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Functional Brain Dysregulation Associated with Psychological Pain in Suicide Attempters: A Systematic Review

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Abstract

Introduction: Suicide is a major global health concern causing over 700,000 annual deaths. Despite research efforts and clinical need, means of stratifying individuals at the highest risk of suicide attempt remain insufficient. Psychological pain is a key feature of ideation-to-action theory and involves a distinct neural network. However, alterations in the neurocircuitry related to psychological pain between suicide attempters (SA) and suicide ideators (SI) have not been firmly established. Such alterations may serve as a biomarker capable of risk stratification and informing therapeutic targets. Thus, this review sought to identify if consistent functional brain alterations associated with psychological pain exist in SA relative to SI.

Methods: A search strategy with terms related to suicide and psychological pain was conducted in Embase, APA PsycInfo, and Ovid MEDLINE databases without any limits. Studies were screened for use of functional neuroimaging, psychological pain measures, and comparisons between adult SA and SI with mood disorders. Relevant data was extracted from six included studies, and study quality was assessed using the Newcastle-Ottawa Quality Assessment Scale adapted for cross-sectional studies.

Results: The anterior cingulate cortex, insula, orbitofrontal cortex, and thalamus, which are central to the experience of psychological pain, showed consistent dysregulation in SA compared to SI across a range of neuroimaging paradigms. Dysregulation in these regions was consistently correlated with psychological pain levels and suicide attempts, although directionality varied. Comparisons of self-reported psychological pain in SA relative to SI were inconsistent.

Discussion: Brain function in SA may be characterized by alterations in a network of regions associated with psychological pain. This dysregulation indicates impairments in processing and top-down control of negative emotion, decision-making, social cognition, and pain avoidance. Such impairments may make individuals more vulnerable to suicide attempt.

Conclusion: Our findings provide insight into functional brain dysregulation associated with psychological pain that may mediate the transition from ideation to attempt. Further research is needed to clarify the generalizability of these findings and to refine a biomarker of suicide risk. Additional longitudinal research is required to assess whether such brain dysregulation predicts future attempt in SI and whether it represents a therapeutic target.

Keywords: functional neuroimaging; suicide risk; psychological pain; mood disorders; three-step theory

Introduction

Suicide accounts for over 700,000 annual deaths [1]. Suicide incidence is highest among adults aged 25–35 years [2]. The majority of individuals who die by suicide also experience mood disorders [3]. Suicidal ideation is also a significant risk factor for suicide attempt, but is not a reliable predictor, as only 29% of suicide ideators (SI) attempt suicide in their lifetime [4]. Efforts at developing clinical models of risk have failed to reliably differentiate between suicide attempters (SA) and SI, remaining a key challenge [5].

The Three-Step Theory (3ST) presents suicide ideation-to-action as three steps, two of which emphasize psychological pain, the lasting, unpleasant feeling resulting from negative appraisal of an inability or deficiency of the self [6, 7]. First, psychological pain and hopelessness create suicidal desire, then desire intensifies when pain overwhelms connectedness, leading to an attempt if capability for suicide is present [6]. It is proposed that suicide attempt functions as a means of escaping unbearable psychological pain, the most common theme reported in suicide notes [8, 9]. Psychological pain is well-established as a risk factor for suicidality, and emerging evidence supports its potential mediating role in the ideation-to-attempt transition. A meta-analysis demonstrated that self-report psychological pain measures reliably differentiate between SA and non-suicide attempters (NSA) without ideation, with SA reporting higher psychological pain even when

depression severity is equal [10]. Additionally, in patients with mood disorders, increased psychological pain has been reported in SA relative to SI and is prospectively associated with higher odds of suicide attempt [11-13].

Capability for suicide, the third step of the 3ST, is the defining step that facilitates the ideation-to-attempt transition. Increased physical pain tolerance has been proposed as a necessary component of capability for suicide [14]. The relationship between psychological pain and physical pain tolerance is somewhat unclear, with mild and severe psychological pain potentially producing opposing sensitizing and blunting effects on physical pain [15]. By this means, mild psychological pain may decrease physical pain tolerance, whereas severe psychological pain in SA may increase physical pain tolerance [16]. The association between psychological and physical pain may be partly explained by the extensive overlap of their neurobiology [17]. This suggests that psychological pain may have a direct role in the capability for suicide and underscores the need to examine its neurobiology in the context of suicide.

A review assessing functional brain activity among varying levels of psychological pain, recalled sadness, and recalled grief, proposed a neural network of psychological pain including the thalamus, anterior cingulate cortex (ACC), posterior cingulate cortex, prefrontal cortex, cerebellum and parahippocampal gyrus [17]. Broadly, the thalamus relays sensory information to other network regions, such as the cingulate cortex, central to the negative affective processing of pain, and to the prefrontal cortex, involved in memory and planning during painful states. Significant overlap exists between this network and the regions involved in physical pain [18]. Moreover, functional neuroimaging studies have associated social pain, a facet of psychological pain, with dysregulation of the ACC and insula, core regions of the affective processing of physical pain [19]. In order to characterize neuroimaging correlates of suicidality in adolescents, a previous review proposed an Emotional paiN and social Disconnect (END) model of suicidality, wherein dysregulation of emotional pain neurocircuitry (cerebellum, amygdala, and hippocampus) contribute to ideation, while dysregulation of social disconnect neurocircuitry (lateral orbitofrontal cortex and temporal gyri) uniquely contribute to suicide attempt [20]. The neuroimaging correlates of psychological pain have not been systematically examined in adults.

Given the potential role of psychological pain in the ideation-to-attempt transition, identification of functional brain dysregulation related to psychological pain may be crucial for identifying a biomarker of suicide risk. Such a biomarker would deepen our understanding of the suicidal brain and may inform risk identification methods and novel clinical interventions for suicide prevention. The present study aims to review the available functional neuroimaging literature on adults to clarify how brain activity associated with psychological pain differs between SA and SI.

Methods

Following PRISMA 2020 guidelines, a search was conducted using the Ovid search tool within the Embase, APA PsycInfo, and Ovid MEDLINE databases on October 13, 2024. The following search strategy was used: (((“suicid*” or “exp suicide”) and (“psychache” or “psychological pain” or “mental pain” or “social pain” or (“psych* or mental adj3 pain”))). No limits were applied to the search. Inclusion criteria consisted of adult SA with mood disorders, psychiatric comparators, validated measures of psychological pain and functional neuroimaging (e.g., fMRI: functional magnetic resonance imaging, and EEG: electroencephalogram). Only full-text peer-reviewed articles written in English were included.

Articles were excluded if they included youth (under 18), aborted suicide attempt, healthy controls as the only comparator, specifically investigated participants with a central nervous system disorder (e.g., Parkinson’s or Alzheimer’s), chronic inflammatory disease, psychosis, cancer, history of severe brain trauma, drug or alcohol substance use disorder in the last year, or were secondary literature (e.g., reviews, case-control studies, conference proceedings, or commentaries). Exclusions aimed to limit confounding through comorbidities that affect brain structure and function. Studies that measured psychological pain over one year apart from neuroimaging were excluded, as psychological pain may be a relatively stable contributor to suicide risk for up to a year [13].

After the initial search, imported studies were de-duplicated for title and abstract screening (Figure 1). Both reviewers (JE and MO) independently screened all studies, and conflicts at each review stage were resolved by reaching a consensus. Forward and reverse reference tracking for included studies was conducted using the OMNI database.

Study quality was assessed using the Newcastle-Ottawa Quality Assessment Scale adapted for cross-sectional studies. Functional brain alterations and their correlations with psychological pain were extracted as the primary outcome. A consensus on extracted data was also reached. Various population and study characteristics were summarized in Supplementary Tables 1 and 2.

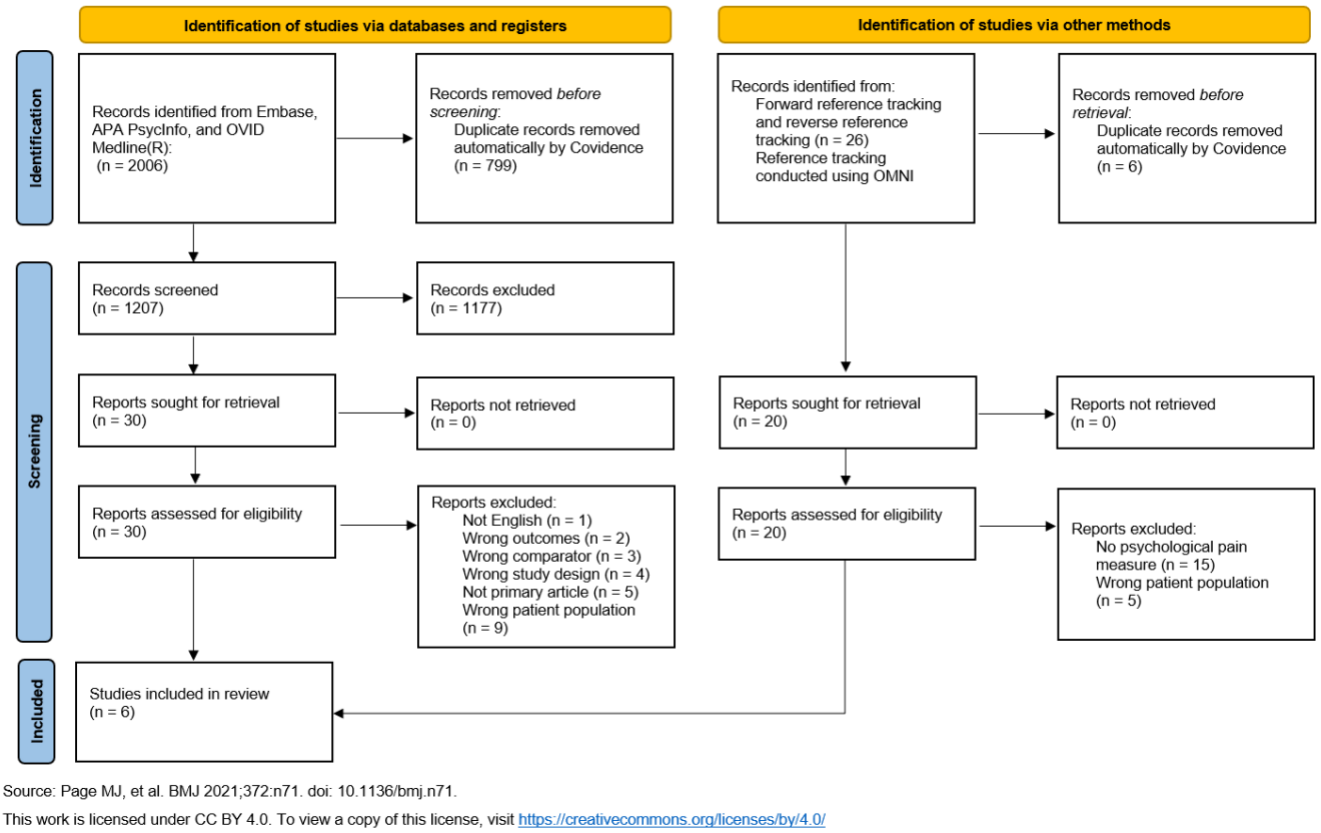

Figure 1. Search Strategy and Screening Process for Systematic Review. This PRISMA (2020) diagram was adapted from a template by Page et al. [21].

Results

Eligibility Screening

Results are summarized in the PRISMA diagram (Figure 1). The initial search yielded 2006 studies. After 799 duplicates were automatically removed by Covidence, title and abstract screening for the remaining 1207 studies was conducted, excluding a further 1177 studies. Of 30 studies screened for full-text, six met eligibility criteria. Forward and reverse citation tracking of the included studies yielded 26 additional studies for full-text screening. Six studies were removed as duplicates and the remaining 20 studies did not meet eligibility criteria, leaving six studies included in the review.

Study Characteristics

Four included studies investigated patients with Major Depressive Disorder [22-25], and two investigated patients with mood disorders [26, 27]. One study did not report ideation levels and thus used NSA as comparators rather than SI [26]. Patient groups had mean ages between 21.60 and 41.45 years. Males accounted for ≤40.6% of all patients and <25% in four out of six SA groups, including one study that exclusively investigated females [22-24, 26]. Three studies involved task-based fMRI: two used a Cyberball task that simulates social exclusion, and one used a Go/No-Go response inhibition task [25-27]. Two studies used resting-state fMRI and one used EEG during a multi-stage reward processing Monetary Incentive Delay (MID) task [22-24]. All studies were cross-sectional, and one included a 1-week longitudinal period using Ecological Momentary Assessment (EMA) to assess psychological pain on a Likert scale [26]. Three studies used the Three-Dimensional Psychological Pain Scale (TDPPS) [22-24], one used a visual analog scale [25], and one used the Psychache Scale and the Physical and Psychological Pain Scale [27]. Study characteristics and outcome data are summarized in Table 1 (All extracted data can be found in Supplementary Tables 1 and 2).

Table 1. Summarized Study Characteristics and Outcome Data

Author, Year	SA (Diagnostic criteria)	SI (Diagnostic criteria)	Imaging technique and task	Psychological pain measure	Functional neural outcome	Psychological pain outcome	Psychological pain and functional neural associations
Caceda et al., 2020 [27]	10 SA (within 3 days) (MDE + mood disorder, DSM-IV criteria)	9 SI (MDE + mood disorder, DSM-IV criteria)	Task-based fMRI (Cyberball)	Psychache scale, Physical and Psychological Pain Scale	↓ right superior anterior insula activity in SA during inclusion.	SA < SI on psychache scale No difference on Physical and Psychological Pain Scale.	Right and left superior anterior insula activity during inclusion correlated positively with usual psychological pain in the last 15 days.
Hao et al., 2023 [23]	25 SA (MDD, DSM-5 criteria, BDI-I score > 17)	45 SI (MDD, DSM-5 criteria, BDI-I score > 17)	Resting-state fMRI	TDPPS	N/A	SA > TDPPS scores than SI including all 3 subscales. Pain avoidance ranked first in all multimodal suicide attempt classification models with 63%–92% accuracy.	Top five features of suicide attempt and pain avoidance classification models using brain imaging data overlapped and included FC between left amygdala and right insula, right OFC and left thalamus, left ACC and left insula, left ACC and right OFC, left ACC and right amygdala, and between the left ACC and left thalamus. The accuracy of brain-only suicide attempt and pain avoidance models was 56%–85%, and 49%–69% respectively.
Hao et al., 2022 [22]	25 SA (MDD, DSM-5 criteria, BDI-I score > 17)	39 SI (MDD, DSM-5 criteria, BDI-I score > 17)	Resting-state fMRI	TDPPS	SA ↑ FC in the right ACC, superior frontal gyrus, left medial OFC, right superior OFC, and left thalamus; and ↓ FC in the MCC, left precuneus, right insula compared with SI. SA had longer dwell time in state I (intra-network connectivity) and shorter state II (inter-network) dwell time than SI.	SA > TDPPS scores than SI including all 3 subscales.	ACC, superior frontal gyrus, and medial OFC connectivity positively correlated with total TDPPS scores and number of suicide attempts. Connectivity in the MCC, insula, and thalamus negatively correlated with total TDPPS scores and number of suicide attempts.

Author, Year	SA (Diagnostic criteria)	SI (Diagnostic criteria)	Imaging technique and task	Psychological pain measure	Functional neural outcome	Psychological pain outcome	Psychological pain and functional neural associations
Olie et al., 2021 [26]	13 euthymic SA (MDE + mood disorder, DSM-IV criteria).	20 euthymic NSA (MDE+ mood disorder, DSM-IV criteria)	Task-based fMRI (Cyberball)	EMA Likert scale	N/A	No significant difference.	SA: daily psychological pain negatively correlated with OFC activation during explicit social exclusion v. inclusion; negative trending correlations in dPFC and ACC reported.
Richard-Devantoy et al., 2016 [25]	25 SA (DSM-IV criteria, HAM-D scale >20)	22 SI (DSM-IV criteria, HAM-D scale >20)	Task-based fMRI (Go/No-Go)	Visual analog scale	SA (Within group): Go v. No-Go contrast ↑ activation difference in precuneus/posterior cingulate gyrus right post-central gyrus/superior temporal gyrus region, temporal cortex, medial supplementary motor area and left putamen.	No significant difference.	Levels of psychological pain correlated with activation in the left inferior frontal gyrus, medial thalamus in the go v. no-go contrast. No-Go v. rest contrast showed left OFC, and right and left angular gyri activation correlated with psychological pain.
Song et al., 2020 [24]	12 SA (MDD, DSM-IV-R criteria, BDI-I >17)	32 SI (MDD, DSM-IV-R criteria, BDI-I >17)	Task-based EEG (MID)	TDPPS	SA: ↑ cue-P3 elicited by reward cues compared to punitive and neutral cues. SA: ↑ feedback-P3 elicited by negative feedback in punitive conditions compared to neutral and reward conditions. SI: ↑ cue-P3elicited by reward cues compared to punitive cues. SI: ↑ feedback-P3 elicited by negative feedback in reward condition compared to neutral condition.	SA > TDPPS scores than SI.	Average amplitude of: Cue-P3 elicited by reward cues negatively correlated with TDPPS and on all subscales. Cue-P3 elicited by punitive cues negatively correlated with pain avoidance subscale of TDDPS. Feedback-P3 elicited by positive feedback in reward and punitive conditions significantly negatively correlated with TDDPS and painful feeling subscale. Feedback-P3 elicited by negative feedback in reward condition showed significant negative correlation with painful feeling subscale and positive correlation with SA.

Abbreviations: ↑: increased/larger; ↓: decreased; >: greater; <: lower; MDD: major depressive disorder; MDE: major depressive episode; dPFC: dorsal prefrontal cortex; MCC: middle cingulate cortex

Psychological Pain Outcomes

Three studies reported higher psychological pain levels in SA than SI [22-24], while two reported no difference between groups [25, 26]. One study reported no difference between groups and higher psychological pain in SI than SA based on different scales [27]. Pain avoidance was the number one feature of all five multimodal (brain and behavioural data) machine learning suicide attempt classification models [23].

Functional Connectivity

Insula: During the social inclusion condition of an fMRI Cyberball task, recent SA exhibited decreased activity in the right superior anterior insula compared with SI [27]. Activity in the left and right superior anterior insula also had a significant positive correlation with average psychological pain in the last 15 days. Similarly, SA had weaker resting-state functional connectivity (FC) in the right insula compared with SI [22]. Resting-state FC in the insula was negatively correlated with psychological pain and number of suicide attempts [22]. Additionally, resting-state FC between the right insula and left amygdala was an overlapping important feature of machine learning classification models identifying both psychological pain avoidance (a TDPPS subscale) and suicide attempt [23].

Cingulate cortex: Hao et al. reported greater resting-state FC in the right ACC and weaker FC in the middle cingulate cortex in SA relative to SI [22]. The study also found ACC connectivity positively correlated with psychological pain and number of suicide attempts, while middle cingulate cortex connectivity negatively correlated with both metrics. In contrast, a negative correlation between ACC activation and daily psychological pain using EMA trended towards significance in SA but not in NSA during explicit Cyberball social exclusion v. inclusion [26]. The left ACC was highly implicated in the overlapping important features of pain avoidance and suicide attempt classification models [23]. Such features included the FC between the left ACC and left insula, right orbitofrontal cortex (OFC), right amygdala, and left thalamus.

Frontal cortex: SA had greater resting-state FC in the left medial and right superior OFC than SI and connectivity in the medial OFC had a significant positive correlation with psychological pain and number of suicide attempts [22]. Following the Cyberball task, OFC activation during explicit social exclusion v. inclusion had a significant negative correlation with daily psychological pain only in SA, with the same correlation trending towards significance in the dorsal prefrontal cortex [26]. In a Go v. No-Go fMRI task, left OFC activation during No-Go v. rest had a significant positive correlation with psychological pain [25]. In pain avoidance and suicide attempt classification models, FC between the right OFC and left thalamus, and the aforementioned FC between the right OFC and left ACC were overlapping important features [23]. Additionally, SA had greater resting-state FC in the superior frontal gyrus than SI and the FC had significant positive correlations with psychological pain and number of suicide attempts [22].

Thalamus: Compared with SI, SA had greater FC in the left thalamus during resting-state fMRI [22]. However, overall thalamus FC had a significant negative correlation with psychological pain and number of suicide attempts. In the Go v. No-Go task contrast, activation in the medial thalamus had a significant positive correlation with psychological pain [25]. As previously mentioned, the FC between the right OFC and left ACC with the left thalamus were important features in both pain avoidance and suicide attempt classification models [23].

Dynamic FC: Hao et al. assessed dynamic FC by specifying two FC states: State I and State II, characterized by independent FC within one network reflecting poor cognitive flexibility and inter-network connectivity, and integrated connectivity, respectively [22]. During resting-state fMRI, SA had more time spent in State I and less time spent in State II.

Central-parietal: Song et al. used EEG to measure P3 event-related potentials from the central-parietal area during the MID task [24]. During negative feedback, the SA group had significantly larger feedback-P3 evoked by punitive conditions than those elicited during reward, whereas no such difference in the SI group was present. Mean cue-P3 amplitude elicited by reward cues was negatively correlated with scores on the TDPPS, and mean cue-P3 amplitude elicited by punitive cues negatively correlated with pain avoidance. Mean feedback-P3 amplitude elicited by positive feedback in reward and punitive conditions showed negative correlations with TDPPS scores. When elicited by negative feedback in the reward condition, mean feedback-P3 amplitude negatively correlated with the painful-feeling subscale of the TDDPS and positively correlated with suicide attempt.

Quality Assessment

All studies were of good quality, with an average score of 7.17 out of 9. No studies provided justification of sample sizes. Further details can be found in Table 2.

Table 2. Quality Assessment Results Using an Adapted Newcastle-Ottawa Quality Assessment Scale [28]

Author, Year	Representative sample	Sample size	Non-respondents	Ascertainment of the exposure (risk factor)	Comparability	Assessment of the outcome	Statistical test	Total /9
Caceda et al., 2020 [27]	*		N/A	**	**	**	*	8
Hao et al., 2023 [23]	*		N/A	**		**	*	6
Hao et al., 2022 [22]	*		N/A	**	*	**	*	7
Olie et al., 2021 [26]	*		N/A	*	**	**	*	7
Richard-Devantoy et al., 2016 [25]	*		N/A	**	**	**	*	8
Song et al., 2020 [24]	*		N/A	**	*	**	*	7

Discussion

Despite significant heterogeneity in imaging paradigms, several brain regions repeatedly exhibited dysregulated functioning in SA compared with SI among patients with mood disorders. Regions most consistently implicated were the insula, ACC, OFC, and thalamus, each exhibiting concurrent functional dysregulation and correlations with psychological pain. These regions are key components of the psychological pain network and of the affective component of both physical and social pain [17-19].

Psychological pain outcomes varied across the studies with only half reporting greater psychological pain in SA [22-24]. Possible explanations for mixed findings include various psychological pain measures capturing its distinct aspects, as theoretical and semantic differences exist between them [29]. Pain avoidance as the top-ranking feature of multimodal suicide attempt models comports with other literature finding pain avoidance to be the strongest predictor of suicide attempt, potentially indicating a motivation to avoid psychological pain through suicide [12,23].

Decreased insular activity in SA during resting state and social inclusion is consistent with previous findings and may be associated with increased physical pain tolerance and impaired social cognition [22, 26, 30, 31]. Insular activity also consistently correlated with psychological pain, although directionality varied. A negative correlation during resting-state may reflect deficits in cognitive pain processing, while a positive correlation during Cyberball inclusion may imply a predisposition to negative affect during positive interactions in individuals with high psychological pain [22, 27]. Consistent with findings by Hao et al. [22], a study in lifetime attempters reported a positive correlation between ventral anterior insula FC with the superior and middle frontal gyri and psychological pain in SI and a negative correlation in SA [31]. The anterior insula is specifically involved in the affective and cognitive processing of pain and for regulating emotions and decision-making through its connection with the prefrontal cortex [32-34]. The authors suggest this represents a shift from state to trait impairment of top-down regulation of emotion and decision-making which may facilitate the transition from ideation to attempt [31].

The ACC has a significant role in affective pain processing, while the OFC appears to modulate pain based on higher-order processing of context [35-37]. Resting-state FC in the ACC and OFC were each found to be increased in SA with positive correlations with psychological pain, while activity in these regions during Cyberball social exclusion v. inclusion were found to be negatively correlated with psychological pain [22, 26]. These results may suggest that at rest, hyperactivity in the ACC and OFC reflect higher psychological pain levels, whereas during the Cyberball task, lower activity in these regions indicates blunted sensitivity and processing of social pain. This is in line with findings of social pain insensitivity in SA with ideation by Risch et al. and may indicate that chronic hyperactivity in regions associated with psychological pain desensitizes them, impairing the response to social pain [38]. This may also contribute to the increased physical pain tolerance in SA that facilitates capability for suicide. Left ACC FC with the insula, OFC, thalamus, and amygdala were all overlapping features of pain avoidance and suicide attempt classification models [23]. This underscores the significant role of dysregulated ACC FC with regions involved in the affective and cognitive processing of psychological pain in classifying suicide risk.

Despite the increased resting-state FC in the left thalamus for SA but not SI, thalamus FC correlated negatively with psychological pain and number of suicide attempts [22]. This seemingly paradoxical finding may indicate differential dysregulated functioning of the thalamus in SA that is obscured in correlations of all

groups, and a need for literature clarifying this relationship. The medial thalamus projects to the ACC, thus the positive correlation of medial thalamus FC with psychological pain during the Go v. No-Go task suggests that hyperactivity of the thalamus may stimulate negative affect networks during cognitively demanding tasks [25, 39]. Furthermore, the importance of left thalamus FC with the right OFC and left ACC in pain avoidance and attempt classification models suggests dysregulated relaying of sensory information to the pain network [23].

Electrophysiological data gathered by Song et al. demonstrated negative feedback-dependent increases in feedback-P3 in punitive conditions relative to reward conditions only for SA [24]. The authors proposed that this result, in combination with the negative correlation observed between mean cue-P3 amplitude elicited by punitive cues and pain avoidance scores on the TDPPS, supports the notion that a characteristic feature of SA is a strong motivation to avoid punishment. Other EEG literature has also shown alterations in cue-P3 responses during the same MID task in SA compared to SI, potentially representing a deficit in reward-cue processing [40].

Together, these findings provide support for a functional neural basis of psychological pain differences in SA that may begin to clarify a biomarker of the ideation-to-attempt transition. In addition to reflecting painful emotional states, the altered function supports impaired processing and top-down regulation of emotion in SA, which may reflect difficulties coping with psychological pain and motivate SI to seek relief through suicide. Moreover, the reported increase in state I dwell time and decreased state II dwell time in SA is indicative of poor inter-network communication and thus impaired executive control [22]. This may contribute to the risky decision-making in SA found in a meta-analysis by Perrain et al. which could mediate the ideation-to-attempt transition as psychological pain becomes unbearable [41].

A significant limitation of this review is the heterogeneity of study methodologies which limits the interpretability of findings. The limited available literature, small sample sizes, and low proportion of males in the included studies also limit the generalizability of findings.

Conclusions

Among the six studies reviewed, the insula, ACC, OFC, and thalamus were most commonly dysregulated in SA relative to SI, each of which correlated with psychological pain and suicide attempts. These results provide context for the development of a biomarker of suicide risk. As self-report measures of psychological pain had inconsistent findings, dysregulations in psychological pain neurocircuitry may serve as a more concrete marker of suicide risk. Further research using social exclusion tasks, such as Cyberball, in transdiagnostic lifetime attempters could help clarify the dysregulation of the pain network in SA. Longitudinal research is needed to explore potential causal relationships between such dysregulation and suicide attempts, which could inform the development of novel preventative interventions.

List of Abbreviations

3ST: three-step theory
ACC: anterior cingulate cortex
dPFC: dorsal prefrontal cortex
EEG: electroencephalogram
EMA: ecological momentary assessment
END: emotional pain and social disconnect
FC: functional connectivity
fMRI: functional magnetic resonance imaging
MCC: middle cingulate cortex
MDD: major depressive disorder
MDE: major depressive episode
MID: monetary incentive delay
NSA: non-suicide attempters
OFC: orbitofrontal cortex
SA: suicide attempters
SI: suicide ideators
TDPPS: three-dimensional psychological pain scale

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Ethics Approval and/or Participant Consent

Not applicable; this review did not collect new data requiring ethical approval or consent.

Authors' Contributions

JHE: made substantial contributions to the study design, collected and interpreted data, drafted the manuscript, gave final approval of the version to be published, and is accountable for all aspects of the manuscript.
MEO: made substantial contributions to the study design, collected and interpreted data, drafted the manuscript, gave final approval of the version to be published, and is accountable for all aspects of the manuscript.

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