A Potential Neural Pathway for Explaining Suicidal Behaviour: Does it Exist?

Ryan Chiu[1]
[1] University of British Columbia, Vancouver, British Columbia, Canada

Abstract Suicide is a major health problem, with a lack of decline in suicide rates over the past few decades suggesting that existing treatment methods are insufficient for dealing with suicidal behaviour. A review of the existing neuroimaging literature on suicidal behaviour suggests that a core, "skeleton" neural pathway exists in most suicidal individuals, who tend to have structural and functional alterations in the anterior cingulate cortex, orbitofrontal cortex, and insular cortex. This altered neural pathway explains the two main cognitive-behavioural characteristics observed in suicidal individuals: impaired decision-making, and emotional dysregulation. Abnormalities in other brain regions may exist in certain suicidal individuals; most notably, the presence of a comorbid mental disorder may be correlated with impairments of specific brain structures depending on the disorder present. Future neuroscientific and psychological research should aim to increase the replicability of neuroimaging studies, determine the extent that a comorbid mental disorder impacts an observed location of neural abnormality, and unify terminology definitions used in the study of suicide to increase validity and compatibility across suicidology research.

INTRODUCTION

Suicide is a major health problem as the 10th leading cause of death in the United States. In 2019 alone, 47,500 deaths occurred by suicide, and 12 million American adults had contemplated suicide (Centers for Disease Control and Prevention [CDC], 2021). Despite the rapidly expanding literature on risk factors contributing to suicidal behaviour and/or thoughts, suicide rates have not declined significantly over the last few decades (Franklin et al., 2017). Additionally, there have been several challenges in the field of suicidology that hinder progress in treating the issue at hand, including a lack of consensus on suicide-related terminology, suicidality measures that are interpreted differently between studies due to the lack of consensus , contrasting perspectives as to whether suicide should be viewed as a state or trait, stigma impacting data collection and analyses, and the low base-rate of suicidal behaviour implying that an extreme sample size in the thousands is required for reliable results (Klonsky et al., 2016).

Given such challenges, a neuroscientific approach to suicide research as opposed to social or personality approaches may be a promising avenue for further research. In particular, neuroimaging techniques seem to circumvent some of the challenges in suicidology. While the subjectivity of defining suicidal behaviour and thoughts may affect the validity and comparability of data, well-established neuroimaging techniques measure objective variables (e.g., brain activity), producing results that are unaffected by social phenomena such as stigmas. Furthermore, neuroimaging studies are not subject to the limitations of self-report measures. Literature reviews of existing neuroimaging studies may provide critical information into the biological factors of suicide and the resulting effects on psychological and social behaviours. This literature review aims to summarise findings regarding potential neural pathways involved in suicide.

LITERATURE REVIEW

Neural networks in psychological pain

Within the ideation-to-action framework, many theories include negative emotional affect – that is, negative moods or emotions such as anxiety -- in some form or another as a key risk factor for suicidal ideation. Joiner's interpersonal theory posits perceived burdensomeness (the irrational belief that one's death is of greater value than their life) as a main risk factor (Joiner, 2019). O'Connor's integrated motivational-volitional theory includes a sense of defeat and entrapment within the individual as a critical factor (O'Connor, 2011). Most

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Correspondence
Address correspondence to **Yi Nok Ryan Chiu** at ryanynchiu@gmail.com

notably, Klonsky's three-step theory explicitly highlights psychological pain as a critical variable in determining intensity of suicidal ideation (Klonsky & May, 2015). While the neural networks of physical pain have been well studied in the general neuroscience literature (Apkarian et al., 2005; Schnitzler & Ploner, 2000), the networks for psychological pain have only been of minor interest (Biro, 2010).

While the definition of psychological pain is not as clear-cut as physical pain, a review of the literature by Meerwijk and Weiss (2011, p. 410) suggests that it be defined as "a lasting, unsustainable, and unpleasant feeling resulting from negative appraisal of an inability or deficiency of the self" that requires considerable time to resolve. When psychological needs such as the need to love or be loved are not met to a sufficient level, intense psychological pain may result (Shneidman, 1998), which has been identified as preceding suicidal ideation and/or behaviour (Troister & Holden, 2010). Psychological pain is clearly relevant in the previously mentioned theories of suicide that highlight negative affect as a key factor. As such, the mechanisms of how such pain manifests within individuals needs to be understood.

Meerwijk et al. (2013) proposed a tentative neural network for psychological pain based on a systematic review of 18 studies that utilised neuroimaging techniques and assessed psychological pain, grief and/or recalled sadness. Across all studies, the medial subcortical area showed significantly greater activation when participants were experiencing any one of the above three affective states, implicating the anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), thalamus and cerebellum. The lateral prefrontal cortex (PFC) and parahippocampal gyrus were also implicated; however, their involvement in psychological pain is not as consistent as that of the medial subcortical area. All the brain areas listed comprise the tentative neural network set forth by the authors. For a visual representation of the system, refer to Figure 2 of Meerwijk et al. (2013). In addition to the tentative network proposed, the authors also found a positive correlation between psychological pain and suicidal ideation, further supporting the role of the former in suicidal thoughts and behaviour.

Neuroanatomical differences in clinical populations

Neuroimaging research investigating suicide aims to provide objective markers for predicting suicidal tendencies. Studies relying on subjective information, such as self-report data from suicidal patients, may present several ethical and practical challenges which could interfere with data collection and analyses. For example, researchers must refer participants with a non-zero risk of suicide to appropriate clinical services (Hom et al., 2017), which may influence the outcome of certain research studies. Furthermore, it has been suggested that the clinical manifestations of suicidal behaviour may vary based on other comorbid psychiatric disorders that are present (Nakagawa et al., 2011). Neuroimaging techniques may be able to identify such differences from a neurobiological perspective with greater power than that of subjective methods.

Zhang et al. (2014) conducted a review of neuroimaging studies examining suicidal behaviour in patients with depression. The review found that, in the studies examined (N = 12), structural and/or functional alterations were exhibited in the orbitofrontal cortex (OFC), ACC, and striatum for depressive patients exhibiting suicidal behaviour. The OFC, thought to be responsible for emotion-based cognitive processes and hedonic valuation of stimuli (Salzman & Fusi, 2010), is crucial for adapting to unexpected outcomes including reversal learning tasks (Bendetti et al., 2011). Suicidal depressive patients exhibited abnormalities in the OFC, which may have resulted in an impairment in affective regulation and contributed to impaired decision-making, increased impulsivity, and susceptibility to subsequent suicidal behaviour. Abnormal activity in the ACC has been reported in depressive suicidal patients, most notably involving reduced dendritic growth in patients who had committed suicide (Hercher et al., 2010). However, as the ACC is involved in a wide variety of functions, a more mechanistic explanation for how ACC is implicated in suicidal behaviour requires further research (Zhang et al., 2014). Finally, a decrease in striatal grey matter volume was associated with suicidal behaviour in depressive patients (Marchand et al., 2012), likely contributing to increased impulsivity (Dombrovski et al., 2012). More specifically, it is hypothesised that abnormalities in the putamen may result in a cognitive shift towards a more short-term, immediately rewarding style of decision-making, thus encouraging impulsive suicidal acts in a state of depression (Luo et al., 2009). In summary, the findings indicate that a frontal-ACC-striatum loop is implicated in depressive suicidal patients and is hypothesized to impair decision-making by increasing patients' impulsivity and impacting affective regulation processes (for a visual representation of the proposed circuit, refer to Figure 2 of Zhang et al., 2014).

Building upon the work of Zhang et al. (2014), Domínguez-Baleón et al. (2018) conducted a systematic review of neuroimaging studies investigating suicidal behaviour in patients diagnosed with a psychiatric disorder. Studies that met the inclusion criteria (N = 33) were sorted into one of five categories: major depressive disorder (MDD; n = 17), bipolar disorder (BIP; n = 6), schizophrenia (SCZ; n = 5), schizoaffective disorders and borderline personality disorder (BPD; n = 3), and other (n = 2). The review corroborated the findings of Zhang et al. (2014) with respect to reductions in grey matter density and cortical thickness in MDD patients' ACC (Wagner et al., 2011, 2012), and decreased cortical volume in the putamen (Dombrovski et al., 2012). However, the review was unable to find additional studies replicating the findings of Monkul et al. (2007) on reduced grey matter volume in the OFC. Additionally, the review identified reduced cortical thickness and reduced grey matter volume in the frontal lobe, temporal lobe, and insular cortex of MDD patients—all hypothesised to contribute to suicidal behaviour through emotional dysregulation (Gosnell et al., 2016; Hwang et al., 2010; Taylor et al., 2015).

Current neuroimaging literature largely focuses on suicidal patients with MDD. Comparatively, studies investigating the relationship between other clinical disorders and suicide are less replicable due to a lack of available studies for review. The review by Domínguez-Baleón et al. (2018) found six studies examining neuroanatomical differences between those with and without suicidal tendencies in the BIP clinical population. BIP suicide attempters had significantly different OFC grey matter volume than BIP non-attempters, but the directionality of the difference has been conflicting, with one study reporting decreased volume (Johnston et al., 2017) and another reporting increased volume

(Duarte et al., 2017). BIP attempters were also reported to have reduced grey matter volume in the hippocampus (Johnston et al., 2017). Other implicated regions have had contradictory evidence, including studies indicating either no differences or a reduction in cerebellar grey matter volume (Baldaçara et al., 2011; Johnston et al., 2017), and bidirectional differences in PFC grey matter volume depending on whether BIP suicide attempters had previously been hospitalised (Lijffijt et al., 2014).

All but one of five studies in the Domínguez-Baleón et al. (2018) review found significant differences in various subcortical regions of the frontal lobe of SCZ patients, including reduced cortical thickness in the right dorsolateral prefrontal cortex (Besteher et al., 2016) and reduced grey matter density in the left OFC compared to non-suicidal patients (Aguilar et al., 2008). Other cortical regions associated with suicidal SCZ attempters included cortical thinning in the temporal lobe (Giakoumatos et al., 2013), ACC, and insular cortex (Bester et al., 2016), among others. Impairment in the insular cortex is thought to contribute to suicidal ideation in SCZ patients by causing an inability to differentiate between internal and external stimuli. It is also a proposed explanation for the hallucinations some SCZ patients experience. The effect of reduced temporal lobe volumes on suicide is corroborated by the observation of an increased prevalence of suicide after epileptic patients have been treated via temporal lobectomy (Bell et al., 2009). With respect to subcortical regions, SCZ attempters were found to have increased right amygdalar volume compared to healthy controls and non-attempters (Spoletini et al., 2011) and reduced thalamic grey matter volume in comparison to non-attempters (Giakoumatos et al., 2013). However, the differences in both subcortical regions have not been consistently replicated across the five studies. Clearly, more studies need to be conducted in this specific clinical population.

Of the three BPD studies included in the Domínguez-Baleón et al. (2018) review, two originated from the same group of authors. Reduced grey matter volume in the left fusiform gyrus, left lingual gyrus, and right middle superior temporal gyrus were found in high-lethality BPD suicide attempters in comparison to low-lethality patients. All of these brain region deficiencies are hypothesised to impair social interactions due to their roles in facial recognition and processing, cognitive appraisal of others' intentions, and reflexive responses to socially-related visual inputs (Soloff et al., 2012, 2014). One of the Soloff et al. (2012) studies found that high-lethality BPD attempters had reduced grey matter volumes in the ACC. More specifically, Brodmann Area 24 was found to be significantly smaller in affected patients (Goodmen et al., 2011). Reduced grey matter volume was also found in the right insula and OFC. It is hypothesised that impairments to the insular cortex may result in patients misjudging the intentions of others and activating responses to perceived rejection, and that similar changes to the OFC may result in disinhibited, impulsive behaviour (Soloff et al., 2012, 2014). Lastly, reduced grey matter volume was found in the left hippocampus of high-lethality BPD attempters in comparison to low-lethality patients. As this area is involved in (episodic) memory encoding and retrieval of information relevant to social settings, as well as identifying sarcasm and processing complex facial features, impairments to the (left) hippocampus is hypothesised to further worsen social functioning and contribute towards suicidal behaviour (Soloff et al., 2012, 2014).

Domínguez-Baleón et al. (2018) found two other neuroimaging studies investigating suicidal patients with a clinical disorder that was not MDD, BIP, SCZ or BPD. One study looked at suicidal panic disorder patients and found no significant differences in grey or white matter volumes in comparison to non-suicidal patients (Kim et al., 2015). Another study examined posttraumatic stress disorder patients that had suicidal thoughts in the past in comparison to healthy controls, finding that the clinical group had significantly increased pituitary volumes, suggesting that these individuals are experiencing hypothalamic-pituitary-adrenal axis dysregulation (Thomas et al., 2004).

Cognitive tasks evaluating decision-making

The idea that neuroanatomical abnormalities contribute to suicidal behaviour has been supported by studies utilising cognitive tasks that evaluate decision-making and/or impulsivity. The Iowa Gambling Task (IGT) simulates decision-making that applies to naturalistic, outside-the-lab contexts. The IGT presents participants with four decks of cards, with two decks generating positive expected values of return (i.e., a "profit") and the other two generating negative expected values of return (i.e., a "loss"). In general, healthy (control) groups are observed to prefer the profitable decks, suggesting that certain cognitive-behavioural processes occur to minimise losses and maximise profits (Bechara et al., 1994). Building upon the pioneering work of Bechara and colleagues, several studies have used the IGT to assess differences in cognition in suicidal populations. Mood disorder patients who have previously attempted suicide performed significantly worse (i.e., chose "loss" decks more often) on the task compared to patients with no suicide history (Jollant et al., 2005). BIP attempters also performed significantly worse compared to other clinical groups (Jollant et al., 2007). The Cambridge Gambling Task (CGT), a similar task to the IGT, has also been used to demonstrate impaired decision-making in suicide attempters in general (Chamberlain et al., 2013; Clark et al., 2011). In both gambling tasks, the concept of loss aversion is key to understanding differences in task performance, since participants' sensitivity to the size and frequency of loss incurred from each deck determines whether they avoid choosing cards from the deck or not (Weller et al., 2010). Loss aversion refers to the humans' desire to avoid losses over making gains of the same magnitude; given an equal chance to win or lose a certain amount of money, participants will refuse to take the gamble (Gächter et al., 2007).

Using this concept, Hadlaczky et al. (2018) utilised a mixed monetary gambling task to measure adolescent participants' tolerance to loss. In this task, various gambles were presented with a 50% chance of winning a fixed amount of money and a 50% chance of losing money, with the loss varying for each gamble. Participants were asked to either accept or reject each gamble (for more specific details, refer to the materials and methods section of Hadlaczky et al., 2018). Loss aversion was found to be significantly lower in suicide attempters compared to non-attempters, and the same relationship was found between attempters and non-attempters at a four-month follow-up after excluding attempters at the beginning of the study. In sum, cognitive studies utilising the IGT, CGT and mixed monetary gambling task have demonstrated that suicidal individuals tend to exhibit signs of impaired decision-making. An impaired sense of loss aversion is hypothesised to arise from increased emotional reactivity and

impulsivity due to neuroanatomical abnormalties, which may contribute to suicidal behaviour (Hadlaczky et al. 2018).

Cognitive tasks evaluating emotional regulation

Other cognitive task experiments have supported the hypothesis that maladaptive emotional regulation is correlated with suicidal behaviour. The concept of emotional dysregulation has been operationalised differently in the literature and includes definitions such as (high) emotional reactivity, difficulty returning to emotional baseline, and a greater tendency to use maladaptive emotional regulation strategies — and a lower tendency to use adaptive ones — compared to healthy individuals (Linehan, 1993). The Computerised Paced Auditory Serial Addition Task (PASAT-C; Lejuez et al., 2003) is a stress-based task that emotionally arouses participants and aims to identify problems with goal-directed behaviour under stress. Using PASAT-C, Neacsiu et al. (2018) found that depressed suicide attempters had significantly greater difficulty returning to baseline heart rate after a stressor compared to both healthy and depressed non-attempter controls. This finding indicates that depressed attempters experience greater emotion dysregulation. Additionally, the depressed attempter group self-reported significantly greater difficulty with emotional regulation, more problematic coping, and more experiences of negative affect. In the same study, researchers found that emotion dysregulation, as measured by the Difficulties in Emotion Regulation Scale (DERS; Gratz & Roemer, 2004), predicted suicidal ideation in both healthy and clinical populations. However, given the various definitions for emotional regulation and dysregulation, more work is needed to unify and clarify operationalisations for the mentioned terms. Other studies appear to support the findings of Neacsiu and colleagues (2018). Healthy and clinical participants who scored higher on the Suicide Cognitions Scale (SCS; Rudd et al., 2010), indicating more severe suicidal thought patterns, experienced greater negative affect during a variant of the Trier Social Stressor Task (TSST; Smith & Jordan, 2015), which is designed to induce psychological distress in participants (Grove et al., 2020).

Although not the focus of this review, research adjacent to the topics of decision-making and emotional regulation are also notable. Researchers found that suicidal attempters, compared to suicidal ideators and healthy controls, have demonstrated significant impairments in a subset of executive functions (working memory, response inhibition, response selection, and task-switching), known as cognitive control (Ranjbar et al., 2021; Brokke et al., 2020). Task-based measures used to evaluate cognitive control performance include the Stroop Task (Strauss et al., 2006) and its variants, such as the Delis-Kaplan Executive Function System Color-Word Interference Test (D-KEFS CWIT; Delis et al., 2001).

CONCLUSIONS

Neuroimaging studies examining neural correlates with respect to suicidal behaviour have implicated certain brain structures. Some neural abnormalities appear to be common across most suicidal individuals, while other abnormalities appear to occur only within certain clinical groups such as MDD, BIP, SCZ and/or BPD. There is strong evidence to suggest that reduced grey matter volume, dendritic growth, and cortical thickness in the ACC and PFC (specifically the OFC) are key factors in suicidal behaviour. It seems that abnormalities in the ACC and PFC are relatively universal across most suicidal individuals and is thought to result in increased impulsivity and impaired decision-making as well as a greater degree of emotional dysregulation (i.e., greater use of maladaptive emotional regulation strategies). These symptoms are suspected to contribute to a greater degree of "indulgence" in suicidal thoughts and/or behaviours. The insular cortex is also implicated across most clinical disorders considered in this review and is also thought to contribute to suicidal behaviour by altering clinical patients' cognition, including perceiving others' actions and intentions more negatively. Therefore, it is proposed that a foundational "skeleton" pathway may exist wherein the cingulate cortex, prefrontal cortex, and insular cortex are the three key neural structures involved in suicidal thoughts and behaviour. Most suicidal individuals are expected to have abnormalities in these three regions, and more abnormalities may exist in other areas depending on the individual and the presence of clinical disorders. Future neuroimaging research should focus on specific clinical populations in suicide (e.g., SCZ-suicide comorbid patients) so that differential methods of treatment for each population may be identified and recommended for maximal efficacy.

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Conflicts of Interest

The author declares no conflicts of interest.

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