# Resting State MRI Amplitude of Low Frequency Fluctuations Associated With Suicidal Ideation in Bipolar Depression

Martin J. Lan, MD, PhD[a,b,*]; Spiro P. Pantazatos, PhD[a,b]; R. Todd Ogden, PhD[a,b]; Harry Rubin-Falcone, BS[a,b]; David Hellerstein, MD[a,c]; Patrick J. McGrath, MD[a,c]; and J. John Mann, MD[a,b,d]

## ABSTRACT

***Objective:*** Suicidal ideation (SI) is a risk factor for completed suicide. Our previous resting state functional magnetic resonance imaging (fMRI) study found that higher amplitude of low frequency fluctuation (ALFF) in right hippocampus and thalamus was associated with SI in major depressive disorder (MDD). The present study aimed to evaluate that association in participants with bipolar disorder (BD).

***Methods:*** Thirty depressed, adult participants with a *DSM-IV* diagnosis of BD had resting state fMRI scans. Region-of-interest (ROI) analyses used ALFF values within areas that were previously associated with SI in MDD. Spearman rank correlation and ordinal regression analyses were performed to assess associations between ALFF values and the SI item of the Montgomery-Asberg Depression Rating Scale. Exploratory whole-brain analyses identified regions where ALFF was associated with SI.

***Results:*** Within the right hippocampus region, SI was positively associated with ALFF (Spearman $R = 0.490$, $P = .0060$). Ordinal regression analysis indicated that for every 0.1-unit increase in ALFF in that region, the odds of having higher SI were increased by 35% (odds ratio = 1.35; 95% confidence interval, 1.08–1.73; $P = .012$). Within the previously identified thalamus cluster, SI was associated with ALFF only at a trend level (Spearman $R = 0.310$, $P = .069$). Whole-brain analyses identified 3 clusters of positive association between SI and ALFF, 1 of which was located in the right hippocampus.

***Conclusions:*** This study found that our previous finding of positive association between SI and ALFF in the right hippocampus extended to bipolar depression. Future studies should examine the clinical utility of this association, and the role of the hippocampus in SI.

***Trial Registration:*** Data used for this secondary analysis came from studies with ClinicalTrials.gov identifiers NCT02239094 (January 2015 through September 2016) and NCT02473250 (January 2015 through December 2019).

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[a]Department of Psychiatry, Vagelos College of Physicians and Surgeons at Columbia University, New York, New York

[b]Division of Molecular Imaging and Neuropathology, New York State Psychiatric Institute, New York, New York

[c]Depression Evaluation Service, New York State Psychiatric Institute, New York, New York

[d]Department of Radiology, Vagelos College of Physicians and Surgeons at Columbia University, New York, New York

**Corresponding author:* Martin J. Lan, 1051 Riverside Dr, Unit 42, New York, NY 10032 (martin.lan@nyspi.columbia.edu).

Assessing the severity of suicidal ideation (SI) in patients is a critical clinical challenge. The severity of SI can inform clinical care decisions, including whether to change medication or increase safety precautions such as hospitalization. In acute care settings, safety for discharge is often based on whether SI has mitigated. Patients seeking to avoid hospitalization or quicker discharge from hospital may minimize SI, or deny the intensity of their SI to themselves and their doctors.[1,2] Suicide remains an enormous public health problem. Approximately 800,000 people die by suicide each year globally.[3] SI is a risk factor for both nonfatal suicide attempts and suicide.[4,5] An objective tool to measure or track SI could potentially have a substantial public health impact.

Amplitude of low frequency fluctuations (ALFF) quantifies the intensity of oscillations of brain activity within a particular frequency range using functional magnetic resonance imaging (fMRI). ALFF signal has been associated with the state when the brain is not engaged in particular cognitive activation.[6,7] The physiologic meaning of ALFF has not been fully elucidated, however. One strength of ALFF is its excellent test-retest reliability, lending itself to the potential use as a non-invasive, low-risk clinical tool.[8]

We previously published an exploratory resting state fMRI analysis[9] that identified 2 clusters of increased ALFF in participants with major depressive disorder (MDD) who reported SI when compared with MDD participants without SI. One cluster was located in the right hippocampus and the other in the thalamus. Others[10] reported higher ALFF in the right hippocampus in MDD participants with a history of a past suicide attempt. In the present study, we used an independent dataset from participants with bipolar depression to further investigate the results of our initial study, by quantifying ALFF within the brain regions that were determined from our initial study to be associated with SI, and determine whether the finding in MDD extends to bipolar disorder (BD).

BD is associated with about a 20-fold higher risk for suicide compared with the general population.[11] BD affects 1%–3% of the population.[12] Major depressive episodes in BD have similar symptoms to those in MDD. BD differs from MDD, however, due to its clinical course that includes manic or hypomanic episodes as well as its prevalence, heritability, and response to medications.[13] Moreover, participants with BD are often excluded from studies of MDD. We therefore chose a dataset from participants with BD to determine if our results from MDD replicate in a BD sample. To our knowledge, this study is the first to measure the association

**Clinical Points**

- There are no objective biomarkers to determine if a patient is experiencing suicidal ideation, limiting the ability to assess for their safety.
- An association was found between the intensity of suicidal ideation and resting state activity of several regions of the brain, including the right hippocampus, in participants with bipolar disorder. The results extended previous findings from participants with major depressive disorder. The work provides proof-of-concept data that a transdiagnostic biomarker for suicidal ideation may be feasible.

between resting state ALFF and SI in BD. We also performed exploratory whole-brain analyses to identify regions whose ALFF may be associated with SI in BD.

## METHODS

### Participants

Thirty participants were recruited at the New York State Psychiatric Institute (New York, New York). The participants were enrolled in 2 studies (15 in each) that originally had been designed to identify neuroimaging markers of antidepressant response. Both studies included participants with *DSM-IV* BD (I, II or not otherwise specified [NOS]) between the ages of 18 and 60 years who were in a current major depressive episode. Both studies excluded participants with current psychosis, recent substance abuse (within the last 2 months) or substance dependence (within the last 6 months), unstable medical conditions, or known metal in the body. The first study used a score > 15 on the Quick Inventory of Depressive Symptomatology–Self Rated version (QIDS-SR)[14] to determine eligibility, and the second study used a 17-item Hamilton Depression Rating Scale[15] score of > 15 when atypical items were included. The first study excluded participants who had an onset of mood disorder after age 40 years or who had a lack of antidepressant response to lurasidone.[16] The second study excluded participants who had failed trials of more than 2 serotonin-based antidepressants (selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors). This is a secondary analysis of those data. Suicidal ideation was measured by the score of Montgomery-Asberg Depression Rating Scale (MADRS)[17] item number 10, which ranges from 0 to 6. The total MADRS score without the value on the suicidal ideation item (ie, MADRS – SI) was calculated for each participant to include as a potential nuisance covariate. The studies were approved by the local Institutional Review Board, written informed consent was obtained, and the studies were registered at www.clinicaltrials.gov. The first study (NCT02239094)[16] was conducted from January 2015 through December 2019; the second study (NCT02473250)[18] was conducted from January 2015 through September 2016.

### Image Acquisition

Brain magnetic resonance imaging (MRI) was obtained on a 3T Signa HDx scanner from General Electric (Fairfield, Connecticut) with a 32-channel head coil. The same scanner was used for both studies. Head motion was constricted by restraining foam pads. Participants were instructed to focus their sight on a black crosshair with a white background for 6 minutes. An echo planar image (EPI) sequence was acquired with the following parameters: repetition time, 2,000 ms; echo time, 28.0 ms; acquisition matrix, 64 × 64; flip angle, 90.0°; slices of 2 mm, with 3 mm voxels. T1-weighted spoiled gradient recalled echo sequence images, obtained in 3 dimensions had the following parameters: repetition time, 6.4 ms; echo time, 2.6 ms; inversion time, 900 ms; flip angle, 9.0°; matrix, 256 × 256 × 1 mm slices, 1 mm voxels.

### Image Processing

Configurable Pipeline for the Analysis of Connectomes (CPAC) was used to process fMRI data.[19] T1-weighted structural MRI scans were spatially normalized using Advanced Normalization Tools into Montreal Neurological Institute (MNI) space.[20] EPI images were transformed into the subject space of the associated T1-weighted structural MRI and then to the common template. The Friston 24-parameter model[21] was used for motion correction, and white matter and cerebrospinal fluid signal were included as nuisance variables. Maps of ALFF were created for each subject with a temporal bandpass filter (0.01–0.08 Hz) before transformation into *Z*-score maps. A 6-mm full-width half-maximum Gaussian filter was used for spatial smoothing.

### Replication Region of Interest (ROI) Analyses

Spatial masks of the clusters that were previously reported[9] to have higher ALFF in MDD participants with SI when contrasted to those without SI were used to obtain mean ALFF values. Spearman rank correlations between SI scores and the mean ALFF in those regions were calculated. Post hoc analyses were performed to assess associations with age, sex, and study protocol using either a Pearson correlation or a 2-tailed *t* test. An ordinal logistic regression analysis with SI as outcome was performed to investigate the relationship between SI and ALFF values calculated using R statistical package 4.0.4.[22]

### Whole-Brain Exploratory Analyses

Whole-brain analyses were performed to identify other brain regions in which ALFF was associated with SI. A linear regression analysis of SI was performed using the FSL tool for nonparametric permutation inference, randomize,[23] with age, sex, and study as covariates.[24,25] Analyses were repeated with MADRS – SI included as an additional covariate. Clusters with a threshold-free cluster enhancement family-wise error–corrected *P* value less than .05 were considered significant.[26]

## RESULTS

### Demographics

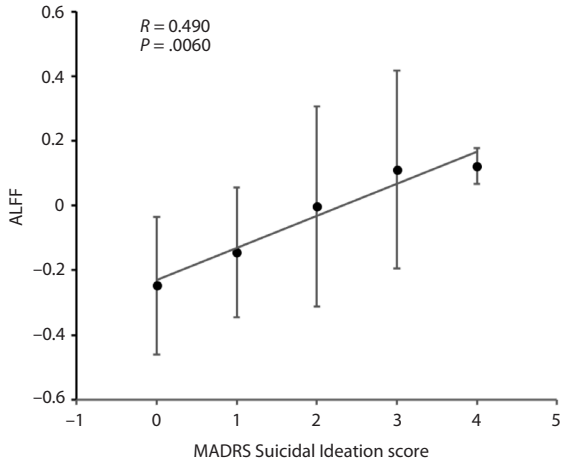
Clinical variables are listed in Table 1. Ten participants had no SI, and the SI value from the MADRS ranged from

**Table 1. Demographic and Clinical Characteristics of the Study Sample (N = 30)[a]**

| Demographic Characteristic | Value | Association With SI |
|---|---|---|
| Age, mean (SD), y | 35.7 (12.2) | $R = -0.213$, $P = .259$* |
| MADRS – SI,[b] mean (SD) | 27.3 (8.3) | $R = 0.484$, $P = .0067$* |
| SI score (from MADRS) | 1.7 (1.5) | NA |
| Male | 17 (57) | $P = .440$** |
| Bipolar disorder diagnosis | | $P = .478$** |
| Bipolar I | 13 (43) | |
| Bipolar II | 11 (37) | |
| Bipolar NOS | 6 (20) | |
| Right-handedness | 26 (87) | $P = .160$** |
| Medications[c] | | $P = .913$** |
| Valproic acid | 13 (43) | |
| Other medication | 2 (7) | |
| No medication | 15 (50) | |
| Comorbid disorders | | $P = .067$** |
| Anxiety disorders | 17 (57) | |
| Other comorbid psychiatric illness | 1 (3) | |
| No comorbid psychiatric illness | 12 (40) | |
| Substance use disorder[d] | | $P = .537$** |
| Alcohol use disorder | 5 (17) | |
| Cocaine use disorder | 3 (10) | |
| Polysubstance use disorder | 2 (7) | |
| No substance use disorder | 20 (67) | |

[a]Values are shown as n (%) unless otherwise noted.
[b]MADRS – SI is the MADRS score without the suicidal ideation item included.
[c]Medications listed are what the participants were taking at the time of the scan.
[d]Substance use disorders are lifetime diagnoses.
*Spearman *R* and *P* value.
**One-way ANOVA.
Abbreviations: ANOVA = analysis of variance, MADRS = Montgomery-Asberg Depression Rating Scale, NOS = not otherwise specified.

**Figure 1. Relation Between Amplitude of Low Frequency Fluctuations (ALFF) Within the Right Hippocampus Cluster and Suicidal Ideation[a,b]**




[a]In a previous study of major depressive disorder, ALFF within the right hippocampus cluster was higher in participants with suicidal ideation than in those without suicidal ideation. Here, ALFF was associated with the Suicidal Ideation score of the Montgomery-Asberg Depression Rating Scale (MADRS), replicating the previous result in participants with a bipolar disorder diagnosis.
[b]*R* = Spearman correlation coefficient; *P* value is from Spearman rank correlation.

1 through 4. The mean SI value for the whole group was 1.7 and was 2.6 for those with some ideation. Associations between demographic variables and SI values are listed in Table 1.

### Region of Interest Analyses

Within the previously identified right hippocampus cluster,[9] SI was positively associated with ALFF (Spearman $R = 0.490$, $P = .0060$; Figure 1). Ordinal regression analysis indicated that for every increase of 0.1 unit of ALFF in the hippocampus cluster, the odds of having higher SI on the scale were increased by 35% (odds ratio = 1.35; 95% CI, 1.08–1.73; $P = .012$). Within the previously identified thalamus cluster, SI was positively associated with ALFF at a trend level (Spearman $R = 0.310$, $P = .069$). Because the clusters had been defined when controlling for age and sex in the initial analysis with MDD participants, these were not included as covariates here. Post hoc analyses were performed to determine if the ALFF values were associated with these other clinical variables. The mean ALFF was not associated with age in the hippocampus cluster (Pearson $R = 0.032$, $P = .868$) or in the thalamus cluster (Pearson $R = -0.143$, $P = .452$). It was not different between sexes in the hippocampus cluster ($P = .542$) or the thalamus cluster ($P = .886$). It was not associated with depression severity when SI was not considered (MADRS – SI) in the hippocampus (Pearson $R = 0.278$, $P = .135$), but it had a trend-level association with MADRS – SI in the thalamus cluster (Pearson $R = 0.336$, $P = .069$). It was not different between the 2 studies in the hippocampus cluster ($P = .719$), but did differ between the studies in the thalamus cluster ($P = .038$). Of note, participants in only 1 study[18] were on a medication at the time of the imaging.

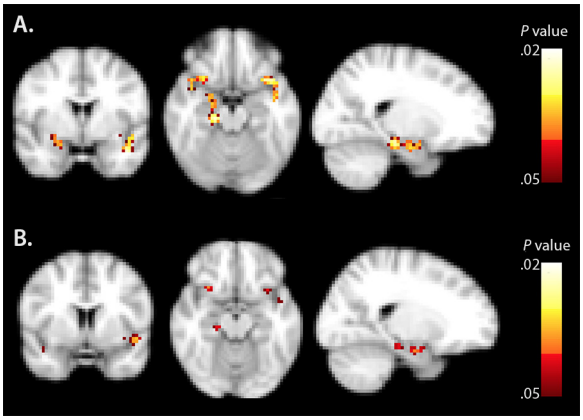
### Whole-Brain Exploratory Analyses

Whole-brain regression analyses of SI and ALFF with age, sex, and study as covariates yielded 3 clusters that were positively associated with SI (Figure 2A). One cluster included the right hippocampus, parahippocampal gyrus, and amygdala (116 voxels, peak $P = .02$, X = 18, Y = −24, Z = −18). A second cluster included the right insula, temporal pole, and frontal orbital regions (164 voxels, peak $P = .02$, X = −48, Y = 6, Z = −9). A third cluster on the left included the same regions as the second, but also included the left planum temporale (90 voxels, peak $P = .03$, X = 30, Y = 18, Z = −15). The whole-brain regression analysis was rerun with age, sex, study and MADRS – SI values included as covariates to assess whether the association between ALFF and SI could be explained by the other symptoms of depression. Five smaller clusters were identified that spatially overlapped with the clusters without the covariate (Figure 2B). No clusters of ALFF were inversely associated with suicidal ideation in the exploratory analyses.

## DISCUSSION

We found that the association between SI and ALFF in the right hippocampus in MDD extends to SI in BD. Higher ALFF in this region was associated with greater SI with an odds ratio of 1.35 per 0.1-unit increase in ALFF. In exploratory

**Figure 2. Coronal, Axial, and Sagittal Brain Views Showing the Results of the Whole Brain Correlation Analysis of Amplitude of Low Frequency Fluctuations (ALFF) Using a Nonparametric Permutation Inference (A) With Age, Sex, and Study as Covariates and (B) With MADRS Score With the SI Value Removed From the Scale (MADRS – SI Value) as an Additional Covariate[a]**




[a]In the initial correlation analysis (A), the ALFF in 3 clusters was positively associated with SI. When the analysis was rerun with age, sex, study, and MADRS – SI values as covariates (B), smaller clusters with similar spatial distribution were positively associated with suicidal ideation.
Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale.

whole-brain analyses, ALFF in regions including the insula, temporal pole, and frontal orbital regions was associated with SI in BD. These findings remained when including MADRS – SI as a covariate in the analysis, indicating that the association between SI and ALFF could not be explained by depression severity alone.

Methodological differences between our study and previous resting state fMRI studies complicate comparisons. Most previous studies have focused on identifying a signal that is associated with a history of suicide attempt, rather than SI.[27–30] Because those studies compared participants with suicide attempts who were experiencing SI to those without suicide attempts who were also experiencing SI, the designs were not optimized to identify a signal that is associated with SI. Many studies also used other methods of analyzing the fMRI data that are distinct from ALFF, most commonly functional connectivity.[31–33]

Previous studies have reported altered resting state signal in the hippocampus with either SI or suicidal behaviors. One study[10] found higher ALFF in the hippocampus and thalamus within a group of participants with SI and a history of suicide attempts when compared to 3 other groups: those with SI without suicide attempts, healthy volunteers, and participants with MDD without any SI or suicide attempts. Another report[34] found that dynamic ALFF in the left hippocampus, among other regions, had lower variability in participants with SI when compared to those without SI. A previous study[35] reported higher seed-based functional connectivity between one hippocampus to its contralateral region in participants with a suicide attempt history when compared to those without an attempt. Another[36] reported higher functional connectivity to the contralateral side in the hippocampus in participants with SI when compared to those without SI. Together, these studies confirm an association between resting state activity in the hippocampus and suicide risk. Future studies could further elucidate how the ALFF signal relates to the functional connectivity in the region.

Our exploratory analyses found that higher ALFF within the amygdala was associated with SI in BD. A primary function of the amygdala is in processing the salience of events and stimuli. Our findings are consistent with previous studies that have found associations between SI and amygdala or "salience network" activity. A previous study[36] reported greater functional connectivity between the amygdala and both the precuneus and posterior cingulate cortex regions in participants with BD and SI. One study[37] reported altered functional connectivity within the "salience network" with participants with SI, and two others[38,39] found altered salience network connectivity in participants with a history of suicide attempts.

Our finding of higher ALFF in the insula associated with SI is also consistent with previous literature. One study[40] reported lower global brain connectivity in the insula within BD participants with suicide attempt history. Two studies[39,41] found altered functional connectivity within the "limbic network" with participants with a suicide attempt history, consistent with an association in insula function.

A recent meta-analysis[42] of functional imaging studies found that alterations in the hippocampus, amygdala, thalamus, and posterior cingulate cortex were associated with either self-injurious thoughts or self-injurious behaviors, consistent with our findings. The authors interpreted these results to mean that there was a pattern of internally oriented emotional processing that could underly resting state activity with suicide risk.[42]

It should be noted that we found the association between hippocampal ALFF with SI both in participants with MDD in our previous study and in participants with BD reported here. However, thalamic ALFF was associated with SI in MDD, but not in BD. Conversely, the insula and amygdala had higher ALFF with BD, but not with MDD. Therefore, there could be both a common and unique resting state patterns associated with SI in the two disorders. Our data suggest that resting brain activity related to SI should be studied further across participants with distinct psychiatric diagnoses. Because SI can occur as part of a number of diagnoses, there has been an initiative to define suicide-specific syndromes such as suicide crisis syndrome[43] or suicide behavior disorder.[44] Subtle neurocognitive deficits have been found to be associated with both suicidal behavior and SI transdiagnostically.[45] It is possible that these deficits may mediate the association between SI and ALFF signal. Of note, we did find an association between the ALFF signal and memory function in our previous study of MDD participants.[9]

This study has several limitations. Acute risk for suicide, including having a suicide plan and intent, was an exclusion for the study. The results therefore may not extend to individuals at imminent risk for suicide. The severity of SI

was based on one item of a depression rating scale. A more thorough scale may have more accurately characterized the SI. The generalizability of the results is limited by the study design and sample size. For example, participants were excluded if they had failed trials of particular medications. Many of the participants also had comorbid psychiatric disorders that could not be controlled for within this sample size.

A biomarker that could measure the risk of future suicide attempt would clearly have clinical utility. Because a history of past attempts is a strong predictor of future attempts, it forms an important clinical characteristic to study. Data on suicide attempt history were not obtained for sufficient numbers of participants here, however, to perform an analysis of this factor. A future study could disentangle the contribution of ideation and past attempt behavior to the resting state signal. Alternatively, a longitudinal study could measure whether ALFF is predictive of future attempts. Future studies could also determine whether ALFF is associated with certain qualities of SI that are linked to the risk for future attempts, including the presence of suicide intent or plan, or the variability of SI over time.[46]

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*Editor's Note:* We encourage authors to submit papers for consideration as a part of our Focus on Suicide section. Please contact Philippe Courtet, MD, PhD, at pcourtet@psychiatrist.com.