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Resting State Amplitude of Low-Frequency Fluctuation is Associated with Suicidal Ideation

Martin J. Lan^{#1,2}, Mina M. Rizk^{#1,2,3}, Spiro P. Pantazatos^{1,2}, Harry Rubin-Falcone^{1,2}, Jeffrey M. Miller^{1,2}, M. Elizabeth Sublette^{1,2}, Maria A. Oquendo⁴, John G. Keilp^{1,2}, and J. John Mann^{1,2,5}

¹Department of Psychiatry, Columbia University College of Physicians and Surgeons, New York, NY, USA

²Division of Molecular Imaging and Neuropathology, New York State Psychiatric Institute, New York, NY, USA

³Department of Psychiatry, Faculty of Medicine, Minia University, Egypt

⁴Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

⁵Department of Radiology, Columbia University College of Physicians and Surgeons, New York, NY, USA

These authors contributed equally to this work.

Abstract

Background: Identifying brain activity patterns that are associated with suicidal ideation (SI) may help to elucidate its pathogenesis and etiology. Suicide poses a significant public health problem, and SI is a risk factor for suicidal behavior.

Methods: Forty-one unmedicated adult participants in a major depressive episode (MDE), 26 with SI on the Beck Scale for Suicidal Ideation and 15 without SI, underwent resting state fMRI scanning. Twenty-one healthy volunteers (HV) were scanned for secondary analyses. Whole brain analyses of both amplitude of low frequency fluctuations (ALFF) and fractional ALFF (fALFF) were performed in MDE subjects to identify regions where activity was associated with SI.

Results: Subjects with SI had greater ALFF than those without SI in two clusters: one in right hippocampus and one in thalamus and caudate, bilaterally. Multi-voxel pattern analysis distinguished between those with and without SI. *Post-hoc* analysis of the mean ALFF in the hippocampus cluster found it to be associated with delayed recall on the Buschke memory task.

Corresponding author: Martin J Lan, 1051 Riverside Dr., Unit 42, New York, NY 10032, martin.lan@nyspi.columbia.edu, Tel: 646 774 7610.

Work was performed at Columbia University College of Physicians and Surgeons, New York, NY USA

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Mean ALFF from the significant clusters was not associated with depression severity, and did not differ between MDE and HV groups.

Discussion: These results indicate that SI is associated with altered resting state brain activity. The pattern of elevated activity in the hippocampus may be related to how memories are processed.

Keywords

Suicidal ideation; resting state; fMRI; major depressive disorder; biomarker; suicide

INTRODUCTION

Suicide is a major cause of mortality worldwide (World Health Organization, 2016). Suicidal behavior is strongly associated with underlying psychiatric illness (Kessler, Berglund, Borges, Nock, & Wang, 2005), particularly major depressive disorder and bipolar depression (Cavanagh, Carson, Sharpe, & Lawrie, 2003). Suicide rates have increased in the U.S. over the last 20 years (Stone et al., 2018) despite advances in psychiatric treatments. Both psychotherapy (Brown et al., 2005; Linehan, Armstrong, Suarez, Allmon, & Heard, 1991) and psychotropic medication treatments (Mann et al., 2005; Zalsman et al., 2016) can reduce the risk for suicide, but there are no objective tests to determine this risk.

Suicidal ideation (SI) is more common than suicidal behavior (Nock et al., 2008) and is a risk factor for suicide attempts (Fawcett et al., 1987; Kessler, Borges, & Walters, 1999; Mann, Waternaux, Haas, & Malone, 1999; Mundt et al., 2013; Oquendo et al., 2004). A suicidal patient may deny SI on interview. This is particularly true in initial evaluations and emergency room settings, when patients and clinicians may be relatively unknown to each other. Patients may avoid discussing SI with clinicians (van Spijker, van Straten, & Kerkhof, 2010), or they may deny or minimize the importance of SI to themselves (Oquendo, Halberstam, & Mann, 2003). Some patients may intentionally try to thwart any intervention to prevent suicide, or they may not perceive a need for care (Brook, Klap, Liao, & Wells, 2006). The neural circuits involved in SI are not known. Elucidating the activity patterns associated with SI may help develop a test to evaluate risk for suicide, or to create more targeted treatment strategies to reverse SI.

Resting state functional magnetic resonance imaging (rs-fMRI) investigates brain processes that occur when subjects are not engaged in any particular mental task. SI often occurs when peoples' thoughts are at rest (Beck, Rush, Shaw, & Emery, 1979). rs-fMRI may therefore help to delineate brain regions that are involved with SI. SI has been linked to stable patterns of negative self-reflection (Bhar, Ghahramanlou-Holloway, Brown, & Beck, 2008; Cox, Enns, & Clara, 2004) including rumination (Miranda & Nolen-Hoeksema, 2007; J. M. Smith, Alloy, & Abramson, 2006). These mental processes have been associated with rs-fMRI activity (J. P. Hamilton, Farmer, Fogelman, & Gotlib, 2015). Few prior rs-fMRI studies have examined SI (Chase et al., 2017; Du et al., 2017; Kang et al., 2017; Kim et al., 2017; Li, Duan, Cui, Chen, & Liao, 2018; Ordaz, Goyer, Ho, Singh, & Gotlib, 2018), and their results are mixed.

We performed an exploratory whole brain analysis and machine learning multi-voxel pattern analysis to identify the differences in rs-fMRI signal that was associated with SI in subjects in a major depressive episode (MDE). A group of healthy volunteers (HV) were included to allow for a secondary analysis of MDE diagnosis effect. We used Amplitude of Low Frequency Fluctuations (ALFF) and fractional ALFF (fALFF) as the outcome measures because they reflect resting brain activity, and have strong test-retest reliability (Zuo et al., 2010). Although the univariate analysis has high interpretability and allows us to map individual regions related to SI, it does not allow us to test whether f/ALFF maps can predict SI on an individual subject basis. Thus, we also applied MVPA to identify regions whose pattern may predict SI.

METHODS AND MATERIALS

Participants:

Participants were recruited through the Molecular Imaging and Neuropathology Area (MIND) Clinic at The New York State Psychiatric Institute (New York, NY, USA). Forty-one participants with major depressive disorder and 21 HV subjects were recruited. One subject was determined after research procedures to have a bipolar disorder diagnosis. Inclusion/exclusion criteria were assessed through clinical interview, physical examination, routine blood tests and electrocardiogram. Inclusion criteria for the major depressive episode (MDE) group were: 1) age range from 18–65 years; 2) DSM-IV diagnosis of a current MDE as assessed using the Structured Clinical Interview (SCID) for DSM-IV (First, Spitzer, Gibbon, & Williams, 1995); 3) Hamilton Depression Rating Scale-17 item score ≥ 16 (HAM-D) (M. Hamilton, 1960); and 4) If on current antidepressant medications, reported lack of significant benefit and considered to be likely to tolerate medication washout. Exclusion criteria included: 1) unstable medical conditions, 2) lifetime psychosis, anorexia nervosa or bulimia nervosa in the past year (comorbid anxiety disorders were allowed); 3) Drug or alcohol abuse within past 2 months, or current drug or alcohol dependence not remitted in the past 6 months; 4) first-degree family history of schizophrenia for subjects less than 33 years old; 5) neurological disease or previous head trauma with evidence of cognitive impairment; 6) electroconvulsive therapy (ECT) within past 6 months; 7) pregnancy, currently lactating, planning to conceive during the course of study participation or abortion in the past two months; and 8) unable to obtain MRI; for example, due to metal within the body or claustrophobia. HV participants were excluded if they had any lifetime psychiatric diagnoses including substance use disorders, other than specific phobia, or first-degree family members with psychiatric disease. All participants provided written informed consent. Study procedures were approved by the New York State Psychiatric Institute Institutional Review Board. MRI scanning at Weill Cornell Medical Center was approved by the Institutional Review Board of Weill Cornell Medical Center. This work was a secondary analysis of data acquired from studies with other scientific aims.

Clinical Procedures:

Patients on antidepressant treatment at time of enrollment (N=8) underwent a medication washout and were medication free for at least three weeks prior to neuroimaging. Short acting benzodiazepines were allowed as needed for anxiety up to 72 before neuroimaging.

Clinical assessments within one week of neuroimaging included the HAMD (M. Hamilton, 1960) and Beck's Hopelessness Scale (Beck, Weissman, Lester, & Trexler, 1974) for depression severity, Columbia Suicide History Form (Oquendo et al., 2003), and the Beck Scale for Suicidal Ideation (SSI) (Beck, Kovacs, & Weissman, 1979). To assess the effect of depression severity independent of SI, the value of the suicide item (item 3) of the HAMD was subtracted from the HAMD to yield a clinical variable (HAMD-SI) for further analyses.

Image Acquisition:

Brain magnetic resonance imaging was obtained at two scan sites, New York State Psychiatric Institute and Weill Cornell Medical Center. Both sites used a 3T Signa HDx scanner from GE (General Electric, Fairfield, CT, USA) with an 8-channel head coil and identical scan parameters. Head motion was limited by restraining foam pads. During resting state sequence acquisition, subjects were instructed to focus their sight on a black cross-hair with a white background for 6 minutes. An EPI sequence was acquired with the following parameters: repetition time 2000, echo time 28.0, Acquisition matrix 64 X 64, Flip angle 90.0, field of view 20.5 cm, 39 contiguous slices of 3 mm with 3 mm voxels. T1 weighted spoiled gradient recalled echo sequence images were obtained in 3D with parameters TE 2.4 ms, TR 6.0 ms, TI 900 ms, Flip angle 9.0° Matrix 256 X 256, 174 X 1 mm slices, 1 mm voxels.

Image Processing:

Resting state fMRI data preprocessing was carried out using the Configurable Pipeline for the Analysis of Connectomes (C-PAC) (Cameron Craddock et al., 2013). T1-weighted structural MRI scans were transformed into Montreal Neurological Institute (MNI) space using Advanced Normalization Tools (ANTS). EPI images were then transformed into the space of their corresponding T1-weighted structural MRI, and finally transformed to the common template. Motion correction was performed using the Friston 24-parameter model. Subject-level maps of ALFF and fALFF were created with a temporal bandpass filtering (0.01–0.08 Hz) and transformed into Z-score maps. Spatial smoothing was performed with a 6-mm full-width half-maximum Gaussian filter.

Whole brain statistical analyses:

Whole brain group level analyses were performed within the MDE subjects. A categorical analysis of participants with and without SI was performed using FSL's tool for nonparametric permutation inference, randomize, with age, sex and scan site as covariates (Winkler, Ridgway, Webster, Smith, & Nichols, 2014). A whole brain analysis was also performed using SSI score as a continuous measure to identify clusters that correlated with SSI score with age, sex and scan site as covariates. Clusters with a Threshold Free Cluster Enhancement family wise error corrected p-value less than 0.05 were considered as significant (S. M. Smith & Nichols, 2009). T-maps of clusters with $t > 2.3$ were also inspected to identify areas that differed between the groups at a more liberal statistical threshold.

Buschke Selective Reminder Task:

Thirty-one MDE subjects and 12 HVs received the Buschke Selective Reminding Test, a list learning task to assess their verbal memory. Because one cluster of ALFF was found in the right hippocampus (see below), and the hippocampus is involved with memory function (Opitz, 2014), we assessed *post hoc* for an association between the ALFF in this cluster and Selective Reminding Task score. The Selective Reminding Task is unique among list learning tasks in requiring examinees to retain information from trial to trial without explicit repetition of words committed to memory, to assess the quality of encoding. Words are only repeated if forgotten ('selective reminding'). Quality of learning across trials, then, can be examined in detail. Buschke Selective Reminding Task performance is commonly affected by depression (Zakzanis, Leach, & Kaplan, 1998), as well as by history of suicidal behavior over and above the effects of depression (Keilp et al., 2014; Keilp et al., 2013; Keilp et al., 2001).

Secondary Analyses:

Secondary tests were performed to examine the association of ALFF in the significant clusters identified from brain-wide analysis with the clinical variables listed below using IBM SPSS Statistics (SPSS Inc., Chicago, Illinois, USA, Version 24.0). We initially checked all quantitative variables for outliers and normal distribution. Pearson correlation analysis was performed between SSI scores, HAM-D-SI scores, Buschke scores, and ALFF. Fisher-Z transformation was used to compare the correlations of ALFF with either Buschke delayed recall score or Buschke immediate recall score. Two-tailed t-tests were used to assess for differences in ALFF within the significant clusters between the two scan sites, subjects with a history of anxiety disorders, or subjects with history of substance use disorders.

Multi-voxel pattern analysis:

We performed classifications using whole-brain fALFF and ALFF maps (not z-scored) from Configurable Pipeline for the Analysis of Connectomes (C-PAC) (C. Craddock et al., 2013) to 1) predict continuous suicide ideation severity scores using Support Vector Regression and 2) classify suicide ideators vs. non-ideators using Support Vector Machines (SVM) (Vapnik, 1999). Analyses were implemented in scikit-learn (Pedregosa et al., 2012) and nilearn using linear kernels with default parameters. Maps were resampled to 6×6×6 mm resolution and masked using the nilearn NiftiMasker function. We applied feature selection using linear regression (or ANOVA for SVMs), leave-one-out cross-validation and significance testing based on non-parametric permutation. Features were adjusted for depression severity (HRDS-SI), age, sex and scan site using linear regression. Classification performance was estimated and plotted as the negative of the Mean Squared Error or Area under the ROC curve (AUC) for real and null data where subjects' scores/labels were shuffled 1,000 times for each top N features selected. We first looked at the top 10, 20... 90%, and then also examined the top 1 through 10 voxels (features). A corrected p-value that combined the separate p-values obtained across the top N tested features was computed using Empirical Brown's Method for combining dependent p-values (Poole, Gibbs, Shmulevich, Bernard, & Knijnenburg, 2016).

RESULTS

Clinical characteristics of the research participants are found in Table 1. Only two subjects had a suicide attempt history, precluding analyses of past suicide behavior. Twenty-three MDE subjects had scans at New York State Psychiatric Institute and 18 subjects had scans at the Weill Cornell Medical Center. All HVs were scanned at New York State Psychiatric Institute. The value of the suicide question (item three) of the HAMD correlated significantly with SSI values ($r=0.629$, $p=1.4 \times 10^{-5}$).

Two clusters of ALFF were higher in MDE subjects with SI compared with MDE subjects without SI, after correcting for age, sex and scan site as covariates. One was located in bilateral thalamus and caudate (239 voxels, peak $p=0.032$, $X=27$, $Y=-21$, $Z=-21$), and the other localized to right hippocampus (48 voxels, $p=0.032$, maximum voxel $X=27$, $Y=-21$, $Z=-21$; Figure 1). No clusters of ALFF were lower in suicide ideators when compared to non-ideators with age, sex and scan site as covariates. No clusters of fALFF differed between suicidal ideators and non-ideators with age, sex and scan site as covariates. No clusters of either ALFF or fALFF correlated with the continuous values of SSI scores when considering all MDE subjects with age, sex and scan site as covariates. When the analysis of MDE subjects with SI compared to without SI was repeated with age, sex, scan site and HAMD-SI included as covariates, similar clusters of smaller size differed between groups (Figure 2; 148 voxels, peak $p=0.032$, $X=-12$, $Y=3$, $Z=-3$; and 9 voxels, peak $p=0.046$, $X=27$, $Y=-24$, $Z=-12$).

Mean ALFF values in the significant clusters as above were used for *post hoc* analyses. When considering all MDE and HV subjects with Buschke test data, mean ALFF in the hippocampus positively correlated with Buschke delayed recall ($r=0.314$, $df=43$, $p=0.040$; Figure 3), but not with immediate recall values ($r=0.173$, $df=43$, $p=0.267$). Mean ALFF in the thalamus and caudate cluster, however was not associated with Buschke scores (immediate recall $r=0.053$, $df=43$, $p=0.734$, delayed recall: $r=0.152$, $df=43$, $p=0.330$). Buschke scores did not correlate with SSI scores when considering within the MDE group (immediate recall: $r=-0.079$, $df=31$, $p=0.671$; delayed recall: $r=0.134$, $df=31$, $p=0.472$) and did not differ between MDE ideators and non-ideators (Table 1). The correlation between ALFF with delayed recall scores and ALFF with immediate recall scores did not significantly differ (hippocampus cluster: $Z=1.04$, $p=0.149$; thalamus cluster: $Z=0.71$, $p=0.24$).

A number of *post hoc* analyses were run to rule out other clinical factors that may have explained the association between SI and ALFF. Mean ALFF in the significant clusters did not differ between MDE and HV groups. When considering the MDE group only, mean ALFF was not correlated with HAMD-SI scores (thalamus cluster, $r=0.059$, $p=0.712$; hippocampus cluster, $r=0.136$, $p=0.401$), or Beck Hopelessness Scale (thalamus cluster, $r=0.078$, $p=0.548$; hippocampus cluster, $r=0.126$, $p=0.437$). Mean ALFF values did not differ between MDE subjects with a history of anxiety disorders when compared to those without anxiety disorders (Thalamus cluster, $t_{(39)}=0.438$, $p=0.663$; hippocampus cluster, $t_{(39)}=0.809$, $p=0.424$), and did not differ between those with remitted substance use disorder and those without substance use disorder history (thalamus cluster $t_{(34)}=0.808$, $p=0.425$;

hippocampus cluster $t_{(34)}=0.242$, $p=0.810$). ALFF was not different between the scans acquired at the two sites (thalamus cluster ($t_{(39)}=0.097$, $p=0.923$, hippocampus cluster $t_{(39)}=1.277$, $p=0.209$).

Multi-voxel pattern analyses also identified associations between SI and resting state fMRI. When selecting the top 10, 20...90% features, neither fALFF nor ALFF maps performed better than chance when predicting either suicide ideation severity or MDE suicide ideators vs. MDE non-ideators. However, selecting the top 1 through 10 features indicated a trend in the fALFF maps when predicting SI severity ($p=0.08$ corrected), and in the ALFF maps when classifying ideators vs. non-ideators ($p=0.0005$ corrected) (Figure 4). For SI severity, best performance was achieved with the top 4 features, approaching significance across all top N features ($p=0.08$ corrected, Figure 4A, left panel) and explained ~20% out-of-sample variance in SI severity (Figure 3A, right panel). Informative features included voxels in dorsolateral PFC, anterior temporal cortex and vmPFC (Figure 4A, right box). For SI binary classification, best performance was achieved with the top 3 features ($AUC=0.72$, Figure 4B, left and right panels) and was significant across all top N features ($p=0.0004$ corrected). Informative features included voxels in the vmPFC and lateral occipital cortex (Figure 4B, right box). The T-map of clusters of ALFF with $t>2.3$ that differed between participants in a MDE with SI compared with MDE subjects without SI, after correcting for age, sex and scan site, demonstrated a region of greater ALFF in the Frontal Cortex of participants with SI, consistent with the informative features from the MVPA analysis. (Supplemental Figure).

DISCUSSION

This is one of the first studies to examine the association between brain amplitude of low frequency fluctuations (ALFF) at rest and current suicidal ideation in unmedicated patients in a MDE, and it is the first to use multi-voxel pattern analysis to characterize an association between SI and rs-fMRI. Depressed individuals with SI had greater ALFF during resting state in two clusters; one in bilateral thalamus and caudate, and one in right hippocampus, compared with MDE without current SI. *Post hoc* analyses showed that the association between ALFF and SI could not be explained by depression symptoms of the MDE participants.

Because the hippocampus is known to have a role in memory functions (Opitz, 2014), secondary analyses were conducted to determine if the greater ALFF in the right hippocampus cluster was related to delayed recall. Our positive result indicates that the association between SI and ALFF signal in the hippocampus may relate to a difference in how the subjects with SI activate the hippocampus to process memory at rest. Participants with SI did not have deficits on the memory task, however, indicating that the difference in activity was not associated with either better or worse memory function. Several previous studies have reported neurocognitive deficits in subjects with a history of suicide attempts in MDE when compared to non-attempters, including memory deficits (Keilp et al., 2014; Richard-Devantoy, Berlim, & Jollant, 2014; Stewart et al., 2017). We could not test this in our sample, however, since only two subjects in our MDE group had made past attempts. Together, the data suggest that SI is associated with different hippocampus activity at rest

that may relate to memory function, but those patients who go on to attempt suicide have gross deficits in memory function. Because the association between memory function and the ALFF signal was found through our secondary analyses of the data, the result needs replication through future studies to assess this *a priori*. Such studies should be powered to detect whether the association is specific to delayed recall, but not to immediate recall. Our study did not find a significant difference between the delayed recall and immediate recall associations with ALFF. Although delayed recall is dependent on initial learning during the immediate recall phase of the Buschke, delayed recall is more demanding (given that information must be retained over a 30 minute delay). An effect that is specific to delayed recall would suggest that more extensive and/or challenging memory tasks provide stronger associations to ALFF in hippocampus.

A recent meta-analysis of resting state fMRI studies in MDD found hyperactivity of right hippocampus, among other regions, when compared to HV (Sundermann, Olde Lutke Beverborg, & Pfleiderer, 2014). Another study showed greater anterior cingulate cortex-hippocampus functional connectivity in MDD (de Kwaasteniet et al., 2013). Major depression is also reported to be associated with greater resting state activity in left thalamus relative to controls (Kuhn & Gallinat, 2013). Our results of an association between SI and ALFF was not explained by depression severity. Future studies of MDD should investigate to what extent SI drives the group differences between MDD and healthy volunteers.

The thalamus acts as an important node in multiple neuronal circuits with a wide range of functions (Sherman, 2016). Suicidal feelings and ideation often appear driven by emotional pain (Shneidman, 1998). The processing of emotional pain has been associated with both thalamus activity (Dalgleish, 2004) and with SI (Olie, Guillaume, Jaussent, Courtet, & Jollant, 2010). Future studies are required to explore whether emotional pain can explain the association between SI and rs-fMRI activity in the region.

Our machine learning analyses identified the ventromedial prefrontal cortex to be driving the differentiation between depressed suicidal ideators and non-ideators. The ventromedial prefrontal cortex is involved with multiple brain functions that are linked to depression (Hiser & Koenigs, 2018), including reward and value based decision making, generation and regulation of negative affect, and aspects of social cognition (Van Overwalle, 2009). Surprisingly, there was little overlap between the statistical parametric maps obtained from the group-level univariate analysis with maps of informative features in the MVPA. This is mostly likely attributed to the fact that group level results applied cluster-extent correction for multiple comparisons, and was thus more sensitive to weaker, but spatially distributed signals, whereas MVPA feature selection was applied to individual (downsampled) voxels. When the group level results were examined at a looser statistical threshold ($t > 2.3$), a region with spatial overlap to the frontal cortex features of the MVPA analysis was identified (Supplemental Figure).

Most previous studies examining the association between SI and rs-fMRI activity (Chase et al., 2017; Du et al., 2017; Kang et al., 2017; Kim et al., 2017; Li et al., 2018; Ordaz et al., 2018), have focused on functional connectivity between regions. Compared to non-ideators, suicidal ideators had greater resting-state functional connectivity between the amygdala and

left superior orbitofrontal cortex (Kang et al., 2017), and the posterior cingulate cortex and middle temporal gyrus (Chase et al., 2017). Others reported that suicidal ideators have lower connectivity between right anterior cingulate cortex and orbitofrontal cortex and right middle temporal pole (Du et al., 2017), and between the orbitofrontal cortex, the left middle temporal gyrus, left postcentral gyrus, and subcortical regions including both caudate, both thalami, and right putamen (Kim et al., 2017). Ordaz et al. (2018) reported lower within-network coherence in the executive control, default mode and salience networks in relation to greater lifetime severity of SI. Li et al. (2018) found that suicidal ideators exhibit less dynamic ALFF, a measure of temporal variability of ALFF, in the dorsal anterior cingulate cortex, orbitofrontal cortex and hippocampus compared with non-ideators. Because of the distinct outcome measures of rs-fMRI activity amongst these studies, a unifying model of activity pattern cannot be discerned at this time.

We found group-level differences in ALFF, and ALFF predicted SI vs. non-SI, whereas fALFF measures predicted continuous SI scores in the MVPA analysis. These differences may be attributed to several reasons: 1) ALFF has been found to have greater test-retest reliability. 2) To calculate fALFF, the low frequency fluctuations are normalized to the amplitude of all fluctuations in the fMRI signal, including those outside of the low frequency oscillation range. This normalization can introduce variance into the data from the other frequencies that may not reflect resting state activity. fALFF can be less disrupted by the pulsatile effects of nearby large blood vessels; this advantage is not as relevant for our study, as our results do not track a clear vascular distribution (Zuo et al., 2010). Other studies have looked at how ALFF changes over the scan, using dynamic ALFF (dALFF) as their dependent variable. We decided not to measure this because two previous studies have shown low reliability for this measure (Lindquist, Xu, Nebel, & Caffo, 2014; Zhang, Baum, Adduru, Biswal, & Michael, 2018).

Our study was limited by its sample size, particularly the number of MDE subjects without SI. As this was a secondary analysis of pooled data, we were unable to control for differences in recruitment among the original studies. A potential confound for the study was the two separate MRI scanning locations. The scanner hardware and scan parameters were identical at the two locations, however. Our analyses included scan site as a covariate, and we did not find a site effect in our *post hoc* analyses.

Taken together, our data suggest that resting state fMRI warrants further study as a tool to elucidate the brain activity patterns that are associated with SI. Knowing the brain patterns associated with SI may lead to a clinical tool either to better predict suicide risk, or to monitor effects of treatment on SI. Future studies may further investigate the interaction between memory function, resting state activity and the etiology of SI.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Coronal, axial and sagittal brain views showing the results of whole brain analysis of Amplitude of Low Frequency Fluctuations (ALFF) using a non-parametric permutation inference (randomise) with age, sex and scan site as covariates. Two cluster had greater ALFF in depressed suicidal ideators (N=26) compared with depressed non-ideators (N=15). One cluster localized to the bilateral thalamus and caudate. The second cluster localized to the right hippocampus.

Figure 2:

Coronal, axial and sagittal brain views showing the results of whole brain analysis of Amplitude of Low Frequency Fluctuations (ALFF) using a non-parametric permutation inference (randomise) with HAMD-SI, age, sex and scan site as covariates. Two cluster had greater ALFF in depressed suicidal ideators (N=26) compared with depressed non-ideators (N=15). The distribution of significant clusters were similar to the analysis without HAMD-SI as a covariate, but with smaller area.

Figure 3.

Plot of the Mean ALFF in the right hippocampus cluster and the delayed recall scores on the Buschke Selective Reminding Task. Green points and regression line are for depressed patients and blue points and regression line are for healthy volunteers. Black regression line includes all subjects. Abbreviation: ALFF= amplitude of the low frequency fluctuation.

Figure 4. f/ALFF maps to predict SI in subjects with MDE (N=41).

A) When predicting suicide severity, best performance was achieved with the top 4 features (voxels in dorsolateral PFC, anterior temporal cortex and vmPFC, top right inset) and was marginally significant across all top N features ($p=0.08$ corrected, left) and explained ~20% out-of-sample variance in SI severity (right). **B)** When classifying SI vs. non-SI, best performance was achieved with top 3 features (AUC=0.72, right) that included vmPFC and lateral occipital cortex (right small box), and was significant across all top N features ($p=0.0004$ corrected). Error bars represent the middle 90% of values about the null mean.

Table 1:

Demographic and clinical characteristics of the study sample. HVs: healthy volunteers; SI: Suicidal Ideators; SD: standard deviation.

Variable	Depressed SI (N= 26)		Depressed Non-SI (N= 15)		HV's (N= 21)		Three-group Comparison	Depressed SI vs. Depressed Non-SI
Demographic Characteristics								
	N	%	N	%	N	%	<i>p^a</i>	<i>p^b</i>
Sex; Female	16	61.5	7	46.7	12	57.1	0.650	0.355
Handedness; Right	25	96.2	11	73.3	18	85.7	0.253	0.174
Medication Naïve	10	38.5	5	33.3				0.864
Suicide Attempters	2	7.7	0	0				0.695 ^{\$}
Anxiety Disorders	11	42.3	8	53.3				0.495
Other comorbid Psychiatric Illness	4	15.4	4	26.7				0.434 ^{\$}
Substance Use Disorders:								
Alcohol Use Disorder	4	15.4	1	6.7				0.636 ^{\$}
Marijuana Use Disorder	4	15.4	1	6.7				0.636 ^{\$}
Other Substance Use Disorder	1	3.9	0	0				0.634 ^{\$}
	<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>	<i>p^c</i>	<i>p^d</i>
Age (years)	33.4	10.6	34.1	8.6	32.4	9.8	0.873	0.821
Education (years)	15.9	2.4	16.9	2.6	15.0	1.9	0.046	0.187
Clinical measures								
Hamilton Depression Rating Scale without SI value.	17.4	5.4	16.1	3.4	1.1	1.6	<0.001	0.421
Beck Hopelessness Scale	13.0	4.7	9.4	5.0	1.0	1.0	<0.001	0.028
Scale for Suicidal Ideation	6.5	4.7	0	0	0	0	<0.001	<0.001
Immediate recall	125.2	14.2	130.2	11.6	125.6	13.5	0.582	0.324
Delayed recall	11.0	1.4	10.8	1.4	11.0	2.0	0.894	0.384

^a Chi-square test (df= 2).

^b Chi-square test (df= 1);

^{\$} Fisher's Exact test.

^c One-way analysis of variance (df= 2, 59)

^d Independent two-sample two-tailed t-test (df= 39).