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More than just statics: temporal dynamics of intrinsic brain activity predicts the suicidal ideation in depressed patients

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Abstract

Background. Major depressive disorder (MDD) is associated with high risk of suicide. Conventional neuroimaging works showed abnormalities of static brain activity and connectivity in MDD with suicidal ideation (SI). However, little is known regarding alterations of brain dynamics. More broadly, it remains unclear whether temporal dynamics of the brain activity could predict the prognosis of SI.

Methods. We included MDD patients ($n = 48$) with and without SI and age-, gender-, and education-matched healthy controls ($n = 30$) who underwent resting-state functional magnetic resonance imaging. We first assessed dynamic amplitude of low-frequency fluctuation (dALFF) – a proxy for intrinsic brain activity (iBA) – using sliding-window analysis. Furthermore, the temporal variability (dynamics) of iBA was quantified as the variance of dALFF over time. In addition, the prediction of the severity of SI from temporal variability was conducted using a general linear model.

Results. Compared with MDD without SI, the SI group showed decreased brain dynamics (less temporal variability) in the dorsal anterior cingulate cortex, the left orbital frontal cortex, the left inferior temporal gyrus, and the left hippocampus. Importantly, these temporal variabilities could be used to predict the severity of SI ($r = 0.43$, $p = 0.03$), whereas static ALFF could not in the current data set.

Conclusions. These findings suggest that alterations of temporal variability in regions involved in executive and emotional processing are associated with SI in MDD patients. This novel predictive model using the dynamics of iBA could be useful in developing neuromarkers for clinical applications.

Introduction

Patients with major depressive disorder (MDD) have higher risk of suicide compared with the general population (Angst *et al.*, 2002). Although suicidal ideation (SI) may be distinct from suicidal attempt and behavior (Klonsky and May, 2014), it is a strong indicator of suicide attempt within the first year after SI onset (Nock *et al.*, 2008). It is crucial to elucidate the biological underpinnings of SI in MDD patients.

Biologically, suicidal individuals exhibit genetic and serotonergic differences compared with healthy controls (HCs) and major depression (Joiner *et al.*, 2005). Clinically, SI differs from other depression symptoms (such as insomnia, sad mood, fatigue, and concentration problems) in important dimensions with regard to risk factors and impact on impairments (for instance, SI patients exhibits high pessimism for future, whereas fatigue most impacts on home management) (O'Connor and Nock, 2014; Fried and Nesse, 2015). Moreover, MDD patients with SI are harder to treat and more likely to relapse than those without SI during continuation treatment (Szanto *et al.*, 2003). However, few studies have specially concentrated on the different intrinsic brain activity (iBA) or/and connectivity patterns between MDD patients with and without SI (Myung *et al.*, 2016; Chase *et al.*, 2017; Du *et al.*, 2017; Kim *et al.*, 2017b).

Previous studies in depressed patients linked SI and suicidal attempt to impulsive behavior and dysfunctional executive and emotional processing (Westheide *et al.*, 2008; O'Connor and Nock, 2014; Myung *et al.*, 2016; Johnston *et al.*, 2017). Notably, executive function and emotional processing involve brain areas such as the orbitofrontal cortex, anterior cingulate cortex, dorsolateral prefrontal cortex, and temporal pole gyrus (Rogers *et al.*, 2004; Olson *et al.*, 2007). Compared with MDD patients without SI, SI patients showed reduced fronto-limbic (Du *et al.*, 2017) and orbitofrontal-thalamic functional connectivity (Kim *et al.*, 2017b) and fronto-subcortical white matter connectivity (Myung *et al.*, 2016). Convergent findings suggest the presence of structural and functional magnetic resonance imaging (fMRI) abnormalities in MDD patients with SI (Myung *et al.*, 2016; Du *et al.*, 2017; Kim *et al.*, 2017b). However,

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these studies relied on the assumption of the 'static' of the brain and did not investigate the dynamic brain alterations over time in SI patients. More recently, studies have focused on investigating dynamic functional connectivity or networks, which can provide information on the variability in the strength or spatial dynamic organization of the brain (Bassett and Sporns, 2017). Despite the dynamics of inter-regional functional connectivity in resting state are successfully applied in many psychiatric and neurological diseases, such as major depression (Kaiser *et al.*, 2016), schizophrenia (Damaraju *et al.*, 2014), epilepsy (Liao *et al.*, 2014b; Li *et al.*, 2018), and Parkinson's disease (Kim *et al.*, 2017a), knowledge about the dynamics of local brain activity is still limited. This local iBA is supposed to be a reflection of mental activity (Raichle and Snyder, 2007), which may cause high time-varying iBA (Fu *et al.*, 2017). In this study, we regard time-varying iBA as a potential way to deepen our understanding of SI in depressed patients.

One approach to measure time-varying iBA is to quantify the temporal variability of the amplitude of iBA (Tagliazucchi *et al.*, 2014; Tomasi *et al.*, 2016; Fu *et al.*, 2017; Yan *et al.*, 2017). The iBA amplitude provides strong temporal information (Zang *et al.*, 2007). Conventional studies on iBA amplitude assume that brain activity is stationarity over a whole resting-state fMRI scan, while recent investigations of brain activity have taken fluctuation over time into account (Allen *et al.*, 2014), which can be quantified by measuring the temporal variability in the iBA amplitude among voxels. One study on temporal dynamics of iBA investigated the relationship between functional connectivity density and temporal variability of iBA (Tomasi *et al.*, 2016). By investigating the temporal variability of the iBA amplitude in MDD patients with SI, we expect to delineate the brain regions or neural systems related to SI, which can be used as targets in subsequent treatments, and to gain a more thorough understanding of the brain's biological details.

In the current work, to characterize the temporal variability of iBA in MDD patients with SI, we employ a dynamic amplitude of low-frequency fluctuation (dALFF) on resting-state fMRI. We sought to determine (i) whether MDD patients with SI show different patterns in temporal variability compared with MDD patients without SI; and (ii) whether these altered temporal variability of dALFF would provide a neuromarker to predict the severity of SI (Woo *et al.*, 2017).

Materials and methods

Subjects

This study was approved by the Local Medical Ethics Committee of the First Affiliated Hospital of Chongqing Medical University. Written informed consent was obtained from all subjects. A total of 51 drug-naïve MDD patients including MDD with SI (SI group, $n = 30$) and without SI (NSI group, $n = 21$) with single depressive episode were recruited. MDD was diagnosed using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (SCID-I/P, Chinese version), with a cut-off score $\geqslant$16 on the 17-item Hamilton Depression Rating Scale (HAMD). Patients were excluded if they had neurological or other psychiatric disorders, history of substance dependence, alcohol, cocaine or other drugs abuse, neurological MRI abnormalities, or any metal or electronic implants.

In addition, the age-, educational level-, gender-matched HCs ($n = 30$) with no mood disorder or neurologic disorders were recruited. Additionally, HCs were interviewed to confirm that there was no history of psychiatric illness among their first-degree relatives. The exclusion criteria also required that subjects have no history of substance, drug, or alcohol dependence. Three MDD patients (two SI patients, one NSI patient) were excluded due to excessive head movements during the scan. Consequently, 48 patients (SI group, $n = 28$; NSI group, $n = 20$) and 30 HCs were included in the final analyses.

Assessment of depression and SI

At enrollment of this study, all MDD patients were assessed for depression severity and SI severity. Depression severity was evaluated using the 17-item HAMD scale. SI severity was measured by the Scale for Suicide Ideation – Chinese Version (SSI-CV) (Li *et al.*, 2010), which was subsequently verified for satisfactory reliability and validity in evaluating the SI of depressed patients (Wang *et al.*, 2012). SSI-CV is a 19-item clinical research instrument designed to quantify the intensity of current conscious suicidal intent. The scoring range of each item was 0–2 points (total range 0–38). Items 4 and 5 were used to estimate the current suicidal thoughts (Marzuk *et al.*, 2005). A score of 0 on either item indicates subjects without SI, while a score above 0 indicates current suicidal thoughts (Marzuk *et al.*, 2005). The SI group subsequently completed the remaining 14 items on current suicidal thoughts, which was not required for the NSI and HC groups. There was no strict cut-off point for SSI score (Cochrane-Brink *et al.*, 2000). Higher scores indicate more severe SI.

Data acquisition

Imaging data were acquired using an echo-planar imaging sequence on 3.0 Tesla GE Medical systems at the First Affiliated Hospital of Chongqing Medical University. During the MRI scan, all subjects were instructed to keep their head still and their eyes closed without falling asleep and do not think of anything in particular. Resting-state fMRI was obtained using the following parameters: repetition time (TR), 2000 ms; echo time, 30 ms; flip angle, 90 degrees; field of view, 240 mm × 240 mm; matrix, 64 × 64; voxel size, 3.75 mm × 3.75 mm × 5 mm; 33 axial slices without slice gap. A total of 240 TRs were collected for each subject.

Data preprocessing

Data preprocessing was performed using the Data Processing & Analysis for Brain Imaging (DPABI, v2.3, www.rfmri.org/dpabi) and SPM12 toolkits (www.fil.ion.ucl.ac.uk/spm/software/spm12). The first 10 volumes were excluded, and the remaining functional images were corrected for slice timing and realignment. Head motion exceeded 2.5 mm translation or 2.5° rotation were excluded from subsequent analyses. The mean frame displacement (FD) was calculated for each subject according to a previously published formula (Power *et al.*, 2012). The functional images were further normalized to a standard template (Montreal Neurological Institute) and re-sampled to 3 mm × 3 mm × 3 mm^3. After normalization, several spurious variances, including 24 head motion parameters (Friston 24-parameter model) (Friston *et al.*, 1996), cerebrospinal fluid signals, and white matter signals, were regressed out by multiple linear regression analysis. For a precise head motion correction, the parameters from scrubbing data were also regressed out. The bad

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points were identified by a threshold of FD (>0.5 mm) as well as one-forward and two-back neighbors (Power *et al.*, 2012). Then each bad point was modeled as a separate regressor in the regression models. Functional images were spatially smoothed with an 8 mm full-width half-maximum isotropic Gaussian kernel. Subsequently, linear trends were removed from time courses. Temporal band-pass filtering was performed between 0.01 and 0.10 Hz. Because of the necessary contiguous time points in ALFF analysis, we did not carry out scrubbing, which altered the temporal structure of the data (Yan *et al.*, 2013). While we used the mean FD as a covariate in group-level analysis to reduce motion-related artifact in the fMRI signal.

Dynamic ALFF computation

The dynamic ALFF was computed using a sliding window approach via DynamicBC (v1.1, www.restfmri.net/forum/DynamicBC) (Liao *et al.*, 2014a). Window length is an important parameter in resting-state dynamics computation. According to previous studies, the minimum window length should be no less than $1/f_{min}$, because shorter window lengths may increase the risk of introducing spurious fluctuations in the observed dynamic ALFF (Leonardi and Van De Ville, 2015). f_{min} was defined as the minimum frequency of time series. Based on this, the optimal window length of 50 TRs (100 s) was selected to compute the temporal variability of ALFF, because a longer window length may hinder the description of the temporal variability dynamics of ALFF. The time series was comprised of 230 TRs (460 s), and the window was shifted by five TRs (10 s). The full-length time series was then divided into 37 windows for each participant. For each sliding window, the ALFF map was obtained. The ALFF of each voxel was divided by the global mean ALFF value to normalize the global effects. To study the temporal variability of the amplitude of iBA, we computed the variance of dALFF maps across sliding-window dynamics. See Fig. 1*a* for analysis steps.

Statistical analysis

Demographic and clinical characteristics were evaluated among three groups. Differences in age and education were analyzed with one-way analysis of variance (ANOVA); χ^2 test was used for gender. Illness duration and HAMD score were compared between the SI and NSI groups by Mann–Whitney *U* test and two-sample *t* test, respectively.

To determine group-level temporal variability of ALFF, we used DPABI toolkit (v2.3, www.rfmri.org/dpabi) (Yan *et al.*, 2016) to perform one-sample *t* test for temporal variability of ALFF within-group comparisons (within the gray matter mask) for each group. Two-sample *t* test analysis was performed to investigate the group differences of temporal variability of ALFF between the SI and NSI groups. Age, gender, educational level, mean FD, and HAMD score were used as covariates. However, liberalizing the statistical threshold can dramatically increase the family-wise error rate (FWER), as recently demonstrated systematically for widely used statistical methods (Eklund *et al.*, 2016). Considering the trade-off between ALFF reproducibility and FWER (Chen *et al.*, 2018), we set the statistical significance level at $P_{FWER} < 0.05$ under permutation test (PT, 5000 times permutations) using in Permutation Analysis of Linear Models (Winkler *et al.*, 2016) implemented in DPABI. Combination of PT-based cluster size inference and height threshold with $p < 0.01$ as the cluster-forming threshold and the cluster extent threshold at $k > 25$ voxels. Post hoc comparisons (SI *v.* HCs and NSI *v.* HCs) were then performed with a two-sample *t* test. Bonferroni-corrected for two planned comparisons was used for multiple comparisons.

SSI symptom prediction

To investigate the relationship between altered temporal variability of ALFF and symptom severity measured by the SSI, we predicted the SSI score for each patient in the SI group using a general linear model according to the previous work (Finn *et al.*, 2015; Shen *et al.*, 2017). We used altered temporal variability of ALFF values in the SI group (compared with the NSI group) as features. We applied a leave-one-out cross-validation (LOOCV) to produce a robust and reliable model. This method is the most popular choice and unbiased strategy (Finn *et al.*, 2015; Shen *et al.*, 2017). In each LOOCV, we selected one subject's data as a test set, and the remaining subjects' data were used as a train set so that this subject's SSI score was predicted based on the building prediction model. Finally, we used the Pearson's correlation to determine whether predicted SSI score is correlated with the observed SSI score in patients with SI. To improve the standards correlation analysis, we identified outliers by bootstrapping the Mahalanobis distance D_s for each observation from the bivariate mean and excluded all points with an average D_s of 6 or greater (Schwarzkopf *et al.*, 2012). If the statistical significance level of $p < 0.05$, we then considered that the altered temporal variability of ALFF could predict SSI and *vice versa*.

In addition, to determine whether dALFF values would provide a neuromarker to predict the severity of SI than static ALFF, we also employed a LOOCV procedure in SSI symptom prediction by static ALFF values.

Validation analysis

To validate our findings of temporal variability of dALFF, we carried out auxiliary analyses. In addition to the window length of 50 TRs (100 s), two additional window lengths [30 TRs (60 s) and 80 TRs (160 s)] were considered to validate the main results.

In addition, the head motion would potentially affect the brain dynamics (Hutchison *et al.*, 2013). We did not perform the produce for scrubbing bad time points identified as image frames because of the necessary contiguous time points in ALFF analysis. However, the mean FD did not differ between two groups [$T_{(46)} = 0.80$, $p = 0.43$]. In addition, the mean FD was considered as a covariate in group-level analysis for correcting motion-related artifact. After we obtained the main results, we additionally performed correlation analysis between head motion parameters (mean FD) and dALFF variance values from group difference regions across subject to further preclude the impact of motion in our results.

Results

Clinical and demographic characteristics

No differences in age (one-way ANOVA, $p = 0.27$), education (one-way ANOVA, $p = 0.83$), gender (χ^2 test, $p = 0.26$), and head motion (one-way ANOVA, $p = 0.54$) were found among the three groups. A significant difference was found in HAMD score (two-sample *t* test, $p = 0.002$) (Table 1). The range of SSI score in the SI group was 9–24.

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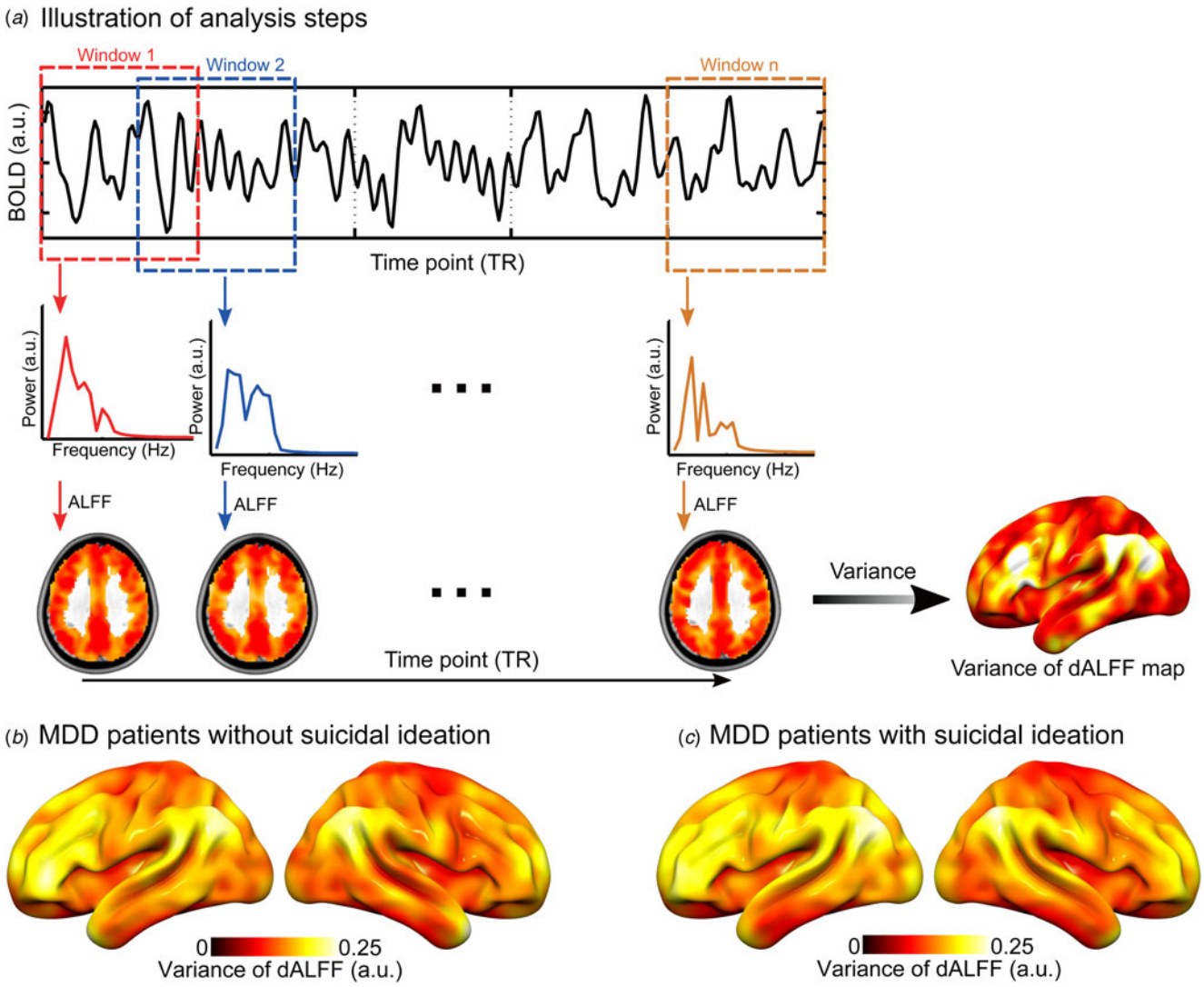

Fig. 1. Illustration of analysis steps and temporal variability of dALFF pattern. (*a*) The preprocessed full-length BOLD fMRI time series was segmented into several sliding windows (50 TRs). For each sliding window, the FFT-based ALFF measure was computed for each voxel for the whole brain. The ALFF was defined as the average square root of the activity in the low-frequency band (0.01–0.10 Hz). The ALFF value of each voxel was standardized by dividing the full-brain mean ALFF value. The sliding window was systematically shifted by five TRs and the corresponding ALFF was computed. This process was performed until the entire data length was covered. The temporal variability of the dALFF was defined as the variance of dALFF maps across the sliding windows. The pattern of temporal variability of the dALFF of the SI (*b*) and NSI group (*c*). The temporal variability of dALFF was averaged at each voxel across all subjects in each group. Low and high variances of dALFF are shown in red and yellow colors, respectively.

Temporal variability of ALFF differences between the SI and NSI groups

Temporal variability of ALFF was quantified at each voxel for the SI and NSI groups (Fig. 1*b*, *c*). The variance of the dALFF displayed a non-uniform spatial distribution across the brain. The largest temporal variability of dALFF was located in the heteromodal association cortex, including the bilateral prefrontal lobes, the temporal–parietal junction, and the posteromedial cortex. The lowest variability was located in limbic cortices. Brain regions showing a moderate level of variability were anchored to the primary sensory and visual cortices, as well as upstream and downstream of the unimodal cortices.

According to two-sample *t* tests, we found that the temporal ALFF variability in the right dorsal anterior cingulate cortex (dACC), the left inferior temporal gyrus (ITG), the hippocampus/parahippocampus gyrus (HIP/ParaHIP), and the orbital frontal cortex (OFC) was significantly different between the SI and NSI groups. Post hoc tests revealed that patients with SI showed decreased temporal ALFF variability in the OFC, left ITG compared with HCs, and patients with NSI showed increased temporal ALFF variability in the dACC and left HIP/ParaHIP compared with HCs (Fig. 2 and Table 2). These results were presented on inflated surface maps by BrainNet Viewer (v1.8, www.nitrc.org/projects/bnv) (Xia *et al.*, 2013).

To determine whether dynamic ALFF and static ALFF provide overlapping or complementary information, we also computed the static ALFF patterns using full-length time series (Zang *et al.*, 2007). The group differences between the SI and NSI groups of static ALFF patterns are shown in online Supplementary Fig. S1.

SSI score prediction from temporal variability of ALFF

We found that dALFF values could predict the severity of SI ($r = 0.43$, $p = 0.03$), while static ALFF values could not ($r = 0.20$, $p = 0.31$) (Fig. 3).

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Table 1. Participant demographic and clinical information

Demographics	SI	NSI	HCs	Statistical	Evaluation
Group size (*n*)	28	20	30	N.A.	N.A.
Handedness (left/right)	0/28	0/20	0/30	N.A.	N.A.
Gender (male/female)	7/21	4/16	12/18	$\chi^2 = 2.73$	$p = 0.26$
Age (years)	32.5 ± 9.9	37.1 ± 10.6	35.7 ± 10.2	$F_{(2,75)} = 1.33$	$p = 0.27$
Education (years)	13.3 ± 2.6	13.3 ± 2.4	12.9 ± 3.2	$F_{(2,75)} = 0.19$	$p = 0.83$
Illness duration (months)	16.6 ± 20.0	19.2 ± 20.0	N.A.	$U = 272.0$	$p = 0.87$
HAMD score	26.0 ± 4.0	22.2 ± 3.8	2.77 ± 1.3	$t_{(46)} = 3.38$[a]	$p = 0.002$
SSI score	15.9 ± 4.4	0 ± 0	0 ± 0	N.A.	N.A.
Mean FD	0.09 ± 0.04	0.10 ± 0.06	0.10 ± 0.05	$F_{(2,75)} = 0.63$	$p = 0.54$

SI, major depression disorder patients with suicidal ideation; NSI, major depression disorder patients without suicidal ideation; HCs, healthy controls; HAMD, 17-item Hamilton Depression Scale; SSI, 19-item Scale for Suicide Ideation. FD, framewise-displacement; *p*, between-group or among-group test *p* value; $t_{(df)}$, between-group *t* statistic and degrees of freedom; $F_{(dfn,\ dfd)}$, one-way ANOVA and degrees of freedom numerator and degrees of freedom denominator; N.A., not available.
Values are mean ± s.d.
[a]*T*-value was calculated between the SI and NSI groups.

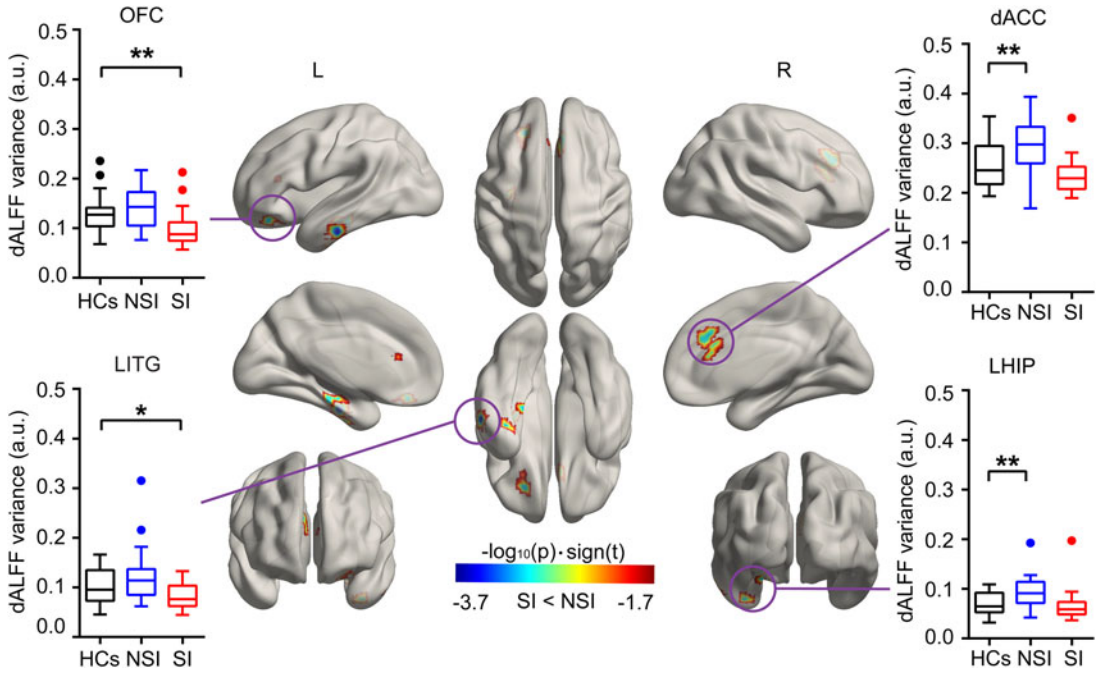

Fig. 2. Group differences of temporal variability of the dALFF. Temporal variability of the dALFF between the SI and NSI groups was identified using two-sample *t* tests. The statistical significance level was set $P_{FWER} < 0.05$ under permutation test-based corrections. The inset box-and-whisker plot indicates the planned post-hoc analysis between SI and HCs, and between NSI and HCs using two-sample *t* tests. *Denotes $p < 0.05$, uncorrected. **Denotes $p < 0.05$ Bonferroni correction with two times planned comparisons, respectively. HCs, healthy controls; NSI, major depressive disorder without suicidal ideation; SI, major depressive disorder with suicidal ideation.

Validation results

The analysis of the data using different sliding-window lengths supported our main results (online Supplementary Fig. S2). There are no significant correlations between motion parameters and variance of dALFF in abnormal brain regions (all $p > 0.05$) (online Supplementary Fig. S3).

Discussion

We demonstrated a novel way, temporal variability of amplitude of low-frequency fluctuations, to explore brain dynamics on MDD with and without SI. Specifically, the SI group exhibited decreased brain dynamics (less temporal variability of dALFF) in the dACC, left OFC, ITG and HIP/ParaHIP compared with the NSI group. More broadly, the altered temporal ALFF variability values in these regions could predict the severity of SI.

Brain dynamics would reflect the aspects of neural system functional capacity (Kucyi *et al.*, 2017) and serve as a novel physiological neuromarker of various neurological and psychiatric diseases (Damaraju *et al.*, 2014; Liao *et al.*, 2014b; Kaiser *et al.*, 2016; Kim *et al.*, 2017a; Li *et al.*, 2018). Although the presence and severity of MDD is associated with abnormal dynamics of inter-regional functional connectivity (Kaiser *et al.*, 2016), the

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Table 2. Decreased dALFF regions in the SI group compared with the NSI group

Brain region	Brodmann area	MNI coordinates (*x*, *y*, *z*)	Cluster size (voxels)	Statistical value
Left inferior temporal gyrus	20	(−57, −18, −27)	46	−3.70
Left orbitofrontal gyrus	11	(−24, 36, −21)	29	−3.00
Dorsal anterior cingulate cortex	24/32	(3, 30, 15)	60	−2.85
Left hippocampus	34	(−33, −18, −18)	31	−2.85

MNI, Montreal Neurological Institute.
Statistical value was computed by the equation: statistical value = $-\log_{10}(p)\cdot\text{sign}(t)$.

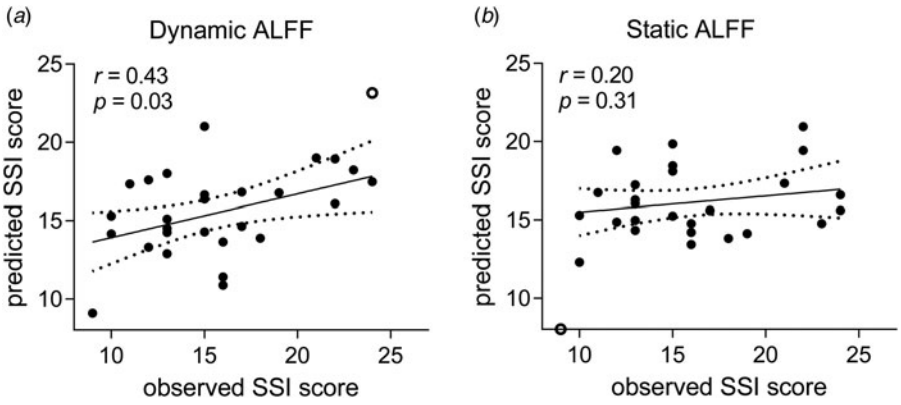

Fig. 3. Temporal variability of the dALFF predicts the severity of SI. (*a*) The results of dynamic ALFF as features to predict the severity of SI ($r = 0.43$, $p = 0.03$). (*b*) The results of static ALFF as features to predict the severity of SI ($r = 0.20$, $p = 0.31$). Filled circles were included in this correlation analysis, while open circles were excluded. Solid lines and dashed lines represented the best-fitted line and 95% confidence interval of the Pearson's correlation analysis, respectively. ALFF, amplitude of low-frequency fluctuation; SSI, Scale for Suicide Ideation.

dynamics of local brain activity itself remains unknown. In contrast to the inter-regional functional connectivity, fluctuations of local brain activity can also be captured using first-order statistics, that is, with time-resolved analysis of instantaneous activity patterns (Fu *et al.*, 2017). The current work expands the dynamics of brain connectivity in depressed patients, and deconstruct the time-varying patterns of iBA in depressed patients with and without SI.

Both OFC and dACC are involved in executive function and emotional processing (Rogers *et al.*, 2004; Schoenbaum *et al.*, 2006; Frodl *et al.*, 2010), which are implicated in MDD with SI or suicidal attempt (Marzuk *et al.*, 2005; Westheide *et al.*, 2008; Pan *et al.*, 2013; Myung *et al.*, 2016). One important aspect of the OFC in executive function is to incorporate emotional salience (e.g. reward and punishment) into decision-making (Mesulam, 2002; Rogers *et al.*, 2004). The current finding of the OFC is consistent with the previous studies, suggesting that the OFC abnormalities are related to suicidal behavior in MDD (Monkul *et al.*, 2007; Jia *et al.*, 2014). The OFC also has a critical role in modulating impulsivity (Matsuo *et al.*, 2009). Impulsivity, one of factors related to personality and individual differences affecting cognitive and emotion, is associated with SI, suicidal attempt, and suicide deaths (O'Connor and Nock, 2014). Therefore, we speculate that decreased dALFF in the OFC may lead to abnormal executive function and emotional processing related to MDD with SI.

We found another considerable decreased dALFF in the dACC. The dACC plays an important role in executive function (Bush *et al.*, 2000; Rogers *et al.*, 2004; Frodl *et al.*, 2010; Lieberman and Eisenberger, 2015) in MDD with SI. The dACC is interconnected with prefrontal cortex, parietal cortex, and motor system, playing a central role in processing top-down activation (Posner and DiGirolamo, 1998; Zhou *et al.*, 2017). Top-down mental processes are needed in executive functions (Diamond, 2013). Aberrant brain distinct connectivity and local activity in the dACC may disturb the balance of the default-mode network, resulting in abnormal emotional regulation (Pannekoek *et al.*, 2014; Zhou *et al.*, 2017). Furthermore, abnormal brain structure and function in the dACC were related to parasuicidal behavior and SI (Whittle *et al.*, 2009; Marchand *et al.*, 2012; Chase *et al.*, 2017). We thus suggest that decreased dALFF activity in the dACC may underlie the phenomenon of abnormal executive function and emotional processing in MDD with SI.

For MDD without SI, previous studies have found altered brain local activity in both dorsal and ventral ACC (Davidson *et al.*, 2002; Mayberg, 2003; Liu *et al.*, 2014; Zhou *et al.*, 2017). In line with previous works, we found increased dALFF in the dACC in MDD without SI compared with HCs. The dACC contributes to online performance monitoring by detecting errors and modifies attention bias based on conflict paradigms (Carter *et al.*, 1998; Kerns *et al.*, 2004; Liu *et al.*, 2014). Therefore, we indicate that increased ALFF in the dACC may disturb error detection and cognitive control in MDD without SI.

The HIP participants in autographical memory and emotional regulation (Bremner *et al.*, 2004; Viard *et al.*, 2007), which are associated with MDD with/without SI and suicidal attempt (Bremner *et al.*, 2004; O'Connor and Nock, 2014; Wang *et al.*, 2015; Johnston *et al.*, 2017). We observed decreased dALFF in the left HIP in MDD with SI relative to the NSI group. The dALFF is a mean of capturing brain instantaneous activity patterns based on high time-resolved (Fu *et al.*, 2017). The brain instantaneous activity, excessive variability (increased temporal variance), or excessive stability (decreased temporal variance) (Christoff *et al.*, 2016) may occur at different times standing as causes of altered cognitive functions and particular pathological state (Preti *et al.*, 2017). Therefore, we speculate that decreased dALFF in the left HIP may underlie the phenomenon of disable to recall specific memories and failure to solve emotional problem in the SI group compared with the NSI group. In addition, we

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found increased dALFF in the left HIP in the NSI group compared with HCs. This finding is consistent with the previous studies demonstrating that MDD exhibits hypoactivation in the HIP in response to positive social stimuli compared with HCs (Fu *et al.*, 2007; Sheline *et al.*, 2009).

We observed that the SI groups showed increased dALFF in the left ITG compared with the NSI group. The ITG is involved in a putative output system, which regulates visceral functions connected with emotions (van Tol *et al.*, 2014). Abnormalities in the ITG may cause emotional disturbances, which not only relate to MDD but also influence SI in MDD patients. Moreover, the ITG showed decreased regional cerebral blood flow and it was considered as one of the top 10 regions to predict suicide in depressed suicidal patients compared with depressed non-suicidal patients (Willeumier *et al.*, 2011). In this respect, impairment in the temporal cortex was not only related to MDD but also associated with the risk of SI in MDD patients. Our study suggests that the ITG may play an important role in detecting NSI development and the risk of SI in MDD patients.

More importantly, the temporal variability of dALFF would predict the severity of SI using. Although several previous studies have found a correlation between neuroimaging features and clinical variables about SI in MDD (Ballard *et al.*, 2015; Pu *et al.*, 2015; Myung *et al.*, 2016), we are not aware of any study that has reported employing dynamic values to predict the severity of SI. Interestingly, we found that dALFF values could successfully predict the severity of SI in the SI group while static ALFF values could not, suggesting that dALFF values may be a more powerful predicted neuromarker in the current sample. However, we did not underestimate the key role of static ALFF in disease prediction modal. In the future work, combining the dynamic ALFF and static ALFF (Fu *et al.*, 2017), even dynamic local brain activity and remote inter-regional connectivity (Rashid *et al.*, 2016) would build better models of brain function and dysfunction.

Limitations and further considerations

Several issues need to be considered. First, although the group size is relatively small, the power analysis showed a large effect size, suggesting the generalizability of our findings to a large sample size. Second, we selected the window size according to the filter bandwidth (0.01–0.10 Hz) utilized in a previous study, which recommended that the minimum window length should be no less than $1/f_{min}$ (1/0.01 = 100 s) (Liao *et al.*, 2014b). Similarly, albeit less reliable, results from the utilization of different sliding window lengths suggest that the findings of the present study are less influenced by this factor. Third, generalizability of brain predictive models is important (Woo *et al.*, 2017). The current model using the dynamics of brain activity should be generalized to new individuals and across different centers in future studies. In addition, LOOCV is unbiased but typically has more variance in prediction error than K-fold (i.e. 10-fold) cross-validation (Kohavi, 1995). However, the K-fold cross-validation can be critical and depends on sample size and effect size in the prediction model (Shen *et al.*, 2017). Considering the small sample size here, we choose the LOOCV for the prediction model. Finally, although we did not perform the produce for scrubbing bad time points, the mean FD was considered as a covariate in statistical analysis and did not correlate with dALFF variance and preclude the impact of motion in our results.

In summary, compared with MDD without SI, the SI group showed decreased brain dynamics (less temporal variability) in the dACC, the OFC, the left ITG, and the left HIP. Our findings suggest that abnormal executive and emotional processing related to MDD with SI. More broadly, these dALFF abnormalities could predict the severity of SI while static ALFF abnormalities could not, indicating the first evidence of changes of brain dynamics in SI. Our findings suggest that this novel predictive model using iBA dynamics could be useful to develop neuromarkers for clinical applications.

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