The Functional Magnetic Resonance Imaging of Major Depressive Disorder in Resting State and Task State

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【Abstract】 **Objective:** We sought to investigate the brain dysfunction in patients with major depressive disorder(MDD) by using combined task-activation and resting-state functional Magnetic Resonance Imaging(fMRI). **Methods:** We investigated 25 MDD patients and 24 healthy controls during a n-back working memory task and resting-state. Task-activated state helped us to identify brain areas that are associated with the processing of n-back task stimuli and its performance. The intrinsic brain resting-state activity was measured by the amplitude of low-frequency fluctuation(ALFF). **Results:** We found that comparing to HC, patients with MDD exhibited increased spontaneous resting state activity in the left thalamus, putamen, insula and middle and inferior frontal gyrus. During the WM task, patients with MDD showed bilateral decreased activities in the right inferior temporal gyrus, thalamus, precuneus, posterior cingulated gyrus, inferior parietal gyrus, and the left superior occipital gyrus and fusiform, relative to HC. **Conclusion:** The present study provides important empirical support for the hypothesis that functional impairment in the cortico-thalamo-striatal circuit is possibly the underlying neuropathological feature of cognitive impairment and severity of depressive symptoms in MDD.

【Key words】 Cortico-thalamo-striatal circuit; Task state; Resting state; Functional Magnetic Resonance Imaging; Major Depressive Disorder

中图分类号: R395.1　　　DOI: 10.16128/j.cnki.1005-3611.2017.03.001

重度抑郁症患者任务态和静息态脑功能磁共振成像研究

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【摘要】 **目的:**本研究通过结合任务态与静息态的fMRI数据探讨导致抑郁症患者脑功能障碍的神经病理学因素。**方法:**采集25例抑郁症患者、24例健康对照N-back任务和静息态fMRI数据,采用双样本t检验进行任务态数据组间比较,低频振幅(ALFF)测量静息态。**结果:**重度抑郁症患者在静息态下,左丘脑、壳核、脑岛、额中回及额下回活跃程度显著增高,在任务态下,双边颞下回、右丘脑、契前叶、后扣带回、顶下回及左枕上回和梭状回活跃程度减弱。**结论:**皮质-丘脑-纹状体回路受损可能是抑郁症患者认知功能障碍和抑郁症状严重程度的潜在神经病理学因素。

【关键词】 皮质-丘脑-纹状体回路; 任务态; 静息态; fMRI; 重度抑郁症

1 Introduction

Functional magnetic resonance imaging(fMRI) has been widely used to examine neurobiological correlates of major depressive disorder(MDD) and has provided insight on the prevailing pathophysiological features of this highly prevalent and disabling disorder (Drevets et al., 2008). Most of these fMRI studies have employed either task- activation(Hammar and Ardal, 2009) or resting- state(Wang et al., 2012) to localize the abnormalities of brain activity. However, it remains elusive to whether brain functional changes during resting state are sensitive to the same brain regions during task activation. Therefore, a study which focuses on investigation of underlying brain disruption in MDD by using cognitive task in conjunction with resting- state fMRI in the same group of patients may be helpful to elucidate the underlying pathogenesis of this disorder.

Cognitive control deficit is thought to be the most important aspect of morbidity in MDD and might be

【基金项目】 江西省科技厅社会发展项目《儿童期创伤与心理弹性对抑郁症患者脑功能影响的fMRI研究》(20151BBG70079)
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lasting long despite symptom reduction and recovery (Ebmeier et al., 2006). N-back task can be used to assess cognitive impairment in patients with MDD, because patients can respond differently to internal or external stimuli(Sliz and Hayley, 2012).

Emerging findings from resting-state studies in MDD revealed that the functional connectivity in anterior cingulate cortex, limbic system and thalamic area to be significantly reduced in patients with depression, suggesting a regulation effect on subcortical emotional circuits on depressive symptoms(Bobb et al., 2012).

Moreover, both task-activation and resting-state fMRI techniques have some advantages and limitations. Cognitive tasks measure the relationship between task demands and brain neurophysiological responses, however, different tasks activate different brain regions, and even different subject has different results on the same task because the task ratings vary with each individual(Zhou et al., 2014). Resting state is a relatively novel approach; participants are typically asked to rest quietly with their eyes closed or fixate to a point for several minutes and do not have to perform a task. Because no task involved, thus, an important advantage of the resting-state approach is that a more direct comparison between brain functions of patients and healthy controls can be made, including differences between patient groups of different conditions as well as subjects at varying stages of disease severity and development(Fox and Raichle, 2007). However, the resting state of the brain is not possible to standardize, as we cannot control a participant's mental state during visual fixation or with eyes closed. Thus, it remains unknown to whether the same patient group can exhibit similar brain functional changes between the two states: resting-state and task-activation fMRI.

Thus, in the current study, we compared the resting-state and task-activation fMRI brain activity from MDD patients with that of healthy controls. The aim of using the combined approach was to obtain a complementary detection of the neuropathology in MDD because the resting state fMRI can be used to investigate baseline brain activity changes as it is relatively easy to perform as does not involved task performance which can be challenging to some patients. We hypothesized that the impairment within the cortico-thalamo-striatal circuit would be correlated with cognitive and severity of depressive symptoms.

2 Materials and Methods

2.1 Participants

Twenty five participants with a diagnosis of major depressive disorder(DSM-5 criteria, American Psychiatric Association 2013) were recruited from inpatient and outpatient units of the Department of Psychiatry, the Second Xiangya Hospital of Central South University. The age of patients were between18 and 45 years, they were all Han Chinese ethnicity and right-handed by a determination of hand preference, they were also required to have nine years of education or above and a 17-item Hamilton Depression Rating Scale (HAMD, maximum=52) score above 17. They were excluded if: a) any contra-indications to MRI scanning; b) additional diagnoses on DSM-V(including schizophrenia, generalized anxiety disorder, substance abuse, panic and obsessive compulsive disorder); c) patients with head trauma with loss of consciousness; d) chronic neurological disorders or severe physical disease.

Healthy controls(HC) were recruited via poster and web-based advertisement in the hospital, plus word-of-mouth requests from staff in the research unit. As shown in Table 1, 24 healthy controls who were age-, gender- and education-matched with MDD patients, were selected from a community sample in Changsha city. The inclusion and exclusion criteria were the same as those of the patients group except that the healthy controls did not meet the DSM-V diagnostic criteria for any mental disorder.

All participants gave their written informed consent for participation in the study after the risks and benefits of their participation were explained in detail. The ethics committee of the Second Xiangya Hospital of Central South University approved the study.

2.2 Clinical characteristics

All participants were assessed for cognitive functions by using the Information and Digit symbol subscales of Wechsler Adult Intelligence Scale-Chinese

Revised(WAIS-CR), the experiences of childhood trauma were assessed with the Childhood Trauma Questionnaire(CTQ) (Bernstein, 1998). Clinical symptoms were assessed by using the Hamilton Depression Rating Scale(HAMD) (Hamilton, 1960) , the 21-item Beck Depression Inventory(BDI) , Beck Suicide Ideation Scale (BSIS) (Beck et al., 1979). Current and previous drug regimens were recorded: 17 out of 25 patients were on medications at the time of the scan, including antidepressant (6), combined antidepressant and anxiolytic drugs (8), combined antidepressant, anxiolytic and anti- epileptic drugs (2), and combined antidepressant, anxiolytic and antipsychotics drugs (1). The anxiolytic, anti- epileptic and anti- pyschotic drugs were used to provide relief of symptoms that accompanied the MDD.

2.3 Experimental design and task

All participants underwent both a resting- state and a subsequent n- back working memory(WM) task fMRI scans. The WM paradigm was a block-design letter n-back WM task, which has been used in previous studies. We used the “2-back” task condition in which participants were instructed to press a button when the letter presented was identical to what they saw two letters prior. Each letter stimulus appeared for 500ms, and the inter-stimulus interval was 1500ms. Each stimulus block consisted of 20 stimuli containing seven targets and was indicated by an instruction cue displayed for 2s before each block. During resting periods, the participants were instructed to fixate on a cross in the center of the screen for 20s.

2.4 Data acquisition and Processing

MR images were acquired on a 3.0 T MR scanner (Philips Achieva XT). The fMRI data were processed by MATLAB 2012a(Mathworks, Natick, MA, USA) and DPARSF(Data processing Assistant for Resting- State fMRI) (Chao-Gan, 2010) software for DICOM transformation, slice timing, head motion correction, and spatial normalization. The general linear mode(GLM) was applied to the task data for detection of activation. The details for each of these steps are provided in Supplemental information(S1).

2.5 Statistical analysis

For resting data, two sample t- tests were performed to examine the voxel- wise difference on the ALFF maps between the MDD and HC groups. For task data, two sample t-tests were performed to examine the voxel- wise difference on the activation maps between the two groups. After then, the cluster size threshold V>2295 mm^3 (35voxels) and T>2.0141 were used to determine statistical significance, which means P<0.05 for each voxel. As for multiple comparison correction, this combined threshold was determined by Monte Carlo simulation with AlphaSim command.

Correlation analysis was performed using SPSS 19.0. We correlated the average ALFF value of significant regions with clinical symptoms in MDD patients. We extracted the average strength of activation from significant brain regions obtained from task-activation fMRI data and we also correlated it with clinical characteristics of the MDD group. The correlation was all performed using Pearson correlation. Statistical significance was set at P<0.05.

3 Results

3.1 Demographic, task performance and clinical characteristics

As shown in Table 1, there was no significant difference between MDD and healthy controls in terms of age, education, gender, reaction time and accuracy of the n-back task(all P>0.05). There were significant differences in scores of digit symbol subscales of WAIS-CR(t=-2.697, P=0.01) and CTQ(t=2.828, P=0.008).

3.2 Functional imaging results

The task and resting fMRI data were analyzed independently. Then the brain functional abnormalities from task and resting- state fMRI in MDD patient group were inspected visually and those showing resemblance of specific anatomical functional features from images of these two functional modalities were described as convergent region. This approach has been successfully used in other studies(Zamboni et al., 2013). To further explore the relevance of the convergent as well as functional abnormalities and from each of the two functional modalities, we extracted task-based and resting-state functional activity signals and correlated it with clinical characteristics obtained from psychological batteries.

3.2.1 Between group differences during n-back WM task As shown in Table 2 and in Figure 1, the MDD group shows decreased activities at bilateral inferior temporal cortices, right fusiform, thalamus and posterior cingulum and left superior occipital gyrus. We did not found any region with decreased activity in the healthy group.

Table 1 Demographic and clinical characteristics of major depressive disorder(MDD) and healthy controls(HC)

Variable	MDD (n=25)	HC (n=24)	Group comparisons
Age(year)	29.52(7.63)	25.75(6.97)	t=1.803, P=0.08
Education(years)	12.60(3.08)	13.42(2.59)	t=-1.003, P=0.321
Illness duration(months)	63.58(83.93)	-	-
Gender(male/female)	14/11	14/10	χ^2=1.00, P=0.317
Accuracy	0.668(0.212)	0.761(0.163)	t=-1.656, P=0.105
Reaction time(ms)	745.979(195.729)	714.184(128.184)	t=0.647, P=0.521
Information	19.22(5.570)	19.76(5.150)	t=-0.348, P=0.729
Digit symbol	71.50(20.117)	85.74(15.702)	t=-2.697*, P=0.01
CTQ score	51.12(7.607)	44.273(3.663)	t=2.828*, P=0.008
SSRS score	35.24(7.584)	40.091(6.549)	t=-1.838, P=0.075
BDI score	29.04(12.181)	-	-
HAMD-17 score	20.88(4.58)	-	-
BSIS score	60.25(18.658)	-	-

Note: Data reflect mean(SD) unless otherwise stated. Information, information subscale of Wechsler Adult Intelligence Scale-Chinese Revised; Digit symbol, Digit symbol subscale of Wechsler Adult Intelligence Scale-Chinese Revised; CTQ, Childhood Trauma Questionnaire; SSRS, Social Support Revalued Scale; BDI, 21-item Beck Depression Inventory; HAMD, Hamilton Depression Rating scale; BSIS, Beck Suicide Ideation Scale.

Table 2 Regions with significant difference during task activation between Major Depressive Disorder (MDD) and healthy controls(HC)

Anatomical Region	AAL	Cluster size (Voxels)	MNI coordinates[b] X	Y	Z	T[a]
R. Inferior temporal gyrus	90	21	45	-33	-21	2.73
R. Fusiform gyrus	56	38	39	-18	-27	3.278
L.Superior occipital gyrus	49	26	-15	-81	21	3.223
L. Inferior temporal gyrus	89	10	-48	-60	-6	2.802
R. Thalamus	78	18	12	-30	9	2.600
R. Precuneus	68	24	12	-48	18	3.092
R. Posterior cingulated gyrus	36	9	9	-42	18	3.227
R. Inferior parietal gyrus	62	18	30	-45	54	2.593

Note: AAL=90 AAL regions, R=right, L=left; [a]Represents the statistical value of peak voxel showing task activity differences comparing MDD and HC. Positive T value indicates the increase of task activity in HC, and negative T value indicates the decrease of task activity in HC respectively, compared with MDD. [b]Coordinates of primary peak locations in the MNI space.

3.2.2 Between group differences in resting state As summarized in Table 3 and Figure 2, the MDD group showed increased spontaneous activities in the left putamen, thalamus, insula, and left frontal areas, including middle and inferior frontal cortices.

3.3 Correlation of abnormal regions with clinical characteristics

To demonstrate the relevance of the functional abnormalities observed during both task-activation and resting state, the regions showing differences in activation between-group and states, the measure of activation response(the first eigenvalue) was extracted from each participant's data, and the effect size(Cohen's d) for group status on brain activation was calculated. Then we correlated these parameters of each abnormal brain region with patients' total HAMD scores, BDI scores, CTQ scores, BSIS scores as well as the scores of Information subscale and Digital symbol subscale of WAIS-CR. As shown in Table 4, we found significant correlations between bilateral inferior temporal cortices with Information and Digit symbol subscale scores on the WM task state, but the left inferior temporal region showed negative correlation while the right region showed positive correlation. The right thalamus was negatively correlated with Digit symbol score on WM task state while the left thalamus was positively correlated with Digit symbol score on resting state. We found significant correlation between the right precuneus and the CTQ score during WM task, especially with the factor of emotion abuse (r=0.437, P=0.029). On the resting state, left putamen was positively correlated with HAMD, and the left insula was correlated with the physical abuse item of CTQ(r=0.410, P=0.042). Moreover, 2-back response time of the patients was found to be correlated with left inferior temporal gyrus(r=0.526, P=0.017).

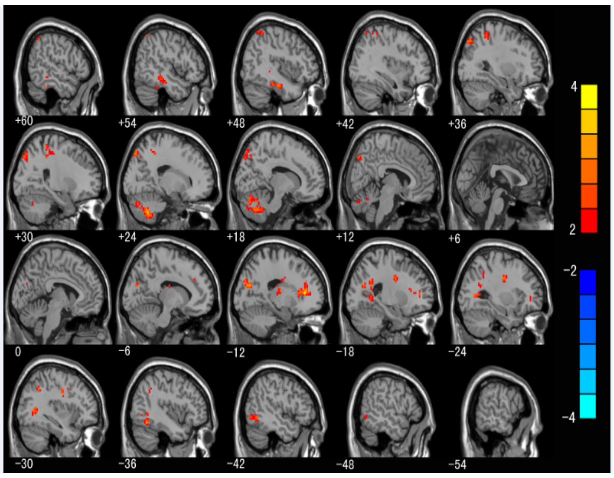

Figure 1 Results of two sample t-test of activation differences during task state between control groups and patients(P<0.05, corrected). The differences map is from X=+45 to X=-48 mm (every 6 mm). Red color indicates that patient subjects had decreased activation compared with the healthy controls

Table 3 Regions with significant difference of ALFF during resting state between Major Depressive Disorder (MDD) and healthy controls(HC)

Anatomical Region	AAL	Cluster size (Voxels)	MNI[b] X	MNI[b] Y	MNI[b] Z	T[a]
L. Putamen	73	11	-33	-9	3	-3.8939
L. Thalamus	77	8	-18	-9	0	-3.1686
L. Insula	29	17	-33	9	12	-3.3753
L. Middle frontal gyrus	7	16	-39	42	27	-3.4489
L.Inferior frontal gyrus(triangular part)	13	71	-45	36	6	-4.1123
L. Inferior frontal gyrus(orbital part)	15	16	-48	39	-9	-4.3128

Note: AAL=AAL regions, R=right, L=left. [a] Represents the statistical value of peak voxel showing ALFF differences comparing HC and MDD. Positive T value indicates the increase of ALFF in HC, and negative T value indicates the decrease of ALFF in HC respectively, compared with MDD. [b]Coordinates of primary peak locations in the MNI space.

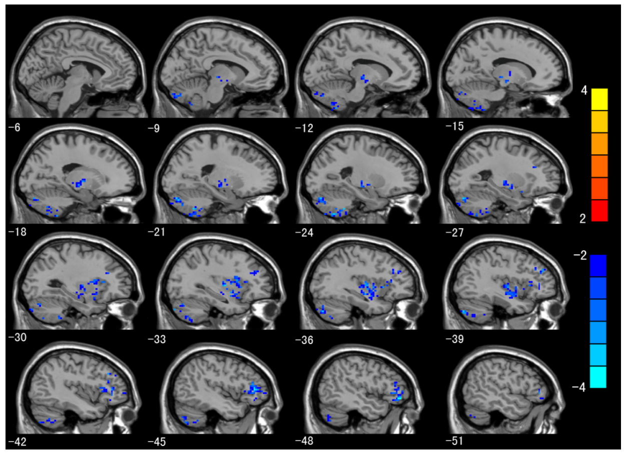

Figure 2 Results of two sample t-test of ALFF differences between health controls and patients (P<0.05, corrected). The differences map is from X=-6 to X=-51 mm(every 3 mm). Blue color indicates that patient subjects had increased ALFF compared with the controls

Table 4 The correlations between clinical characteristics and brain regions with functional abnormalities

Anatomical Region	Information r	Information P	Digit symbol r	Digit symbol P	CTQ score r	CTQ score P	HAMD score r	HAMD score P
[a]R. Inferiortemporalgyrus	-0.432*	0.031	-0.598*	0.002	0.223	0.284	0.301	0.152
[a]L.Inferior temporal gyrus	0.409*	0.042	0.241	0.257	0.069	0.745	0.108	0.614
[a]R. Thalamus	-0.095	0.652	-0.502*	0.012	0.350	0.086	0.044	0.839
[a]R. Precuneus	0.053	0.800	-0.216	0.310	0.434*	0.030	0.063	0.769
[b]L. Putamen	-0.255	0.218	-0.122	0.571	-0.109	0.604	0.405*	0.045
[b]L. Thalamus	0.171	0.414	0.542**	0.006	-0.373	0.066	-0.113	0.591

Note: a: abnormal regions in task state; b: abnormal regions in resting state; L=left, R=right; Information: information subscale of Wechsler Adult Intelligence Scale-Chinese Revised; Digit symbol, Digit symbol subscale of Wechsler Adult Intelligence Scale-Chinese Revised; CTQ, Childhood Trauma Questionnaire; HAMD: Hamilton Depression Rating scale.

4 Discussion

We analyzed the intrinsic resting- state activity measured by the ALFF and brain activation obtained during the WM task performance in both MDD as compared to HC. We found patients with MDD to exhibit increased spontaneous resting state activities in the left hemisphere of the thalamus, putamen, insula and middle and inferior frontal gyrus. During task performance, patients with MDD showed bilateral decreased activities in the inferior temporal gyrus, right hemisphere of the thalamus, precuneus, posterior cingulated gyrus, inferior parietal gyrus, and left superior occipital gyrus and fusiform gyrus. The increased ALFF during resting state might be a compensatory mechanism, while the task-activation might be representing pathological abnormality in MDD. Moreover, when the regions with abnormalities were correlated with clinical symptoms we found precuneus, inferior temporal gyrus, thalamus, and putamen to be correlated with childhood trauma experience, general information and WAIS digital symbol coding scores, and severity of depressive symptoms, respectively, in MDD patients. These regions are found within the cortico-thalamo-striatal circuit, which is consistent with several other studies on MDD(Greicius et al., 2007; Salomons et al., 2014).

In this study, we obtained both task-activation and resting-state fMRI data from MDD patients and HC by using the same scanner. Since task-activation fMRI studies are likely to suffer from intra and inter-subject variability, scanner variability, and often involve lengthy scan times with complex study designs that are hard to standardize, and cognitive tasks are difficult to be individuals with impaired cognitive control (Fleisher et al., 2009). On the other hand, the resting state fMRI does not suffer from variability related to task performance and may be easier to standardize across studies. Nevertheless, the resting state of the brain is not possible to standardize, as we cannot control a participant's mental state during visual fixation or with eyes closed. Therefore, the use of task activation and resting state fMRI in the same patient group might be a more sensitive complementary marker of functional abnormalities with potentials to reveal the underlying pathophysiology in MDD patients.

Though from different hemisphere, we found convergent abnormality between ALFF and 2-back WM task-evoked activation in the thalamus in MDD patients. The resting state activity was increased in the left thalamus, while task-stimulated activity was decreased in the right thalamus. Moreover, WAIS-Digital symbol coding score were correlated with bilateral thalamus and left inferior temporal gyrus. Thalamus and inferior temporal gyrus are important regions in the default mode network which also contains the precuneus, parahippocampal gyrus, anterior cingulate cortex, hippocampus, posterior cingulate cortex and medial prefrontal cortex and plays an important role in self-referential activity(Raichle et al., 2001), and individuals with MDD have been found with difficulties in regulating self-focused thinking in order to engage in more goal-directed behavior(Belleau et al., 2015). Taken together, this finding may imply that the disruptions in the thalamus and inferior temporal gyrus may be the neurosubstrates for cognitive impairment and negative symptoms observed in MDD patients.

In the current study, we found putamen to be activated more than in healthy controls and were positively correlated with HAMD scores during resting-state. Putamen plays a role in the motor system, perceptions, contempt and disgust, and its activity has been correlated with the amount of declares on hate a person(Zeki and Romaya, 2008). Moreover, putamen which is found in striatum is an important component in the hate circuit, it was found to exhibit increased and decreased responses to negative and positive emotional stimuli, respectively(Tao et al., 2013). Consistent with this study, a recent meta-analysis study on brain activation, though reported other regions such as superior frontal gyrus and insula to be abnormal in MDD patients, also revealed studies to report putamen abnormalities (Fitzgerald et al., 2008). Moreover, Kapornai K, et al(Kapornai et al., 2007) found putamen to be associated with increased severity of depressive symptoms. Taken together, this evidence suggests putamen to be the underlying pathological features for severity of depressive symptoms in MDD.

The mechanism underlying cortico-thalamo-striatal circuit in MDD is widely unclear. However, the precuneus, thalamus, inferior temporal gyrus and putamen are organized in highly integrated manner to support diverse motor, cognitive and emotional processes(Bora et al., 2012). The precuneus, thalamus and inferior temporal gyrus are important component in the DMN, which has been robustly reported to associate with depressive symptoms in MDD (Liston et al., 2014; Marchetti et al., 2012; Sheline et al., 2009). Some resting state studies implicated that the lower cortico-thalamic, cortico-striatal, and cortico-limbic connectivity is associated with better treatment outcomes in MDD(Salomons et al., 2014). Similarly, task- induced activation studies reported the neural network linking limbic, thalamic, cortical, and striatal regions to mediate executive functions of working memory. Collectively, these evidences suggest that the neuronal dysfunction in the cortico-thalamo-striatal circuit might be mediating the cognitive impairment and negative symptoms observed in MDD.

The main limitation of this study pertains to the discordant exposure to medications between the depressed group and the healthy controls. There is firm evidence that depressed patients as a group are characterized by cognitive impairment as compared to the health controls, especially during the acute phase due to medications and motivations(Scheurich et al., 2008). Therefore, it is conceivable that the brain functional connectivity differences between these two groups reflect the fact that most of the depressed subjects were taking psychotropic medications and none of the healthy controls. Secondly, since task- related BOLD signal is a difference contrast between the baseline signal and the signal change associated with the task, therefore, it is possible that the extraction of this signal may have differentially affected the resting state baseline signal. Perhaps studies which employ independent component analysis to compare the difference of activation between task and rest would be helpful to validate our findings(Greicius et al., 2007).

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(收稿日期:2016-11-18)

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(收稿日期:2016-11-30)