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Research paper

Resting-state neural mechanisms of capability for suicide and their interaction with pain – A CAN-BIND-05 Study

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ABSTRACT

Background: Suicidal ideation is highly prevalent in Major Depressive Disorder (MDD). However, the factors determining who will transition from ideation to attempt are not established. Emerging research points to suicide capability (SC), which reflects fearlessness of death and increased pain tolerance, as a construct mediating this transition. This Canadian Biomarker Integration Network in Depression study (CANBIND-5) aimed to identify the neural basis of SC and its interaction with pain as a marker of suicide attempt.

Methods: MDD patients ($n = 20$) with suicide risk and healthy controls ($n = 21$) completed a self-report SC scale and a cold pressor task measuring pain threshold, tolerance, endurance, and intensity at threshold and tolerance. All participants underwent a resting-state brain scan and functional connectivity was examined for 4 regions: anterior insula (aIC), posterior insula (pIC), anterior mid-cingulate cortex (aMCC) and subgenual anterior cingulate cortex (sgACC).

Results: In MDD, SC correlated positively with pain endurance and negatively with threshold intensity. Furthermore, SC correlated with the connectivity of aIC to the supramarginal gyrus, pIC to the paracingulate gyrus, aMCC to the paracingulate gyrus, and sgACC to the dorsolateral prefrontal cortex. These correlations were stronger in MDD compared to controls. Only threshold intensity mediated the correlation between SC and connectivity strength.

Limitations: Resting-state scans provided an indirect assessment of SC and the pain network.

Conclusions: These findings highlight point to a neural network underlying SC that is associated with pain processing. This supports the potential clinical utility of pain response measurement as a method to investigate markers of suicide risk.

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1. Introduction

The number of deaths by suicide and suicide attempts (SA) globally represents a major health issue (World Health Organization, 2019), yet the prediction of an SA remains poor (Franklin et al., 2017). Notably, suicide ideation (SI) is not itself a reliable predictor of SA, given only 24 % of individuals with SI make an attempt in the subsequent year (Chan et al., 2014); indeed, this is true for many suicide risk factors (Khazem and Anestis, 2016; Klonsky et al., 2017; Klonsky and May, 2014; May and Klonsky, 2016). The immense challenge identifying individuals who will ultimately make an attempt among those with SI significantly limits our ability to stratify suicide risk and provide interventions to those who would most benefit.

The Interpersonal Theory of Suicide proposes that suicide capability (SC), which reflects fearlessness of death and increased tolerance to pain, contributes to SA when someone has a desire to die (Van Orden et al., 2010). Evidence has indicated that high SI predicts attempts only among individuals with high SC (Anestis et al., 2015; Chu et al., 2017). In other words, SC may mediate the transition from SI to SA. Importantly, several small studies suggest that people with a history of SA experience blunted pain processing with increased threshold and tolerance to pain, and lowered subjective pain sensitivity (i.e., intensity ratings) (Cáceda et al., 2017; Deville et al., 2020; Kim et al., 2019; Orbach et al., 1997, 1996b, 1996a). Pain tolerance has also been associated with SC both subjectively (self-reported pain response) among individuals with suicide risk and objectively (using a pain task) among community participants (Förtsch et al., 2021; Franklin et al., 2011; Preece et al., 2020; Teismann et al., 2014). However, the association between SC and objective pain processing of physical stimuli has not been examined in a suicidal population. Furthermore, there are no published studies to date that directly examine the neural underpinnings of SC and the links to pain processing. Importantly, developing such a mechanistic understanding of SC could advance efforts to stratify suicide risk.

Pain and SA share overlapping neural circuitry, which could underlie the neural basis of SC. Pain and SA both heavily recruit brain regions including the prefrontal cortex (PFC), anterior cingulate cortex (ACC), insula, and amygdala (Rizvi et al., 2017). The salience network (including anterior mid-cingulate (aMCC), and anterior insula (aIC)) is implicated in coordinating brain responses to salient stimuli such as pain (Menon, 2011), and has been frequently implicated in SA (Ambrosi et al., 2019; Cao et al., 2020; Gosnell et al., 2019; Hu et al., 2021; Kang et al., 2017; Malhi et al., 2020; Qiu et al., 2020; Schreiner et al., 2019; Stumps et al., 2021; Yang et al., 2020; Zhang et al., 2020, 2016). Additionally, regions such as the posterior insula (pIC) that are important for sensory aspects of pain perception have shown abnormal connectivity in individuals with lifetime SA (Ambrosi et al., 2019; Deville et al., 2020; Hu et al., 2021; Zhang et al., 2020). The subgenual ACC (sgACC) is also involved in higher-order pain processing and is implicated in SA (Olié et al., 2021; Vanneste et al., 2017). Given the potential role of pain processing in SC, the current study focuses on these 4 regions implicated in both pain and suicide: aIC, pIC, aMCC, and sgACC.

Given the clinical challenge in identifying the individuals with MDD and suicidal ideation who will make an attempt, as well as the lack of characterization of this sample in the literature, this study aims to identify the resting-state neural correlates of SC in MDD and its association with behavioral measures of pain. This will be done by investigating the relationships among a clinical scale of SC, a cold pain task, and resting-state functional magnetic resonance imaging (rsfMRI). As it is not *clinically* relevant to have a biomarker to distinguish between MDD with suicide risk and healthy controls, our goal is to detect the within group patterns in MDD that can stratify suicide risk and distinguish subgroups. Thus the healthy control (HC) group will be used as a normative control (i.e., to see if identified mechanisms are unique within the MDD group), rather than as a direct comparison to maximize between-group differences.

2. Methods

2.1. Participants

The data was obtained from a longitudinal prospective study of suicide biomarkers within the Canadian Biomarker Integration Network in Depression program (CANDIND-5). A total of 20 MDD participants and 21 HC were recruited. Participants were recruited through self- or physician-referrals at St. Michael's Hospital, community or online advertisements.

Inclusion criteria for the MDD group included: age 18–70 years; current Major Depressive Episode based on DSM-5 criteria, confirmed by the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1997); and a Hamilton Rating Scale for Depression-17 item (HAMD-17) (Hamilton, 1960) total score $\geq$ 14; current suicide risk with either SI (HAMD-17 suicide item $\geq$2) or lifetime SA(s) (confirmed by the Columbia Suicide Severity Rating Scale, C-SSRS) (Posner et al., 2011). Suicide attempt was defined as a behavior with potential harm to oneself which was acted with at least some intent to die as a result of the behavior. Exclusion criteria were: pregnancy/lactation, unstable medical conditions, substance use disorder in past 6 months, lifetime history of psychosis or bipolar disorder, current diagnosis of a personality disorder, and use of a stimulant/benzodiazepine within 2 weeks of fMRI scan (unless on a stable dose for $\geq$4 weeks before the scan). HC participants were required to be aged 18–70 with no lifetime history of a psychiatric diagnosis, antidepressant use, lifetime SI or SA. The HC cohort was selected to ensure comparable mean age and proportion of sexes between groups.

2.2. Procedures

Following written informed consent, participants completed a screening visit and a demographic form to assess eligibility. Eligible participants attended a baseline visit within 30 days. At this visit, depression severity was measured using the HAMD-17 and the self-report Quick Inventory of Depressive Symptomatology (QIDS-SR) (Rush et al., 2003). SI and SA were measured with the C-SSRS. SC was measured using the 20-item Acquired Capability for Suicide Scale (ACSS) (Van Orden et al., 2008). A fMRI scan was also conducted. The cold pressor task was administered in which a hand was submerged into a container with 2 °C ice water for up to two minutes (Fig. 1) (Franklin et al., 2011; Teismann et al., 2014). The time at pain onset (*pain threshold*) and when pain became intolerable (*pain tolerance*) were recorded, at which time participants could remove their hand. The time between pain threshold and tolerance was defined as *pain endurance*. At both timepoints, participants rated pain intensity on a scale from 1 (no perceptible pain) to 10 (the most intense pain imaginable) (defined as *threshold intensity* and *tolerance intensity*, respectively).

2.3. Clinical assessments

The Acquired Capability for Suicide Scale (ACSS) is a 20-item self-reported scale that measures the self-perceived ability to perform dangerous tasks, comfort level with dangerous situations, and fearlessness of death (Van Orden et al., 2008). The ACSS total score of all 20 items, as consistently utilized in other investigations of SC, was used in the current study as the measure of SC.

The Columbia Suicide Rating Scale (C-SSRS) is a semi-structured clinical interview for suicidal ideation, behaviors, and attempt (Posner et al., 2011). During the interview, the details and numbers of lifetime SA were recorded. Suicidal ideation was also scored for the participants' worst lifetime level and current level (score 1 if they never had a wish to be dead, 2 if they have non-specific thoughts of suicide, 3 if they have active SI with methods in mind, without intent to act, 4 if they have active SI with some intent to act, without a specific plan, and 5 if they have active SI with a specific plan and intent to act).

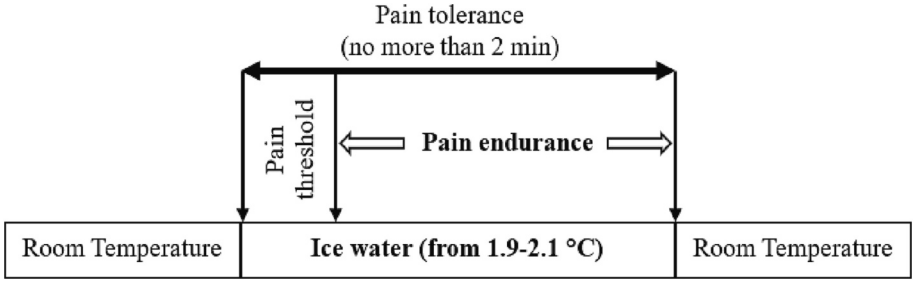

Fig. 1. A diagram of the cold pressor pain task. The figure illustrated the timing of pain task measures.

Depression severity was assessed using the clinician-administered Hamilton Rating Scale for Depression – 17 item (HAMD-17; Hamilton, 1960), and the 16-item self-report Quick Inventory of Depressive Symptomatology (QIDS-SR; Rush et al., 2003).

2.4. Neuroimaging

A 3T MRI scan (Siemens Magnetom Skyra) incorporated a structural MRI and a rsfMRI protocol. An T1-weighted anatomical scan was acquired at 1.0 mm3 resolution with a rapid gradient-echo sequence (echo time = 3.4 ms, repetition time = 1840 ms, 176 sagittal slices, field of view = 256 mm, flip angle = 15°). Resting-state blood-oxygen-level-dependent (BOLD) activity was assessed with a 10-minute whole-brain T2*-weighted 2D Echo Planar Imaging (EPI) sequence (echo time = 30 ms, repetition time = 2000 ms, 37 axial slices with 4.0 mm thickness, voxels = 4 × 4 × 4 mm3, field of view = 256 mm, flip angle = 75°). Participants received instructions to close their eyes and not fall asleep during the rsfMRI. Respiratory and cardio-pulmonary phases were recorded simultaneously using a respiratory belt and photoplethysmography, to remove physiological noise during preprocessing.

Neuroimaging data were preprocessed with the Analysis of Functional Neuro Images (AFNI) (Cox, 1996) and the FMRIB Software Library (FSL) (Jenkinson et al., 2012). First, each subject's T1-weighted anatomical scan was processed to remove non-brain tissue using the FSL Brain Extraction Tool (BET) (Smith, 2002). Second, the individual-subject 4D resting-state fMRI data underwent the following preprocessing steps: correction of outlier volumes (3dDespike), regression of physiological noise (3dRetroicor), removal of the first 5 volumes (10 s) of the data, estimation of motion correction parameters (FMRIB's Linear Image Registration Tool, MCFLIRT) (Jenkinson et al., 2002), interleaved slice-time correction and spatial smoothing (5 mm) with the FSL fMRI Expert Analysis Tool (FEAT) (Woolrich et al., 2001). Functional data were then registered to the structural brain image and transformed into a standardized MNI152 2 mm brain with FSL FMRIB's Linear Image Registration Tool (FLIRT) (Jenkinson et al., 2002) and FSL FMRIB's Non-Linear Image Registration Tool (FNIRT) (Jenkinson et al., 2012). To optimally denoise the rsfMRI data, the Python 2.7 script ICA-AROMA (ICA-based Automatic Removal of Motion Artifact) was implemented to remove motion-related components using the MCFLIRT-estimated parameters (Pruim et al., 2015). After denoising, nuisance regression was performed to remove the timeseries in the white matter and cerebrospinal fluid, and a high-pass temporal filtering was applied (0.01–0.1 Hz).

After preprocessing, first-level seed-based connectivity was analyzed for each subject using four regions of interest (ROIs) that have been implicated in both SA and pain: the bilateral aIC (±36, 14, 4), pIC (±38, −4, 10), aMCC, (±2, −12, 44), and sgACC (±4, 15, −11) (Rizvi et al., 2017). All ROIs were 5 mm spheres with the center on the MNI coordinates reported from previous studies on pain or SA (Ibinson and Vogt, 2013; Olié et al., 2021; Vogt et al., 2016). These masks were utilized to extract the mean time-series within the corresponding ROIs from the preprocessed functional data for each subject. The resting-state functional connectivity (rsFC) maps were then calculated as the Pearson correlation of each voxel with the seed time-series.

2.5. Statistical analysis

All statistical analyses for clinical and behavioral data were performed with IBM SPSS version 27 (IBM Corp, 2020). Demographic and clinical measures were compared between groups using independent *t*-tests, Mann-Whitney *U* tests, or Chi-Square tests, based on variable characteristics. A *p*-value of 0.05 was used for determining statistical significance for all tests.

2.6. Correlations between SC and pain variables

Bivariate correlational analyses examined the associations between pain measures and SC in each group. Partial correlations were also performed by adding lifetime and current SI as covariates. Based on normality, Pearson's product-moment or Spearman rank correlation coefficients were used. A Benjamini-Yekutieli procedure was used to correct for false-discovery rate (FDR) under dependency for all correlation analyses (Benjamini and Yekutieli, 2001). To compare the correlations between MDD and HC groups, a Fisher's r to z transformation was performed with R package "cocor" (Diedenhofen and Musch, 2015), where two-tailed *t*-tests were performed on the z scores with a confidence level of 0.95.

2.7. Correlations of SC with resting-state functional connectivity in MDD

First-level connectivity maps for the MDD group were entered to higher-level analysis using the demeaned ACSS score as a regressor, to identify regions where rsFC with the ROIs showed a significant correlation with ACSS. Higher-level analyses were performed using FSL mixed-effects model FLAME 1 (FMRIB's Local Analysis of Mixed Effects) (Woolrich et al., 2004). Multiple comparisons were corrected with a Gaussian random field theory cluster-defining thresholding ($z > 3.0$).

To examine if connectivity findings were unique within the MDD group, we conducted an analysis with HCs as a normative control. Parameter estimates (mean z scores) within the clusters whose rsFC had a significant association with ACSS scores were extracted from each participant from both MDD and HC groups. To explore the differences of rsFC values, the extracted mean z scores were compared between groups. Furthermore, to examine whether the correlation between ACSS scores and rsFC was only observed in MDD, a bivariate correlational analysis was performed between ACSS scores and the mean z score for each ROI, in both the MDD and HC groups (the HC data was used as a normative control). Between-group analyses were performed on the correlation coefficients using R package "cocor", as per the behavioral analysis above. The effect of age and sex on the rsFC of SC was assessed using likelihood ratio tests for both groups. Additionally, for the MDD group, the effect of age, sex, depression severity (HAMD total score) and SI (from C-SSRS) on the rsFC of SC was examined.

2.8. The effect of pain on SC connectivity in MDD – exploratory mediation analysis

As a secondary aim to preliminarily explore whether any pain measures mediated associations between ACSS scores and rsFC within the MDD group, an exploratory mediation analysis was performed. Exploratory mediation analyses have been useful to identify potential relationships among variables of interest in previous studies (Ammerman et al., 2018; Misra et al., 2021; O'Loughlin et al., 2021; Serang et al., 2017). Correlations between pain variables and rsFC mean Z in the MDD group were first examined to identify pain variables that showed both significant correlations with ACSS scores and the rsFC mean Z scores. Only the variable sets that were correlated with each other were entered to the subsequent mediation models. A simple mediation model was utilized with bootstrapping (5000 times) using the SPSS 27 package PROGRESS macro (Hayes, 2018). The indirect effects of SC on the rsFC mean z-values were then examined through the mediation of selected pain variables. Given the cross-sectional nature of the study, the exploratory mediation analysis was only utilized to examine the relationship between ACSS score, pain variables, and rsFC strengths.

3. Results

3.1. Demographic and clinical characteristics

There were no differences in demographic variables between groups (Table 1). Clinically, the MDD group had higher depression severity, lifetime and current SI. Groups also did not differ in ACSS scores (U = 138.50, $p = 0.062$), although the MDD group showed a trend of higher ACSS scores than HCs.

3.2. Relationship between ACSS scores and pain measures

Correlations between variables in each group are summarized in Table 2. In MDD, ACSS scores positively correlated pain endurance ($r_s = 0.64$, $p = 0.002$, 95 % CI [0.23, 0.86]) and negatively correlated with threshold intensity ($r_s = -0.61$, $p = 0.004$, 95 % CI [−0.84, −0.19]), while a positive correlation with tolerance did not survive the FDR correction ($r_s = 0.51$, $p = 0.021$, 95 % CI [0.06, 0.79]). After controlling for SI, the correlation of ACSS scores with endurance remained significant ($r_s = 0.64$, $p = 0.004$), while effects for tolerance ($r_s = 0.48$, $p = 0.042$) and threshold intensity ($r_s = -0.58$, $p = 0.011$) did not survive correction. In HCs, the positive correlation with threshold did not survive correction ($r_s = 0.49$, $p = 0.023$, 95 % CI [0.05, 0.77]), and ACSS scores did not correlate with any other pain measures. Comparing the correlation coefficients between groups, only the correlation between threshold intensity and ACSS scores significantly differed ($z = -2.13$, $p = 0.033$).

3.3. Resting-state functional connectivity associated with ACSS scores in MDD

For all four ROI seeds, functional connectivity was significantly associated with ACSS scores in the MDD group (thresholded clusters shown in Fig. 2 and Table 3). Higher ACSS scores correlated with higher rsFC from the aIC seed to the left posterior supramarginal gyrus (SMG), from the aMCC seed to the right cuneus, and from the sgACC seed to the right dorsolateral prefrontal cortex (DLPFC, Brodmann Area 46). Additionally, higher ACSS scores correlated with lower rsFC from the pIC seed to the right paracingulate gyrus (PCG). As a normative control, HCs showed no correlations between ACSS scores and rsFC strength, using the same SC connectivity identified within the MDD group (aIC-SMG: $r = -0.099$, pIC-PCG: $r = 0.084$, aMCC-cuneus: $r = -0.354$, sgACC-DLPFC: $r = 0.097$).

The mean rsFC strength did not differ between groups in any SC connectivity (aIC-SMG: U = 183, $p = 0.481$; pIC-PCG: U = 183, $p = 0.481$; aMCC-cuneus: $t = -0.772$, $p = 0.512$; sgACC-DLPFC: U = 190, $p = 0.602$). Comparing the correlation coefficients between ACSS scores and the rsFC strength, MDD showed a larger positive correlation than HCs for aIC-SMG ($z = 3.26$, $p = 0.001$), aMCC-cuneus ($z = 4.46$, $p <$

Table 1
Demographic and clinical characteristics.

Variables	MDD (n = 20)	HC ($n = 21$)	p
Age (years, Mean ± SD)	39.60 ± 13.34	42.48 ± 16.06	0.537
Sex (% female)	60.00 %	47.62 %	0.536
Education (years, Mean ± SD)	17.85 ± 2.50	18.75 ± 2.12	0.076
Employment Status (n)			0.067
Employed	7	14	
Student	3	2	
Retired	1	2	
Disabled/On Leave	5	0	
Unemployed	4	2	
Unknown	0	1	
Marital Status (% of married or common-law)	25.00 %	10.53 %	0.407
Household Income (n)			0.648
Less than $25, 000	6	5	
$25, 000–$49, 999	2	5	
$50, 000–$74, 999	5	4	
$75, 000 or more	3	5	
Unknown	4	2	
Ethnicity (n)			0.066
White	14	9	
Black	1	1	
Asian	2	10	
Portuguese	1	0	
Jewish	1	1	
Other	1	0	
Depression severity (HAMD, Mean ± SD)	18.45 ± 2.91	1.10 ± 1.34	<0.001
Depression severity (QIDS, Mean ± SD)	20.50 ± 6.33	2.14 ± 2.03	<0.001
Duration of current MDE (in Months, Mean ± SD)	15.40 ± 18.89	/	/
Lifetime SI (score from 0 to 5, Mean ± SD)	2.05 ± 1.57	0.05 ± 0.22	<0.001
Current SI (score from 0 to 5, Mean ± SD)	4.30 ± 1.03	0.05 ± 0.22	<0.001
Lifetime SA (n)		/	/
None	6		
One SA	3		
More than One SA	11		
Number of Lifetime SA (Mean ± SD)	2.35 ± 2.32	/	/
Non-Suicidal Self-Injury (n)		/	/
Lifetime NSSI	9		
Current NSSI	1		
Number of Psychiatric Comorbidities (n)*		/	/
= 0	10		
= 1	3		
= 2	4		
≥ 3	3		
Comorbidity with MDD (n)		/	/
Post-Traumatic Stress Disorder	5		
Panic Disorder	5		
Social Anxiety Disorder	4		
General Anxiety Disorder	3		
Agoraphobia	3		
Obsessive-Compulsive Disorder	2		
Anorexia Nervosa	1		
ACSS Score (Mean ± SD)	47.45 ± 10.65	41.00 ± 10.65	0.062

Notes: clinical variables not applicable to the HC were left empty and no between-group statistics were performed; MDD = Major Depressive Disorder or participants with Major Depressive Disorder; HC = healthy controls; HAMD = Hamilton Rating Scale for Depression total score; QIDS = Quick Inventory of Depressive Symptomatology total score; MDE = Major Depressive Episode; SI = suicidal ideation; SA = suicide attempt; NSSI = non-suicidal self-injury.

Table 2
Correlation analyses between ACSS total and pain measures in MDD and HC.

Measures	ACSS Score			Mean ± SD	
	MDD - Bivariate	MDD - Controlling SI	HC	MDD	HC
Threshold (time)	0.130	0.093	0.493*	14.10 ± 10.24	11.02 ± 7.48
Tolerance (time)	0.511*	0.483*	0.348	49.59 ± 39.33	39.61 ± 34.69
Endurance (time)	**0.640****	**0.638****	0.217	35.45 ± 33.65	28.52 ± 35.25
Threshold Intensity	**−0.614****	−0.583*	0.005	4.80 ± 2.61	4.93 ± 1.75
Tolerance Intensity	−0.404	−0.469*	0.101	7.50 ± 2.21	7.95 ± 1.50

Notes: ACSS = Acquired Capability for Suicide Scale; MDD = participants with Major Depressive Disorder; HC = healthy controls; SI = suicidal ideation; SA = suicide attempt; All coefficients here are the Spearman correlation; **Bolded are the correlations that survived correction for false-discovery rate.**
* $p < 0.05$.
** $p < 0.01$

0.001), and sgACC-DLPFC rsFC (z = 2.73, $p = 0.006$), as well as a larger negative correlation for the pIC-PCG rsFC (z = −3.497, $p < 0.001$) (Supplemental Fig. 1).

In the MDD group, a model that included age and sex as co-predictors (in addition to SC) did not significantly improve the original model (with only SC as the predictor) for aMCC-cuneus rsFC ($\chi^2(2) = 1.60$, $p = 0.422$), sgACC-DLPFC rsFC ($\chi^2(2) = 5.88$, $p = 0.079$), pIC-PCG rsFC ($\chi^2(2) = 2.95$, $p = 0.332$), or aIC-SMG rsFC ($\chi^2(2) = 7.927$, $p = 0.198$), using likelihood ratio tests. In the HC group, a model that included age and sex as co-predictors did not significantly improve the original model for aMCC-cuneus rsFC ($\chi^2(2) = 1.53$, $p = 0.706$), pIC-PCG rsFC ($\chi^2(2) = 9.07$, $p = 0.255$), or aIC-SMG rsFC ($\chi^2(2) = 6.39$, $p = 0.643$). For sgACC-DLPFC rsFC, adding age and sex predictors significantly improved the model ($\chi^2(2) = 15.80$, $p = 0.001$). In addition, when including age, sex, depression severity and SI as co-predictors in the MDD group, the model also did not significantly improve the original model for aMCC-cuneus rsFC ($\chi^2(2) = 3.15$, $p = 0.506$) or pIC-PCG rsFC ($\chi^2(2) = 3.08$, $p = 0.73$). However, they significantly improved the prediction for sgACC-DLPFC rsFC ($\chi^2(2) = 11.279$, $p = 0.017$) and or aIC-SMG rsFC ($\chi^2(2) = 24.228$, $p = 0.005$).

3.4. The effect of pain with SC connectivity in MDD

The correlation analyses showed that only pain threshold intensity, tolerance and endurance significantly correlated with both ACSS scores (Table 2) and some rsFC strengths (Supplemental Table 1). The mediation analysis in the MDD group (Fig. 3) demonstrated that pain threshold

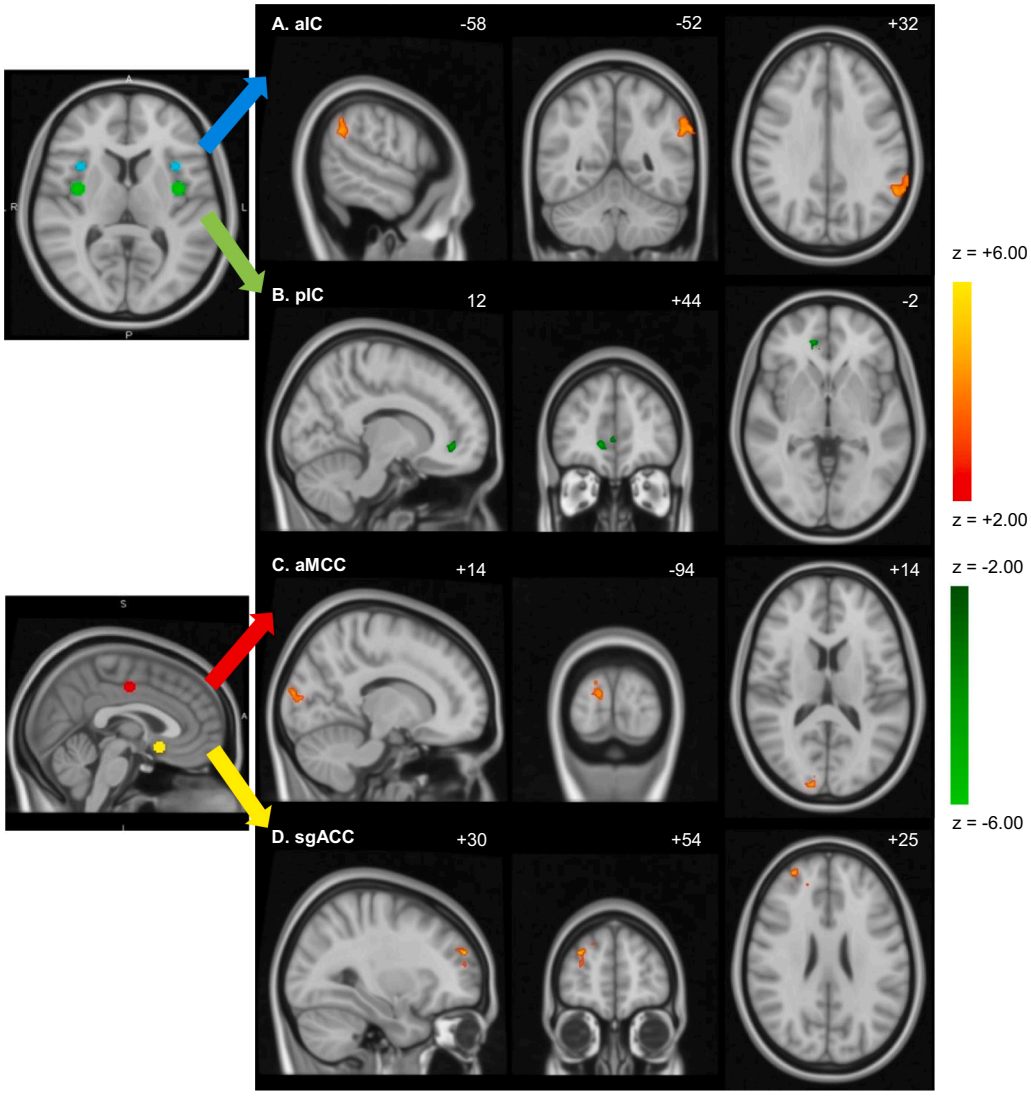

Fig. 2. Seed-based functional connectivity analysis results: Brain clusters connected with the ROIs that showed significant correlation with ACSS scores. The seeds (left) aIC (blue) and pIC (green) are shown in slice z = 8, and the seeds aMCC (red) and sgACC (yellow) were show in slice x = 2.
Regions that showed maximal correlation with ACSS total scores in terms of their resting-state functional connectivity (rsFC) with the seeds aIC (A), pIC (B), aMCC (C), and sgACC (D). All figures were displayed in the MNI152 1.0 mm standard space within radiological orientations in sagittal (left), coronal (middle), and axial (right) views (z threshold from 2.0 to 5.0). The rsFC from the seeds to the regions in yellow-red was positively correlated with ACSS score (A, C, and D); those in green-light green was negatively correlated with ACSS score (B). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 3
Cluster-seed connectivity associated with ACSS scores in the MDD group. Local maximum intensity within the significant voxel clusters is listed by their functionally connected seeds, Brodmann area, anatomical location, and MNI coordinates in standard space.

Seed	BA	Location	Max MNI Coordinates			Max z	Voxels	*p*
			x	y	z			
aIC	40	Left supramarginal gyrus (posterior)	−68	−44	30	4.22	210	<0.001
pIC	32	Right paracingulate gyrus	12	44	−2	−4.42	100	0.018
aMCC	17–18	Right occipital pole (cuneus)	14	−94	14	4.00	95	0.036
sgACC	10	Right dorsolateral prefrontal cortex	30	54	26	4.81	90	0.022

Notes: ACSS = Acquired Capability for Suicide Scale; MDD = participants with Major Depressive Disorder; BA = Brodmann area; x, y, z = correlates in MNI standard space; Max z = maximum z values representing the correlation between ACSS scores and the connectivity; Voxels = number of voxels that passed the threshold.

intensity significantly mediated the relationship between ACSS score and rsFC of the pIC-PCG (ab = −0.037, BCa CI [−0.070, −0.006], standardized β = −0.224, effect size 29.1 %) and the sgACC-DLPFC (ab = −0.033, BCa CI [0.002, 0.087], standardized β = 0.199, effect size 25.9 %). Mediation models using other pain mediators did not significantly affect the SC connectivity across the 4 ROIs (see Supplemental Table 2 and Table 3).

4. Discussion

To our knowledge, this study is the first to directly examine the neural correlates of SC and its association with pain in MDD patients with suicide risk compared to HCs. Overall, in MDD participants we observed a positive correlation between SC and pain endurance, a negative correlation between SC and threshold intensity, as well as an association between SC and rsFC of the insula and cingulate with brain regions involved in pain. This association was partially mediated by pain threshold intensity, but not tolerance or endurance.

Our findings of SC associations with pain in MDD using both objective (time in water) and subjective (intensity rating) measures of pain were consistent with prior literature using the same task in individuals with a history of self-harm and in young males (Förtsch et al., 2021; Franklin et al., 2011; Teismann et al., 2014). We reported that the associations between SC and pain measures were different in MDD compared to HC groups, which indicates a need to further explore this relationship in different patient subgroups in order to potentially stratify suicide risk.

As the first study to directly probe the neural correlates of SC with a focus on an MDD group, the rsfMRI results suggest that the pain network underlies SC in MDD patients. To our knowledge, only one study examined the neural correlates of proposed endophenotypes of SC using a non-suicide risk sample (Deshpande et al., 2016). The authors conducted a meta-analysis of previous neuroimaging studies examining fear, pain, emotion, and reward networks and determined whether they overlapped with networks identified from previous MDD studies. The authors proposed an SC network consisting of the putamen, insula, claustrum, cingulate, and thalamus. Our finding that the ACC and insula underlie SC aligns with this preliminary work.

Notably, the aIC is important for emotional aspects of pain through its rich limbic connections, while the pIC plays a central role in the sensory aspects of pain via primary and secondary somatosensory cortices (AD, 2011; Farb et al., 2013; Wiech et al., 2014). We also observed that SC was linked to higher aIC-SMG rsFC. The SMG as part of the somatosensory association cortex is activated during pain sensation, involved in the cognitive modulation of pain (Wager et al., 2013), and has been associated with the neural response to social exclusion in SA (Giakoumatos et al., 2013; Olié et al., 2017). Therefore, higher aIC-SMG connectivity may be involved in abnormal cognitive and emotional responses to pain. In the present study, controlling for depression SI severity significantly improved the model of SC predicting aIC-SMG, suggesting that this marker may be particularly sensitive to varying depression and current SI levels. SC was also associated with lower pIC rsFC to a region that extended anteriorly to the ventral ACC (vACC). The pIC and vACC are involved in the initial unconscious noxious response and the conscious affective perception of pain, respectively (Bastuji et al., 2016). Thus, SC may indicate weakened transmission from the ascending pathway of pain to higher-order regions involved in emotional aspects of pain.

In addition, we found that SC was linked to higher aMCC-cuneus rsFC. The aMCC is important for the cognitive and emotional modulation of pain and negative affect (Shackman et al., 2011), while the cuneus is primarily involved in visual processing. In a previous study, the cuneus was activated when participants read a suicidal act script compared to a neutral script (Reisch et al., 2010). Therefore, higher aMCC connectivity to the visual regions in SC may suggest heightened mental imagery associated with suicide. We also reported here that a model that controls for depression SI severity significantly improved the model of SC predicting aMCC-cuneus rsFC, suggesting that this marker may also be more associated with patients with depression and current SI. Finally, we demonstrated that SC was associated with higher sgACC-DLPFC rsFC. Importantly, the sgACC and DLPFC are involved in pain modulation (Duerden and Albanese, 2013; Olié et al., 2021; Reisch et al., 2010; Vanneste et al., 2017), and the DLPFC is particularly important for top-down cognitive regulation of pain (Cieslik et al., 2013). Reduced DLPFC volume and activity have been reported in groups with suicide risk, which suggests impaired cognitive control and decision-making (Jollant, 2016; Schmaal et al., 2020). The current finding of higher sgACC-DLPFC connectivity may indicate that increased cognitive

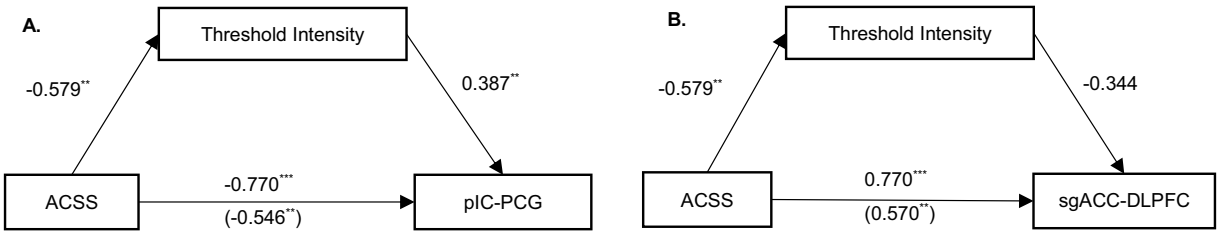

Fig. 3. Mediation analyses of SC and rsFC through pain threshold intensity in the MDD group ($n = 20$). The Simple mediation models tested how pain threshold intensity mediate the association between ACSS scores and SC connectivity, including the connectivity between the posterior insula and paracingulate gyrus (pIC-PCG, A), and subgenual anterior cingulate and dorsolateral prefrontal cortex (sgACC-DLPFC, B). Note: standardized beta scores are presented here; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

resources are utilized at rest due to heightened top-down pain regulation. In summary of the results from 4 ROIs, in MDD, SC may not be associated with a global decrease in pain network connectivity, but instead is associated with decreased connectivity in the ascending pathway of pain perception, and increased connectivity in the top-down pain regulatory network.

Importantly, although the mean SC connectivity strength in MDD observed did not differ from HCs, the correlations between ACSS scores and SC connectivity in MDD were significantly stronger. These results support the possibility that the observed rsfMRI markers for SC may be more present among individuals with suicide risk. This study focused on SC in MDD given the majority of suicide attempts/deaths occur within this group, as well as the significant clinical challenge identifying risk. Therefore, we used the HC group as a normative control, rather than examining the interactions of the correlations of ACSS scores and rsFC between two groups. This allowed us to better identify the rsFC pattern associated with SC within the MDD group rather than the regions that showed a maximal difference between groups. However, SC is a transdiagnostic construct, thus, future studies should examine the present neuroimaging findings transdiagnostically to evaluate their generalizability or if there are biomarkers unique to a diagnostic group.

Our mediation results show that only threshold intensity, but not other pain variables, mediated the effect of SC on pIC-PCG and sgACC-DLPFC rsFC in the MDD group, and accounted for 25–30 % of the total effect. This finding is aligned with prior literature in healthy subjects, where pain sensitivity was linked to similar network connectivity (Kim et al., 2020; Niddam et al., 2021; Tu et al., 2019; Yu et al., 2020). However, given the modest effect sizes, there may be other potential variables involved in this relationship. Furthermore, since this study is cross-sectional in nature, we cannot make any inference about causality based on the mediation analysis done here.

4.1. Limitations

This study has several limitations. First, we were unable to explore grouping based on the presence of SI. Nevertheless, our analyses still demonstrated the correlates of SC while controlling for SI severity. We also did not have a non-suicidal control group with MDD, which limits our ability to differentiate the effect of depression and suicide risk. Another limitation is that while the ACSS is the most frequently utilized in suicide research (Kramer et al., 2020), conceptualization of SC has evolved since the start of this study to include practical aspects of SC (e.g., accessibility of methods) (Klonsky and May, 2015). Thus, it would be prudent to replicate these findings with newer scales (George et al., 2016; Klonsky and May, 2015; Shahnaz et al., 2020). Thirdly, we noted high variability in pain tolerance measured by the cold pressor pain task, similar to prior studies (Deville et al., 2020; Förtsch et al., 2021; Teismann et al., 2014). Variability of the cold-pressor task is common and may be ameliorated by implementing other pain task modalities that have less variability (Birnie et al., 2014). Lastly, rsfMRI indirectly assessed the association between SC and the pain network, so we can only infer the role of these neural markers in pain. Nevertheless, prior evidence suggests that rsFC of regions within the pain network predicts differences in pain threshold and sensitivity (Kim et al., 2020; Niddam et al., 2021; Tu et al., 2019).

5. Conclusions

This study found that SC strongly correlated with pain processing among individuals with MDD and suicide risk. Using rsfMRI, we found that SC was associated with the neural network of pain perception and modulation, which can be partially explained by the mediation of pain sensitivity. These findings advance our understanding of the neurobiological basis of suicide risk, specifically, the neurocircuitry of SC and its association with pain. Furthermore, this work signals there may be a utility in exploring the use of pain and the neurocircuitry of pain to stratify suicide risk, which may also inform novel treatment avenues. Future studies should explore the possibility of differential effects within a population at risk of suicide (e.g., SI only vs. SI/SA) to better understand the clinical utility of pain processing as a marker of suicide risk.

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CRediT authorship contribution statement

SW: substantial contributions to the conception or design of the work; the acquisition, analysis, or interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

SHK: substantial contributions to the conception or design of the work; revising the work critically for important intellectual content; and final approval of the version to be published.

TVS: substantial contributions to the conception or design of the work; revising the work critically for important intellectual content; and final approval of the version to be published.

AKC: the acquisition, analysis, or interpretation of data for the work; revising the work critically for important intellectual content; and final approval of the version to be published.

SJM, YB, DAP, NF, GT, TAS, NC, MS: revising the work critically for important intellectual content; and final approval of the version to be published.

SJR: substantial contributions to the conception or design of the work; revising the work critically for important intellectual content; final approval of the version to be published; and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of interest

Dr. Sidney H. Kennedy has received research funding or honoraria from Abbott, Alkermes, Allergan, Boehringer Ingelheim, Brain Canada, Canadian Institutes for Health Research (CIHR), Janssen, Lundbeck, Lundbeck Institute, Ontario Brain Institute, Ontario Research Fund (ORF), Otsuka, Pfizer, Servier, Sunovion and Xian-Janssen. He also has received stock options from Field Trip Health.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2023.02.147.

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