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The MRI study of the change rules and the correlate mechanisms of amygdale and hippocampus's morphous and function of the depression

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Abstract: *Object Combined with the morphology's measurement and fMRI, the amygdale and hippocampus' morphous and function of the depressive patients were researched, in order to explore the changing regularity and mechanisms. Method Sixty patients (divided equally into mild, moderate and major groups by patient's condition) and 20 healthy control groups were scanned by T1-MR and fMRI for the amygdale and hippocampus' morphous and function, and analyzed the morphous and function's changing regularity comparably. Result The hippocampal volumes of depressive patients were smaller than that of control groups, and the major ones were the most apparent, while the moderate ones were next and the mild ones were last. The amygdale's volumes changed from big to small based on the patient's condition, the mild groups were bigger apparently and the moderate groups were next, but the major groups were smaller. fMRI manifested there were more apparent brain's active signals of the amygdale, hippocampus and their contacts under the stimulations of negative events, and also there is was a regularity of it. The mild groups signals were most significant , the moderate one were degraded, and the major one were weakest while it is higher than the control groups. Conclusion 1.The hippocampal volumes of depressive patients were smaller, maybe made by the effect of the amygdale, and the amygdale's volumes were different based on the patient's condition. 2. There were more apparent brain's active signals of the amygdale, hippocampus and their contacts of depressive patients to the stimulation of negative images.*

Key Words: *Amygdale, Hippocampus, Depression, Volume,*

Depression is a group of mood disorder or emotional disorder taking depression as the major symptom and caused by various reasons, being a mental disease significantly threatening human physical and psychological health. About 2 to 3 in 100 people suffer from depression disorder, while the morbidity keeps increasing. Studies on depressive order have been popular. It has been demonstrated in a great deal of reports that limbic system, including amygdale, hippocampus and other nucleus groups, is closely related with depression [1-2]. Therefore, there are increasing amounts of studies on gray matter nuclei in depression patients, including studies adopting fMRI, MRS, morphological measurements and other measures. Certain outcomes have been achieved, yet there are inadequacies, including inconsistency, no convincing explanations on causes of different nuclei changes, and few control studies concerning depression patients with different disease conditions. Therefore, fMRI and morphological measurements are integrated in this paper to discuss morphological and functional changing rules of amygdale and hippocampus as well as the mechanisms in depression patients with different disease conditions.

I. Material and Method

1. Subject of the Study

The Patient Group: A total of 60 depression patients who were outpatients of Department of Psychiatry in Affiliated Hospital of Jiangsu University and Affiliated No. 4 People's Hospital from December 2008 to March 2010 were enrolled based on the criteria, including inclusion of unipolar depression patients who were affected by this disorder for the first time and exclusion of ones with other mental disorder or drug dependence, ones with severe physical disease or severe drug allergy, and ones with previous cerebral organic disease or other diseases which possible affected brain structure and functions. Based on disease condition, the patient group was divided into three groups, the mild, moderate and severe depression groups. For the mild depression group (male=11 & female=9), the age range is 20 to 37yr with an average age of (26±5)yr, the schooling year is 9 ~ 19(13.4±3.8)yr, the height is 154 ~ 176(161±23)cm, the weight is 49 ~ 79(63±11)kg, and 18 cases are right handedness. For the moderate depression group (male=12 & female=8), the age range is 23 to 40yr with an average age of (28±6)yr, the schooling year is 8 ~ 16(11.3±2.7)yr, the height is 154 ~ 178 (159±16)cm, the weight is 51 ~ 73 (59±8)kg, and 19 cases are right handedness. For the severe depression group (male=13 &

female=7), the age range is 20 to 42yr with an average age of (27±5)yr, the schooling year is 5 ~ 15 (12.3±2.0)yr, the height is 156 ~ 177 (165±19)cm, the weight is 48 ~ 70 (58±9)kg, and 18 cases are right handedness.

The Control Group: The 20 healthy volunteers are employees of our hospital and their relatives, including 16 males and 4 females. The age range is 19 to 39yr with an average age of (27±6)yr, the schooling year is 8 ~ 19 (14.8±2.9)yr, the height is 157 ~ 177 (163±23)cm, the weight is 45 ~ 76 (57±11)kg, and 18 cases are right handedness.

This study was approved by the Hospital Ethics Committee. All volunteers were informed with the study and signed informed consents.

2. Image Collection

Collection of Morphological Images. All study objects sat and rested for 30 min before examinations, were explained with examination procedures to guarantee calmness and high compliance during the procedures; in addition, no head movement was emphasized to guarantee examination quality. Siemens Magnetom Trio Tim 3.0T MR was used for head MRI. The machine was positioned to the median sagittal plane for coronary diagonal plane scan which was parallel to the long axis of brainstem, reaching anterior white commissure for the anterior demarcation and posterior commissure level for the posterior demarcation. The scanning parameters were as follows. Three-dimensional fast low-angle shot (FLASH) sequence was adopted, the radio-frequency pulse TR (time of repetition) was 14ms, the TE (time of echo) was 4.92ms, the Nex (number of excitation) was 2, the FOV (field of view) was 230cm, the matrix was 256×192, the slice thickness was 1.5mm, and no interval was set. The receiving coil was head coil. (2) Collection of Functional Images. Subjects lay on MRI examination couch in the supine position and saw projections on wall through a small mirror on head coil, which were all selected from IAPS (International Affective Picture System). Firstly, the subjects watched a total of 50 pictures which caused negative emotions. One picture was watched once and for 10 seconds. Subjects were required to try their best to memorized contents of the pictures. The scanning parameters were as follows. Single shot GRE-EPI sequence was adopted for scanning of the transverse section, the TR was 3000ms, the TE was 39ms, the FA was 90°, the matrix was 64×64, the NEX was 1, the FOV was 192mm, the slice thickness was 1.5mm, the interval was 0.75mm, and the scan was totally identical to T1WI axial position.

3. Image Processing

Processing of Morphological Images. Segmentation of amygdala and hippocampus images were conducted according to method presented in Brabec J, Nikolai V et al [3-4]. MRIs of all subjects were sketched by three trained physician of the department with the blind method on the basis of high field intensity MRI. Kappa values were analyzed to determine whether there was a high consistency of tested results made by the three physicians; average values were taken for computation. Areas sketched for every slice were added one by one and multiplied by the slice thickness to achieve unilateral volume [V= (S1+S2+……Sn) × the slice thickness]. In order to eliminate the impacts of individual head size on above data, original volumes were processed with normalization to achieve relative volumes. (2) Processing of Functional Images. SPM5 software was used. Images were firstly adjusted and matched, corrected for head movements, and then spatially normalized according to Talairach standardized human brain atlas. With 3mm×3mm×3mm as the volume unit for sampling, normalized data smoothing was realized with FWHM8mm. Corresponding to experimental duties in every sequence, functional models were then constructed. Finally, functional data of same duty were added together and averaged to achieve brain activation maps of the subjects.

4. Statistical Process:

Morphology Measurements: This study is a cross-sectional study with complete random design and data is expressed in $\overline{X} \pm s$. Levene's was adopted for homogeneity test of variance; variance analysis and Dunnett-t test comparing average values between multiple experimental groups and a control group were adopt for achieved data. SPSS12.0 software was used for statistical analysis and $P<0.05$ was determined to be statistical significant. Functional Measurements: Active areas appeared in subjects' functional images were recorded and signals of different brain active regions were compared. Methods provided by SPM5 software was adopted for all statistical processing of fMRI data.

II. Results

1. The Case Group and the Control Group show no statistically significant differences of age, gender, handedness, schooling year, weight and height ($P>0.05$; See Table 3). It is determined by Kappa value that results measured by the three physicians show high consistency (a Kappa value of 0.73). Bilateral amygdala and

hippocampus volumes conform to normal distributions and show homogeneity of variance in the Control Group as well as the Minor, Moderate and Severe Depression Groups. The averages of amygdala and hippocampus volumes are not completely equal in the Control Group and the three Depression Groups (See Table 2). For the bilateral amygdala volumes in the Patient Group, the volume in the Mild Depression Group is significantly larger than the Control Group (left Dunnett-t=4.78, P <0.001; right Dunnett-t=5.05, P <0.001); the volume in the Moderate Depression Group is also larger than the Control Group, but not as significant as the Mild Depression Group (left Dunnett-t=2.83, P <0.05; right Dunnett-t=2.76, P <0.05); and the volume is significantly smaller in the Severe Depression Group than the Control Group (left Dunnett-t=-6.81, P <0.001; right Dunnett-t=-6.97, P <0.001) . See Fig 1-4. Bilateral hippocampus volumes in the three Depression Group are all smaller than the Control Group, but with different significant levels. The volume in the Severe Depression Group decreases most significantly (left Dunnett-t=-10.03, P <0.001; right Dunnett-t=-9.15, P <0.001), the decrease in the Moderate Depression Group is secondly significant (left Dunnett-t=-3.01, P <0.05; right Dunnett-t=-2.99, P <0.05) and the difference between the Mild Depression Group and the Control Group is least obvious and shows no statistical significance (Left Dunnett-t=-1.44, P >0.05; right Dunnett-t=-1.57 , P >0.05). See Fig 1-4.

Table 1--Comparison of Data between the Control Group and the Depression Groups

	CG	MIDG	MODG	SDG	*P*
Age（years）[a]	27±6	26±5	28±6	27±5	>0.05[a]
Male/Female[b]	16/4	11/9	12/8	13/7	>0.05[b]
Handedness (right/left)[b]	18/2	18/2	19/1	18/2	>0.05[b]
Schooling Years (yr)[b]	14.8±2.9	13.4±3.8	11.3±2.7	12.3±2.0	>0.05[b]
Weight (KG)[a]	57±11	63±11	59±8	58±9	>0.05[a]
Height (cm)[a]	163±23	161±23	159±16	165±19	>0.05[a]

CG: the Control Group; MIDG: the Mild Depression Group; MODG: the Moderate Depression Group; SDG: the Severe Depression Group; a signifies variance analysis, P>0.05; b signifies chi-square test.

Table 2--Bilateral Amygdala and Hippocampus Volumes of the Control Group and the Depression Groups

	Amygdala		Hippocampus	
	Left	Right	Left	Right
CG	1762±184.8	1749±182.0	2296±201.8	2283±198.7
MIDG	1992±199.6	1989±190.9	2207±189.0	2210±191.4
MODG	1889±192.2	1896±194.7	2127±180.1	2135±183.2
SDG	1539±178.5	1543±180.4	1978±176.5	1981±171.1
	$F_{(3, 76)}$ =7.6, *P*<0.001	$F_{(3, 76)}$ =7.1, *P*<0.001	$F_{(3, 76)}$ =11.2, *P*<0.001	$F_{(3, 76)}$ =10.7, *P*<0.001

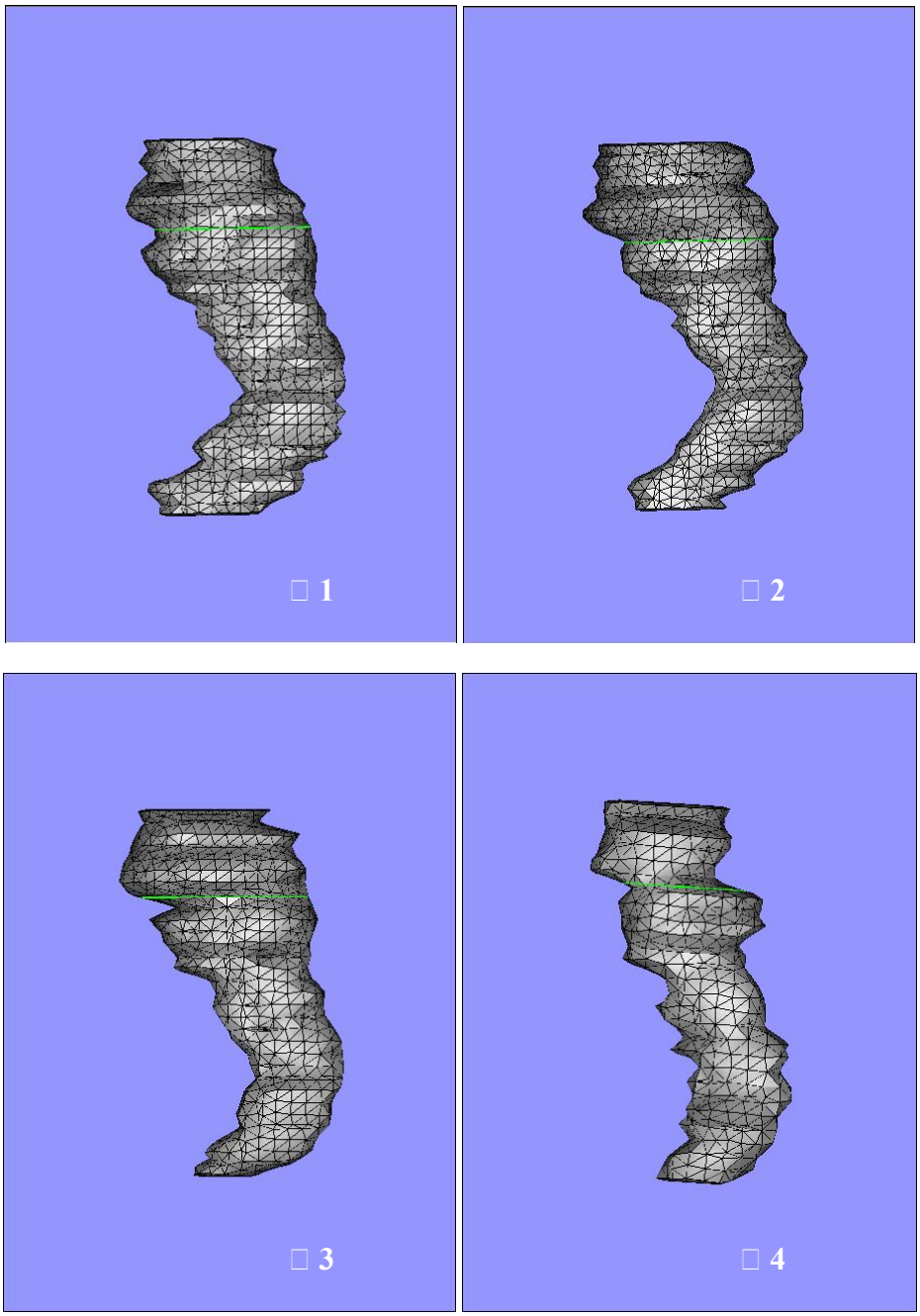

Fig. 1-4 Reconstructed images of amygdala and hippocampus in the Control Group and the Mild, Moderate and Severe Depression Groups. The parts above the green lines represent the amygdala and the parts below represent the hippocampus. It is shown in the figures that the volume of amygdala of amygdala shows a tendency of increasing to decreasing in the Depression Groups, while the volume of hippocampus shows a continuously decreasing trend.

2. It is indicated by fMRI that amygdala, hippocampus and interconnection of the two all show obvious bran active signals to negative picture in the Control Group and the Patient Group (See Fig. 5) and there is a certain rule. The signals showed by amygdala and the interconnection are most significant in the Mild Depression Group and are reduced in the Moderate Depression Group, yet both are higher than in the Control Group; the signals in the Severe Depression Group is weakest among the groups and lower than the Control Group (See Fig. 6-9).

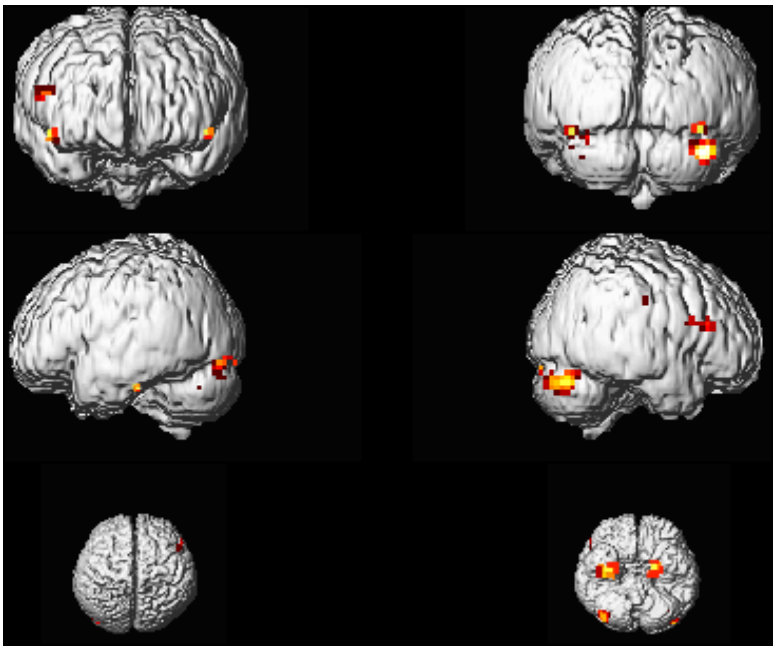

Fig. 5: It is indicated by 3-D brain functional images that amygdala, hippocampus and the interconnection show obvious brain active signals in the depression patients.

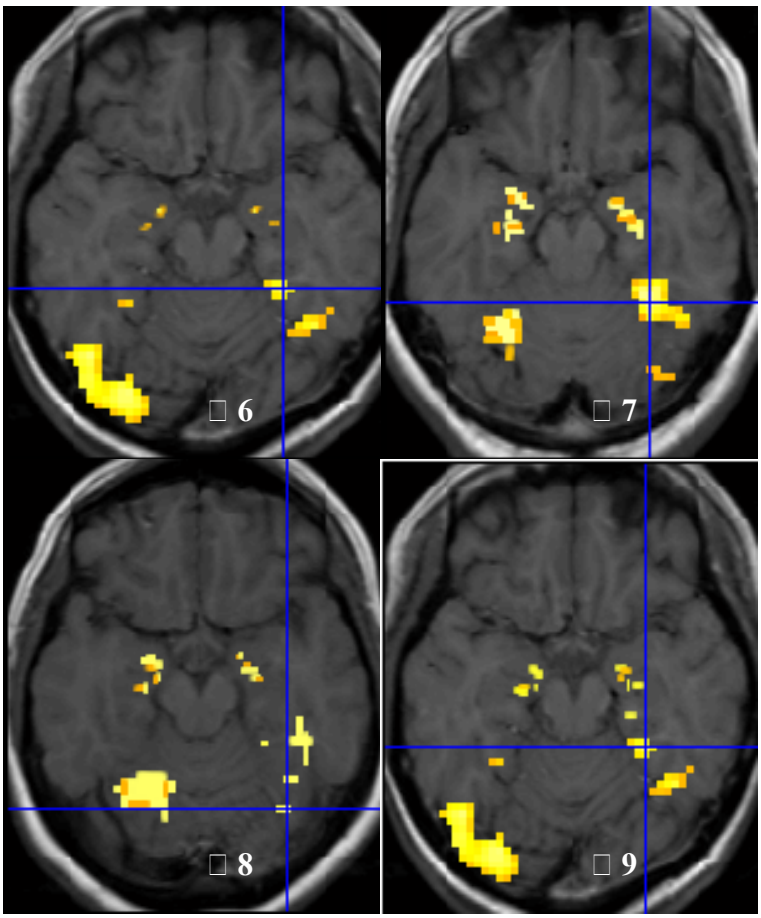

Fig. 6-9 Brain active signals under stimulations of negative pictures of the Control Group and the Depression Groups are showed. Image 6, 7, 8 and 9 represent images of the Control Group, the MIDG, the MODG and the SDG respectively. It is ranked as the MIDG, the MODG, the SDG and the Control Group from ones with intense signals to weak signals.

III. Discussion

Both amygdala and hippocampus are important nuclei of limbic system, majorly involving awakening, behavior, autonomic nerve reaction, reward reaction, generation and introduction emotions trusted by various information of cerebral cortex and nonspecific control of emotional reaction. It has been demonstrated that amygdala, hippocampus and other related gray nuclei structural changes exist in patients with mental disorder, especially depression [1-2]. Many scholars attempted to study pathogenesis of depression on the basis, but achieved different outcomes. For example, it is reported in Velakoulis D et al [5] that amygdala volume increases in depression patients, but it is showed in Savitz J et al [6] that the volume of amygdala decreases. In addition, there is little report on volume and functional changes of amygdala and hippocampus in patients with different disease severities. Therefore, this study aims at analyzing morphological and functional changes of amygdala and hippocampus in patients with depression of different severities and to discuss pathogenesis of depression.

After comparative analysis on bilateral amygdala and hippocampus volume measurements between the Control Group and the Patient Groups, it is found that the volume of normal left hippocampus is 2296±201.8 mm3 and the right is 2283±198.7 mm3, which are basically consistent with results of LI Yue-Feng's study [7] (Our previous study on measurements of hippocampus volumes was published in Volume 43 of Chinese Journal of Radiology). However, results concerning amygdala volume are different. In our measurements, the relative volume of left amygdala is 1762±184.8 mm3 and the right is 1749±182.0 mm3 in the Control Group; the absolute volume of the left side is 1927±194.1 mm3, and the right is 1935±187.8 mm3. As it was reported that the measurement of amygdala specimen is 0.6-1.6 cm3, it was once believed that measurement values achieved by MR were mostly slightly than actual values. It was believed by Brabec J et al., [3] that the phenomenon was caused by relatively small sample sizes (all below 3 cases) for specimen measurements and adoption of different measurement schemes. It is believed by the author that moisture loss, tissue collapse and other factors of specimen tissues should be considered for cases of specimen measurements. It was reported that volume of amygdala is measured as 1-4 $cm^3$with MR technique. Our measurement results fall in the range and are basically consistent with reports of recent years [8].

It is indicated in this paper that volumes of bilateral hippocampus in the Depression Groups are all smaller than the Control Group. The decrease of hippocampus volume has been reported a lot, such as the hypothesis of catecholamine and the receptor, the hypothesis of 5-hydroxytryptamine and the receptor, the hypothesis of multiple amine metabolic disorders, the hypothesis of cholinergic-adrenal gland balance disorder, and the hypothesis of memory neuroendocrine. Similarities of these hypotheses lie on organic damage of hippocampus caused under stress conditions and final volume reduction caused by decrease of neuron amount. However, viewed from Mild, Moderate and Severe Depression Groups, the volume decrease is most significant in the Severe Group, while the decrease of the Mild Group is merely numerical reduction without statistical difference and the decreases in the Moderate Group is between the two, suggesting a gradual change of hippocampus in the Depression Groups. Viewed from functional structure, amygdala realizes memory and emotion activities by regulating and controlling hippocampus and amygdala and hippocampus depend on each other to realize their own functions. It is found by using fMRI that when patients are receiving negative stimulations, activities of amygdala, hippocampus and the interconnection increase obviously. The result is basically identical to Surguladze S [9]. Therefore, we can believe that the reduction of hippocampus volume might be resulted from stress of amygdala.

The change of amygdala volume seems to show certain regularity that the volume of amygdala increases significantly in the MIDG and less significantly in the MODG, but decreases in the SDG, being considerably different from previous literatures, which showed sole increasing or decreasing of amygdala in depression patients. When integrating changes of hippocampus volume, which slightly decreases in mild depression cases, obviously decreases in moderate cases and significantly decreases in severe cases, and fMRI results, that amygdala, hippocampus and the interconnection show relatively remarkable brain active signals to negative picture stimulations (the signals are mostly significant in mild cases, are slightly reduced in the moderate cases and are weakest in the severe cases), it is believed that, when the depression is mild, amygdala shows more intensive reactions to negative picture stimulations [10] with increased activities, increased blood flow and increased volume compensation, posing impacts on hippocampus functions and structure via amygdala-hippocampus functional axis; when the depression is moderate, activities of amygdala are slightly decreased for excitatory toxicity, while functions and structure of hippocampus changes continuously to obvious levels; when the depression is severe, activities of amygdala decrease significantly, resulting in decreased volume, and hippocampus structure and functions show significant decrease, eventually leading to significant decreases of both volumes. It was also found by Hamilton JP [11] that amygdala and hippocampus showed significant correlations with disease severity in depression patients. The changes of amygdala and hippocampus in depression patients might explain why amygdala in depression patients was reported to be increased or decreased by different scholars, as different results might be caused by different severities in subjects.

By integrating morphological and functional methods, changing rules of amygdala and hippocampus and the mechanism in depression patients are preliminarily discussed in this paper. Due to the limitations of sample size and trial condition, a study with follow-ups as well as multiple and comprehensive MRI analysis could not be conducted and further study is required.

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