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Dissociating default mode network resting state markers of suicide from familial risk factors for depression

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Neural signatures of suicide risk likely reflect a combination of specific and non-specific factors, and clarifying specific factors may facilitate development of novel treatments. Previously, we demonstrated an altered pattern of resting state connectivity between the dorsal and ventral posterior cingulate cortex (d/vPCC) and the dorsal anterior cingulate cortex (dACC), as well as altered low frequency oscillations in these regions, in individuals with a history of suicidal thoughts and behaviors (STBs) compared to healthy controls. It remains uncertain, however, whether these markers were directly related to STBs or, more generally, reflect a trait-level risk factor for depression. Here, we examined data from a 3-generational longitudinal study of depression where resting state fMRI data were analyzed from 2nd and 3rd generation offspring of probands with (FH+ = 44: STB+ = 32, STB− = 12) and without (FH− = 25: STB+ = 15, STB− = 10) a family history of major depressive disorder (MDD). Standard seed-based methods and a frequency-based analysis of intrinsic neural activity (ALFF/fALFF) were employed. FH of MDD, but not a personal history of STBs or MDD, was associated with relatively reduced dPCC-dACC, and enhanced vPCC-dACC functional connectivity. FH of MDD showed a pattern of reduced ALFF in the dPCC whereas an STB history was associated with an increase. All findings were invariant to confounding by lifetime MDD and current depression severity. Overall, contrary to predictions, resting state functional connectivity within the default mode network (DMN) was associated with FH of depression rather than STBs. These findings confirm the relevance of DMN functional connectivity for mood disorders and underscore the importance of disambiguating biological factors that differentially relate to mental disorders versus STBs.

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INTRODUCTION

Major depressive disorder (MDD) is prevalent world-wide at around 3–5% [1] and is a significant risk factor for suicide [2, 3]. Although promising neural markers of MDD have been identified [4], biological markers specifically associated with suicidal thoughts and behaviors (STBs) remain unclear. Recent comprehensive reviews in youth [5] and adults [6, 7] highlight frontal and limbic alterations in STBs, but many of these effects are non-specific, perhaps reflecting the etiopathophysiology of the underlying mood disorders [8].

One approach to tackling the complexity of the neural systems underlying STBs is to perform hypothesis-driven analyses, focusing on particular neural circuits implicated in prior work [9–11]. This may complement data-driven strategies (e.g., [12]), in which neural alterations are identified via unbiased multivariate statistical methods. A neural system consistently implicated in MDD [13] and STBs [5–7], and thus a focus for a hypothesis-driven analysis in the present study, is the default mode network (DMN). The DMN is a network of anatomically and functionally connected regions that include posterior cingulate cortex, medial prefrontal cortex, inferior parietal cortex, and hippocampus [14], which typically de-activate, rather than activate, during difficult cognitive tasks. Hyper-connectivity within the DMN has been observed for MDD [15], as well as those at-risk for MDD [16, 17], which may

underlie processes related to rumination or negatively-biased cognition [18]. In addition, previous studies have demonstrated alterations in DMN functional connectivity at rest in individuals with STBs [10, 11, 19]. Taken together, these findings suggest that DMN alterations may serve as stable and transmittable biomarker for depressive illness.

We recently evaluated DMN resting state functional connectivity related to STBs [9], given that suicidal ideation is strongly associated with rumination and brooding [20]. As there is increasing evidence for dissociable components within the DMN (e.g., [21]), we employed distinct seed regions for dorsal and ventral posterior cingulate cortex (dPCC/vPCC) which would capture more fine-grained connectivity patterns than a unitary region of interest. The ventral PCC is better associated with classical DMN regions, while the dorsal region shows slightly enhanced functional connectivity with central executive and salience network regions. We observed different patterns of functional connectivity between these seed regions and the dorsal anterior cingulate cortices (dACC). Whereas healthy adults showed greater functional connectivity between the *dorsal* PCC and dACC, STB+ individuals exhibiting current suicidal ideation (including a subset with a suicide attempt history) showed greater dACC connectivity from the *ventral* PCC. Further, the frequency spectrum of all three regions (vPCC, dPCC, dACC) was altered in

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the STB+ group, with a relative reduction of low frequency oscillatory activity compared to healthy adults. However, the STB+ group also reported greater depressive symptom severity and higher rates of lifetime trauma. Thus, although promising, it is unclear whether these neural correlates directly relate to STBs, or rather, reflect a risk factor associated with depression.

There are two core methodological considerations to consider when probing the DMN, which may impact the interpretation of DMN-STB related findings. First, the dACC region that was identified in prior research [9] was placed at a possible transitional zone between the DMN and salience network [22]. In this light, it is notable that the distinct PCC regions we employed as ROIs were originally defined on the basis of their interactions with 'task-positive' regions under different cognitive loads [21]. Thus, these findings might point to altered interactions between the DMN and salience networks, the latter of which also is implicated in STBs [23]. Second, contrary to expectations, low frequency oscillatory activity in the DMN was not clearly associated with altered functional connectivity across individuals. Such activity shows good psychometric properties [24] and distinguishes individual differences [25], suggestive of trait-like properties. However, although low frequency BOLD is associated with other measures of neural activity, it is difficult to decisively distinguish neural activity from physiological noise or variation [26]. In practice, related metrics often correlate with a region's anatomical and functional properties, particularly the position of the region in the neural processing hierarchy, and can show task modulation [27]. In the absence of a complete neural model of the DMN's intrinsic activity and functional connectivity, these two classes of metrics may be used to provide complementary information into the network's functional properties.

In the present study, we addressed the limitation of the healthy control versus STB design by using an ongoing longitudinal family study of MDD, in which second (Gen 2) and third (Gen 3) generation offspring of first generation (Gen 1) probands with and without MDD were followed prospectively over time to understand the course of depression within families [28, 29]. We have shown over the years that Gen 2 and 3 offspring at high familial risk for depression (based on the MDD status of the first generation) had higher rates of anxiety and depressive disorders, and greater functional impairment [30, 31]. As suicidal ideation and attempts also were assessed at each time point, blind to the individual's family history of depression [28, 29], we were afforded greater discrimination in comparing the effects of personal history of STBs versus familial predisposition to mood disorders on default mode function.

Building on our prior work [9], we hypothesized that individuals with a lifetime history of STBs (STB+) would demonstrate stronger vPCC-dACC over dPCC-dACC functional connectivity, and individuals without a clinical history of STBs (STB−), would exhibit the opposite pattern of activity (dPCC-dACC>vPCC-dACC), independent of their family history (FH), lifetime MDD, and current depression symptoms. Similarly, we hypothesized that low frequency intrinsic activity in these same regions of interest (dPCC, vPCC and dACC) would be reduced in STB+ compared to STB− individuals, accounting for FH, lifetime MDD, and current depression symptoms. As the sample was optimized for evaluating the effects of FH of depression on neural function, we also considered the hypothesis that a positive FH of MDD would be associated with the vPCC-dACC>dPCC-dACC pattern of functional connectivity described previously. Together, this directly addresses the key ambiguity in our previous work; namely, the confounding of STBs with trait-level risk factors for MDD.

METHODS

Description of cohort
The study began in 1982 with the recruitment of two groups of first generation probands (G1). The first group was recruited from outpatient clinics and included probands with moderate to severely impairing major depressive disorder (MDD), but no history of schizophrenia, antisocial personality disorder, bipolar disorder, or primary substance use disorder. The second group included non-depressed probands, selected from an epidemiologic sample in the same community, who had no lifetime history of psychiatric illness, as confirmed through several interviews. The second (Gen 2) and third (Gen 3) generation offspring of these probands form the cohort for this study. Offspring of probands with MDD constitute the high-risk (family history, FH+) group, and those of probands without depression, the low-risk (FH−) group.

There were six waves to the study at the timepoint of this analysis, corresponding to baseline, time (~year) 2, 10, 20, 25 and 30. G2 entered the study at baseline or time 2; G3 offspring were enrolled at time 10 or 20 as they aged in. The average number of interviews was 4.6 for 2nd generation, and 2.0 for 3rd generation offspring. However, as each interview assessed the complete time period subsequent to the preceding interview, total follow up was from birth to current age. The overall design of the study has been detailed in several previous publications [28, 29].

Informed consent was obtained from adults for themselves and for their minor children; verbal assent was also obtained from minors. All participants provided consent and all procedures were approved by the New York State Psychiatric Institute's IRB. One hundred and twenty G2 and G3 biological offspring of G1 probands underwent an MRI scan at time 30 of the study. We excluded five participants with high motion (>3 mm). All included participants showed a framewise displacement of between 0.05 and 0.56 (see Section 2.3 for further details; see Supplement for additional tests of movement parameters). Forty-six individuals under the age of 25 were removed to mitigate the statistical impact of confounding related to age, depression, and suicide symptoms. An age 25 was selected as a cutoff because this often defines a transitional period from adolescence to early adulthood (i.e., 18−25) [32]. In our own sample, this reduced the relationship between STBs and age considerably (partial η^2 reduced from 0.66 to 0.41). Thus, the final sample included 69 participants, after excluding individuals with excessive head motion ($n = 5$) and who were under age 25 ($n = 46$) (note: sixty-two of these individuals also are included in a prior publication [16] examining the role of the DMN in family history of depression; that study, however, did not test PCC subregions).

Clinical interviews
Clinical interviews were conducted at each wave using the semi-structured Schedule for Affective Disorders and Schizophrenia, lifetime version [33] (the child/adolescent version was used for participants when they were 6–17 years old [34]). Each family member was interviewed blind to the clinical status of other family members by trained doctoral- and/or master-level mental health professionals, allowing us to generate independently derived measures of FH and STBs. Interview training and reliability have been documented elsewhere; reliability ranged from good to excellent. Final diagnoses were confirmed by an M.D. or Ph.D. using the best-estimate procedure [35].

As part of the interview, a gate question (*Have you ever wished you were dead or thought about dying or killing yourself?"*) prompted entry into a suicide module, where the frequency and severity of STBs were probed. For individuals who reported suicide attempts, number and age at each attempt was recorded along with severity of suicidal intent and medical threat. For minors, both parent and child reports were obtained, and when reports were discrepant, a clinician assigned a summary score based on all available information. To rule out spurious ideation reports, we required moderate-to-higher severity for inclusion into STB+. A subgroup of 8 individuals reported having made a suicide attempt (7 of whom reported significant ideation). We defined the STB+ group as individuals who reached the suicidal ideation criterion

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Table 1. Demographic and clinical characteristics.

	FH+/STB+	FH+/STB−	FH−/STB+	FH−/STB−	Statistics
Sex, N (Female/Male)	17/15	8/4	8/7	6/4	FH: $x^2 < 1$ STB: $x^2 < 1$
Age, mean (SD)	46.73 (7.54)	35.38 (14.15)	47.90 (5.48)	29.37 (4.94)	FH: $F(1,65) = 1.18$, $p = 0.28$ STB: $F(1,65) = 44.75$, $p < 0.001$ STB*FH: $F(1,65) = 2.58$, $p = 0.11$
Lifetime mental disorders, N (%)					
Major depressive disorder	24 (75)	7 (58)	5 (33)	3 (30)	FH: $x^2 = 9.59$, $p = 0.002$ STB: $x^2 = 1.61$, $p = 0.20$
Any anxiety disorder	14 (44)	7 (58)	2 (13)	3 (30)	FH: $x^2 = 5.22$, $p = 0.022$ STB: $x^2 = 0.83$, $p = 0.36$
Any substance use disorder	15 (47)	5 (42)	6 (40)	1 (10)	FH: $x^2 = 2.04$, $p = 0.15$ STB: $x^2 = 1.90$, $p = 0.17$
Any of the above disorders	29 (91)	12 (100)	9 (60)	5 (50)	FH: $x^2 = 13.63$, $p = 0.0002$ STB: $x^2 = 0.12$, $p = 0.73$
Any suicide attempt	6 (19)	0	2 (13)	0	n/e
Depression severity, mean (SD)	2.97 (4.27)	2.67 (3.26)	2.067 (5.39)	0.40 (0.84)	FH: $F(1,63) = 2.24$, $p = 0.14$ STB*FH/STB: $F < 1$
Medication use, N (%)	10 (31)	3 (25)	1 (7)	1 (10)	FH: $x^2 = 4.35$, $p = 0.037$ STB: $x^2 = $ n/e
Antidepressant use, N (%)	7 (22)	3 (25)	1 (7)	1 (10)	FH: $x^2 = 2.40$, $p = 0.12$ STB: $x^2 = $ n/e
Motion (Framewise displacement)	0.21 (0.12)	0.16 (0.14)	0.19 (0.12)	0.13 (0.084)	STB: $F(1,65) = 2.40$, $p = 0.13$ F's<1

Depression severity scores for two participants were missing. These scores were measured on the date of the scan and reflect symptoms from the past two weeks. Medication/antidepressant use reflects usage within the last 3 months. Analyses of medication distributions using Fisher's exact tests were null for all cases (p's > 0.06).
FH+ High-Risk for MDD, *FH−* Low-Risk for MDD, *STB+* Lifetime Suicidal Thoughts and Behaviors, *STB−* No Lifetime of Suicidal Thoughts and Behaviors, *n/e* not estimatable.

and/or had a history of suicide attempt, and the STB- group as individuals with no lifetime history (see Table 1). To control for the effects of current mood on DMN connectivity, current depressive symptoms were assessed using the 17-item Hamilton Depression Rating Scale (HDRS$_{17}$), a standard instrument used to assess clinical depression in the last two weeks [36].

Image acquisition and parameters
Neuroimaging data were acquired at New York State Psychiatric Institute using a GE Signa 3.0 T scanner with an 8-channel head coil. During the resting state acquisition, participants were instructed to remain still, with their eyes closed, and allow their minds to wander freely. Two runs, 8 min 50 s each, were collected per participant. Only the first run was used, unless maximum motion in any direction during the scan was greater than 3 mm, in which case the second was used, provided it too had a maximum motion of <3 mm [37]. Including both runs would have led to inconsistencies regarding numbers of runs used per participant and/or fewer subjects given our motion criterion. Resting state images were acquired using an axial echoplanar imaging (EPI) sequence (TE/TR = 23.6/2800 ms, 90° flip angle, receiver bandwidth = 62.5 kHz, single excitation per image, slice thickness = 3.0 mm, 0.5 mm spacing, 43 slices, 24 × 24 cm field of view, 64 × 64 matrix; effective resolution of 3.75 × 3.75 × 3.0 mm). A structural FSPGR scan, which was used for normalization, was acquired using the following parameters (TE/TR = 2.39/6.036 ms, slice thickness = 1.0 mm, 162 slices, 25 × 25 cm field of view, 256 × 256 matrix).

fMRI resting state data preprocessing
Data were analyzed using a combination of SPM, FSL and AFNI scripts implemented in Nipype [38]. Preprocessing involved co-registration, slice time correction, normalization (SPM - DARTEL), despiking (AFNI), rescaling following linear detrending, and smoothing using SUSAN (FSL: 6 mm kernel). Seed-based and (fractional) amplitude of low frequency fluctuation ((f)ALFF) analyses were conducted using routines in the C-PAC software (https://fcp-indi.github.io). Seed-based analysis employed the 8 mm diameter spheres centered on dorsal (x = 0, y = −58, z = 28) and ventral (x = 0, y = −58, z = 28) PCC coordinates defined by Leech and colleagues [21], and employed in our previous study. Following preprocessing, nuisance parameters included a global signal timeseries, five a/tCompCor timeseries obtained from white matter/cerebrospinal fluid and high temporal standard deviation voxels [9, 39] and 6 motion parameters, as well as the derivatives of all 12 timeseries and a linear trend. Following nuisance regression, bandpass filtering was employed (42.56/4.26 s). Finally, Pearson's correlation was performed between the seed region and each voxel in the brain, which were then converted into z statistics. These seed-based analyses were supplemented by an analysis—analogous to one performed in previous study [9]—using unfiltered data. Unfiltered time series were extracted from preprocessed, nuisance corrected images using the dorsal and ventral PCC seeds, and a dorsal anterior cingulate seed defined by [40], as employed by the previous study [9] (ROIs displayed in Supplementary Fig. 1). Our reasoning for examining both filtered and unfiltered timeseries here was to ensure the generalizability across different methods, similar to our previous work [9]. Correlation coefficients between the regions' timeseries were computed, which were then z transformed.

The Amplitude of Low Frequency Fluctuations (ALFF) method [24] was implemented using C-PAC. Briefly, this method involves computing the power in each voxel time series between 0.1 and 0.01 Hz. This metric is then Z-transformed relative to the mean and standard deviation of every voxel in the individual's brain, and this measure is used for further analysis. The fractional ALFF method (fALFF) uses the same calculation of low frequency power, but

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relative to the total power across all frequencies within the voxel, which can provide some correction for arbitrary physiological confounding [24]. As with ALFF, the voxel-wise measure is Z-transformed relative to the mean and standard deviation across the whole brain. Broadly, the goal of employing the methods was to obtain an estimate of the power of low frequency oscillations in the brain, relative to the rest of the individual's brain activity. Of the two methods, fALFF is closest conceptually to the method employed in our previous work [9], but a variety of arbitrary differences – especially the different scan duration and temporal resolution of image acquisition—might influence the capacity to identify differences in oscillatory power, so both approaches were adopted. In general terms, the (f)ALFF technique was employed in this study as it is both widely used and affords exploratory whole brain analysis.

Hypothesis testing and data analysis
In line with our previous work [9], we focused on the difference between dPCC-dACC and vPCC-dACC connectivity. Our strategy employed region of interest (ROI) analyses using the same ROIs (dPCC, vPCC, dACC) used in that study (Supplementary Fig. 1: [9]). For functional connectivity analyses, ROI analyses were performed using generalized estimating equations (GEE) with a single dependent measure (dPCC-dACC minus vPCC-dACC) and between-subject effects of STBs and FH. Sequential testing of factors was performed, assessing the effects of the predictors independently and together. In addition, follow up regression analyses were performed with the connectivity measures, assessing the effects of lifetime MDD, current depression symptoms, and medication (i.e., coded as present or absent). Final models were performed using a generalized estimating equation (GEE) approach (PROC GENMOD in SAS 9.4, Cary, N.C) to account for potential non-independence of outcomes for offspring from the same family; age, sex and motion (framewise displacement) also were included in all models.

For each dependent measure, a finding was considered significant if it reached a corrected significance threshold of $p < 0.025$ (0.05/2 for STB/FH), for all regression models examined. To ensure comparability with our previous study [9], we examined the effects of bandpass filtering by comparing the results of filtered and unfiltered timeseries. For ALFF/fALFF analyses, a similar GEE model was used, but including ALFF/fALFF measures from dPCC/vPCC/dACC as dependent measures in separate models. As a post-hoc analysis to establish whether functional connectivity and intrinsic activity dependent measures predict FH, we examined the inter-relationship between d/vPCC-dACC connectivity and dPCC ALFF scores and used logistic regression (modeling of familial relationships was not performed for this analysis). We estimated joint and separate models, reporting Wald scores as well as classification accuracy, sensitivity, and specificity.

Supplementary whole brain analyses explored (filtered) dPCC versus vPCC maps, and mean dPCC and vPCC maps, and ALFF and fALFF measures (see Supplement). Statistical analyses included whole brain corrected analyses ($p < 0.001$ uncorrected, pFWE<0.05 cluster corrected). The independent measures (between-subject predictors) were the same as those used in the ROI analyses (i.e., STB, FH and lifetime MDD with age, sex and motion as covariates). Neither familial relationships nor current depression symptoms were modeled in these exploratory analyses.

RESULTS
Demographics
Participant demographic and clinical information are summarized in Table 1. Relative to STB−, STB+ individuals were older ($t(67) = 6.60$, $p < 0.001$), but there were no significant age-related differences regarding FH (see Table 1). Consistent with prior research (e.g., [41, 42]), FH+ individuals were more likely to have

experienced lifetime MDD ($\chi^2 = 9.59$, $p = 0.002$), but no significant relationship between lifetime MDD and STBs was observed ($\chi^2 = 1.61$, $p = 0.20$).

Dissociation of dorsal versus ventral PCC connectivity with dACC
We first tested whether differential dPCC/vPCC to dACC functional connectivity was related to STBs or FH individually. No significant differences emerged when comparing STB+ and STB−; however, it was related to FH ($b = −0.147$, 95% CI [−0.267, −0.028], $p = 0.0156$; Table 2, **Model A**). Further examination of mean connectivity values for each FH group and each PCC region (plotted in Fig. 1A) showed overall differences between dPCC and vPCC in the high-risk group; namely, greater ventral, relative to dorsal, PCC connectivity to the dACC (beta = −0.1464 [95% CI: −0.274, −0.018], $p = 0.0247$) but not in the low-risk group, where dPCC and vPCC connectivity to the dACC were similar (beta = 0.033 [95% CI: −0.1092, 0.174], $p = 0.653$).

The overall FH effect (Model A) remained significant ($p < 0.025$ in all cases) when accounting for STBs (Table 2, **Model B**), lifetime MDD history (Table 2, **Model C**), and current depression symptom severity and medication usage (Table 2, **Model D**). As a test of sensitivity, we re-ran the model after excluding the 8 suicide attempters from the STB group, and the model remained significant, $b = −0.10728$ [−0.39, −0.05], $p = 0.0057$. Finally, there also were no differences by generation (generation-by-risk interaction, $p = 0.595$; see also Table S1).

To ensure consistency with our previous work [9], which employed unfiltered data for post-hoc analysis, we also performed the same analysis using unfiltered data. We observed a similar pattern of findings with FH as a predictor of d/vPCC-dACC connectivity (Fig. 1B; Table S2)—specifically, the dPCC-dACC>vPCC-dACC pattern of functional connectivity in FH− individuals, but the reverse pattern (vPCC-dACC>dPCC-dACC) in FH+ individuals.

Oscillations within the anterior and posterior cingulate cortex
We next tested whether STB or FH were associated with overall oscillatory power in the three cingulate regions of interest using ALFF and fALFF. No findings which consistently reached our corrected significance threshold ($p < 0.025$) across models were observed, although several findings emerged at uncorrected levels ($p < 0.05$) which were generally dependent on the regression model employed. Using ALFF, FH+ was associated with reduced low frequency power in the dPCC in the combined models (Table 3, Fig. 2; **Models C and D**), but STB+ (**Models A, B, and C**) and the presence of lifetime MDD (**Models C and D**) were associated with increased power (Table 3). STB+ individuals showed increased oscillations in the dorsal ACC (Table 3, **Models A, B, and C**). For fALFF, STB+ was associated with increased low frequency oscillations in the dPCC (Table S3, **Models A, B, C and D**). To assess potential confounding of STBs with age, we plotted ALFF/fALFF against age (Fig. S2), observing no relationships that might account for our findings.

Combined effects of functional connectivity and ALFF
The above analyses showed that FH is associated with both reduced ALFF in the dPCC and an increase from dorsal to ventral PCC functional connectivity to the dACC. However, further zero-order correlations revealed that these two measures were not significantly related to each other ($rs < 0.19$, $ps > 0.13$). Thus, these measures may reflect complementary manifestations of FH. Accordingly, we performed a post-hoc analysis using logistic regression, in which we attempted to classify FH using both measures. A logistic regression model including both d/vPCC-dACC (filtered: Wald = 6.11, $p = 0.013$) and dPCC ALFF (Wald = 4.26, $p = 0.039$: the region evincing the largest group difference), as well as motion/age/sex covariates, accurately classified 73.9% of FH+/FH− cases (sensitivity: 86.4%; specificity: 52.0%). Both metrics

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Table 2. d/vPCC to dAcc connectivity as a function of suicidal behaviors (STBs) and family history for depression (FH).

Model[a]	Betas[b]	Standard error	Lower 95%	Upper 95%	Z	p value
A. Individual models for STBs and FH						
STBs	0.12	0.10	−0.075	0.32	1.22	0.22
FH	−0.15	0.061	−0.27	−0.028	−2.42	**0.016**
B. Combined model with STBs and FH						
STBs	0.13	0.096	−0.060	0.32	1.34	0.18
FH	−0.15	0.060	−0.27	−0.031	−2.47	**0.014**
C. Combined model (B) + Lifetime MDD						
STB	0.13	0.096	−0.060	0.32	1.33	0.18
FH	−0.17	0.054	−0.28	−0.067	−3.21	**0.0013**
Lifetime MDD	0.062	0.056	−0.048	0.17	1.10	0.27
D. Full model						
STB	0.10	0.10	−0.097	0.30	1.00	0.32
FH	−0.18	0.057	−0.29	−0.071	−3.19	**0.0014**
Lifetime MDD	0.040	0.068	−0.094	0.17	0.58	0.56
Current symptoms[c]	0.063	0.029	0.0069	0.12	2.20	0.028
Medication Use[d]	−0.018	0.080	−0.17	0.14	−0.22	0.83

STBs Suicidal traits and behaviors, FH Family history for depression.
[a]All models are adjusted for participant age, sex, and motion, and for family structure to account for potential non-independence of outcomes among related individuals.
[b]Betas reflect estimates of the effect of the independent variable (e.g., STB, FH) on connectivity between PCC subregions (dorsal, ventral) and the dorsal ACC. An estimate of 0 reflects the null hypothesis, namely, that connectivity between dorsal PCC-dorsal ACC, and ventral PCC-dorsal ACC do not significantly differ from each other. Positive estimates indicate that PCC-dACC connectivity is greater from the dorsal, relative to ventral, PCC; negative estimates indicate greater connectivity from the ventral PCC.
[c]Within two weeks of scan date, based on the Hamilton Rating Scale for Depression.
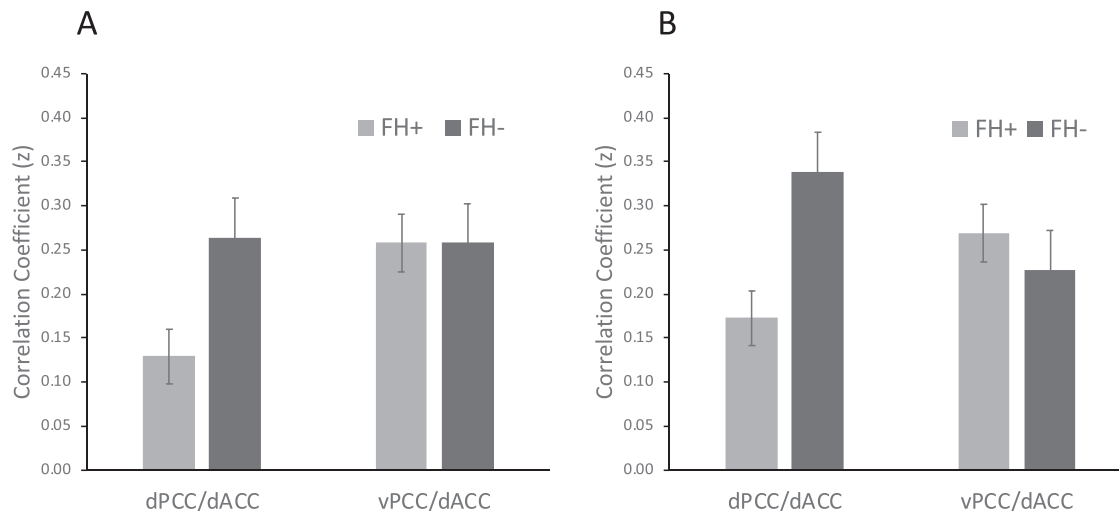[d]Past three months.

Fig. 1 PCC-ACC functional connectivity as a function of Family History. A PCC-ACC functional connectivity, split by FH, from the present study (filtered data). **B** PCC-ACC functional connectivity, split by FH, from the present study (unfiltered data).

could independently predict FH within similar logistic model, but with a somewhat diminished capacity to classify FH (d/vPCC-dACC: Wald = 6.10, $p = 0.014$; classification 66.7%; sensitivity 84.1%; specificity 36.0%; dPCC ALFF: Wald = 4.34, $p = 0.037$, overall classification 65.2%; sensitivity 86.4%; specificity 28.0%).

DISCUSSION
In the present study, we evaluated resting state functional connectivity within the DMN to clarify whether previously identified neural correlates of STBs may reflect an MDD risk factor. There were several notable findings. Contrary to our original hypotheses, stronger functional connectivity between the dorsal PCC and the dACC versus the ventral PCC and the dACC was related to FH but not lifetime history of STBs. Specifically, FH+ individuals showed greater vPCC-dACC than dPCC-dACC functional connectivity, whereas FH− individuals showed the reverse pattern. This pattern of altered functional connectivity remained significant when accounting for lifetime MDD history, current depression symptom severity, and psychotropic medication use, suggestive of a stable trait marker rather than a consequence of having the disorder.

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Table 3. Amplitude of low frequency fluctuations in the cingulate regions as a function of suicidal ideation and family history of depression.

Dorsal Posterior Cingulate (dPCC)

Model[a]	Estimates[b]	SE	Lower 95%	Upper 95%	Z	p value
A. Individual models for STBs and FH						
STBs	0.39	0.13	0.13	0.64	2.96	**0.0031**
FH	−0.20	0.13	−0.46	0.058	−1.52	0.13
B. Combined model with STBs and FH						
STBs	0.29	0.11	0.069	0.52	2.56	**0.010**
FH	−0.18	0.14	−0.45	0.09	−1.30	0.19
C. Combined model (B) + Lifetime MDD						
STB	0.20	0.095	0.013	0.38	2.10	**0.036**
FH	0.31	0.15	−0.61	−0.013	−2.05	**0.041**
Lifetime MDD	−0.26	0.12	0.027	0.50	2.19	**0.029**
D. Full model						
STB	0.14	0.089	−0.035	0.31	1.57	0.12
FH	−0.35	0.15	−0.64	−0.051	−2.30	**0.022**
Lifetime MDD	0.36	0.15	0.070	0.66	2.43	**0.015**
Current symptoms[c]	0.0069	0.044	−0.078	0.092	0.16	0.87
Medication Use[d]	−0.16	0.17	−0.50	0.17	−0.97	0.33
Ventral Posterior Cingulate (vPCC)						
A. Individual models for STBs and FH						
STBs	0.016	0.19	−0.36	0.39	0.08	0.93
FH	−0.22	0.17	−0.54	0.11	−1.31	0.19
B. Combined model with STBs and FH						
STBs	0.022	0.20	−0.37	0.41	0.11	0.91
FH	−0.22	0.17	−0.54	0.11	−1.31	0.19
C. Combined model (B) + Lifetime MDD						
STB	0.023	0.19	−0.36	0.40	0.12	0.91
FH	−0.26	0.19	−0.63	0.10	−1.42	0.16
Lifetime MDD	0.13	0.20	−0.27	0.53	0.64	0.52
D. Full model						
STB	0.014	0.19	−0.37	0.40	0.070	0.94
FH	−0.28	0.19	−0.65	0.093	−1.47	0.14
Lifetime MDD	0.065	0.24	−0.40	0.53	0.27	0.79
Current symptoms[c]	0.10	0.12	−0.13	0.33	0.87	0.39
Medication use[d]	0.028	0.14	−0.25	0.31	0.20	0.84
Dorsal anterior cingulate (dACC)						
A. Individual models for STBs and FH						
STBs	0.26	0.12	0.017	0.4967	2.10	**0.036**
FH	0.099	0.11	−0.12	0.3144	0.90	0.37
B. Combined model with STBs and FH						
STBs	0.25	0.12	0.014	0.50	2.070	**0.038**
FH	0.096	0.11	−0.11	0.31	0.90	0.37
C. Combined model (B) + Lifetime MDD						
STB	0.27	0.12	0.028	0.50	2.19	**0.029**
FH	0.055	0.090	−0.12	0.23	0.61	0.54
Lifetime MDD	0.16	0.094	−0.020	0.35	1.75	0.080
D. Full model						
STB	0.25	0.13	−0.013	0.51	1.86	0.063
FH	0.067	0.086	−0.10	0.24	0.77	0.44
Lifetime MDD	0.21	0.10	0.0086	0.42	2.040	**0.041**
Current symptoms[c]	0.0086	0.063	−0.12	0.13	0.14	0.89
Medication Use[d]	−0.10	0.15	−0.39	0.19	−0.69	0.49

STBs Suicidal traits and behaviors, *FH* Family history for depression.
[a]All models are adjusted for participant age, sex, and motion, and for family structure to account for potential non-independence of outcomes among related individuals.
[b]Betas reflect estimates of the effect of the independent variable (e.g., STB, FH) on amplitude within each ROI within the cingulate cortex.
[c]Within two weeks of scan date, based on the Hamilton Rating Scale for Depression
[d]Past three months.

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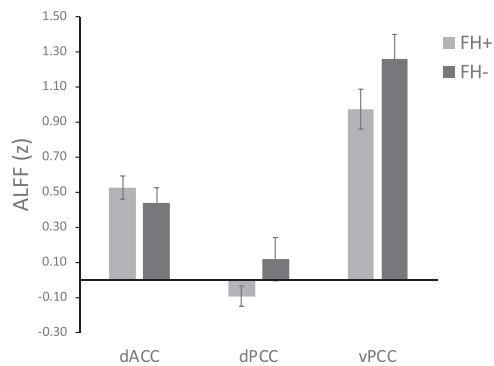HW Chase et al.

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Fig. 2 ALFF values within dPCC, vPCC and dACC regions of interest.

In line with our prior work [9], we hypothesized that low frequency oscillations of BOLD activity would be reduced in the cingulate cortex in STB+ individuals compared to STB−. However, STB+ was associated with a numerically *heightened* ALFF and fALFF, particularly in the dorsal PCC and dorsal ACC, which reached uncorrected thresholds across several of the models tested. In addition, there was evidence that FH+ was associated with numerically *reduced* ALFF signal, particularly in the dPCC. In general, the (f)ALFF findings were more dependent on the regression model employed (i.e., separate versus combined), suggesting that confounding within a simple patient vs control design might potentially suppress effects of different factors (e.g., FH, STB, lifetime MDD), which move in opposing directions [43]. One interesting point to note is that whole brain analysis suggested that STBs were more strongly reflected in fALFF, while FH was more strongly reflected in ALFF. Such a pattern might be observed if FH had a broadband effect— oscillatory power was reduced across the spectrum, while the STB effect was highly restricted to a particular frequency band within the 0.01–0.1 Hz window. If these phenomena are spectrally independent, both could co-exist but would be difficult to differentiate statistically unless focused analysis were performed on crucial frequencies. Overall, our current findings suggest that our prior research [9] might have been unduly influenced by FH effects, given that low frequency oscillations were lower in STB than HC. More importantly, if suppression is important in this context, it requires that both STB and FH are concurrently measured in future studies to determine their relative contribution accurately.

Although both frequency (ALFF) and connectivity (d/vPCC-dACC) connectivity were related to FH, the two measures were not correlated with one another and are independently associated with family history. This is interesting to consider, as a re-analysis of our prior work [9] shows a similar level of classification (~70%) of STBs versus HC using equivalent metrics (d/vPCC-dACC connectivity; dPCC low frequency signal; age/sex/ motion covariates) obtained within that study. Together, these findings suggest that d/vPCC-dACC functional connectivity is a sensitive marker of depression-related individual differences, rather than being specific to STBs, again underscoring the importance of disentangling neural factors related to MDD versus STBs [5, 44].

The three generation family study provided important insights into underlying trait-level risk factors of MDD [45, 46], which are distinct from the standard case-controlled design of a depressed or suicidal cohort versus a healthy control group. Indeed, many prior studies examining relationships between the DMN connectivity or low frequency BOLD and rumination [18, 47, 48] or suicide [10, 11, 49] have adopted this type of cross-sectional approach. The contribution of our findings, however, is to suggest

that DMN functional connectivity may *be influenced by a familial predisposition to depression*, and interestingly, a recent study examining reliable, trait-like functional connectivity markers [50] showed that these factors were often located in the DMN. This further supports our contention that d/vPCC-dACC connectivity may reflect a trait-like marker of MDD and confirms the importance of delineation of subregions within the DMN [51, 52] for identifying reliable trait-like patterns of DMN functional connectivity. Together, such findings may offer potential to describe objective and reliably predictive markers of major depression, as well as offering potential to provide targets for neuromodulation-based interventions [53].

Furthermore, the findings suggest a way to reconsider the complex, emerging literature examining neuroimaging measures of suicide [7]; namely, many of the findings identified within prior studies employing healthy controls may be confounded by correlates of general illness severity or risk, as well as state confounds such as mood. One strategy to address this, should the neural correlates of such confounds be relatively reliable, would be to use these correlates to stratify patients, and determine whether the proposed neural correlate of suicide was broadly independent of this stratification. Within the resting state field, such a strategy may help to parse the already complex literature that is rapidly emerging [10, 11, 19, 23].

Limitations
The study has several limitations. First, the presence of suicidal ideation was assessed within the context of a diagnostic interview, rather than self-report measure (e.g., [54–56]). Self-report measures can be sensitive to different aspects of suicidal ideation, including its severity, frequency, content and duration, and these dimensions may be important for more detailed understanding of the neural basis of STBs. Additionally, the STB group is heterogenous with regards to the inclusion of ideators and attempters, and more broadly, differences in the severity and persistence of suicidal thinking may unduly influence our capacity to detect unique effects related to FH versus STBs. Relatedly, we could not test the associations between family history for STBs and DMN outcomes, as families with multiple generations of STBs were embedded within those with family history for depression. Second, the overall sample size was small and thus, limited the power for detecting interaction effects. Moreover, data collected per participant were relatively modest, in light of calls to increase resting state data acquisition to ~12–13 min [57] to enhance reliability. Third, the confounding of STBs by age may have reduced statistical power to detect STB related effects in the presence of age covariates. Nevertheless, there was no evidence that such confounding was related to our findings. Last, the sample was primarily of European ancestry, as was the standard at the time when the study originated in 1982, and it is unclear whether findings would generalize to other population sub-groups.

Summary
Systematic study of the neural correlates of suicide is an emerging field. We used a hypothesis-based approach, building on previous work examining DMN functional activity in STBs [9]. Contrary to our predictions, an altered pattern of posterior and anterior cingulate functional connectivity was associated with FH but not STBs. Likewise, low frequency BOLD oscillations, which were previously shown to be reduced in STBs, were generally *reduced* in individuals with a FH+ but increased in STB+. Together, in line with considerable prior research, the findings confirm the importance of the DMN as a key neural correlate of mood disorders, and suggest that trait-level, familial influences are important. They also indicate that identification of neural markers of STBs will require careful modeling of state- and trait-level factors that account for MDD.

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