Modes of Resting Functional Brain Organization Differentiate Suicidal Thoughts and Actions:
A Preliminary Study

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ABSTRACT

Objective: A major target in suicide prevention is interrupting the progression from suicidal thoughts to action. Use of complex algorithms in large samples has identified individuals at very high risk for suicide. We tested the ability of data-driven pattern classification analysis of brain functional connectivity to differentiate recent suicide attempters from patients with suicidal ideation.

Methods: We performed a cross-sectional study using resting-state functional magnetic resonance imaging in depressed inpatients and outpatients of both sexes recruited from a university hospital between March 2014 and June 2016: recent suicide Attempters within 3 days of an attempt (n = 10), Suicidal Ideators (n = 9), Depressed Non-Suicidal Controls (n = 17), and Healthy Controls (n = 18). All depressed patients fulfilled *DSM-IV-TR* criteria for major depressive episode and either major depressive disorder, bipolar disorder, or depression not otherwise specified. A subset of suicide attempters (n = 7) were rescanned within 7 days. We used a support vector machine data-driven neural pattern classification analysis of resting-state functional connectivity to characterize recent suicide attempters and then tested the classifier's specificity.

Results: A binary classifier trained to discriminate patterns of resting-state functional connectivity robustly differentiated Suicide Attempters from Suicidal Ideators (mean accuracy = 0.788, signed rank test: $P = .002$; null hypothesis: area under the curve = 0.5), with distinct functional connectivity between the default mode and the limbic, salience, and central executive networks. The classifier did not discriminate stable Suicide Attempters from Suicidal Ideators (mean accuracy = 0.58, $P = .33$) or presence from absence of lifetime suicidal behavior (mean accuracy = 0.543, $P = .348$) and was not improved by modeling clinical variables (mean accuracy = 0.736, $P = .002$).

Conclusions: Measures of intrinsic brain organization may have practical value as objective measures of suicide risk and its underlying mechanisms. Further incorporation of serum or cognitive markers and use of a prospective study design are needed to validate and refine the clinical relevance of this candidate biomarker of suicide risk.

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Identifying individuals at imminent risk of suicide with urgent need of acute medical care remains a subjective process. Thousands of individuals contemplate suicide, but only a fraction act upon those thoughts during their lifetime.[1,2] Consummation of suicidal behavior represents the highest level of suicide risk, apart from completed suicide.[3] Thus, a major target for intervention is identifying and interrupting the progression from suicidal thoughts to action.

An ideal, although costly and lengthy study design would be to characterize prospectively large at-risk cohorts at frequent intervals to capture emergent suicidal thoughts and behaviors. Use of complex algorithms based on risk factors in large samples has prospectively identified individuals at very high risk for suicidal behavior within 1 year.[4–8] In an alternative cross-sectional approach, the present study examined recent suicide attempters as an imminent high-risk group while controlling for suicidal ideation and depression using resting-state functional magnetic resonance imaging (rs-fMRI).

rs-fMRI is an increasingly prevalent technique for measuring intrinsic connectivity between functional brain networks in resting, awake individuals who are not engaged in overt tasks.[9] The growing popularity of rs-fMRI stems from its independence of task performance, thus circumventing the confound of study-specific task properties. rs-fMRI has been increasingly used to investigate the relationship between the functional organization of neural networks and behavior[10,11] and clinical outcomes.[12] For instance, changes in intrinsic connectivity of the default mode network (DMN), central executive network (CEN), salience network (SAL), and limbic network (LIM) have been shown to correlate with changes in depression severity.[13–15]

By using rs-fMRI in a cross-sectional design, we attempted to study intrinsic brain activity associated with acute suicidal behavior as an acute and transient state, not a lifetime trait. We built on previous work[16,17] that found significant transient abnormalities, independent of previous lifetime suicidal behavior, in cognitive impulsivity and pain processing within 3 days of a suicide attempt that resolve within a week. Thus, in this pilot study, we examined the use of rs-fMRI to differentiate individuals who had attempted suicide in the previous 3 days from individuals at lesser acute suicide risk. We hypothesized

Clinical Points

- There is a lack of biology-based markers of acute risk for suicidal behavior.
- A support vector machine neural pattern classifier based on baseline brain function was able to discriminate depressed patients who attempted suicide in the previous 72 hours from those currently endorsing suicidal ideation.
- Replication and validation in a larger independent sample, further incorporation of serum or cognitive markers, and the use of a prospective study design are needed to validate and refine the clinical relevance of this candidate biomarker of suicide risk.

that a data-driven pattern classification analysis of brain functional connectivity could differentiate recent suicide attempters from those with current suicidal ideation.

METHODS

Patients

Four groups of adults of both sexes, aged 18–65 years, were recruited between March 2014 and June 2016. Consecutive subjects were screened from the psychiatric inpatient units (groups 1 and 2) and outpatient clinics of the University of Arkansas for Medical Sciences (UAMS) (groups 2 and 3) and the local community (groups 3 and 4). All subjects in groups 1, 2, and 3 fulfilled *DSM-IV-TR* criteria for major depressive episode and major depressive disorder, bipolar disorder, or depression not otherwise specified. The depressed outpatients and healthy controls were recruited through flyers posted in the community.

Exclusion criteria were (*a*) inability to read, write, and speak English; (*b*) inability to provide informed consent; (*c*) history of dementia or neurovascular or neurodegenerative conditions; (*d*) current pain of any kind; (*e*) opioid use within the last month; (*f*) history of non-suicidal self-harm; (*g*) undergoing alcohol, benzodiazepine, opioid, or barbiturate withdrawal; (*h*) non-removable ferromagnetic objects; (*i*) history of claustrophobia; (*j*) positive pregnancy test; and (*k*) involuntary hospitalization. The UAMS Institutional Review Board approved all procedures.

The 4 groups were as follows: Group 1 (Suicide Attempters; n = 10): currently depressed subjects with a recent (within the previous 3 days) suicide attempt of moderate to high intent and lethality as defined by a score of ≥ 2 on the actual lethality/medical damage subscale of the Columbia Suicide Severity Rating Scale (C-SSRS)[18] (35 contacted and 10 met inclusion/exclusion criteria and agreed to participate); Group 2 (Suicidal Ideators; n = 9): currently depressed subjects with current suicidal ideation but no suicidal behavior in the previous 6 months (31 contacted and 9 met inclusion/exclusion criteria and agreed to participate); Group 3 (Depressed Non-Suicidal Controls; n = 17): currently depressed subjects with no suicidal ideation or suicidal behavior in the last 6 months (all met inclusion/exclusion criteria); and Group 4 (Healthy Controls; n = 18): subjects without a psychiatric history.

Our study focused on the neurobiology of acute suicidal behavior as a state rather than a trait; thus, recent suicidal behavior was an exclusion criterion for the Suicidal Ideator and Depressed Non-Suicidal Control groups, and suicidal ideation in the last 6 months was an exclusion criterion for the Depressed Non-Suicidal Control group. Our group and others[16,17,19–21] have previously used this empirical 6-month cut-off for remote suicidal behavior to identify cognitive and physiological changes associated with recent suicidal behavior. There were individuals with lifetime suicide attempts in the 3 depression groups (ie, Groups 1–3; see Table 1).

Procedure

After they gave written informed consent, participants underwent an interview to provide demographic data, psychiatric and medical history, behavioral ratings, and measurement of pressure pain threshold.[22] Psychiatric diagnosis was established with the Structural Clinical Interview for *DSM-IV-TR* Axis I Disorders (SCID).[23] The C-SSRS and Beck Depression Inventory-II (BDI-II)[24] were used to quantify suicidal ideation and behavior as well as depression severity. Known risk factors associated with suicide were characterized with the Beck Anxiety Inventory (BAI)[25] and Beck Hopelessness Scale (BHS)[26] and choice impulsivity with the Monetary Choice Questionnaire.[27]

After the intake interview, participants underwent rs-fMRI and task-based fMRI, the latter to be discussed in separate reports. Suicide attempters who were still hospitalized and who agreed to further evaluation (n = 7) underwent a second study visit that included rating scales and fMRI scanning.

Analysis of clinical data. Analysis of variance (ANOVA) was used to compare continuous variables. Significant results were followed by the Tukey test. Chi-square tests were used to compare categorical data. All tests were 2-tailed. Adjusted *P* values are reported.

MRI acquisition. Imaging data were acquired using a Philips 3T Achieva X-series MRI scanner (Philips Healthcare, Eindhoven, The Netherlands). Anatomic images were acquired with a MPRAGE sequence (matrix = 256 × 256, 220 sagittal slices, TR/TE/FA = shortest/shortest/8°, final resolution = 0.94 × 0.94 × 1 mm^3 resolution). Resting state images were acquired using a 32-channel head coil with the following echo-planar imaging sequence parameters: TR/TE/FA = 2000 ms/30 ms/90°, FOV = 240 × 240 mm, matrix = 80 × 80, 37 oblique slices, ascending sequential slice acquisition, slice thickness = 2.5 mm with 0.5 mm gap, final resolution 3.0 × 3.0 × 3.0 mm^3 for 7.5 minutes. Parameters for the 32-channel coil were selected to reduce orbitofrontal signal loss due to sinus artifact.

fMRI preprocessing. All MRI data preprocessing was conducted in AFNI[28] unless otherwise noted. Anatomic data underwent skull stripping, spatial normalization to the ICBM452 brain atlas, and segmentation into white matter (WM), gray matter, and cerebrospinal fluid (CSF) with the FMRIB Software Library (FSL).[29] Functional data underwent

Table 1. Clinical and Demographic Characteristics of Study Participants[a]

Characteristic	Suicide Attempters		Suicidal Ideators	Depressed Non-Suicidal Controls	Healthy Controls	Adjusted *P*
	Recent	Stable				
n	10	7	9	17	18	
Age, mean ± SD, y	34.2 ± 10.9	35.7 ± 11.3	31.5 ± 9.9	37.2 ± 9.8	32.6 ± 10.9	.087
Male	1 (10)	1 (14)	3 (33)	8 (47)	7 (39)	.266*
Race						.200*
White	8 (80)	6 (86)	9 (100)	11 (65)	14 (78)	
Black	2 (20)	1 (14)	0 (0)	6 (35)	4 (22)	
Marital status						.362*
Single	5 (50)	5 (71)	6 (67)	11 (65)	10 (56)	
Long-term relationship	3 (30)	1 (14)	2 (22)	2 (12)	5 (29)	
Divorced/widowed	2 (20)	1 (14)	1 (11)	4 (24)	3 (17)	
Education, mean ± SD, y	12.8 ± 1.3	12.3 ± 1.9	13.9 ± 2.3	13.5 ± 1.8	15.0 ± 2.0	.091
Employment status						.081*
Student or working	4 (40)	2 (28)	6 (67)	9 (53)	6 (33)	
Unemployed, disabled, or retired	6 (60)	5 (71)	3 (33)	8 (47)	12 (67)	
Clinical characteristics						
Diagnosis						.583*,†
Major depressive disorder	6 (60)	5 (71)	8 (89)	12 (71)	0 (0)	
Bipolar disorder	2 (20)	2 (28)	1 (11)	4 (24)	0 (0)	
Depression NOS	2 (20)	0 (0)	0 (0)	2 (12)	0 (0)	
Anxiety disorder	5 (50)	5 (71)	5 (56)	4 (24)	0 (0)	.196†
Substance use disorder	5 (50)	4 (57)	6 (67)	12 (71)	0 (0)	.719†
Antidepressant use	10 (100)	7 (100)	9 (100)	10 (59)	0 (0)	**.008***,†
Depression (BDI) score, mean ± SD	33.5 ± 16.8	15.3 ± 6.3**	39.0 ± 6.7	31.5 ± 8.9	2.0 ± 2.5	.135†
Anxiety (BAI) score, mean ± SD	23.0 ± 17.1	7.1 ± 2.5**	26.8 ± 9.4	26.4 ± 12.4	2.8 ± 3.6	.767†
Hopelessness (BHS) score, mean ± SD	10.3 ± 1.6	9.8 ± 0.4**	10.6 ± 1.6	10.2 ± 2.1	8.6 ± 0.9	.878†
Suicidal ideation severity (C-SSRS) score, mean ± SD	1.0 ± 1.6	0.1 ± 0.1**	1.6 ± 1.0[b]	0 ± 0[c]	0 ± 0	**< .001**†
Pressure pain threshold score, mean ± SD	13.8 ± 4.5[b,c,d]	9.2 ± 3.0**	9.8 ± 4.6[e]	10.2 ± 5.1[e]	8.8 ± 3.2[e]	**.041**
Delay discounting rate, mean ± SD	0.79 ± 0.29[b]	0.49 ± 0.39**	0.58 ± 0.34	0.53 ± 0.32	0.31 ± 0.27[e]	**.003**
Suicide-related measures						
Presence of suicidal ideation	4 (40)	0 (0)	9 (100)	0 (0)	0 (0)	**< .001***,†
Lifetime history of suicide attempts	10 (100)	7 (100)	5 (56)	6 (35)	0 (0)	**.004***,†

[a]Values shown as n (%) unless otherwise noted. The 7 stable Suicide Attempters were a subset of the 10 recent Suicide Attempters. Analysis of variance was performed for all demographic variables for recent Suicide Attempters, Suicidal Ideators, Depressed Non-Suicidal Controls, and Healthy Controls. Generalized linear model with correction for age, gender, race, marital status, education years, and functioning level was performed to compare all clinical variables between the 4 groups, except for *Yates χ^2. Boldface indicates statistical significance.
[b]Compared to Healthy Controls.
[c]Compared to Ideators group.
[d]Compared to Depressed Non-Suicidal Controls.
[e]Compared to Recent Attempters group.
**Comparison of Stable with Recent Attempters group.
†χ^2 between Recent Attempters, Suicidal Ideators, and Depressed Non-Suicidal Controls.
Abbreviations: BAI = Beck Anxiety Inventory, BDI = Beck Depression Inventory, BHS = Beck Hopelessness Scale, C-SSRS = Columbia Suicide Severity Rating Scale, NOS = not otherwise specified.

despiking; slice correction; deobliquing (to $3 \times 3 \times 3$ mm^3 voxels); motion correction (using the 10th time point); transformation to the spatially normalized anatomic image; regression of 6 motion parameters (lateral movement in x, y, and z; rotational movement in roll, pitch, or yaw) and regression of mean time course of WM voxels and mean time course of CSF voxels; spatial smoothing with a 6-mm FWHM Gaussian kernel; and scaling to percent signal change. Using the Matlab Statistics Toolbox (The Mathworks, Inc, 2015), time points with brief spikes in head motion were identified via the framewise displacement method[30]; any time point for which the sum of these differentials exceeded 0.5 in magnitude was excluded from the time series, as these sudden head movements introduce greatest fMRI artifact.

Independent Components Analysis (ICA). We used the GIFT Matlab toolbox to perform group ICA.[31] We utilized ICASSO[32] to estimate component reliability. All components exhibited high stability index, $I_q \geq 0.9$, sampled from 20 runs, randomly initialized. GIFT was configured to compute Principal Components Analysis using expectation maximization, compressing to 60 principal components in the first step and 30 principal components in the second step, as well as to use infomax to solve for ICAs and scale the resultant ICAs to *z*-scores. The size of our component set (30) is comparable to the number of ICAs typically found usable in machine learning–derived analysis. Nine components were identified as noise or ventricular activation and excluded from further analysis.

Feature Generation. We projected each participant's fMRI data into group-mean-ICA-space, yielding 21 time-series (1 time-series for each component). ICA-based functional connectivity was computed for each subject via Pearson correlation of pairwise component time-series. Due to symmetry of the functional connectivity matrix, the upper triangular matrix was extracted and vectorised, forming the subject's classification feature.

Multivariate Pattern Classification. Multivariate Pattern Classification was implemented via linear support vector machine (SVM) classification[33] using the default implementation found within the Matlab Statistics Toolbox

Table 2. Neural Activity Within Independent Components Identified Through Independent Component Analysis During the Resting State in Suicide Attempters, Suicidal Ideators, Depressed Non-Suicidal Controls, and Healthy Controls[a]

Region (Brodmann Area)	Cluster Size (no. of Voxels)	Peak Voxel t-Score	Peak Voxel MNI Coordinates x	y	z
Limbic network					
Component 13					
Putamen (l 34)	1,581	20.81	−25.5	7.5	5.5
Component 14					
Parahippocampal gyrus (r 38)	1,414	22.15	25.5	−1.5	−18.5
Component 18					
Thalamus (r 27)	524	22.18	−4.5	−31.5	−3.5
Central executive network					
Component 26					
Middle frontal gyrus (r 8)	1,318	19.01	25.5	25.5	53.5
Inferior parietal lobule (r 40)	456	20.10	49.5	−52.5	41.5
Component 29					
Middle frontal gyrus (l 10)	1,112	18.83	−43.5	43.5	5.5
Inferior parietal lobule (l 40)	456	17.12	−43.5	−46.5	41.5
Component 30					
Inferior frontal gyrus (r 9)	806	19.96	52.5	25.5	11.5
Inferior frontal gyrus (r 46)	379	16.22	−43.5	34.5	5.5
Salience network					
Component 22					
Superior temporal gyrus (r 13)	564	21.40	46.5	16.5	−6.5
Superior temporal gyrus (l 13)	513	19.51	−49.5	13.5	−6.5
Component 24					
Medial frontal gyrus (r 6)	1,465	28.37	4.5	19.5	38.5
Insula (l 13)	364	21.28	−40.5	16.5	8.5
Insula (r 13)	342	23.88	46.5	13.5	−0.5
Component 28					
Dorsal insula (r 13)	1,428	23.66	40.5	−10.5	11.5
Dorsal insula (l 13)	1,214	21.10	−61.5	−13.5	11.5
Default mode network					
Component 4					
Cuneus (18)	2,210	28.33	−1.5	−67.5	8.5
Component 6					
Dorsal precuneus (7)	996	22.51	−1.5	−62.5	44.5
Component 11					
Ventral precuneus (31)	1,146	26.41	1.5	−37.5	26.5
Component 16					
Medial frontal gyrus (9)	1,794	30.57	−4.5	43.5	2.5
Cingulate (31)	252	19.37	−1.5	−22.5	41.5
Component 17					
Retrosplenial cortex (l 31)	846	28.10	−7.5	−58.5	14.5
Component 20					
Superior frontal gyrus (l 8)	889	20.10	−1.5	52.5	35.5
Precuneus (l 31)	337	25.68	−1.5	−58.5	26.5
Superior temporal gyrus (l 39)	243	15.13	−46.5	−55.5	23.5
Sensorimotor network					
Component 21					
Post central gyrus (l 6)	2,581	26.19	1.5	−13.5	50.5
Component 23					
Inferior parietal lobule (r 40)	781	26.19	1.5	−13.5	50.5
Inferior parietal lobule (l 40)	520	21.92	37.5	−43.5	41.5
Component 27					
Precentral gyrus (l 4)	233	15.70	−52.5	−10.5	41.5
Precentral gyrus (r 4)	213	15.00	52.5	−10.5	35.5
Inferior parietal lobule (r 40)	150	−15.14	52.5	−37.5	29.5
Occipital network					
Component 5					
Lingual gyrus (l 18)	1,287	19.47	−4.5	−76.5	−9.5
Component 15					
Middle occipital gyrus (r 19)	1,220	18.35	25.5	−46.5	−9.5
Middle occipital gyrus (l 19)	773	18.47	−28.5	−52.5	−12.5
Cerebellum network					
Component 9					
Culmen (l 19)	1,773	19.99	−28.5	−43.5	−24.5

[a]Independent component analyses used data from all voxels. These clusters were arbitrarily thresholded at cluster > 20 and $P < .005$ to aid visualization of the networks.
Abbreviation: MNI = Montreal Neurological Institute.

(The Mathworks, Inc, 2015). All scripts are available upon request.

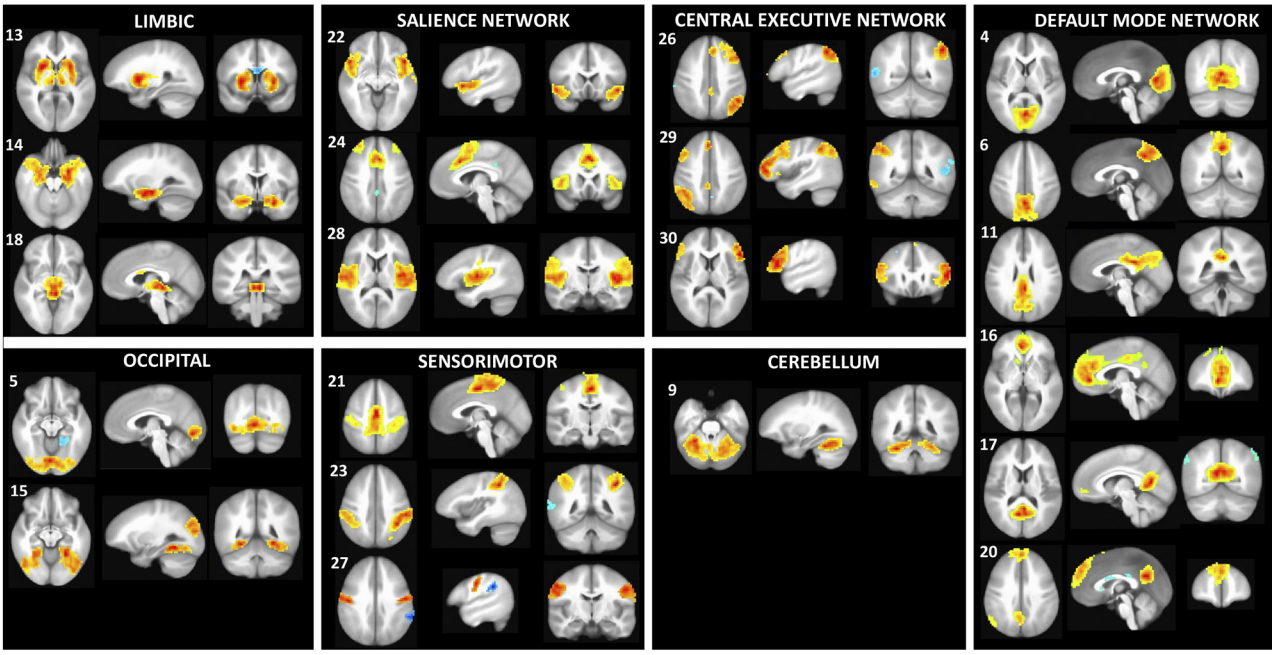
Of note, differentiation of groups by breaking into training/testing groups is the gold standard but is practicable only with larger samples than the current one. Leave-one-out-cross-validation (LOOCV) is the next best practice to approximate the true underlying distribution of the data. We took this one step further and conducted a randomly balanced LOOCV experiment. This is the most accurate methodology given the data set size.

Intersubject cross-validation. LOOCV was performed subject-wise (number of total subjects = Nsubjects). Thus, Nsubjects – 1 subjects' data were used to predict the data of the remaining subject. For each of the Nsubject test subjects, the training fold was formed as follows. The labels of training subjects were binned and counted. The size of the minority group was identified, and a subset of the majority group's data having the same size as the minority group was uniformly, randomly sampled from the majority data. The testing fold was formed from the remaining subject's data.

Training convergence. The entire LOOCV training process was iterated until group classification accuracy converged to steady state. Loop termination criterion was iterative difference of mean classification vector magnitude (root sum of squares) evaluating to less than 1E-6. Training convergence stepcounts were 216 (Suicide Attempters vs Suicidal Ideators), 414 (Suicide Attempters vs Depressed Non-Suicidal Controls), and 103 (Healthy Controls vs Suicide Attempters + Suicidal Ideators + Depressed Non-Suicidal Controls).

Testing of classifier specificity. To control for possible confounds of clinical state and suicide attempt history, we tested the specificity of the classifier's by differentiating (*a*) recent Attempters from all depressed patients (Ideators and Depressed Non-Suicidal Controls); (*b*) clinically stable Suicide Attempters, mostly asymptomatic (rescanned after 5–7 days of treatment), from Suicidal Ideators; and (*c*) patients with and without lifetime history of suicide attempt. We also tested the prediction accuracy of the multivariate classifier by adding clinical variables implicated in suicidality: depression (BDI-II),[34] anxiety (BAI),[35,36] suicidal ideation severity

Figure 1. Brain Networks Identified by Independent Component Analysis During Resting State in the Pooled Sample of Suicide Attempters, Suicidal Ideators, Non-Suicidal Depressed Controls, and Healthy Controls[a]



[a]Images are arbitrarily thresholded at |t| > 3 to depict voxels with strongest contribution to the network time series.

(C-SSRS), hopelessness (BHS),[37] pressure pain threshold,[17] and impulsivity (delay discounting rate from the Montreal Choice Questionnaire)[16,35] to the rs-fMRI variables.

RESULTS

Demographic and Clinical Characteristics

Table 1 provides demographic and clinical characteristics of the 54 participants included in the analysis. There was a nonsignificantly higher representation of women in the Suicide Attempter and Suicidal Ideator groups ($\chi^2 = 3.954$; $P = .266$). Depression ($F = 2.108$, $P = .135$), anxiety ($F = 0.301$, $P = .767$), and hopelessness severity ($F = 0.112$, $P = .878$) did not differ between the depression groups. Whereas all subjects in the Suicide Attempter and Suicidal Ideator groups were taking antidepressant medications, only 59% of the Depressed Non-Suicidal Control group were taking antidepressants ($\chi^2 = 9.335$; $P = .008$). As expected, suicidal ideation severity was greater in the Suicide Attempter and Suicidal Ideator groups ($F = 7.74$, $P < .001$). Lifetime history of suicide attempts was higher in the Suicidal Ideator group (56%) than in the Depressed Non-Suicidal Control group (35%) ($\chi^2 = 8.414$; $P = .01$).

Follow-Up Assessment

On the follow-up assessment, performed 5–7 days after the initial interview in a subset of patients in the Attempter group (7/10), there was a reduction in severity of depression ($t = 5.352$, $P < .001$), suicidal ideation ($t = 5.83$, $P < .001$), and pressure pain threshold ($t = 2.763$, $P = .041$).

Independent Component Analysis

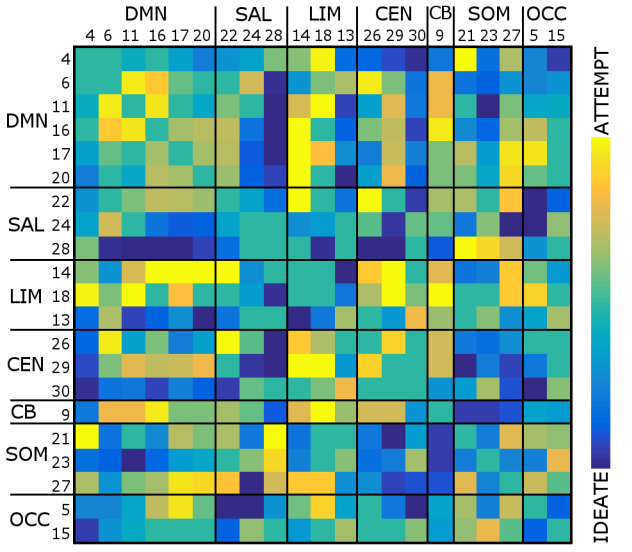
ICA of the rs-fMRI reduced data dimensionality to 30 components (ie, spatially independent networks of brain activity). Nine components were identified as noise (eg, head motion, ventricular CSF fluctuation) and excluded from further analysis. The ICA components correspond to well-documented resting-state functional networks that can be grouped into 7 cognitions/modalities (Table 2 and Figure 1).[38] The LIM was represented by components 13, 14, and 18. The DMN was denoted by components 4, 6, 11, 16, 17, and 20. The CEN was reflected in activity in components 26, 29, and 30. The SAL was represented by components 22, 24, and 28. An occipital network comprised components 5 and 15. A sensorimotor network was represented by components 21, 23, and 27. Lastly, a cerebellar network was defined by component 9.

Multivariate (ie, Multivoxel) Pattern Classification

Our binary SVM classifier significantly discriminated Suicide Attempters from Suicidal Ideators (mean accuracy = 0.788, sign rank test: $P = .002$; null hypothesis: area under the curve = 0.5). Figure 2 depicts the functional connectivity matrix for the 21 components predicted by the mean (over LOOCV iterations) learned separating hyperplane (Suicide Attempters vs Suicidal Ideators) when the SVM's decoding weights are transformed into encoding weights via Haufe transformation.[39] This transformation allows the maximum margin hyperplane that separates the labeled groups to be visualized in its encoding form, ie, feature components activated in concert with a class

label. This representation differs from the raw hyperplane (decoding) parameters, which may represent nonclass properties such as noise attenuation. Attempters displayed positive functional connectivity between both the dorsal and ventral precuneus subnetworks of the posterior DMN and the parahippocampal subnetwork of the LIM network and between frontoparietal CEN networks and parahippocampal and thalamic subnetworks of the LIM network while exhibiting negative functional connectivity between the dorsal and ventral precuneus, between medial prefrontal subnetworks of the DMN and dorsal insula subnetwork of the SAL network and between frontoparietal CEN networks and dorsal insula subnetwork of the SAL network.

Figure 2. Representation of the Predicted Pairwise Connectivity Between the 21 Independent Components (ICs) That Differentiated Recent Suicide Attempters and Suicidal Ideators[a]



[a]Predicted connectivity was calculated as the mean (over leave-one-out-cross-validation iteration) support vector machine separating hyperplane parameters transformed according to the Haufe method of predicted connectivity. Warm colors (orange to yellow) indicate pairwise connections for which correlations predict Suicide Attempters, whereas cold colors (blue to purple) indicate pairwise connections for which negative correlations predict Suicide Ideators. ICs are grouped by canonical resting state functional networks, which include the default mode network (DMN), salience network (SAL), limbic network (LIM), central executive network (CEN), cerebellum network (CB), sensorimotor network (SOM), and occipital network (OCC).

Testing of Classifier Specificity

None of the potential confounding outcomes were significantly discriminated by our classifier: (*a*) recent Attempters from all depressed patients (mean accuracy = 0.531, $P = .551$), (*b*) clinically stable Suicide Attempters from Suicidal Ideators (mean accuracy = 0.58, $P = .33$), and (*c*) presence vs absence of lifetime history of suicide attempts (mean accuracy = 0.543, $P = .348$). The non-imaging variables (depression, anxiety, and hopelessness severity; pressure pain threshold; and impulsivity) did not significantly discriminate Suicide Attempters and Suicidal Ideators on their own (mean accuracy = 0.381, $P = .236$) and did not improve the accuracy of the binary neural pattern classifier (mean accuracy = 0.736, $P = .002$; see Table 3).

DISCUSSION

A binary classifier trained to discriminate patterns of resting state brain functional connectivity robustly differentiated patients who had attempted suicide in the previous 3 days from those endorsing current suicidal ideation but no suicide attempts in at least the previous 6 months. This classifier seems specific to recent suicidal behavior, since it did not discriminate clinically stable suicide attempters and lifetime suicide attempt history and was not improved with the addition of clinical variables associated with acute suicide risk.

Our findings suggest that differential states of functional engagement of the anterior and posterior DMN may reflect distinct levels of imminent suicide risk. Different imaging modalities have shown alterations in suicidal patients. For instance, decreased prefrontal cortex metabolism has been associated with suicide attempt lethality[40] and suicidal intent and plans.[20] Recently, decreased resting state functional connectivity between the rostral anterior cingulate, the orbitomedial prefrontal cortex, and the right middle temporal pole was described in depressed patients with suicidal ideation.[41] Anomalies in DLPFC function and connectivity are meaningful in the context of its central role in the regulation of processes closely associated with suicidal behavior such as impulsivity,[16] control inhibition,[42] emotional reactivity,[43] and anhedonia.[44] Other studies have examined resting state functional connectivity in depressed patients with lifetime history of suicide attempts, reporting

Table 3. Support Vector Machine Classification of Recent Suicidal Attempters Versus Suicidal Ideators Based on Functional Brain Connectivity and Estimation of the Influence of Other Participant Risk Factors on Classifier Performance[a]

Classifier	Mean Accuracy, %	*P*	Mean FPR	Mean TPR	Mean AUC
Recent Suicide Attempters vs Suicidal Ideators (FC only)	78.8	**.002**	0.222	0.788	0.9
Recent Suicide Attempters vs all depressed (Suicidal Ideators + Depressed Non-Suicidal Controls)	53.1	.551	0.423	0.531	0.565
Stable Suicide Attempters vs Suicidal Ideators	58.0	.330	0.222	0.58	0.635
Presence vs absence of lifetime suicidal behavior	54.3	.348	0.45	0.543	0.613
Recent Suicide Attempters vs Suicidal Ideators (clinical and behavioral data)	38.1	.236	0.556	0.375	0.319
Recent Suicide Attempters vs Suicidal Ideators (FC + clinical and behavioral data)	73.6	**.023**	0.222	0.750	0.833

[a]Null hypothesis: AUC = 0.5. Boldface indicates statistical significance.
Abbreviations: AUC = area under the curve, FC = functional connectivity, FPR = false-positive rate, TPR = true positive rate.

increased functional connectivity of the superior temporal gyrus, middle temporal gyrus, and middle occipital gyrus[45,46] or a specific pattern of functional connectivity of superior orbitofrontal area, insula, amygdala, and middle temporal area.[47] When focusing on the DMN, increased connectivity of the left cerebellum and lingual gyrus, and decreased connectivity of the right precuneus was found.[48] On the other hand, a study of depressed adolescents with lifetime history of suicide attempts[43] showed distinct prefrontal activity and reduced functional connectivity between the anterior cingulate and amygdala during a facial emotion processing task. A recent report by Just et al,[49] using a machine learning approach to identify neural signatures associated with specific emotional and life/death–related words, successfully differentiated depressed patients with suicidal ideation from healthy controls and differentiated suicidal ideators with and without lifetime history of suicide attempts. Lastly, abnormal patterns of functional connectivity between the medial prefrontal cortex and posterior cingulate during an N-back task were reported in schizophrenic patients at high risk for suicide.[50] Even though these data did not come from directly comparable studies, ie, patients with lifetime history of suicide attempts or presence of suicidal ideation, resting state or task related, a consistent pattern of functional connectivity abnormalities in 3 major brain networks (DMN, LIM, and CEN) seems to emerge in suicidal patients.

Our finding of increased DMN-LIM (parahippocampal gyrus) functional connectivity in recent suicide attempters suggests that imminent suicide risk may be related to disruption of the integration of precuneus-mediated self-cognitions (eg, empathy, intentionality judgment, attribution of emotional state, and perspective taking) with the emotion-processing functions of the LIM subnetworks. Furthermore, the finding of decreased DMN-insula functional connectivity suggests a neurobiological substrate for distinct future-oriented self-cognitions within emotional contexts associated with acute suicidal behavior.[51] This view is compatible with findings of impaired cognitive control associated with emotion dysregulation[43,52] and anhedonia[8,53,54] described in suicidal patients. Nonetheless, future studies may shed light on identifying specific downstream cognitive or physiologic effects of changes in DMN connectivity that may be more proximal to suicidal behavior and potential intervention targets.

Our findings support the notion that a neural classifier is specific for a state very temporally close to suicidal behavior rather than to the trait of lifetime suicidal behavior. The lack of improved performance of the neural pattern classifier with the incorporation of clinical and behavioral measures associated with suicide risk seems in agreement with the notion that complex algorithms that combine a host of risk factors, rather than the focus on individual ones, may hold better promise to identify acute risk for suicide.[55] This view is also supported by the recent successful use of complex algorithms that combined large numbers of individual measures of either variables from medical or administrative records[4–8] or a combination of clinical and protein expression variables[4,56] to predict suicide risk.

We aimed to discriminate individuals who were currently contemplating suicide from those who acted on these thoughts within the previous 72 hours based on their brain function. In other words, we attempted to identify those who crossed the ultimate threshold toward suicidal action based on the function of the brain—the organ that was the agent of that action—and who, after integrating all available input, made the decision to engage in suicidal behavior. Noteworthily, this approach is not based on self-report or task performance and required 7.5 minutes of lying in the scanner without engagement in any overt task. By incorporating measures of depression and anxiety severity in our model, we controlled for possible confounds associated with these variables. Even though our subjects were not medication free, all subjects in the Suicide Attempter and Suicidal Ideator groups had been taking antidepressant medications up to the day of scanning; thus, we do not anticipate that medications will have an effect on our classifier.

This approach is not yet ready for clinical practice; it needs replication and validation in a larger independent sample. We envision a potential use of this approach in the assessment of suicidal individuals in hospital-based settings, such as emergency departments or inpatient units, where clinical MRI is readily available. Examination of patterns of resting state functional connectivity in a patient who is currently endorsing suicidal ideation would provide an objective measure of the likelihood of progression to suicidal behavior and inform, but not replace, the clinician's overall assessment of suicide risk.

An intrinsic limitation to all studies hoping to understand suicide is that individuals who survive a suicide attempt may differ from those who complete suicide. We had a limited sample size (10 Suicide Attempters and 9 Suicidal Ideators) and lack a replication sample, which may have an impact on the generalizability of the data, hence the need for replication and validation in a larger independent sample. Sex has a particular effect on both resting state connectivity[57] and suicidal behavior (3/1 female/male ratio of suicide attempters and 4/1 male/female ratio of suicide completers); our limited sample size did not allow for generation of a sex-specific classifier or for testing of the differential effectiveness of the classifier for women and men. Other limitations include lack of assessment of serum biomarkers and of a physical trauma control group. The study did not include subjects with suicide attempts that resulted in treatment in intensive care units who were not medically stable enough for psychiatric services to be consulted (ie, patients who were comatose, had altered mental status, or were nonverbal). Even though we did not characterize the subjects' attitudes toward the unsuccessful suicide attempt—which could have had an impact on their current psychological status—both Suicide Attempter and Suicidal Ideator groups showed severe depression and moderate anxiety (Table 1). The cross-sectional design

prevented inference of a causal relationship between observed functional brain organization and future suicidal behavior.

Despite these limitations and the considerable obstacle of identifying predictors for an event of relative rarity such as suicide,[33] the use of intrinsic brain activity to differentiate acute suicidal acts from current suicidal thoughts with greater accuracy than clinical measures is a promising step toward the development of an objective measure of imminent suicide risk. The use of rs-fMRI within 3 days of a suicide attempt, and a follow-up within a week, allowed for a glimpse into intrinsic brain activity shortly following a suicidal crisis, showing the temporal specificity of our neural pattern classifier. Further incorporation of serum or cognitive markers[4,58] and prospective studies are needed to validate and refine the clinical relevance of this candidate biomarker of suicide risk; these markers are already showing promising results in the Alzheimer's disease field.[58]

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