with the observed volume reduction, suggest that an actual memory deficit may play some role in the characteristics of OCD. It is worth noting here that no correlations could be found between the volume and shape deformities, suggesting that shape deformities can be considered as independent measures, which provide information that is separate from the information gleaned from volumetric measurements. Also, the rostrocaudal division of the hippocampus with regard to memory function has been suggested in previous studies [28, 29]. In that regard, the shape deformity findings obtained in the present study, which demonstrate a rough contrast pattern between the anterior and posterior portion of the hippocampus, appear to have some significance. At the present time, however, any conclusions beyond the presumption of a possibility would be premature.

Considering the series of evidences for hippocampal projections into the orbitofrontal cortex (OFC) with topographical specificity within the hippocampus [25–27] as well as within the OFC [27], it remains possible that the hippocampus plays a role within the frontostriatal circuitry model of OCD. However, thus far, evidences as to what is special about these connections in OCD patients, or how they differ from those in normal individuals, are lacking. Showing that the hippocampal sites of those projections are anatomically different in OCD patients may constitute one of these evidences. The hippocampal surface deformity patterns observed in this study, therefore, reflect some type of alteration in the connections of the hippocampus with other structures, thus indirectly suggesting that something in OCD patients occurs via these altered connections. This is a speculation, albeit a primitive one, which could not have been formulated with the results of volume studies. Of note is that the rostral portion of hippocampal fields CA1 and CA1′ was considered to be the primary source of hippocampal projection into the OFC in the aforementioned monkey studies [25, 27]. It was, though, still difficult to elaborate on any of the field-specific or projection-specific shape deformity findings from the results of the present study. This is unfortunate, but it is a point we had missed in the design stage of our study.

There is still a different way to interpret the results of our study. The hippocampal shape deformities found in this study, which demonstrated a marked downward displacement in its head, may in fact reflect a secondary change that results from anatomical alterations of adjacent structures, or it may also be considered as the result of functional influences from distant structures. For example, expansions in the volume of the amygdala might create a pressure effect in the hippocampal head, or the orbitofrontal projection into the hippocampus may somehow stimulate deformations of its surface. Amygdala volume expansion has, in fact, been previously demonstrated in OCD patients, but it was confined only to the left [8], and orbitofrontal projection into the hippocampus requires further investigation for a definitive demonstration of its existence [27]. In any case, the functional significance of hippocampal shape deformities in patients with OCD remains an issue for which further research is required, after which the question as to whether it is primary or secondary may turn out to be of little importance.

Conclusion

Shape analysis appears to efficiently complement conventional volumetric study methods, and provides an alternative point of view in the study of neuroanatomical structures. Of these structures, the hippocampus, the structure of interest in this study, was determined to be significantly deformed in OCD patients relative to that of the normal controls. Further research to determine whether the hippocampus is abnormal in OCD patients and, if it is, in what manner the hippocampus is abnormal in those patients, together with further sophistication of shape analysis methodology are both needed.

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