Voxel-based morphometry study of the insular cortex in bipolar depression

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ABSTRACT
Bipolar depression (BD) is a common psychiatric illness characterized by deficits in emotional and cognitive processing. Abnormalities in the subregions of the insula are common findings in neuroanatomical studies of patients with bipolar disorder. However, the specific relationships between morphometric changes in specific insular subregions and the pathogenesis of BD are not clear. In this study, structural magnetic resonance imaging (MRI) was used to investigate gray matter volume abnormalities in the insular subregion in 27 patients with BD and in 27 age and sex-matched controls. Using DARTEL (diffeomorphic anatomical registration through exponentiated lie algebra) for voxel-based morphometry (VBM), we examined changes in regional gray matter volumes of the insula in patients with BD. As compared with healthy controls, the BD patients showed decreased gray matter volumes in the right posterior insula and left ventral anterior insula and increased gray matter volumes in the left dorsal anterior insula. Consistent with the emerging theory of insular interference as a contributor to emotional-cognitive dysregulation, the current findings suggest that the insular cortex may be involved in the neural substrates of BD.

1. Introduction

Bipolar depression (BD) is a common psychiatric illness characterized by depressive and manic phases alternating with variable inter-episode periods of remission (Nikolaus et al., 2012). Among the two primary episodes (depression and mania) in BD, depressive symptomatology predominates during the pervasive illness phase and is associated with the greatest burden of depressive morbidity (Judd et al., 2002, 2003). Moreover, depressive symptomatology is related to poor psychosocial functioning (Altshuler et al., 2006; Bonnin et al., 2010) and to the risk of disability and suicide (Baldessarini et al., 2010; Reinares et al., 2013). In spite of the burden of depressive morbidity, treatment options for BD are limited (Hirschfeld and Vornik, 2004; Baldessarini et al., 2010; Sienaert et al., 2013). For these reasons, there is a compelling need to investigate the pathophysiologic mechanisms of BD.

A brain area with potential significance in BD is the insula. According to cytoarchitectural, functional, and fiber tract tracing studies, the insula has three distinct subregions (Mesulam and Mufson, 1982a, 1982b; Mufson and Mesulam, 1982; Deen et al., 2011). On a large scale, the insular cortex is divided into anterior and posterior portions by the central insular sulcus (Affif and Mertens, 2010). The anterior insula can be further separated into a ventral and a dorsal part according to cytoarchitecture (Flynn et al., 1999). The ventral anterior insula is composed of agranular cells with indistinct laminar structure, while the dorsal anterior...
insular is composed of dysgranular cells with incomplete laminar structure. The posterior insula is composed of a granular region and an adjacent dysgranular region (Wyllie and Tregellas, 2010). The ventral anterior insula is interconnected with the limbic regions, e.g., the amygdala and the ventral striatum; the dorsal anterior insula is interconnected with the frontal operculum or anterior cingulate cortex; and the posterior insula is interconnected with the parietal, occipital and temporal cortices (Deen et al., 2011). Importantly, the human insula, which links to number of cortical areas through different neural pathways, may have multiple functional roles, including emotion, cognition, and sensory perception (Nieuwenhuys, 2012).

Functional studies have supported this tripartite subdivision of the insula by associating the dorsoanterior, ventroanterior, and posterior insular regions with cognitive, affective-chemosensory, and sensorimotor processing, respectively (Nelson et al., 2010; Cauda et al., 2011; Deen et al., 2011; Kelly et al., 2012; Chang et al., 2013). Furthermore, meta-analyses of task-based functional magnetic resonance imaging (fMRI) studies have further documented functional differences between the anterior insular subregion and the posterior insular subregion: the former subregion is more relevant to cognition and emotional/social behaviors, while the latter is more related to sensory perception and motor-related functions (Mutschler et al., 2009; Kurth et al., 2010; Cauda et al., 2012; Kelly et al., 2012; Chang et al., 2013). Taken together, the findings from structural and functional neuroimaging studies suggest that the insular cortex is an interface for integrating the disparate functional systems involved in feelings, cognition, and action (Erberich et al., 2006; Craig, 2009; Kurth et al., 2010; Menon and Uddin, 2010), and different subregions may serve different roles. However, the specific relationships between dysfunctions in insular subregions and the pathogenesis of BD are not clear. In this study we examine the hypothesis that morphometric changes in one or more insular subregions are related to BD.

Studies on structural and functional brain changes in BD patients have found alterations in cortico-limbic systems, including the inferior frontal gyrus, anterior cingulate cortex, amygdala, and insula (Bora et al., 2010, 2012; Ellison-Wright and Bullmore, 2010; Selvaraj et al., 2012). As one of the core regions in the limbic system, the insular cortex may be implicated in the etiology of BD. Chai et al. (2011) found positive correlations between the medial prefrontal gyrus and the anterior insula. Xu et al. (2014) showed increased amplitude of low-frequency fluctuations in the insula of patients with bipolar disorder, and Liu et al. (2012a) reported that BD patients had increased amplitude of low-frequency fluctuations in the left insula relative to healthy controls. Matsuo et al. (2012) reported reduced left anterior insular gray matter volumes in BD type I patients and their unaffected first degree relatives. Lochhead et al. (2004) reported larger volumes in the left insular cortex of 11 BD patients compared with 31 healthy volunteers using optimized voxel-based morphometry (VBM). Takahashi et al. (2010) found an inverse correlation between the number of depressive episodes and the volume of the anterior insular cortex in BD patients. Taken together, these findings suggest that insular dysfunction may play a role in the pathogenesis of BD.

Previous region of interest (ROI) analyses are limited because they rely upon the manual identification of anatomical areas and, as a result, have been inconsistently validated (Konarski et al., 2008). Furthermore, ROI analyses are user-dependent and focus only on specific hypothesized brain regions (Lee et al., 2011). Magnetic resonance imaging (MRI) studies using VBM (Ashburner and Friston, 2000) provide an alternative and complementary image analysis technique, which is largely operator-independent and allows voxel-wise comparison of the brain (Ridgway et al., 2008). It also permits comprehensive and systematic assessment without operator bias (Bora et al., 2010). Thus, this method is suitable for the exploration of subtle volume abnormalities in the subregions of the insular cortex that are hypothetically related to BD.

The current study used VBM to investigate potential differences in insular subregions between BD patients and healthy controls and to examine clinical correlates of anatomical findings. We hypothesized that (1) BD patients would show volumetric changes in specific insular subregions when compared with control subjects and (2) the VBM changes in these insular subregions would be correlated with clinical parameters.

2. Methods

2.1. Participants

The participants were 27 BD patients who were currently depressed and 27 age-, sex- and educational level-matched healthy subjects. Ages in the two groups were 32.04 ± 11.20 years for the BD patients, and 32.59 ± 11.76 years for the healthy control participants (t = −0.18, p = 0.86). All of the BD patients in the present study are BD type 1 patients who met the following criteria: (1) right handedness; (2) no history of neurological or chronic medical illness; (3) no history of the DSM-IV criteria for psychiatric disorders other than BD including schizophrenia, schizoaffective disorder, obsessive–compulsive disorder, or anxiety disorder as a primary diagnosis; (4) met the Structured Clinical Interview for DSM-IV Axis I/II Disorders (SCID) criteria for bipolar disorder and were currently depressed (Young Mania Rating Scale (YMRS; Young et al., 1978) score < 7) or were in the midst of a depressive episode (17-item Hamilton Depression Rating Scale (HAMD; Hamilton, 1967) score ≥ 17); (5) no history of trauma resulting in loss of consciousness; (6) no other axis-I comorbidities, such as attention deficit hyperactivity disorder, substance abuse, substance dependence or axis-II disorder.

The BD patients were recruited consecutively from the outpatient clinic in the Center of the Treatment for Depressive Disorders, Beijing Anding Hospital. Thirty-nine patients were excluded as follows: three were excluded based on criterion 1 (not right handed); 10 were excluded based on criterion 2 (a history of neurological or chronic medical illness); eight were excluded based on criterion 3 (five patients with schizoaffective disorder and three patients with obsessive–compulsive disorder); six were excluded based on criterion 4 (HAMD < 17); and 12 were excluded based on criterion 6 (other axis-I-II comorbidities).

Inclusion in the BD group was based on clinical assessments by two psychiatrists, one of whom was a senior psychiatrist. Diagnostic criteria were determined according to the Structured Clinical Interview for DSM-IV (SCID), a structured and interviewer-administered diagnostic tool (First et al., 1998). The SCID is composed of questions about behavioral and emotional disorders in adults, such as depression, bipolar disorder, anxiety, and obsessive–compulsive disorders. The healthy controls were recruited through advertisements in local newspapers. They were screened by psychiatrists using the non-patient version of the SCID. They were screened and determined not to have a history of psychiatric or neurologic illness, such as dementia, mental retardation, emotional disorders, affective disorders, and other axis I/II psychiatric disorders. The inter-rater reliability of the SCID, HAMD and YMRS between the two raters was satisfactory: the intra-class correlation coefficients (ICCs) for the sum scores of HAMD and YMRS ranged from 0.85 to 0.87, and the kappa value for the SCID was 0.895.

This study was approved by the Research Ethics Review Board of Beijing Anding Hospital, Capital Medical University and Beijing Normal University Imaging Center for Brain Research. After the study procedures were fully described, all subjects signed informed consent.

2.2. Imaging procedure

MRI data were acquired with a 3.0 T Siemens Trio (Siemens Medical Solutions, Erlangen, Germany) scanner in the National Key Laboratory for Cognitive Neuroscience and Learning at Beijing Normal University. The parameters for three-dimensional structural MRE were as follows: 20 axial slices, echo-planar imaging, pulse sequence, thickness/gap = 1.33/0 mm, in-plane resolution = 64 × 64, repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, inversion time (TI) = 1100 ms, flip angle = 7°, field of view = 256 × 256 mm², and 128 volumes.

2.3. Data preprocessing

MR images were assessed by two experienced radiologists (Dr. Chun-Hong Liu and Dr. Yu Zhang). Preprocessing was performed using the DARTEL algorithm (diffeomorphic anatomical registration through exponentiated lie algebra) in the Statistical Parametric Mapping software (SPM8, http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) under the MATLAB R2008a platform (Mathworks, Sherborn, MA, 2008). Statistical analysis was performed using SPM8 software.
USA). Briefly, the segmentation function was used to divide the regions into gray matter, white matter, and cerebrospinal fluid (CSF) using the ‘new segment’ tool implemented in SPM8, while non-brain features, such as scalp, skull, and dural venous sinus, were removed from consideration. During spatial normalization, more accurate inter-subject registration was achieved by respectively registering individual structural images to an asymmetric customized T1-weighted template based on different groups (BD group and healthy group). A ‘modulation’ step was used to ensure that the overall amount of tissue in a class was unaltered (Ashburner, 2007). The segmented images were normalized to the Montreal Neurological Institute (MNI) template and were smoothed with an 8-mm full-width at half-maximum (FWHM) Gaussian filter. The voxel size of data acquisition is 1×1×1 mm³ and the voxel size of normalized data is 2×2×2 mm³.

2.4. Statistical analysis

To validate our rationale for focusing on the insula, we conducted a whole-brain on VBM measure between the BD and control groups. Age, sex, and total gray matter and white matter volumes of the subjects were included as covariates. The statistical threshold was set at p<0.001 (uncorrected) and the spatial extent threshold k value > 10 voxels within whole brain mask. Given the exploratory nature of this whole-brain analysis, we did not perform a strict multiple comparison correction in order to capture small structures like insular subregions (Chepenik et al., 2010; Liu et al., 2012a; Matsuo et al., 2012). In the specific regional analysis, we defined the regions in bilateral insular cortices based on the WFU Pickatlas software from the automated anatomical labeling (AAL) template (Tzourio-Mazoyer et al., 2002; Maldjian et al., 2003). As the voxels with probability densities below 10% are unlikely to be gray matter, the threshold was set at 0.1. This threshold has been commonly used in VBM studies (e.g., Mané et al., 2009; Streitbürger et al., 2012; Arnone et al., 2013). For the regional analysis, we determined clusters showing significant between-group differences using a family-wise error (FWE) correction approach based on Monte Carlo simulations (AlphaSim program in AFNI; Forman et al., 1995; Xiong et al., 1995; Ledberg et al., 1998). With a pre-specified single-voxel significance level, the program randomly generates false activated voxels and examines the probability (family-wise type I error) of observing a continuous cluster of activated voxels that is larger than a specific size. We set a threshold of single-voxel significance at p<0.005. According to the simulation results, a cluster size of six voxels yielded a FWE level of p<0.05. Cerebral regions displaying significant differences in the two-sample t-test were identified as significant clusters. The mean volumes of each significant cluster were measured using a Matlab program (http://www.cs.ucl.ac.uk/staff/G.Ridgway/vbm/get_totals.m). After that, a partial correlation analysis was performed to reveal the relationship between age, sex, years of education, disease duration, number of depressive episodes, number of manic episodes, HAMD score, and the mean volume in each ROI using SPSS 13.0 (SPSS, Inc., Chicago, IL). To examine lithium effects, BD patients were assigned to receive lithium treatment (n=9) or to not receive lithium treatment (n=18). Two-sample t-tests were used to identify differences between BD patients who received lithium treatment, BD patients who did not receive lithium treatment, and healthy controls who did not receive lithium treatment.

3. Results

3.1. Demographic information and standardized test findings

As shown in Table 1, there were no significant differences between the BD group and the control group with respect to age, gender distribution, and years of education. The mean HAMD score for the BD group was 19.67 ± 2.43.

3.2. Between-group VBM differences

The whole-brain analysis revealed that there was a significant difference in the gray matter volumes of the bilateral insula between the BD and healthy control groups (Fig. 1). The detailed differences at the whole brain level between the BD and healthy control groups are presented in Supplementary Table S1. Analysis of the specific regions found that the BD group showed decreased gray matter volumes in the right posterior insula and the left ventral anterior insula as well as increased gray matter volumes in the left dorsal anterior insula relative to healthy controls (p<0.05, corrected) (Fig. 2). Fig. 3 shows the degree of volumetric change in the left dorsal anterior insula, left ventral anterior insula, and right posterior insula for the healthy controls and bipolar disorder patients. Table 2 details all the brain regions showing significant inter-group differences.

Table 1

<table>
<thead>
<tr>
<th>Measure (mean ± S.D.)</th>
<th>BD patients (n=27)</th>
<th>Healthy controls (n=27)</th>
<th>Statistics</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M/F)</td>
<td>10/17</td>
<td>11/16</td>
<td>χ²=0.078</td>
<td>0.78</td>
</tr>
<tr>
<td>Age (years)</td>
<td>32.04 ± 11.20</td>
<td>32.59 ± 11.76</td>
<td>t(152)=−0.18</td>
<td>0.66</td>
</tr>
<tr>
<td>Range</td>
<td>20–57</td>
<td>20–58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education level (years)</td>
<td>12.56 ± 2.38</td>
<td>13.37 ± 2.37</td>
<td>t(152)=−1.61</td>
<td>0.21</td>
</tr>
<tr>
<td>HAMD-17</td>
<td>19.67 ± 2.43</td>
<td>17–27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>10.4 ± 0.94</td>
<td>0–2</td>
<td></td>
<td></td>
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<tr>
<td>YMRS</td>
<td>4.19 ± 1.71</td>
<td>0.5–6.5</td>
<td></td>
<td></td>
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<tr>
<td>Range</td>
<td>3.41 ± 1.42</td>
<td>1–6</td>
<td></td>
<td></td>
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<tr>
<td>Number of depressive episodes</td>
<td>1.26 ± 0.53</td>
<td>1–3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>4.67 ± 1.54</td>
<td>2–8</td>
<td></td>
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<tr>
<td>Antidepressants</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Citalopram</td>
<td>7</td>
<td></td>
<td></td>
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<tr>
<td>Sertaline</td>
<td>8</td>
<td></td>
<td></td>
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<tr>
<td>Paroxetine</td>
<td>1</td>
<td></td>
<td></td>
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<tr>
<td>Mood-stabilizer</td>
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<tr>
<td>Lithium</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium valproate</td>
<td>6</td>
<td></td>
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<tr>
<td>Divalproex</td>
<td>15</td>
<td></td>
<td></td>
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<tr>
<td>Antipsychotics</td>
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<tr>
<td>Quetiapin</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Olanzapine</td>
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<td></td>
<td></td>
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<tr>
<td>Risperidone</td>
<td>5</td>
<td></td>
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</tbody>
</table>

Abbreviations: S.D., standard deviation; BD, bipolar depression; and HAMD, Hamilton Depression Rating Scale.
3.3. Correlation with clinical and demographic variables

No significant correlation was found between the volume of the right posterior insula, the left ventral anterior insula, the left dorsal anterior insula and age, sex, years of education, disease duration, number of depressive episodes, number of manic episodes, or HAMD scores for the BD group.

3.4. Lithium effects

Compared with the healthy controls, the BD patients who did not receive lithium treatment showed decreased volumes in the right posterior insula and the left ventral anterior insula and increased volumes in the left dorsal anterior insula. The volume of the left dorsal anterior insula was significantly increased in BD patients receiving lithium treatment vs. volume in the healthy controls (Fig. 4).

4. Discussion

The insular cortex, which includes the ventroanterior, dorsoanterior, and posterior insula subregions, is a nexus of self-relevant feelings, empathy, and uncertainty prediction in the brain (Singer et al., 2009). The ventroanterior subregion is associated with socio-emotional processing (Sanfey et al., 2003; Chang et al., 2011); the dorsoanterior network region is associated with higher cognitive processing (Dosenbach et al., 2006; Eckert et al., 2009); and the posterior insula subregion is associated with interoceptive information processing (e.g., somatovisceral sensations) (Craig, 2002, 2003) and auditory information processing (Bamiou et al., 2003). Feelings of worthlessness may be associated with the ventroanterior subregion as it seems to be related to socio-emotional processing. Feelings of increased cognitive impairment may be associated with the dorsoanterior subregion as it seems to be related to higher cognitive processing (Culpepper, 2010). Given the existing findings on the functional roles of the insula, our findings of volume changes in the insular subregions of BD patients may provide some indications of functional dysfunction in the insula.

Fig. 1. Two-sample test between the bipolar depression group and the healthy group using whole brain mask. The statistical threshold was set at $p < 0.001$ and cluster size > 80 mm$^3$.

Fig. 2. Statistical maps showing two-sample t-test results of the VBM maps between the BD group and the healthy control group. Red and blue denote decreased and increased gray matter volumes, respectively, and the color bars indicate the t value from two sample t-test analysis of the two groups. The left side corresponds to the right side of the brain. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
found to have increased gray matter volumes in the left dorsal anterior insula. Considering the functional integration between the dorsal anterior insular and the ventrolateral prefrontal cortex, the increased gray matter volumes in the left dorsal anterior insula might be associated with an increased effort to effectively inhibit subcortical brain activity (Jiao et al., 2011). Lochhead et al. (2004) reported increased left dorsal anterior insular volume in BD patients who had been medication free for 14 days before scanning, and Pompei et al. (2011) demonstrated that euthymic BD patients have a mutual augmentation of the ventrolateral prefrontal cortex and the insula. Moreover, the current study also observed decreased gray matter volumes in the left ventral anterior insula in BD patients. Considering the links between the ventral anterior insula and the limbic regions, the decreased gray matter volumes in the left ventral anterior insula may be related to ventral limbic overactivity. Matsuo et al. (2012) found that BD type I patients have smaller left ventral anterior insula volumes compared with healthy subjects, and a recent meta-analysis of automated VBM methods reported that BD patients have a reduced volume in the bilateral ventral anterior insula (Selvaraj et al., 2012). Our findings support the notion that BD is associated with a dysfunctional integration of the prefrontal and limbic regions. If the findings in the BD depressed and manic phase groups are different from those in the bipolar euthymic group, these differences may be inferred to be state-related markers. In contrast, trait markers of BD would be expected to occur in the euthymic BD group as well as in the depressed and manic BD groups (Hulvershorn et al., 2012; Liu et al., 2012b). The differences that have thus far been documented between the BD group and the HC group cannot clarify mood state- and trait-related features for BD. Future studies involving subjects in different phases of BD are needed to better elucidate trait- vs. state-related markers.

Lithium has been suggested to have complex neuroprotective or neurotrophic effects that increase cellular plasticity and resilience, and altered synaptic plasticity and neuronal morphology (Manji et al., 1999; Bachmann et al., 2005). We found a trend for larger volumes in the right posterior insula and left ventral anterior insula in lithium-treated BD patients in contrast to those not receiving lithium treatment. Our results are in line with a number of previously published studies: Usher et al. (2010) reported that lithium-treated BD in a euthymic phase had larger right amygdala volumes than healthy controls. Benedetti et al. (2011) showed that long-term lithium treatment was associated with increased gray matter volumes, including in the anterior cingulate cortex and left insula. Javadapour et al. (2010) reported that lithium-treated BD patients had larger right anterior cingulate cortex volumes. A recent meta-analysis even suggested that lithium treatment may attenuate gray matter reductions in the anterior cingulate cortex (Bora et al., 2010). In the current study, lithium treatment was also related to larger volumes of the right posterior insula and left ventral anterior insula, providing indirect support for neuroprotective effects. Further studies with a larger sample are required to verify this speculation.

The current study has several limitations: First, almost all patients were taking medication(s) at the time of the scan, so...
the potential effects of medication in our study must be considered. Second, the age range is very large. We intend to control for the differences found between the BD group and the HC group might be attributable to a distinction between BD subjects who are currently depressed and those who are currently euthymic, and which might be attributable a distinction between BD patients and unaffected individuals. Fourth, our study does not consider the differences between bipolar and unipolar depression patients in order to distinguish between the specific characteristics of these different types of depression. Future studies involving subjects in different phases of bipolar disorder and unipolar depression are needed to better elucidate the underlying mechanisms of BD.

In conclusion, the current structural MRI study found significantly decreased gray matter volumes in the right posterior insula and the left ventral anterior insula, and increased gray matter volumes in the left dorsal anterior insula in BD patients. This result suggests that the insular subregion may be related to pathogenic affective regulation during depressive phases of bipolar disorder.

Acknowledgments

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.pscychresns.2014.08.004.

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