ABSTRACT
BACKGROUND: Suicidality involves thoughts (ideations and plans) and actions related to self-inflicted death. To improve management and prevention of suicidality, it is essential to understand the key neural mechanisms underlying suicidal thoughts and actions. Following empirically informed neural framework, we hypothesized that suicidal thoughts would be primarily characterized by alterations in the default mode network indicating disrupted self-related processing, whereas suicidal actions would be characterized by changes in the lateral prefrontal corticostriatal circuitries implicating compromised action control.

METHODS: We analyzed the gray matter volume and resting-state functional connectivity of 113 individuals with late-life depression, including 45 nonsuicidal patients, 33 with suicidal thoughts but no action, and 35 with past suicidal action. Between-group analyses revealed key neural features associated with suicidality. The functional directionality of the identified resting-state functional connectivity was examined using dynamic causal modeling to further elucidate its mechanistic nature. Post hoc classification analysis examined the contribution of the neural measures to suicide classification.

RESULTS: As expected, reduced gray matter volumes in the default mode network and lateral prefrontal regions characterized patients with suicidal thoughts and those with past suicidal actions compared with nonsuicidal patients. Furthermore, region-of-interest analyses revealed that the directionality and strength of the ventrolateral prefrontal cortex–caudate resting-state functional connectivity were related to suicidal thoughts and actions. The neural features significantly improved classification of suicidal thoughts and actions over that based on clinical and suicide questionnaire variables.

CONCLUSIONS: Gray matter reductions in the default mode network and lateral prefrontal regions and the ventrolateral prefrontal cortex–caudate connectivity alterations characterized suicidal thoughts and actions in patients with late-life depression.

https://doi.org/10.1016/j.bpsc.2021.11.011

Suicidality is a serious health issue worldwide, accounting for almost 1 million deaths annually (1). Suicidality involves thoughts (ideations and plans) and actions related to self-inflicted death (2). Individuals with past or current suicidal thoughts are particularly vulnerable to future suicidal actions (3), and those with past suicidal actions are particularly likely to attempt suicide again (4). To improve management and prevention of suicidality, it is essential to understand the key brain mechanisms underlying suicidal thoughts and actions. Notably, with advancing knowledge about principal brain networks involved in internal self-related mental processing and in adaptive action selection, it is now possible to examine the key neural processes related to suicidality adopting empirically informed neural frameworks.

In most countries, old age (≥60 years) is associated with the highest rates of attempted and completed suicides (1,3,5,6), and late-life depression (LLD) is a strong correlate with suicidality (4). However, key features that distinguish nonsuicidal individuals with LLD and those with suicidal thoughts and actions are yet to be found. Common factors such as poor physical and mental health, impaired functionality, and low social support and financial status bear only limited relationship with suicide risk (4,7,8). Furthermore, questionnaires assessing suicidality uniformly show equivocal prediction for suicidality (9). Thus, identifying neural patterns that help pinpoint suicidality among individuals with LLD may confer important clinical values for early identification and intervention strategies. Notably, alterations in the gray matter volume (GMV) and resting-state patterns may be particularly implicated in late-life suicidality because LLD is associated with pronounced GM atrophy in frontoparietal cortical regions (10), and suicidality involves excessively negative and death-related self-referential associations indicating disrupted resting-state functioning (11).
Suicidal actions and thoughts may be respectively linked to aberrations in the lateral prefrontal-striatum-limbic network and in the default mode network (DMN) (Figure 1). Specifically, the ventrolateral prefrontal cortex (VLPFC)/orbitofrontal cortex (OFC) performs crucial top-down regulatory functions on lower-level affective, cognitive, and behavioral processes and is among the most critical structures for emotion regulation and action control (12,13). Notably, the lateral OFC and VLPFC might be crucially involved in the signaling and regulation of nonreward and punishment (14), abnormality of which was proposed to underlie anhedonia and negative-biased processing in major depression (15). Through extensive connection with the caudate (16,17), the VLPFC/OFC has been consistently demonstrated to implement flexible actions adjusted on changing environmental contingencies (18,19), a crucial function that is deficient in older suicide attempters (20).

The DMN comprises the core components of the dorsomedial PFC (DMPFC), inferior parietal cortex (IPC), and posterior cingulate cortex (PCC) with the adjacent precuneus and is principally involved in self-referential and self-related processes during resting state (21). Among suicidal patients, the thoughts of killing oneself may be closely related to disruptions in these processes (11).

Existing evidence indicates that suicide attempt in patients with LLD and younger patients with depression is associated with volumetric reductions in the lateral prefrontal executive control network. Specifically, the VLPFC/OFC along with the neighboring anterior insular cortex (22–25), and the dorsolateral PFC (DLPFC) (23–25), showed decreased GMVs in suicide attempters. Altered OFC, insular, and amygdala resting-state functional connectivity (rsFC) was also found in suicidal versus nonsuicidal patients with depression (26,27). Changes in striatal rsFC strength were also observed in depressed patients with suicide history (28) and in bipolar type II patients with suicide attempt (29). Nevertheless, only one of the above studies was conducted in patients with LLD (23).

Relatively few studies have examined the GM or resting-state correlates of suicidal thoughts (25). Functional activation studies using cognitive or motor tasks generally pointed to altered recruitment of the DMN linked with suicidal thoughts among individuals with depression, including the DMPFC, IPC, and PCC/precuneus (30). The involvement of these regions in suicidal ideation was also observed in schizophrenia (31) and other mood disorders (32,33). The DMPFC was also recruited when people recalled mental pain associated with suicidality (34). Notably, one study used deep-learning method to classify suicidal ideators from healthy control subjects and found that the most discriminating brain regions were the DMPFC and the left IPC (35). Moreover, repetitive transcranial magnetic stimulation on bilateral DMPFC effectively reduced suicidal impulse in borderline personality disorder (36). Nevertheless, to our knowledge, no study has examined the neural correlates of suicidal thoughts in older adults.

Therefore, we aimed to identify key GM and rsFC measures associated with suicidal thoughts and actions among individuals with LLD. To elucidate the network mechanistic nature of the key rsFC, we conducted follow-up dynamic causal modeling (DCM) analysis to examine its functional directionality. Finally, we performed complementary post hoc support vector machine (SVM) analysis to quantify whether the neural measures significantly improved classification of suicidal thoughts and actions. We hypothesized that suicidal action would be associated with GM reductions in the VLPFC and DLPFC, whereas suicidal thoughts would be associated with volumetric reductions in DMN regions including the DMPFC, IPC, and PCC/precuneus. In addition, suicidal patients would exhibit altered directed connectivity from the VLPFC/OFC to the subcortical striatal and amygdala regions.

**METHODS AND MATERIALS**

**Participant and Instruments**

This study was approved by the institutional review board of Chang Gung Memorial Hospital of Taiwan and complied with the Declaration of Helsinki. In total, 113 older adults (age 60–79 years) formally diagnosed with LLD by board-certified psychiatrists were included. Written informed consent was obtained from all participants. Patients’ depressive and anxiety symptom levels were respectively assessed with the Hamilton Depression/Anxiety Rating Scale. Patients’ cognitive function was assessed with the Mini-Mental State Examination. Individual patients’ medication load was calculated as an aggregated score over all psychotropic drugs that the patient was taking at the time of study (for each patient, the same drug treatment protocol had been maintained for at least 2 months preceding the study), which was recorded using the Antidepressant Treatment History Form (37). Details of the participants’ demographic, clinical, and suicide-related information are included in Table 1.
### Table 1. The Demographic, LLD-, and Suicidality-Related Information of the Participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>NS, n = 45</th>
<th>I/P, n = 33</th>
<th>SA, n = 35</th>
<th>Between-Group Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, Years, Mean (SD) [Range]</td>
<td>67.73 (5.68) [60–79]</td>
<td>67.48 (5.64) [60–79]</td>
<td>64.74 (5.22) [60–79]</td>
<td>( \chi^2 = 7.037, p = .039^{d,e} )</td>
</tr>
<tr>
<td>Sex, F/M, n</td>
<td>32/13</td>
<td>27/6</td>
<td>33/2</td>
<td>Pearson ( \chi^2 = 6.993, p = .03^{d,e} )</td>
</tr>
<tr>
<td>Education, Years, Mean (SD)</td>
<td>7.93 (3.00)</td>
<td>8.76 (4.05)</td>
<td>8.34 (3.47)</td>
<td>( \chi^2 = 1.03, p = .998^{d} )</td>
</tr>
<tr>
<td>MMSE, Mean (SD)</td>
<td>27.09 (2.05)</td>
<td>27.24 (1.85)</td>
<td>27.11 (2.21)</td>
<td>( \chi^2 = 0.266, p = .876^{d} )</td>
</tr>
<tr>
<td>LLD Onset Age, Years(^{f}), Mean (SD)</td>
<td>58.25 (8.22)</td>
<td>55.66 (12.32)</td>
<td>52.29 (10.44)</td>
<td>( F_{2,107} = 3.248, p = .043^{c} )</td>
</tr>
<tr>
<td>LLD Number of Episodes(^{g}), Mean (SD)</td>
<td>1.98 (1.58)</td>
<td>3.00 (2.18)</td>
<td>3.15 (3.23)</td>
<td>( \chi^2 = 11.729, p = .003^{c} )</td>
</tr>
<tr>
<td>LLD Duration, Months(^{h}), Mean (SD)</td>
<td>112.91 (80.95)</td>
<td>141.00 (118.56)</td>
<td>147.88 (107.72)</td>
<td>( \chi^2 = 1.702, p = .427^{g} )</td>
</tr>
<tr>
<td>Medication Load, Mean (SD)</td>
<td>3.56 (1.12)</td>
<td>3.79 (1.02)</td>
<td>3.67 (1.05)</td>
<td>( \chi^2 = 0.638, p = .727^{g} )</td>
</tr>
<tr>
<td>HAMD, Mean (SD)</td>
<td>8.44 (6.42)</td>
<td>9.82 (6.81)</td>
<td>9.57 (6.36)</td>
<td>( \chi^2 = 0.941, p = .625^{g} )</td>
</tr>
<tr>
<td>HAMA, Mean (SD)</td>
<td>11.27 (8.64)</td>
<td>13.30 (7.75)</td>
<td>12.03 (9.55)</td>
<td>( \chi^2 = 2.239, p = .326^{g} )</td>
</tr>
<tr>
<td>TSII(^{i}), Mean (SD)</td>
<td>2.26 (1.77)</td>
<td>3.62 (2.08)</td>
<td>2.59 (1.94)</td>
<td>( \chi^2 = 7.045, p = .03^{c} )</td>
</tr>
<tr>
<td>BSS(^{j}), Mean (SD)</td>
<td>2.62 (4.14)</td>
<td>4.14 (5.08)</td>
<td>6.94 (5.41)</td>
<td>( \chi^2 = 17.516, p &lt; .001^{l,h} )</td>
</tr>
<tr>
<td>SAD PERSONS(^{k}), Mean (SD)</td>
<td>3.36 (1.01)</td>
<td>4.55 (1.24)</td>
<td>5.32 (1.12)</td>
<td>( \chi^2 = 39.084, p &lt; .001^{l,h} )</td>
</tr>
<tr>
<td>Medication Type, n</td>
<td>19</td>
<td>12</td>
<td>11</td>
<td>( \chi^2 = 2.009, p = .366^{g} )</td>
</tr>
<tr>
<td>SSRI</td>
<td>4</td>
<td>6</td>
<td>11</td>
<td>( \chi^2 = 5.425, p = .066^{g} )</td>
</tr>
<tr>
<td>SNRI</td>
<td>8</td>
<td>7</td>
<td>7</td>
<td>( \chi^2 = 0.158, p = .924^{g} )</td>
</tr>
<tr>
<td>Others—NaSSA, NDRI, TCA</td>
<td>7</td>
<td>7</td>
<td>5</td>
<td>( \chi^2 = 0.938, p = .628^{g} )</td>
</tr>
<tr>
<td>Nonantidepressants—benzodiazepine, antipsychotics, zolpidem</td>
<td>35</td>
<td>27</td>
<td>28</td>
<td>( \chi^2 = 1.881, p = .39^{g} )</td>
</tr>
</tbody>
</table>

The participants were divided into NS (the LLD group without suicidal ideation, plan or action), I/P (the LLD group with suicidal thoughts, ideation and/or plan), and SA (the LLD group with suicidal thoughts as well as previous suicide action). BSS, Beck Scale for Suicide Ideation; HAMA, Hamilton Anxiety Rating Scale; HAMD, Hamilton Depression Rating Scale; I/P, ideation and/or plan; LLD, late-life depression; MMSE, Mini-Mental State Examination; NaSSA, noradrenergic and specific serotonergic antidepressant; NDRI, norepinephrine-dopamine reuptake inhibitor; NS, nonsuicidal; SA, suicidal action; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; TSII, Triggers of Suicidal Ideation Inventory.

\(^{a}\)All post-hoc pairwise comparisons used Bonferroni correction.

\(^{b}\)Nonparametric independent-samples Kruskal-Wallis test was used, and the associated \( \chi^2 \) statistics were reported, for variables that had non-normal distribution (Kolmogorov-Smirnov test \( p < .05 \)).

\(^{c}\)Significant effects at \( p < .05 \) (two-tailed) after post hoc correction.

\(^{d}\)Marginal effects that did not survive post hoc correction.

\(^{e}\)\( \chi^2 \) test was used to analyze the binary variable of sex and medication use.

\(^{f}\)A small number of cases for these variables had missing data. LLD onset age, episode number, and duration were based on 44 NS, 32 I/P, and 34 SA. Medication load was based on 45 NS, 33 I/P, and 33 SA. TSII and SAD PERSONS scores were based on 39 NS, 29 I/P, and 34 SA. BSS scores were based on 39 NS, 28 I/P, and 32 SA.

\(^{g}\)Significant effects at \( p < .01 \) (two-tailed) after post hoc correction.

\(^{h}\)Significant effects at \( p < .001 \) (two-tailed) after post hoc correction.

\(^{i}\)The number of patients in each group who were taking the medication at the time of study.
The LLD sample consisted of 45 patients (32 females) without suicidal thoughts (ideation or plan) or action—nonsuicidal (NS); 33 patients (27 females) reporting past and/or present suicidal thoughts—ideation and/or plan (I/P) but no action; and 35 patients (33 females) with both suicidal thoughts and previous suicidal action (SA). All patients completed the Beck Scale for Suicidal Ideation (38), the SAD PERSONS Scale that assesses suicide potential (39), and the Triggers of Suicidal Ideation Inventory (40).

No participant was diagnosed with bipolar, psychotic, or substance use disorders or major physical or neurologic conditions. However, 3 patients had comorbidity of generalized anxiety disorder (GAD). All participants were taking psychotropic medication at the time of study (Table 1). Further details about participants are included in the Supplement.

### Imaging Acquisition and Preprocessing

Both structural T1-weighted and resting-state functional T2*-weighted magnetic resonance imaging images were acquired on a clinical 3T scanner equipped with an 8-channel head coil (GE Healthcare). For structural images, a total of 160 sagittal slices were acquired with repetition time = 8.2 ms, echo time = 3.2 ms, flip angle = 12°, field of view = 250 × 250 × 160 mm³, voxel size = 0.98 × 0.98 × 1 mm³. For the resting-state functional magnetic resonance imaging data, a total of 180 volumes were acquired with slice number = 36, repetition time = 2000 ms, echo time = 30 ms, flip angle = 90°, field of view = 220 × 220 × 144 mm³, voxel size = 3.44 × 3.44 × 4 mm³. During scanning, participants were instructed to stay awake with eyes closed.

Structural data processing and analyses were performed using CAT12 (http://dbm.neuro.uni-jena.de/cat/) and embedded functions of SPM12 (Wellcome Department of Cognitive Neurology). The bias-corrected T1 images were segmented and normalized following the DARTEL procedure (41), using customized normalized DARTEL template. The resulting modulated normalized GM images were smoothed using an 8-mm full width at half maximum Gaussian kernel. Two participants’ structural data were absent owing to acquisition failure, resulting in 111 patients with LLD (43 NS, 33 I/P, and 35 SA) in structural data analyses.

The resting-state data preprocessing was conducted using DPARSFA v.4.3 (42) and SPM12. The first five volumes were discarded for magnetic resonance signal equilibrium. The data were corrected for slice timing and head motion. Procedures for minimizing confounding motion effect are detailed in the Supplement.

### Behavioral Analysis

Data processing was conducted using SPSS v.26 (IBM Corp.). Data normality was assessed using the Kolmogorov-Smirnov test. The demographic, clinical, and suicidal characteristics were tested for between-group effects, using either univariate analysis of variance or the nonparametric independent-samples Kruskal-Wallis test. Significant between-group effects were further delineated with post hoc pairwise comparisons, using Bonferroni multiple-testing correction. The statistical threshold was $p < .05$, two-tailed.

### Imaging Data Analysis

The GMV data were analyzed using a general linear model including the NS, I/P, and SA group variables and controlling for the total intracranial volume, age, and sex. We specifically conducted two $t$ tests to examine the effects of a priori interest: first, the contrast $NS − (I/P + SA)/2$ assessed the effect of general suicidality on GMV; second, the contrast $(NS + I/P)/2$-SA assessed the specific effect of suicidal action on GMV. We focused on the a priori regions of interest (ROIs), including the DMPFC (bilateral medial superior frontal gyri, Brodmann area [BA] 9/9), lateral parietal cortex (bilateral superior cortex and IPC, BA 7/39/40), and the PCC/precuneus (BA 7/31) for the general suicidality effect and the DLPFC (bilateral superior and middle frontal gyri, BA 9/46) and VLPFC/OFC (bilateral inferior and orbitofrontal gyri, including the adjacent insular cortex, BA 11/13/44/45/47) for the suicidal action effect. All ROIs were extracted and constructed using the WFU-PickAtlas toolbox (https://www.nitrc.org/projects/wfu_pickatlas/) based on the Automatic Anatomical Labeling templates. Additional whole-brain analyses were performed for completeness. Statistical thresholds were determined using the threshold-free cluster enhancement method with 5000 permutations (43), as ROI-based or whole-brain familywise error (FWE)–corrected $p < .05$. To correct for the number of ROIs, additional Holm-Bonferroni corrections were performed on the $p_{\text{FWE}}$ values. The mean GMV values of the ROI clusters showing significant effects were extracted and subjected to further linear regression analyses in SPSS showing how suicidal ideation and/or suicidal behavior are related to each ROI. Additional analyses were conducted to test whether the effects persisted after controlling for the demographic and clinical variables.

Resting-state analyses examined the functional connectivity of the VLPFC/OFC. The seed region was constructed as a 6-mm sphere centered at the peak coordinate within the VLPFC/OFC mask that showed significant effects in the structural analysis, in order to locate key VLPFC/OFC region that showed suicidality-related alterations in both structural and functional connectivity patterns. Time-series signals of the seed were extracted, and the correlations between the rest of the brain and the seed were computed for each participant. These correlations were forward to a second-level general linear model assessing between-group effect, controlling for age and sex. We focused on the rsFC between the VLPFC/OFC seed and two ROIs: the bilateral amygdala and striatum, both generated using the WFU PickAtlas toolbox. Statistical thresholding and the follow-up regression analyses on extracted rsFC values were the same as in the GM analyses.
Spectral DCM Analyses
We conducted spectral DCM (spDCM) analysis to establish the causal interactions and directionality of the rsFC patterns (44). The following steps were conducted: 1) selecting the seed regions to be the VLPFC/OFC, and the region(s) of which the rsFC with the VLPFC/OFC showed significant suicide group effect; 2) drawing the voxels of interest from 6 mm (for the VLPFC/OFC) or 3 mm (for the amygdala/striatum) spheres centered at the peak coordinates; 3) extracting the first eignvariate of the time series of the voxels of interest, which had been corrected for mean, motion, white matter, and cerebrospinal fluid signals; 4) specifying three spDCM models, namely VLPFC/OFC-to-target, target-to-VLPFC/OFC, and bidirectional; 5) performing a family-level Bayesian model selection (45) to identify the winning model for each suicide group; 6) estimating the amplitudes of intrinsic connections using Bayesian model average, which weighted each model according to its evidence; and 7) conducting linear regression analyses to test whether the connectivity strengths showed significant group effect, controlling for demographic and clinical variables.

Post Hoc Classification Analyses
We formally tested the classification utility of both the structural and rsFC features on the suicide groups. The SVM is a common machine learning approach to compute the classification strengths of both models and individual features, through permutation testing (10,000 times) and internal validation (leave-one-out cross-validation). The leave-one-out cross-validation procedure was performed to avoid the circularity issue that weight vectors that were generated by a given cross-validation procedure was performed to avoid the circularity. General suicidality effect represented by the contrast NS – (IP + SA)/2 revealed GMV differences in the bilateral DMPFC (p_FWE < .05, Holm-Bonferroni–corrected p < .06) and the right IPC (p_FWE < .05, Holm–Bonferroni–corrected p < .06), whereas suicidal action effect represented by the contrast (NS + IP)/2 – SA revealed GMV differences in the right VLPFC/OFC (p_FWE < .05 at both ROI and whole-brain levels, Holm-Bonferroni–corrected p < .05). Contrary to the hypotheses, the contrast NS – (IP + SA)/2 revealed no significant PCC/precuneus cluster, but exploratory analysis revealed significant bilateral precuneus regions to the (NS + IP)/2 – SA contrast (p_FWE < .05). Conversely, while no significant DLPFC cluster was observed to the (NS + IP)/2 – SA contrast, we found areas in this ROI showing marginal effect to the NS – (IP + SA)/2 contrast (p_FWE = .077) (Table 2). Whole-brain analysis revealed no additional significant effect.

Follow-up regression analyses controlling for age, sex, and total intracranial volume confirmed that for the bilateral DMPFC, the right IPC, and right DLPFC, both the I/P and the SA groups showed significantly less GMV than the NS group (t_{Bonf} < −2.86, p_{corrected} < .01), while no significant difference was found in the non-electrode region (NS + IP)/2 – SA.

Table 2. Regional Gray Matter Volume That Showed Significant Between-Group Effect

<table>
<thead>
<tr>
<th>Contrast/Effect</th>
<th>Region(^2)</th>
<th>BA</th>
<th>Locus of Maxima</th>
<th>K(_{m})</th>
<th>TFCE</th>
<th>p(_{FWE})</th>
</tr>
</thead>
<tbody>
<tr>
<td>NS – (IP + SA)/2</td>
<td>Bilateral DMPFC</td>
<td>8</td>
<td>0, 48, 41</td>
<td>123</td>
<td>342.64</td>
<td>.026</td>
</tr>
<tr>
<td></td>
<td>Right inferior parietal lobule</td>
<td>40</td>
<td>42, −39, 53</td>
<td>52</td>
<td>388.15</td>
<td>.039</td>
</tr>
<tr>
<td></td>
<td>Right DLPFC</td>
<td>10(^2)</td>
<td>26, 48, 30(^2)</td>
<td>80(^2)</td>
<td>341.26(^2)</td>
<td>.072(^2)</td>
</tr>
<tr>
<td>(NS + IP)/2 – SA</td>
<td>Right VLPFC/OFC</td>
<td>47</td>
<td>41, 20, −14</td>
<td>231</td>
<td>574.4</td>
<td>.009</td>
</tr>
<tr>
<td></td>
<td>Bilateral precuneus</td>
<td>7</td>
<td>3, −45, 44</td>
<td>79</td>
<td>410.68</td>
<td>.032</td>
</tr>
</tbody>
</table>

The contrast NS – (IP + SA)/2 assessed general suicidality effect, and the contrast (NS + IP)/2 – SA assessed suicidal action effect.

\(^2\)Results computed within a priori regions of interest.

\(^2\) The DLPFC results are marginally significant. The results are presented in Table 2, which shows the significant regions for each contrast. The analyses were conducted using the NumPy library (http://www.numpy.org) built for Python. For each group classification, we first tested the model including only the significant clinical and suicide characteristics, then the model additionally incorporated the significant neural features. Comparison between these models revealed the additional classification value of the neural features, and respective classification strengths of individual features were calculated based on the comprehensive model. All features were z-transformed for standardization of strength. As the features included in the models were already found to show significant group difference, the SVM analyses were post hoc in nature, similar to the method used previously (46). Additional details about the SVM are included in the Supplement.

Supplementary Analyses
Given that our patients were predominantly female (71%, 82%, and 94% for the NS, I/P, and SA groups, respectively), we replicated the main analyses using female samples only. Additional analyses controlling for medication type and comorbidity with GAD are presented in the Supplement.

RESULTS
Participant Characteristics
Table 1 presents between-group statistical comparisons on the demographic, clinical, and suicide questionnaire measures. No significant group difference was observed for the ratio of patients taking each type of medication around the time of study, the average number of medication type received by patients, or the medication load (all p > .05).

GMV Analyses
The two planned contrasts respectively generated significant GMV results in the a priori ROIs (Table 2 and Figure 2). As hypothesized, general suicidality effect represented by the contrast NS − (IP + SA)/2 revealed GMV differences in the bilateral DMPFC (p_FWE < .05, Holm–Bonferroni–corrected p < .06) and the right IPC (p_FWE < .05, Holm–Bonferroni–corrected p < .06), whereas suicidal action effect represented by the contrast (NS + IP)/2 − SA revealed GMV differences in the right VLPFC/OFC (p_FWE < .05 at both ROI and whole-brain levels, Holm–Bonferroni–corrected p < .05). Contrary to the hypotheses, the contrast NS − (IP + SA)/2 revealed no significant PCC/precuneus cluster, but exploratory analysis revealed significant bilateral precuneus regions to the (NS + IP)/2 − SA contrast (p_FWE < .05). Conversely, while no significant DLPFC cluster was observed to the (NS + IP)/2 − SA contrast, we found areas in this ROI showing marginal effect to the NS − (IP + SA)/2 contrast (p_FWE = .077) (Table 2). Whole-brain analysis revealed no additional significant effect.

Follow-up regression analyses controlling for age, sex, and total intracranial volume confirmed that for the bilateral DMPFC, the right IPC, and right DLPFC, both the I/P and the SA groups showed significantly less GMV than the NS group (t_{Bonf} < −2.86, p_{corrected} < .01), while no significant difference was found in the non-electrode region (NS + IP)/2 − SA.
between the I/P and SA groups \((p > .67)\) (Figure 2B, C). In contrast, for the right VLPFC/OFC and bilateral precuneus, the SA group showed reduced GMV than both the NS and the I/P groups \((t_{105} < -3.07, p_{\text{corrected}} < .01)\), which did not differ from each other \((p > .2)\) (Figure 2A, D).

The results did not change after additionally controlling for education, LLD onset, duration and episode number, medication load, and Hamilton Depression/Anxiety Rating Scale and Mini-Mental State Examination scores. In the DMPFC, IPC, and DLPFC regions, both the I/P and SA groups showed substantially less GMV than the NS group \((t_{94} < -2.628, p_{\text{corrected}} < .01)\), while the I/P and SA groups did not differ \((p > .72)\). In the VLPFC/OFC and precuneus regions, the SA group showed lower GMV than both the NS and the I/P groups \((t_{105} < -3.013, p_{\text{corrected}} < .01)\), which did not differ from each other \((p > .55)\).

All the above results were replicated using female and non-GAD samples only and after controlling for medication type (see the Supplement).

### rsFC Analyses

Following our a priori hypothesis and the structural results that the right VLPFC/OFC GM reduction was the most prominent feature of the SA group, we specifically examined the rsFC of this region with the striatum and amygdala. Controlling for age and sex, we found that the rsFC between the VLPFC/OFC and the bilateral caudate nucleus (locus of maxima = 9, 6, 15; 47 voxels, threshold-free cluster enhancement = 78.95, \(p_{\text{FWE}} = .012\)) was significant to the NS - (I/P + SA)/2 contrast (Figure 3A). While the rsFC was significantly negative in the NS group \((t_{42} = -4.221, p < .001)\), it was insignificantly positive in the I/P group \((t_{35} = 1.591, p = .12)\) and insignificantly negative in the SA group \((t_{32} = -0.512, p = .61)\). Follow-up regression analyses confirmed that the VLPFC/OFC-caudate RSFC was more positive in both the SA \((t_{100} = 2.298, p = .024)\) and the I/P \((t_{100} = 3.999, p < .001)\) groups compared with the NS group (Figure 3B). The SA and I/P groups were not significantly different \((p = .129)\). The effects did not change after additionally controlling for the nuisance factors as outlined above (NS vs. I/P: \(t_{87} = 3.733, p < .001\); NS vs. SA: \(t_{87} = 2.029, p = .046\); I/P vs. SA: \(t_{87} = 1.584, p = .117\)). All the above results were replicated using female and non-GAD samples only and after controlling for medication type (see the Supplement).

No significant effect was found for the rsFC with the amygdala to either the NS - (I/P + SA)/2 or the (NS + I/P)/2 - SA contrast. No other whole-brain results were found.

### spDCM Analyses

Initial model diagnostic confirmed that the DCM models explained reasonable variance of participants’ seed time series (all >17%). Moreover, all participants showed largest connectivity well above the baseline of 1/8 Hz, supporting the assumption that model fitting was satisfactory. The best model for the NS and SA groups was characterized by the VLPFC/
OFC-to-caudate connectivity, whereas for the I/P group it was defined by a caudate-to-VLPFC/OFC connectivity (Figure 3C-E). In all cases, the best model received greater than or almost 95% posterior probability and Bayes factors \( > 16 \), indicating high confidence over model selection (45). The VLPFC/OFC-to-caudate connectivity was significantly negative in the NS group \( t_{42} = -21.85, p < .001 \) but not in the SA group \( t_{21.85} = -1.15, p = .273 \). The caudate-to-VLPFC/OFC connectivity was marginally positive in the I/P group \( t_{28} = 1.61, p = .1 \).

After controlling for age and sex, the NS group showed more negative VLPFC/OFC-to-caudate than the SA group \( t_{72} = -11.883, p < .001 \), even after controlling for all the nuisance factors \( t_{60} = -10.778, p < .001 \). All the above results were replicated using female and non-GAD samples only and after controlling for medication type (see the Supplement).

**Post Hoc SVM Analyses**

All the significant clinical, suicide questionnaire, and neural measures were fed into SVM models to quantify their classification strength, using leave-one-out cross-validation. Model 1 included only non-neural variables, while model 2 additionally incorporated neural (GMV and rsFC) features (Table 3). For the NS versus SA classification, the GMV measures improved classification sensitivity by 20% and specificity by 8.57%, resulting in the final accuracy of 85%. SAD PERSONS score and LLD episode number were the top features, followed by the VLPFC/OFC-caudate rsFC at the third highest feature. For the I/P versus SA classification, the GMV features improved sensitivity by 37.5%, resulting in the final accuracy of 68.33%. The VLPFC and precuneus GMV were the top highest features.

**DISCUSSION**

In this study, we demonstrated that lateral prefrontal and DMN regional GM volumetric reductions characterized suicidal thoughts and behaviors, and that the directed rsFC between the VLPFC/OFC and the caudate showed differential alterations in LLD patients with suicidal thoughts, and in those with past suicidal actions, compared with nonsuicidal patients. The neural measures improved classification accuracy of both nonsuicidal versus ideators/planners and ideators/planners versus attempters by more than 15% compared with that based on clinical and suicide questionnaire measures alone, suggesting that the neural measures could be potentially used to identify LLD patients with high suicide risk. However, it should also be noted that our findings were obtained on predominantly female samples, and their generalization to male patients with LLD is not warranted. This is an important consideration, given that although females may constitute the majority of patients with LLD, males may indeed carry higher risk for suicide (4).
The VLPFC/OFC is among the most implicated neural structures in suicidality (22-25). As expected, the VLPFC/OFC GM reduction was specifically observed in suicide attempters, while no significant difference was evident between the non-suicidal patients and suicide ideators. VLPFC/OFC volume was also the most important feature in distinguishing suicidal ideators from attempters. Along with other GM features, the VLPFC/OFC volume boosted the classification sensitivity by 37%, representing a substantial increase in the power to classify individuals with LLD who acted on their suicidal thoughts. The VLPFC/OFC plays a crucial role in implementing goal-directed response selection, particularly in volatile environments where actions need to be flexibly adjusted based on joint consideration of immediate and distant reinforcement histories (18,19). Notably, the GM loss in the suicide attempters was mostly located on the pars orbitalis portion of the inferior frontal gyrus and the OFC. These regions are heavily involved in making goal-directed decisions based on adaptive reinforcement processing (47-51). Furthermore, the VLPFC/OFC connects extensively with the caudate nucleus (16,17), which is also particularly involved in implementing instrumental processing and goal-directed behaviors (51-54). Thus, our results supported the notion that taking the critical step toward suicide results from failure in selecting the more beneficial (less detrimental) action under situations where hardships may seem to outweigh the positive prospects. This notion is consistent with the proposed specialized role of the lateral OFC and VLPFC-insular systems in signaling and regulating nonreward or aversive processing (15), which is an integral component of the extended VLPFC/OFC functioning in top-down inhibitory control of emotion, cognition, and actions (14).

We found little DLPFC volumetric difference between the suicide attempters, while no significant difference was evident between the non-suicidal patients and suicide ideators. The DLPFC may be principally engaged in high-level executive control processes such as attention and working memory (55) and may also be recruited during deliberate reasoning and reframing of cognitive schemata (56). In this regard, our results suggest that rather than being chiefly involved in action selection and control, the role...
of the DLPFC might be more related to initiating, reappraising, and regulating thoughts related to death and suicide, which are prevalent in both ideators and attempters (20). As expected, both the anterior DMPFC and the IPC volumes showed comparable reductions in the ideators and attempters compared with the nonsuicidal patients, indicating their involvements in general suicidality. More specifically, based on the role of these regions in social cognition, episodic memory, and automatic attention (57,58), their structural deficiency may lead to reduced responsiveness to other people’s concern (8), failure to recall positive autobiographic memory (59), and a tendency to attend to death and suicide-related thoughts about oneself (11), a combination of which may drive an individual toward suicidality. Owing to the cross-sectional nature of this study, it was not known with certainty which ideators would commit suicide in future years. However, based on the close association between suicide thoughts and action (2,4), it could be that the deficient DMPFC and IPC structures are among the shared brain mechanisms underlying the prevalent transition from ideators to attempters.

The lack of PCC/precuneus volumetric difference between nonsuicidal patients and ideators was somewhat unexpected. Rather, the PCC/precuneus volume distinguished suicide attempters from both nonsuicidal patients and ideators. The PCC/precuneus plays a prominent role in self-referential processing, self-consciousness, and first-person perspective taking (60). Our previous work identified this region as central to a network crucial for self-referential emotional regulation and attachment/detachment from the affective self-viewpoint (61). The structural deficit of the PCC/precuneus could result in disregard of the affective well-being of oneself, which in the long run may predispose the individual to engage in suicidal acts (3).

On the functional network level, we discovered that the rsFC between the VLPFC/OFC and the caudate was less negative in the suicide ideators compared with that in the nonsuicidal patients. A similar result was observed when comparing attempters and nonsuicidal patients, albeit to lesser extent. Critically, while the rsFC was directed from the VLPFC-OFC to caudate in the nonsuicidal patients and attempters, the reverse direction was found for the ideators. Existing evidence suggests that the head and body of the caudate are respectively implicated in cognitive emotional and perceptual motor processing (62). Through connectivity with the VLPFC/OFC, the caudate may act as an interface mediating cognitive and affective control of behaviors (63). In particular, the OFC (inhibiting) and caudate (facilitating) are considered to play opposing roles in initiation and control of compulsive behavior, namely, habitual, ritualistic behaviors aimed to prevent perceived negative consequences (64). Therefore, the markedly more negative connectivity directed from the OFC to the caudate in the nonsuicidal group may indicate better capacity to regulate the compulsive suicidal behavior, which is deficient in the attempters.

Contrary to our hypothesis, we found no suicidality-related difference in the VLPFC/OFC-amygdala rsFC, which was previously found to be increased in patients with depression who attempted suicide (27). The finding discrepancy could arise from the difference in patient age. Aging is particularly associated with reduction in corticostriatal dopaminergic circuitries (119), which might render the VLPFC/OFC-caudate connectivity the key determining factor for late-life suicidality. Our LLD findings suggest that old age suicidality is primarily associated with altered value-based decision making and behavioral control, while negatively biased emotion processing associated with changes in the ventral PFC–amygdala connectivity may play more important roles in suicidality among younger adults.

The reversed caudate-to-VLPFC/OFC connectivity in ideators is particularly noteworthy because it may mean that for ideators, emotional and behavioral regulation operates in a largely bottom-up manner, governed by instrumental computations that is under intensive dopaminergic modulations (65). Aging is associated with significant declines in dopaminergic levels in the corticostriatal circuitries, which may lead to older people’s impaired capacity to learn from positive outcomes but enhanced learning from negative experience (19). Therefore, the qualitatively positive caudate-to-VLPFC/OFC connectivity may reflect the increased efforts of the ideators to seek positive life experiences to combat suicide-related thoughts. However, owing to deficient corticostriatal dopaminergic functioning, the caudate output may be progressively declining, hampering this positivity process.

Our findings have potential clinical implications, particularly in view of the long-remaining difficulties in pinpointing suicidality among patients with LLD (1). LLD individuals tend to be less voicing and attract less medical and social care (3), meaning that it is important to derive objective, unbiased indices that could help identify high-risk older adults for suicide. Building on these findings, we can progress toward more reliable and earlier identification of old age suicidality, which in turn informs contingent management and intervention plans. Our finding also has translational implication and offers support for the application of neuromodulation methods targeting on key brain regions, such as the VLPFC/OFC and DMPFC, in treating depression symptoms (66,67) and improving suicidal impulse (36).

This study is inevitably limited by its cross-sectional nature, which demands further validation with longitudinal design. While we were only able to distinguish based on participants’ past suicidal action, the findings should also inform on predicting future attempts, given the very close association between past and future suicide attempts. Our sample size was larger than or comparable to that of most imaging studies on suicidality but was still insufficient to address possible modulatory effect of psychosocial (e.g., loneliness) or personality (e.g., impulsivity) measures. Such investigations could be conducted in future studies with more focused research question. The patients with LLD in this study, while all being on medication, showed varied symptom severity levels. Although we could not account for each patient’s potentially distinct treatment regime or comorbidity in the distant past, we did control for patients’ medication type and load, which stayed unchanged for at least 2 months prior to the study, and patients’ comorbidity at the time of study. In addition, we had no direct measure of the patients’ historical illness severity, although we controlled for other clinical variables such as cumulative illness duration and number of depression episodes throughout the analyses. Our ROI approach is an empirically informed, powerful method to identify key neural measures using limited patient samples, but it may not guarantee to include all potential suicide-related brain regions. With more substantial patient samples, future studies may extend our findings by adopting more comprehensive whole-brain...
approach. Finally, our sample consisted predominantly of females. While we verified that the main findings were replicated on female-only samples, the findings may not necessarily generalize to male patients with LLD, which needs to be tested in future studies.

In conclusion, among individuals with LLD, we identified key lateral prefrontal and DMN regions where volumetric decreases characterized suicidal thoughts and action, and the strength and direction of the VLPFC/OFC-caudate circuitry distinguished nonsuicidal patients from ideators and attempters. The findings advanced our knowledge on the neurobiological mechanisms of suicidality in LLD, with potential clinical implications in early identification and intervention.

ACKNOWLEDGMENTS AND DISCLOSURES

The project was supported by the Ministry of Science and Technology of Taiwan (Grant Nos. NMRPG3G6031/32 and NMRPG3J0121 [to S-HL]), Chang Gung Memorial Hospital (Grant No. CRRPG2G2K0021 [to CL]), Ministry of Science and Technology of Taiwan (Grant No. NRRPG2G6011 [to CL]), the Key-Area Research and Development Program of Guangdong Province (Grant No. 2018B03334001 [to TMCL]), and The University of Hong Kong May Endowed Professorship in Neuropsychology (to TMCL). The funding bodies played no role in the original study conductance or the preparation of the present manuscript.

RS contributed to data analysis, interpretation, and manuscript drafting; MG contributed to data analysis and interpretation; CL contributed to study conceptualization, design and data collection; C-MH contributed to study conceptualization, design and data collection; C-HT contributed to study conceptualization and design; CW contributed to study conceptualization and design; Y-FT contributed to study conceptualization and design; DQ contributed to data analysis and interpretation; S-HL contributed to study conceptualization, design and data collection; TMCL contributed to study conceptualization, design and manuscript drafting.

We thank Dr. Clive Wong for his kind advice on data analysis. All data included in this manuscript are available on reasonable request from the corresponding author. The SVN analysis codes are available on reasonable request from the corresponding author.

The authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

From the State Key Laboratory of Brain and Cognitive Sciences (RS, MG, DQ, TMCL) and the Laboratory of Neuropsychology & Human Neuroscience (RS, MG, DQ, TMCL), The University of Hong Kong, Hong Kong; Department of Psychiatry (CL) and Community Medicine Research Center (CL), Chang Gung Memorial Hospital, Keelung; College of Medicine (CL, S-HL), Chang Gung University, Taoyuan County; Department of Biological Science and Technology (C-MH), National Chiao Tung University, Hsinchu; Center for Intelligent Drug Systems and Smart Bio-devices (C-MH), National Chiao Tung University, Taipei; Department of Medical Imaging and Intervention (C-HT), Chang Gung Memorial Hospital at Linkou, Linkou, Taoyuan County; Brain and Consciousness Research Center (CW), Shuang-Ho Hospital, New Taipei; Graduate Institute of Mind, Brain and Consciousness (CW), Taipei Medical University, Taipei; School of Nursing (Y-FT), College of Medicine, Chang Gung University, Taoyuan City; Department of Nursing (Y-FT), Chang Gung University of Science and Technology, Taoyuan City; Department of Psychiatry (S-HL), Linkou Chang Gung Memorial Hospital, Taoyuan County, Taiwan; Guangdong-Hong Kong-Macao Greater Bay Area Center for Brain Science and Brain-Inspired Intelligence (TMCL), Guangzhou, China; and the Department of Imaging Physics (H-LL), University of Texas M D Anderson Cancer Center, Houston, Texas.

This work was conducted in the Chang Gung Memorial Hospital, Taiwan. Address correspondence to Tatia M.C. Lee, Ph.D., at tmcllee@hku.hk, or Shwu-Hua Lee, M.D., at shihee@cgmh.org.tw.

Received Aug 24, 2021; revised Oct 13, 2021; accepted Nov 20, 2021. Supplementary material cited in this article is available online at https://doi.org/10.1016/j.bpsc.2021.11.011.

REFERENCES

Corticostriatal Circuitry Underpinning Suicidality


