

Examining the Neural Basis of Pain Tolerance and Fearlessness About Death in Suicide Risk

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Abstract

Introduction: Suicide is a global health concern accounting for over 700,000 deaths each year worldwide. Suicide capability – including heightened pain tolerance and fearlessness about death – may explain the progression from suicidal ideation to a suicide attempt. Thus, investigating the neural circuitry associated with pain, fear, and suicide risk presents a unique opportunity to identify biomarkers of suicide capability and contribute to our understanding of the transition from suicidal ideation to suicide attempt.

Methods: A total of 90 adults aged 18 to 65 will be recruited from Toronto, Canada. Participants will either be 1) patients with current suicidal ideation but no previous suicide attempt (ideators; n=30), 2) patients with current suicidal ideation and a suicide attempt within the past six months (attempters; n=30), or 3) healthy controls (n=30). Participants will complete self-report measures and magnetic resonance imaging tasks measuring pain tolerance and fearlessness about death.

Results: It is expected that those who have attempted suicide will exhibit significantly higher pain tolerance and fearlessness about death than suicide ideators or healthy controls. It is also predicted that self-reported suicide capability will be negatively associated with pain- and fear-related neural activation.

Discussion: Findings of the present study may contribute to the validation of ideation-to-action models of suicide by providing neurobiological evidence supporting the distinction between suicide ideators and attempters.

Conclusion: By examining the neural underpinnings of suicide capability, this work contributes to the understanding of biomarkers indicating those at greatest risk of suicide.

Keywords: suicide; suicide attempt; suicide capability; pain tolerance; fearlessness about death; biomarkers; magnetic resonance imaging

Introduction

Suicide is a global health concern that takes the lives of over 700,000 people each year [1]. The majority of people who experience suicidal ideation will never attempt suicide [2]. However, the mechanisms underlying the transition from suicidal ideation (SI) to a suicide attempt (SA) are not widely understood. Understanding the distinct mechanisms involved in this transition is critical for developing targeted prevention and intervention strategies for those at the highest risk.

Suicide Capability

According to two leading theories on suicide, the Interpersonal Theory of Suicide [3,4] and the Three-Step Theory of Suicide [5], the progression from SI to SA is contingent on an individual's suicide capability. In these ideation-to-action models of suicide, SI and SA have distinct pathways. While suicide desire arises from feelings of thwarted belongingness (i.e., a lack of belonging and isolation), perceived burdensomeness, and a sense of

hopelessness, it is proposed that an individual will only attempt suicide if they have acquired suicide capability [3, 4]. Indeed, recent work has highlighted the role of suicide capability, particularly when combined with heightened arousal, in predicting suicide death [6].

Suicide capability comprises two core components: 1) heightened pain tolerance (PT) and 2) fearlessness about death (FAD) [3, 4]. An individual's PT refers to the maximum level of pain they can tolerate, while FAD represents a decreased fear of dying. Joiner (2005) suggests that these components increase during the lifespan in response to painful and provocative events. As individuals become habituated to the pain and fear associated with dying, they become capable of carrying out a potentially lethal self-injurious act [3,4]. Accordingly, elevated PT has been observed in individuals with a history of SA [7,8], and evidence suggests that FAD is higher in suicide attempters than ideators [7,9]. Thus, suicide capability (i.e., an increased PT and FAD) may be a key factor in the progression from SI to SA.

Pain Tolerance and Suicide Risk

Repeated exposure to pain can result in heightened pain tolerance, thereby increasing suicide capability [3,4]. As such, existing functional and structural neuroimaging studies indicate a significant overlap in the neural circuitry associated with both pain and suicide (see [Figure 1](#)) [10]. Pain has been consistently associated with activation in brain regions such as the anterior cingulate cortex (ACC), prefrontal cortex (PFC), insular cortex (IC), somatosensory cortex (SC), thalamus, and amygdala [11,12,13]. While few studies have examined the neurobiology of suicide, some evidence suggests that suicide risk may be reflected in brain areas related to stress, emotion regulation, cognitive control, and pain [14,15]. Particularly, abnormalities in the ACC, PFC, IC, and amygdala may be associated with a greater risk for suicide [14,15]. Impaired structural and functional connectivity between the PFC and amygdala is associated with low inhibitory control and difficulties in emotion regulation [14]. To our knowledge, only one study (2016) to date has examined the neurobiology of suicide capability [16]. Deshpande and colleagues (2016) used magnetic resonance imaging (MRI) technology to identify the ACC, IC, and striatum as brain regions underlying suicide capability [16].

Fearlessness About Death and Suicide Risk

FAD may increase suicide risk as individuals who are less frightened of the factors associated with dying (e.g., pain of death, existential uncertainty, leaving loved ones behind) are more capable of carrying out a lethal SA [3,4].

Studies examining FAD have primarily used the Acquired Capability for Suicide Scale – Fearlessness About Death [17]. However, the validity of this measure has come into question. Notably, a meta-analysis by Chu and colleagues (2017) has called for future work to improve measures of suicide capability and its components as few assessments have been empirically validated and few studies have evaluated the psychometric properties of capability measures across populations [18]. Neurobiological measures may more accurately capture underlying constructs of FAD, such as a diminished fear response toward death and suicide-related stimuli [18]. As fear responses – including those related to death and suicide – have a neural basis, measures of neural activation and functional connectivity can provide a more direct link to the underlying constructs [19]. If fear response *is* altered in individuals at risk of suicide, then these alterations should be reflected in the brain. However, no studies to date have explored the use of brain imaging techniques to measure FAD directly.

Activation in brain regions such as the PFC, amygdala, and hypothalamus (HT) is associated with fear and emotional responses [19]. Interestingly, there seems to be considerable overlap between brain regions associated with pain and fear processing as well as suicide risk (see [Figure 1](#)). While no work to date has explored this area, investigating the neurocircuitry and activation of brain areas related to pain, fear, and suicide risk presents a unique opportunity to identify biomarkers of suicide capability.

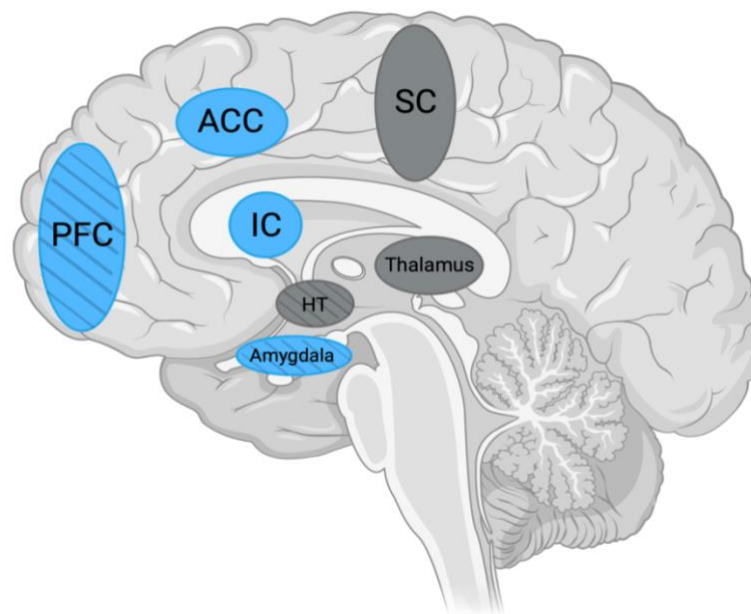


Figure 1. Brain regions associated with pain are in grey and regions associated with fear are represented by shaded grey lines. Areas relevant to suicide risk are highlighted in blue. This image was created using BioRender software.

Study Objectives

The main objective of the study is to examine the neural basis of two main components of the Interpersonal Theory of Suicide that theoretically increase suicide capability: PT and FAD. Specifically, the study aims to:

1. Explore differences in PT (i.e., self-reported PT and pain-related neural activation and functional connectivity) between healthy controls, suicide ideators, and attempters.
2. Investigate differences in FAD (i.e., self-reported FAD and fear-related neural activation and functional connectivity) between healthy controls, suicide ideators, and attempters.
3. Examine associations between pain-related neural activation and self-reported PT.
4. Assess associations between fear-related neural activation and self-reported FAD.

Hypotheses

1. Suicide attempters will demonstrate higher self-reported PT and decreased neural activation and impaired connectivity in pain-related brain regions during a PT task, compared to suicide ideators and healthy controls.
2. Suicide attempters will exhibit higher self-reported FAD and decreased neural activation and impaired connectivity in fear-related regions during an FAD task, compared to suicide ideators and healthy controls.
3. Pain-related neural activation will be negatively associated with self-reported PT.
4. Fear-related neural activation will be negatively associated with self-reported FAD.

Methods

Participants

A total of 90 adults aged 18 to 65 will be recruited from Toronto, Canada. Recruitment will take place over multiple sites in Toronto, and will be monitored and adjusted accordingly to maximize the sample's diversity. The study will recruit patients with current SI but no previous SA (n=30), patients with current SI and an SA within the last six months (n=30), and healthy controls (n=30).

Inclusion criteria for patients:

- Beck Scale for Suicidal Ideation total score equal to or greater than 1 (ranges from 0 to 40)
- SA group only: Positive history of at least one suicide attempt within the last six months, as confirmed by a clinician

Exclusion criteria:

- Taking medication for chronic pain
- Have a medical condition requiring immediate investigation or treatment
- Have a recent history of drug use or dependence (excluding caffeine or nicotine)

- HC group only: Lifetime history of mental disorders

Measures

Acquired Capability for Suicide Scale (ACSS) [20]: The ACSS is a 20-item self-report questionnaire measuring components of suicide capability. The ACSS will be used to assess participants' PT and FAD. Sample items include, "I can tolerate a lot more pain than most people" and "The fact that I am going to die does not scare me." Items are answered on a 5-point Likert scale where 0 = *Not at all like me* and 4 = *Very much like me* where cumulative scores range from 0 to 80. Scores on the PT items will be summed together, while accounting for reverse coded items, to provide a total score of PT. Scores from the FAD items will also be summed together, while accounting for reverse coded items, to provide a total score of FAD. Higher sums of scores indicate higher PT and FAD. The ACSS has been found to have high internal consistency reliability in a diversity of samples [21].

MRI pressure pain task: Pressure pain assessments involve applying pressure to specific points on the body using a pressure algometer. The point at which painful sensation can no longer be tolerated is recorded as a subject's PT [22]. During the task, controlled pressure will be applied at one time to a participant's left calf while brain activity is recorded. Participants will be instructed to press a button when they can no longer tolerate the pain. At this point, a member of the study team will turn off the pressure pain. This task has been validated and implemented in neuroimaging studies of chronic pain [23].

MRI suicide image viewing task: The novel MRI suicide image viewing task has been designed to measure FAD by recording brain activation in fear-related brain regions while participants view neutral and suicide-related images. This task adopts similar methodology from eye tracking tasks measuring gaze behaviour toward suicide images [24]. Each participant will view a set of 10 neutral images, followed by a set of 10 suicide-related images, summing to 20 trials. Images will be presented for 10 seconds, preceded by a one-second fixation cross, and followed by a one-second blank screen. To ensure the relevance and validity of the images, the stimuli have been selected based on prior validation in a study conducted by Li and colleagues [24].

Procedure

At the study visit, participants will review the letter of information with a member of the study team and provide written and verbal informed consent. Mental health resources will be available to participants and listed on the consent form. Participants will first complete an online questionnaire on Qualtrics collecting demographic and clinical information as well as scores on the ACSS. In rare cases, concerning information (e.g., imminent suicide risk) will be flagged and an on-site psychiatrist will be present to

intervene. An MRI scan will then be conducted to collect the neuroimaging data. The scanning session will consist of a structural MRI and task-based functional MRI protocol comprising: 1) a whole-brain T1-weighted anatomical scan at 1mm³ resolution, 2) an event-related BOLD series during a pressure pain task, and 3) an event-related BOLD series during a suicide image task. Functional magnetic resonance will be acquired using a 2D spin echo EPI sequence 30, 4 mm thick slices over a 200 mm field of view. TR / TE are 2000 ms and 30 ms respectively, 70 degree flip angle encoding 64x64 pixels at 2298 Hz / pixel to produce 3.1.x3.1x4 mm voxels.

Statistical Analysis

All MRI data will first undergo preprocessing, involving standard motion and physiological correction, spatial normalization, and smoothing. Next, a whole brain analysis will be conducted using FMRIB Software Library to explore patterns of activation associated with the PT and FAD tasks [25]. Region of interest (ROI) analyses (see [Figure 1](#)) will assess brain activity and functional connectivity in regions related to PT and FAD. Due to the exploratory nature of the study, group differences between suicide ideators and suicide attempters, suicide ideators and HC, suicide attempters and HC, and ideators and attempters versus HC will be examined. Independent t-tests will be performed to assess group differences in PT and FAD as assessed by self-report measures and MRI tasks. Pearson simple linear correlations will be conducted to examine associations between self-report and MRI measures of PT and FAD. Demographic variables (e.g., gender, socioeconomic status) will be included in all analyses as covariates to control for any potential effects. Statistical analyses will be performed using SPSS v.28 [26].

Results

Pain Tolerance and Suicide Risk

It is anticipated that suicide attempters will exhibit statistically significantly higher self-reported PT compared to suicide ideators and healthy controls, aligning with previous findings [7,8]. Neuroimaging results are expected to show statistically significantly lower neural activation and impaired functional connectivity in pain-related brain regions, including the ACC, PFC, IC, thalamus, amygdala and SC during the PT task in suicide attempters compared to ideators or healthy controls supporting findings from previous work [10]. A statistically significant negative association between self-reported PT and pain-related neural activation is predicted.

Fearlessness About Death and Suicide Risk

Higher levels of self-reported FAD in suicide attempters compared to ideators is expected, in line with previous work [7,9]. It is predicted that suicide attempters will exhibit statistically significantly less activity and impaired functional connectivity in fear-related brain

regions, including the PFC, amygdala, and hypothalamus compared to ideators or healthy controls. A statistically significant negative association between self-reported FAD and fear-related neural activation is predicted.

Discussion

The findings of the proposed study may contribute to the validation of ideation-to-action models of suicide by providing neurobiological evidence supporting the distinction between suicide ideators and attempters. Identifying specific brain regions associated with suicide capability could provide a biomarker to indicate treatment efficacy and outcomes. This knowledge has the potential to inform therapeutic strategies, such as repetitive transcranial magnetic stimulation or deep brain stimulation, by pinpointing specific brain regions that could be targeted for intervention.

Limitations

While the study seeks to minimize limitations, several exist despite these efforts. First, demographic characteristics of participants, such as sex, gender, age, and socioeconomic status, may limit the generalizability of findings. Particularly, while more women attempt suicide, more men are likely to die by suicide [27]. Individuals with lower socioeconomic status are also more likely to engage in suicidal behaviour [28]. Second, this study used a cross-sectional design, limiting the ability to establish causal or temporal relationships between variables. The inability to determine whether observed changes in brain activity and functional connectivity precede or result from heightened suicide risk highlights the need for longitudinal investigations. Third, the novel MRI suicide image viewing task employed in this study warrants further investigation regarding its validity in measuring FAD. Fourth, the exclusive focus on suicide attempts in the current study neglects other self-injurious or suicidal behaviours, such as nonsuicidal self-injury (NSSI), aborted suicide attempts, and interrupted suicide attempts. Particularly, NSSI may be a particularly potent event that increases one's capability for suicide as it habituates an individual to the pain and fear associated with more serious self-injury [29]. Recognizing the spectrum of suicidal behaviours is crucial for a comprehensive understanding of suicide capability. Lastly, findings from this study cannot discern whether differences in the brain directly cause or precede suicidal thoughts and/or behaviours, or whether they function bidirectionally. Understanding the temporal relationship is essential for establishing cause and effect; if the study could determine that differences in neurobiology are present prior to the onset of suicidal thoughts/behaviors, it would provide more insight into potential risk factors for suicide.

Future Directions

Future research should strive for diverse participant samples to ensure the broader applicability of the results to different populations, considering the potential influence of

sex or sociodemographic factors on suicide risk. Moreover, it is suggested that future work employ a longitudinal design to explore whether components of suicide capability and their neural underpinnings possess state or trait qualities. It is further recommended that a multi-modal research approach is used to enhance the robustness of future studies. Incorporating ecological momentary assessment techniques and more objective measures of PT and FAD, such as physiological responses or eye-tracking, could provide a more nuanced understanding of these constructs. Future investigations should also adopt a more inclusive approach, considering a broader range of self-injurious and suicidal behaviours to provide a holistic perspective on suicide risk.

Conclusions

Suicide remains a pressing public health issue and identifying those at greatest risk is a critical challenge. This study is the first to evaluate differences in brain regions associated with pain, fear, and suicide, between suicide ideators and attempters. By examining the neural underpinnings of suicide capability, this work contributes to the understanding of biomarkers indicating those at greatest risk of suicide.

List of Abbreviations Used

ACC: anterior cingulate cortex
FAD: fearlessness about death
HC: healthy controls
HT: hypothalamus
IC: insular cortex
MRI: magnetic resonance imaging
NSSI: nonsuicidal self-injury
PFC: prefrontal cortex
PT: pain tolerance
ROI: region of interest
SA: suicide attempt
SI: suicidal ideation

Conflicts of Interest

The author declares that they have no conflicts of interest.

Ethics Approval and/or Participant Consent

As this study will involve human participants, Research Ethics Board (REB) approval will be obtained.

Authors' Contributions

SR: made significant contributions to the design of the study, drafted the manuscript, and gave final approval of the version to be published.

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