Multimodal Neuroimaging Approaches to Understanding Suicide-Related Thoughts, Behaviours and Clinical Risk Factors in Treatment Resistant Depression

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Truths are rarely in extremes, but lie somewhere in the middle

ABSTRACT

Despite extensive research contributions, suicide risk assessment still relies heavily on subjective and clinician judgement. In recent years, the search for suicide biomarkers has gained significant momentum, and an expansive body of literature has provided diverse and convincing evidence of biological involvement in suicide. This thesis is presented as a collection of articles with three primary aims. First, to use structural and resting-state functional magnetic resonance imaging (MRI) techniques to study gray matter volume, cortical thickness, and functional connectivity correlates of suicidal ideation (SI) severity in treatment-resistant depression (TRD). Second, to use resting-state functional MRI to examine functional connectivity differences among healthy controls and participants with TRD and a lifetime history of SI only (SI group), and those with a lifetime history of both SI and suicide attempt (SA group). Additionally, associations between functional connectivity alterations and clinical features that may differentiate SI and SA groups were examined, including hopelessness, anxiety, depression, aggression, impulsivity, and childhood trauma. Third, to use proton magnetic resonance spectroscopy (^{1}H-MRS) to compare levels of glutamate (Glu), Glx (combined glutamine/glutamate), myo-inositol (mI), N-aceylaspartate (NAA), and creatine (Cr) in the dorsal anterior cingulate cortex (ACC) in participants with TRD and a lifetime history of SI to a healthy control group. Associations between neurometabolite concentrations and suicide-related symptoms and traits, including depression, suicidal ideation severity, impulsivity, and aggression were also investigated. Participants underwent a single MRI session, and structural, resting-state functional, and ^{1}H-MRS data were collected. Overall, findings included: 1) increased SI severity correlated with reduced right lateral occipital cortical thickness, and widespread functional connectivity correlates centered on the right posterior parietal cortex (Manuscript 1), 2) functional connectivity differences in fronto-temporo-

limbic regions differentiating participants with SA history from those with SI only, with connectivity markers meaningfully related to clinical features in the SA group (Manuscript 2), and 3) glutamatergic alterations in the dorsal ACC in participants with TRD and SI associated with higher trait impulsivity (Manuscript 3). Collectively, this thesis provides evidence of neural abnormalities associated with suicide risk in TRD, thereby advancing the search for clinically meaningful suicide biomarkers which may inform identification of treatment targets.

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DEDICATION

This thesis work is dedicated to my parents, Floride Zaninka and Baudouin Burhunduli.

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ii. **Burhunduli, P**., Fang, Z., Vandeloo, K.L., Sharmin, F., Blier, P., Phillips, J.L. (2025). Differentiating suicide risk in treatment-resistant depression: clinical and functional imaging correlates of suicidal ideation and attempt. Submitted to NeuroImage: Clinical on August 3, 2025.

iii. **Burhunduli, P**., Taylor, R., Tremblay, S., Cuda, J., Vandeloo, K.L., Blier, P., Phillips, J.L. (2025). Brain metabolite signatures of suicide risk in treatment-resistant depression: a proton magnetic resonance spectroscopy study. Completed and prepared for submission to Progress in Neuro-Psychopharmacology and Biological Psychiatry.

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LIST OF ABBREVIATIONS

ACC	Anterior Cingulate Cortex
BIS-11	Barratt Impulsivity Scale
BOLD	Blood Oxygen Level Dependent
BPAQ	Buss Perry Aggression Questionnaire
C-SSRS	Columbia-Suicide Severity Rating Scale
CVSD	Canadian Vital Statistics Death Database
DMN	Default Mode Network
DSM-5	Diagnostic and Statistical Manual for Mental Disorders Fifth Edition
DWI	Diffusion Weighted Imaging
ENIGMA	Enhancing Neuro Imaging Genetics through Meta Analysis
FID	Free Induction Decay
fMRI	Functional Magnetic Resonance Imaging
GABA	Gamma-Aminobutyric Acid
Gln	Glutamine
Glu	Glutamate
Glx	Combined Glutamine/Glutamate
GUI	Graphic User Interface
^{1}H	Hydrogen Nuclei
HC	Healthy Control/Comparison
^{1}H-MRS	Proton Magnetic Resonance Spectroscopy
LCModel	Linear Combination of Model Spectra
LTP	Long-Term Potentiation

MADRS	Montgomery-Åsberg Depression Rating Scale
MDD	Major Depressive Disorder
MDE	Major Depressive Episode
mI	Myo-Inositol
MRI	Magnetic Resonance Imaging
MTG	Middle Temporal Gyrus
NAA	N-Acetylaspartate
NBS	Network Based Statistics
OFC	Orbitofrontal Cortex
PFC	Prefrontal Cortex
PPC	Posterior Parietal Cortex
QDEC	Query, Design, Estimate, Contrast
RF	Radiofrequency
ROI	Region of Interest
SA	Suicide Attempt
SCID-5-RV	Research Version of the Structured Clinical Interview for DSM-5
SI	Suicidal Ideation
SNR	Signal-to-Noise Ratio
STG	Superior Temporal Gyrus
T	Tesla
TRD	Treatment-Resistant Depression
WHO	World Health Organization

PREFACE

This doctoral dissertation investigates the neuroimaging correlates of suicidal ideation (SI) and attempts in patients with treatment-resistant depression (TRD) using three magnetic resonance imaging (MRI) techniques: structural MRI, resting-state functional MRI, and proton nuclear magnetic resonance spectroscopy (^{1}H-MRS). In accordance with the guidelines set forth by the University of Ottawa Faculty of Medicine Graduate and Postdoctoral Studies, this dissertation is presented as a collection of manuscripts. In Chapter 1, the public health burden of suicide is introduced, underscoring the urgency for studying suicide-related thoughts and behaviours. Current challenges in suicide research are summarized, along with discussion of how this body of work addresses certain limitations. This chapter closes with an overview of the neurobiological underpinnings of SI and suicide attempts (SA), and with a review of existing neuroimaging literature. Chapter 2 provides an in-depth overview of the study design and neuroimaging methodological approaches utilized for this thesis. Chapter 3, 4 and 5 comprise the completed manuscripts exploring the structural, resting-state functional, and neurometabolic correlates of SI and SA in treatment-resistant depression. Chapter 3 presents a manuscript submitted to the International Journal of Neuropsychopharmacology entitled "*Structural and functional neuroimaging correlates of suicidal ideation in treatment-resistant major depressive disorder*". Work in Chapter 3 used structural MRI and resting-state functional MRI (fMRI) techniques to study gray matter volume, cortical thickness, and functional connectivity correlates of SI. Chapter 4 presents a manuscript submitted and under review in NeuroImage: Clinical entitled "*Differentiating suicide risk in treatment-resistant depression: clinical and functional imaging correlates of suicidal ideation and attempt*". This work integrates resting-state fMRI data with clinical risk factors including hopelessness, childhood trauma, impulsivity and aggression, a novel

perspective often overlooked in suicide neuroimaging research. Chapter 5 presents a completed manuscript draft to be submitted to Progress in Neuro-Psychopharmacology and Biological Psychiatry entitled "*Brain metabolite signatures of suicide risk in treatment-resistant depression: a proton magnetic resonance spectroscopy study*". This work used ^{1}H-MRS to investigate neurometabolic involvement in depression and suicide. Chapter 6 provides a comprehensive discussion integrating information presented in chapters 3, 4 and 5, describing the significance and future directions of this work. Annex A outlines the acknowledgments, funding sources, statement of interest and data availability for the overarching project. Beyond academic requirements set by the University, Annex B presents a summary of additional scholarly contributions completed throughout the doctoral program, including additional manuscripts, conferences, awards, scholarships, grants and knowledge translation activities.

Chapter 1: General Introduction

1.1 Global Burden of Suicide

Suicide has long been recognized as a critical public health concern. Over the past two decades (2000-2019), an estimated 15.7 million individuals died by suicide globally (Ilic and Ilic, 2022). With over 720,000 recorded annual global deaths, suicide surpasses mortality rates of malaria, HIV/AIDS, breast cancer, war and homicide (World Health Organization, 2021c, 2025c). In 2019 alone, more than one in every 100 (1.3%) deaths were the result of a suicide, equating to nearly 2,000 lives lost every day (World Health Organization, 2021c). The global burden of suicide is alarming yet not evenly distributed regionally. Most deaths by suicide occur in low- and middle-income countries (~73%), and the highest 2021 crude suicide rates were observed in Europe (12.4 per population of 100,000), followed by South-East Asia (10.1), the Americas (9.9; includes North, Central and South America, and the Caribbean), West Pacific (9.5; includes East Asia, Oceania, and numerous Pacific Island nations and territories), Africa (7.3; includes sub-Saharan Africa, Algeria and several island nations) and Eastern Mediterranean Regions (3.6; includes North Africa, the Middle East and Central Asia) (World Health Organization, 2025b) (Figure 1).

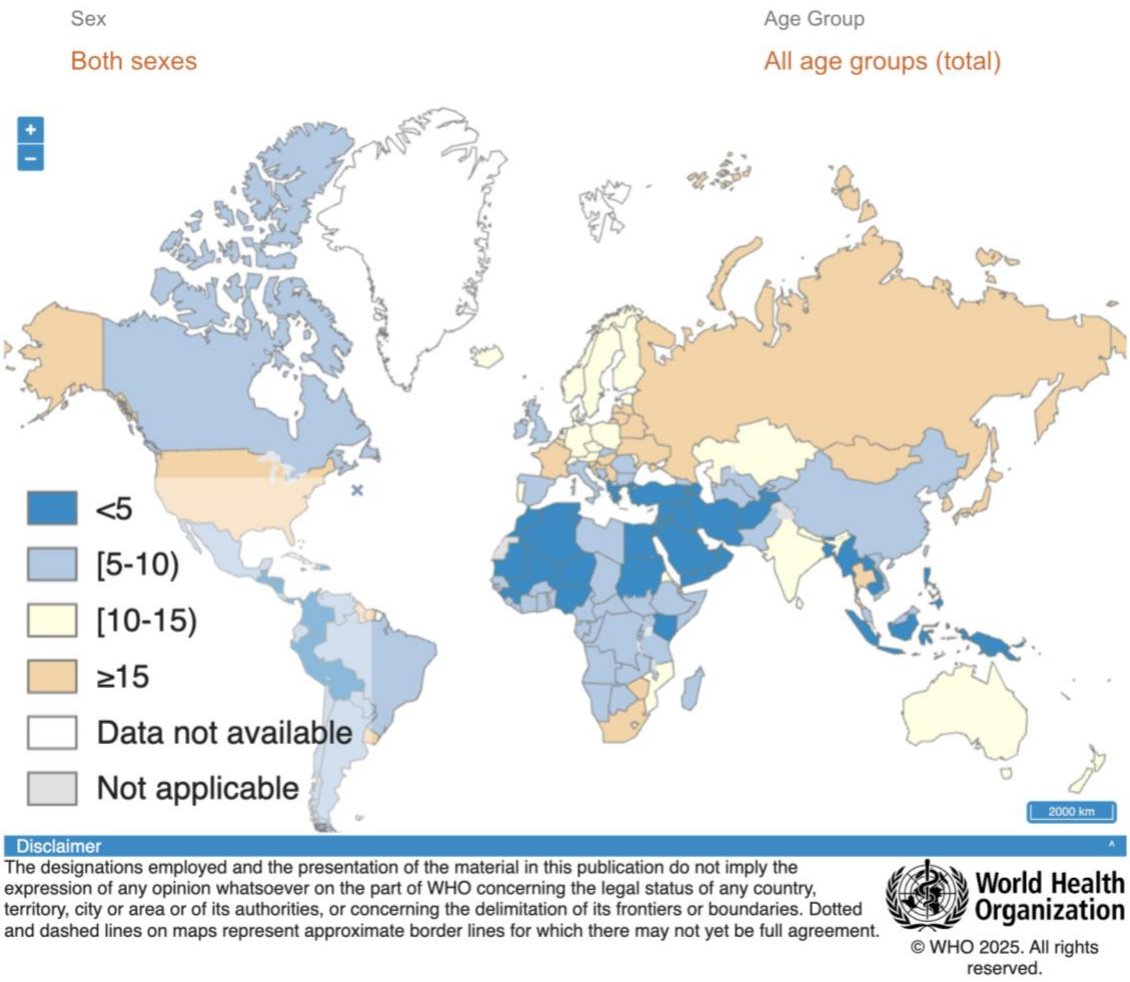

Figure 1. Global crude suicide rates (per 100,000 population) in 2021

While global burden remains heavy, recent trends point to a modest, yet meaningful global shift. The latest edition of the World Health Statistics reports a decrease in total global suicide deaths, from an estimated 762,000 in 2000 to 717,000 in 2021 (World Health Organization, 2024b), potentially attributed to global suicide prevention efforts. However, this global decline masks regional and country level variations, and has not been uniform across nations. The Americas is the only region in the world where overall suicide deaths increased over the past two decades, rising from 7.2 per 100,000 in 2000 to 9.8 per 100,000 in 2021 (World Health Organization, 2024b). Furthermore, seven countries in the Americas exceeded the global crude death rate value of 9.2 in 2021 (Guyana, 24.78; Uruguay, 24.75; Suriname, 22.26; United States of America, 15.63;

Cuba, 13.79; Trinidad and Tobago, 13.34; and Canada, 9.44). In Canada specifically, despite a rate exceeding the global average, there has been a notable decrease, from 12.5 per 100,000 in 2000 to 9.4 per 100,000 in 2021. Conversely, the United States of America has experienced a rise, with a crude suicide rate increasing from 11.2 per 100,000 in 2000 to 15.6 per 100,000 in 2021.

In Canada, suicide is a critical public health issue and stands as the second leading cause of death among youth and young adults (15-34 years old) (Public Health Agency of Canada, 2023a). Every year, approximately 4,500 individuals lose their lives to suicide, equating to nearly 12 lives lost per day, a rate more than 2.5 times greater than deaths caused by motor vehicle accidents (Public Health Agency of Canada, 2023a; Transport Canada, 2024). As previously mentioned, Canada's crude suicide rate stands at 9.4 per 100,000, surpassing the 2021 global average (World Health Organization, 2025b). To monitor these trends, the Canadian Vital Statistics Death Database (CVSD), a national administrative database, collects and reports data on all registered deaths from medical certificates and coroner reports and classifies them according to the World Health Organization (WHO)'s International Statistical Classification of Diseases and Related Health Problems (Statistics Canada, 2025a; World Health Organization, 2025a), facilitating standardized reporting. Leveraging data derived from the CVSD, a 2021 population-based study reported a total of 138,548 deaths by suicide over a 37-year period (1981 to 2017) in individuals aged 10 and older (Varin *et al.*, 2021). Considering age-standardized suicide mortality rates, Canadian mortality suicide rates have declined from 15.0 deaths per 100,000 in 1981 to 11.4 deaths per 100,000 in 2017, decreasing at a rate of approximately 1.2% per year until 2007, and remaining stable from 2008 onwards (Varin *et al.*, 2021). Recent updates indicate this plateau continued until a notable drop in 2023, with a total of 3,811 suicide deaths, the lowest recorded count since 2008 (Statistics Canada, 2025b). Whether the decline merely reflects gains in

population health in general, as it parallels global trends, or is the result of targeted suicide prevention efforts warrants further research.

1.2 Suicide Prevention Efforts

The urgency to prevent suicide has been recognized and prioritized on the global stage. As part of international efforts, reducing suicide mortality rates by one third by 2030 has been included as a target (the only one for mental health) in the United Nations Sustainable Development Goals, and in the WHO Comprehensive Mental Health Action Plan 2013-2030 (Sustainable development, 2015; World Health Organization, 2021a). Despite this, not all countries have demonstrated commitment to suicide prevention, and some, such as the United States of America, have even seen rising suicide rates over time. The WHO cautions that the world is not on tract to reach these international targets and urges nations to take action through comprehensive national suicide prevention strategies (World Health Organization, 2021b). To guide and support countries in this effect, the WHO has created a guide called LIVE LIFE, an approach designed to serve as a starting point for developing and implementing a comprehensive national suicide prevention strategy (World Health Organization, 2021b). This guide focuses on four key evidence-based suicide prevention interventions: 1) limiting access to suicide means, 2) interacting with the media for responsible reporting of suicide, 3) fostering socio-emotional life skills in adolescents and 4) early identification, assessment, management and follow up of anyone who is affected by suicide behaviours. Nationally, Canada has recently made substantial strides in advancing national suicide prevention efforts. In a long overdue, yet pivotal step forward, the federal government released its first-ever national suicide prevention action plan (‘The Action Plan’) in June 2024, acting in alignment with the WHO’s call for national suicide prevention frameworks (Public Health Agency of Canada, 2024). This marks a foundational step forward for Canada, addressing a longstanding

need. This three-year evergreen plan presents a pragmatic approach to suicide prevention, acknowledging that, as a new initiative, requires adaptability and evolution over time. Rather than aiming to replace existing efforts, it is designed to complement active initiatives, fostering increased collaboration in order to advance shared interests and priorities. The Action Plan is structured around four pillars: 1) data and monitoring, 2) research and evaluation, 3) supports and services, and 4) governance. The work comprising this thesis directly contributes to pillar 2, research and evaluation, with details elaborated in the chapters that follow.

Notably, an effective suicide prevention strategy is to reduce the lethality of suicide acts by limiting access to highly lethal suicide methods (Cai *et al.*, 2022). This strategy, although challenging to accomplish in practice, can substantially reduce suicide deaths without necessarily changing underlying suicidal behaviours (Yip *et al.*, 2012; Barber and Miller, 2014). Nonetheless, the prime paradigm in current suicide prevention strategies usually focuses on how to remove upstream causes of suicidal behaviours (Cai *et al.*, 2022). However, mitigating the causes of suicidal behaviors in practice is difficult due to the complex and diverse nature of factors that contribute to suicidal behaviors. Nonetheless, suicide risk factors have predictive potential, and hold value to preventing suicide-related attempts and fatalities.

1.3 Suicide Risk Factors

Suicide-related thoughts and behaviours are rarely the result of a single cause. The sheer volume and heterogeneity of suicide risk factors, ranging from genetics, cytokines and neurobiology to psychiatric diagnoses, personality traits, beliefs, culture, lived experiences, and beyond, forms the complex web at the core of our struggle to understand, prevent, and effectively identify and help those at imminent risk of a fatal SA. These factors can be categorised as state-dependent or trait-dependent, or as distal (i.e. long-term, relatively constant) or proximal (i.e.

immediate, ongoing circumstances) factors. Distal risk factors include genetics, personality characteristics (e.g., impulsivity, aggression), early traumatic events and neurobiological disturbances. Proximal factors encompass psychiatric and physical disorders, psychosocial crises, availability of means and exposure to role models (Hawton and van Heeringen, 2009). The challenge of understanding and managing suicide lies in the inherently interconnected and synergistic nature of risk factors, a complexity made glaringly evident when examining suicide rates following psychiatric hospital discharge. Presumably, hospitals are the best-suited environments for individuals experiencing suicide-related thoughts and behaviours, equipped with the most highly trained medical experts, researchers, and resources necessary to understand the full context of the patient lived experience, pinpoint the deeply rooted motives driving the suicidal thoughts and behaviours and deliver effective evidence-based interventions. Current approaches rely primarily on clinicians conducting brief screening for suicide risk, completing suicide safety assessments and determining appropriate disposition (Horowitz *et al.*, 2023). In principle, these methods should allow clinicians to recognize elevated risk and intervene effectively. Yet paradoxically, suicide deaths at times occur during hospitalization, and the period immediately following discharge from a psychiatric inpatient admission is one of the most high-risk time timeframes, with death by suicide up to 200 times the global rate (Walsh *et al.*, 2015; Chung *et al.*, 2017). This is particularly concerning, as the very setting designed to offer safety and stabilization, at times, appears to fall short of its intended impact. This discrepancy is often attributed to the idea that patients are falling through gaps of care, but evidence suggests that the challenge may rather be partly attributed to the fact that suicidal thoughts and motivations are remarkably fluid, and current instruments are not developed to capture these fluctuations (Rudd, 2023).

As with much of psychiatry, there is no one size fits all approach to suicide. In practice, an individualistic, patient-centered approach is likely the most effective way to help a patient de-escalate their own suicidal thoughts and behaviours and decrease risk. With that said, in order to have adequate knowledge and the skillset required to offer these tailored approaches, a comprehensive understanding on the broader context and key risk factors are the essential first steps. Despite there being no unique profile to describe a person at risk of suicide, there are important risk factors that warrant attention. Previous SA may be by far among the strongest risk factors for future attempts, although relying on any one factor is insufficient and risks potentially independent of treatments administered (Simon and Savarino, 2007; Franklin *et al.*, 2017; Nobile *et al.*, 2025a). It is important to keep in mind that in the literature, risk factors for suicide are often presented generally, with little differentiation between those contributing specifically to suicidal thoughts, behaviours, non-fatal and fatal attempts. Regarding neuroimaging research, considering suicide risk factors is essential both for interpreting the clinical relevance of neuroimaging findings, and for appropriately including them as covariates in statistical analyses. The sections below will explore additional prominent suicide risk factors. Of note, the risk factors highlighted are not exhaustive, and important contributors, such as substance use and chronic pain, among others, also warrant consideration within the broader suicide risk assessment.

1.3.1 Age

The relationship between age and suicide is complex and varies across different populations. While suicide can occur at any point in the lifespan, there are notable age-specific risk factors to consider. Suicide ranks alarmingly high among youth, standing as the third leading cause of death worldwide for individuals aged 15 to 29 (World Health Organization, 2025c). In Canada, suicide ranks as the second leading cause of death among youth and young adults aged

15 to 34 (Public Health Agency of Canada, 2023a). Youth aged 15 to 19 far surpass all age groups in terms of self-inflicted injuries requiring hospitalizations (166 per 100,000 compared to the total population at 61 per 100,000) (Public Health Agency of Canada, 2023b). Among all age groups, middle-aged adults (30-59 years old) have the highest rates of suicide, accounting for 56% of suicide deaths in 2022 (Public Health Agency of Canada, 2025). In contrast, suicide rates are lowest among the elderly population in Canada, with rates at 25 per 100,000 at 65 years of age and above, well below the national average rate of 61 per 100,000 (Public Health Agency of Canada, 2023b). A caveat when interpreting these age-related suicide statistics is that because overall mortality rates are relatively low among youth, suicide accounts for a disproportionally large share of deaths. Conversely, the higher overall mortality rates from various causes among older adults reduces the relative contribution of suicide to total deaths.

There are no formally established theories to explicitly explain these age-related differences in suicide risk, however, several plausible explanations have been proposed in the literature. Higher suicide rates among youth may be linked to the growing prevalence of serious psychological distress and mood disorders in this cohort (Twenge *et al.*, 2019). This distress may be amplified by the increase social media and smartphone use, which has been associated with reduced in-person interaction, poor sleep hygiene, and, in some cases, engagement with suicide-related content online, such as searching information on suicide methods (Twenge *et al.*, 2019). Additionally, research has demonstrated that youth are vulnerable to the influence of reports and portrayals of suicide in mass media (Gould, Jamieson and Romer, 2003). A phenomenon known as suicide contagion, describes the increase in suicide-related thoughts and behaviours following the exposure to suicide-related behaviours within one's family, peer group, or through media reports (Walling, 2021).

Reports have indicated that adolescents who knew someone (such as a friend or family member) who had attempted suicide were three times more likely to attempt suicide themselves compared to those who had no exposure (Gould and Lake, 2013). Regarding older adults, particularly those aged 50 and above, suicide rates may be attributed to inadequate risk assessment completed by healthcare providers. Compared to younger patients, older adults at high suicide risk are less likely to receive a comprehensive risk assessment, education on safety planning, referrals to mental health care services, psychiatric evaluations or consideration for hospitalization, even when presenting with similar clinical profiles (Arias *et al.*, 2017; Simons *et al.*, 2019).

Despite limited understanding on the reasons driving age-related differences in suicide risk, their impact is undeniable. These effects are acknowledged across suicide research, with epidemiological studies routinely applying age-standardized suicide mortality rates, and biological studies including age as key confounding effects. Age-standardized mortality rates are adjusted to a standard age distribution, allowing for comparisons across populations with different age structures. This adjustment is crucial because it accounts for the fact that populations with a higher proportion of older individuals might naturally have higher mortality rates due to age-related factors.

1.3.2 Sex and Gender

The study of sex differences in suicide research has been extensive, although it is important to highlight that until more recently, most studies have used the terms sex and gender interchangeably (Barrigon and Cegla-Schvartzman, 2020). Sex and gender are not mutually exclusive. Sex refers to biological characteristics that define humans as female or male, while gender refers to the socially constructed characteristics of women and men, comprising social, environmental, cultural and behavioural factors and choices that influences a person's self-identity

(Clayton and Tannenbaum, 2016). Given the pronounced sex- and gender-based differences in suicide-related outcomes, understanding these constructs is imperative for research and preventative efforts.

Sex and gender are among the most markedly distinguishing variables in suicide epidemiology. Males account for over two thirds of the 15.7 million global suicide deaths recorded between 2000 and 2019 (Ilic and Ilic, 2022), and they account for higher mean crude suicide rates than females across every country around the world (World Health Organization, 2025b). Globally, the age-standardized suicide rate was 2.3 times higher in males than in females (World Health Organization, 2021c). While mortality from suicide is higher among males than females, nonfatal suicidal behaviours are typically higher in females (Canetto and Sakinofsky, 1998). This discrepancy between the overrepresentation of women experiencing suicidal thoughts and nonfatal suicide attempts, and the predominance of men in suicide mortality is often referred to as the *gender paradox of suicidal behaviour*. The term gained attention in the late 1990s through the work of Canetto and Sakinofsky, who argued that this paradox was not merely an artifact of data collection, but instead a true phenomenon rooted in deeply ingrained gender-specific factors (Canetto and Sakinofsky, 1998). To explain the reasons behind the gender paradox, they proposed several theories, supported by work from an earlier review of epidemiological studies on gender differences in fatal and non-fatal suicide attempts (Moscicki, 1994). In summary, four theories were proposed based on method of lethality, recall bias, depression and alcohol use, and socialization. The lethality hypothesis suggests that men tend to use more lethal means in SAs, such as firearms or hanging, which reduces the likelihood of rescue or survival from a SA compared to women. This perspective may partly explain the higher suicide mortality observed in males as a consequence of using higher lethality methods. Ultimately, the likelihood of SAs

resulting in death largely depends on the method used. A systematic review and meta-analysis of epidemiological studies showed that firearms were the most lethal method of suicidal acts resulting in death or hospitalization, followed by hanging/suffocation, drowning, gas poisoning, jumping and drug/liquid poisoning (Cai *et al.*, 2022). The full picture is likely nuanced, as lethality of suicidal acts remain higher in men even within the same method (Mergl *et al.*, 2015). Sociocultural factors may also contribute to gender-specific method selection. For instance, some suggest that women may avoid methods that would cause disfiguration, leading to a preference of self-poisoning or drowning. In contrast, men may gravitate towards more lethal methods influenced by a desire not to "fail", even in suicide. One study even reported that more men than women expressed disappointment when their SA did not result in death (Tóth *et al.*, 2014). Another theory to consider is the *recall bias theory*, which posits that women are more likely to report suicidal thoughts and behaviours to health professionals compared to men, and the underreporting among men may contribute to apparent sex/gender differences in non-fatal suicidal behaviours. The role of comorbidities is also important to consider, particularly depression and alcohol use. The involvement of alcohol or drug use is more often found in males than in females and is likely to increase the lethality of SA, especially in mood disorders (Sher *et al.*, 2009). It should be noted that men have a higher prevalence of heavy drinking and intoxication than women in the general population, so a higher prevalence of alcohol use among males who have attempted suicide may not reflect any susceptibilities to suicide-promoting effects of alcohol (Sher *et al.*, 2009). The final theory to be discussed is the *gendered socialization hypothesis*, which argues that cultural norms associate femininity with nonfatal suicidal behaviours, whereas masculinity with fatal self-directed violence, reinforcing patterns observed in suicide data. Despite these theories being presented almost three decades ago, they seem to have stood the test of time (Schrijvers, Bollen and Sabbe,

2012). Schrijvers et al. aimed to expand on knowledge of the paradox, reporting that gender-dependent variation in reporting suicide (particularly, men remain difficult to identify and reach), help seeking behaviour, psychosocial stressors and cultural beliefs have important influence (Schrijvers, Bollen and Sabbe, 2012). Overall, recognizing and incorporating sex and gender in suicide research is crucial for accurately capturing the complexity of suicide, and for informing intervention strategies.

1.3.3 Major Depressive Disorder

The presence of a psychiatric diagnosis is one of the largest contributors to SA risk. Over 90% of individuals who die by suicide have a psychiatric diagnosis at the time of their death (Manoel Bertolote and Fleischmann, 2002). Studies employing psychological autopsies, a well-established method for investigating psychological and contextual factors of the deceased by collecting collateral information, report a sixteen-fold increase in the risk of suicide in individuals with mental health disorders compared to those without such diagnoses (Sutar, Kumar and Yadav, 2023). Major depressive disorder (MDD) is one of the most prevalent diagnoses among those who die from suicide, indicating that depression may be of greatest concern in terms of suicide risk (Bachmann, 2018; McMorrow *et al.*, 2022).

Within MDD, difficult-to-treat depression, better known as treatment-resistant depression (TRD) poses a significant suicide risk. TRD is broadly conceptualized as a partial or lack of response to an adequate evidence-based treatment trial (Rybak *et al.*, 2021) Specifically, TRD is often defined as lack of response after at least two adequate trials of antidepressant medication from different drug classes at adequate doses and durations (Berlim and Turecki, 2007; Gaynes *et al.*, 2020). While numerous antidepressant medications have been studied for the treatment of major depressive episodes (MDEs), available evidence suggests that 20-30% of patients do not

adequately respond to treatment (Rush *et al.*, 2006). TRD imposes a significant disease burden and close to one third of patients with TRD attempt suicide at least once in their lifetime (Bergfeld *et al.*, 2018a). Given the high vulnerability to suicide within this population, investigating suicide-related outcomes in TRD is imperative to furthering understanding the neurobiology and clinical manifestations of suicide.

1.3.4 Clinical Features and Behavioural Traits

An influential meta-analysis published in 2017 by Franklin et al., drew striking conclusions regarding suicide risk factors, reporting that the predictive ability of commonly studied suicide risk factors (most of which were clinical) have not improved in over 50 years (Franklin *et al.*, 2017). At first glance, factors contributing risk for SI, SA and suicide deaths appear to differ (Table 1). However, these risk factors are weak predictors of suicide in general, and reasons for this discordance are unclear (Franklin *et al.*, 2017).

Table 1. Top 5 predictors of SI, non-fatal and fatal SA (adapted from (Franklin *et al.*, 2017))

Rank	SI Predictors	Non-Fatal SA Predictors	Fatal SA Predictors
1	Prior SI	Non-suicidal self-injury	Prior psychiatric hospitalization
2	Hopelessness	Prior SA	Prior SA
3	Depression diagnosis	Reponses to screening instruments (mostly consisted of questions about prior suicide-related thoughts and behaviours)	Prior SI
4	Any abuse history	Any Axis II personality disorder diagnosis	Lower socioeconomic status
5	Anxiety diagnosis	Prior psychiatric hospitalization	Stressful life events

These findings are subject to methodological constraints and do not suggest that widely accepted suicide risk factors are invalid or hold little relevance. Instead, they highlight that single risk factors are inherently limited in their ability to accurately predict future suicide-related thoughts and behaviours. To support clinical information, biomarkers have emerged as a promising

complement, capturing objective measures of suicide-related thoughts and behaviours to improve prediction and understanding (Sudol and Mann, 2017a). Among emerging biomarkers, neurobiological risk factors represent an important piece to this complex puzzle, and ongoing biomarker research continues to highlight its value. Additionally, advances in machine learning are making progress to overcome these limitations, offering promise by enabling researchers to develop algorithms capable of considering complex combinations of numerous neurobiological, genetic, inflammatory, clinical, behavioral, psychological and social variables to enhance risk stratification across suicide outcomes (Kusuma *et al.*, 2022; Somé, Noormohammadpour and Lange, 2024).

Mental health characteristics, such as severity of depressive symptoms, feelings of anxiety and hopelessness, and difficulties managing aggression and impulsivity, are all risk factors commonly associated with both treatment-resistant and non-resistant MDD and suicidal thoughts and behaviours. These associations are arguably intuitive, where individuals with suicide-related thoughts, behaviours and attempts tend to exhibit a more severe clinical presentation in general than those without. Studies have reported that patients with TRD and SA history have a more complex course of illness, with earlier onset of depressive symptoms, earlier diagnosis of MDD, more years spent in depressive illness, more severe depressive severity, and more antidepressant medication trials with suboptimal response (Civardi *et al.*, 2024; de Leon *et al.*, 2025). Findings are similar in studies comprising non-resistant MDD cohorts, with higher scores on depression, anxiety and SI scales, earlier depression onset, and longer duration of illness in patients with a history of SA compared to those without (Claassen *et al.*, 2007; Kim *et al.*, 2011; Tong *et al.*, 2023).

Closely tied to depressive symptoms, hopelessness remains among one the most cited risk factors for suicidal behaviours, and findings from a 10-year longitudinal study concluded that hopelessness is best conceptualized as a risk factor for SI but not SA (Qiu, Klonsky and Klein, 2017). Hopelessness as a concept in suicide research was originally derived from Beck's cognitive theory of depression, which suggests depression is largely derived by negative cognitive distortions and refers to hopelessness as negative expectations about the future and a desire to escape from what one considers an insoluble problem (Beck, Kovacs and Weissman, 1975; Baryshnikov *et al.*, 2020). Theoretical models have postulated that hopelessness is an essential precondition for the development of suicidal thoughts and is the key variable linking depression and suicidal behaviour (Wenzel and Beck, 2008; David Klonsky, Saffer and Bryan, 2017). Renowned psychiatrist Aaron Beck and his colleagues have conducted over 30 years of empirical research demonstrating that hopelessness is more strongly related to suicidal intent than is depression (Wenzel and Beck, 2008). A meta-analysis of longitudinal studies reported diagnosis of MDD, and higher depression and hopelessness scores increase the risk of suicide-related ideation, attempts and deaths, although effects were weak, potentially due to methodological constraints (Ribeiro *et al.*, 2018). Taken together, despite variations between studies, there is little doubt that hopelessness plays a central role in understanding suicide.

In further refining our understanding of variables contributing to suicide risk, trait versus state components of suicide risk factors are also important considerations, as they may suggest an underlying construct associated with vulnerability (Goldston, Reboussin and Daniel, 2006). Hopelessness can be a state (activated within a specific moment) or a trait (stable over time), where activating trait hopelessness can escalate state hopelessness and contribute to suicide risk (Beck, 1986; Wenzel and Beck, 2008). Impulsivity and aggression are also important traits that warrant

attention for their association with suicide, particularly SA. Both impulsivity and aggression are heterogeneous constructs, with conceptual inconsistencies on subtyping and a known association with suicide. Aggression is a behavioural trait characterized by actions intended to cause harm or assert dominance (Buss and Perry, 1992; Lee *et al.*, 2025). Impulsivity is a behavioural construct characterized by a tendency toward rapid, unplanned reactions to internal or external stimuli without fully considering the consequences (Patton, Stanford and Barratt, 1995; Stanford *et al.*, 2009; Lee *et al.*, 2025). Broadly speaking, individuals with higher levels of aggression and impulsivity scores are more vulnerable to suicidal behaviours (Lee *et al.*, 2025). Most studies that use self-reported impulsivity metrics found positive relationships between impulsivity scores and suicide risk, including SI and SA (Lee *et al.*, 2025). Impulsivity has been shown to help distinguish between patients with MDD with and without a history of SA (Perroud *et al.*, 2011). In general, impulsive and aggressive traits have been shown to strongly correlate in patients with mood disorders and a history of SA but not among patients without SA history (Dumais *et al.*, 2005; Perroud *et al.*, 2011).

Among the state-related symptoms, anxiety symptoms and SI severity have both been identified as risk factors for suicide. A recent study reported persistent moderate and severe anxiety symptoms were associated with increased SI risk and proposed that this may be due to persistent anxiety acting as chronic stress, potentially altering cortisol levels which have been implicated in suicidal behaviours (Chen et al., 2025). An earlier study found anxiety symptoms (in particular, worrying) contributed to greater risk of depression onset and SI than did core depressive symptoms (Batterham, Christensen and Calear, 2013).

Beyond emotional or psychological states, early life experiences, particularly childhood trauma, has also proven to leave lasting impacts that extend to adulthood. Physical, sexual and

emotional abuse, as well as psychological abuse and neglect are among the most common types of maltreatment towards children and youth (Bernstein *et al.*, 2003; Spinhoven *et al.*, 2014). The relationship between childhood trauma and suicide have been embedded in some contemporary theories of suicide, a popular one being the *interpersonal theory of suicidal behaviour*. This theory suggests that repeated exposure childhood maltreatment, in addition to other physically painful and/or fear-inducing experiences, produce a state of habitation to pain (i.e., increased pain tolerance) and a reduced fear of death which gradually builds to the person's capacity for suicide (Van Orden *et al.*, 2010). The most comprehensive cross-diagnostic systematic review and meta-analysis on childhood trauma and suicide published to date demonstrated a two- to three- fold increase in risk of SI and SA in adults who have experiences sexual, physical or emotional abuse as children (Angelakis, Gillespie and Panagioti, 2019). In the context of TRD, the literature is sparse. To our knowledge, Yrondi et al., is the only study to directly investigate associations between childhood adversities and suicide in a TRD population (Yrondi *et al.*, 2021). Their findings revealed an association between childhood trauma (particularly physical neglect) and suicide risk, mediated by the intensity of the MDE (Yrondi *et al.*, 2021). Surprisingly, no associations were found between childhood trauma and SI, personality traits and impulsivity. Additionally, an earlier study comprising patients with TRD and comorbid Axis 1 and/or Axis 2 disorders revealed childhood adversity predicted lifetime SA, further underscoring the relationship between childhood trauma and suicide (Tunnard *et al.*, 2014).

Rather than affecting suicide risk in isolation, clinical and behavioural risk factors often interact in meaningful ways to shape suicide vulnerability. A notable relationship between hopelessness, suicide and impulsivity has been reported, where impulsivity may mediate the relationship between depression severity and hopelessness (Wang *et al.*, 2015). Further, research

has shown that individuals with a history of physical or sexual childhood abuse have higher impulsivity and aggression scores and are at increased risk of making a SA (Brodsky *et al.*, 2001).

An important caveat to note is that correlation does not imply prediction. The focus throughout this thesis will be placed on identifying and understanding associations between suicide risk factors and suicide-related outcomes rather than predictive modeling. Specifically, the thesis will examine how clinical and behavioural features relate to suicidal thoughts and behaviours and neurobiological correlates in a TRD cohort. Acknowledging that single risk factors capture only part of the underlying mechanisms, correlational analyses illuminate nuances related to suicide, while acknowledging the limits of their predictive value.

Overall, robust evidence exists linking clinical and behavioural risk factors to SI and SA among patients with MDD. Where the literature falls short is in differentiating between those with thoughts of suicide and those who progress to behaviours and attempts, particularly when relying on psychosocial data (May and Klonsky, 2016). Wiebenga et al. recently sought to address this gap, yet similar to previous reports, reported that clinical, personality and psychosocial characteristics including anxiety, depression severity, hopelessness, aggression, risk aversion, rumination and loneliness could not distinguish patients with SA from those who had only thought about suicide (Wiebenga *et al.*, 2021). Despite limitations, suicide risk factors hold important clinical value, though further research is needed to clarify their interplay and enhance their utility to informing clinical risk stratification and prediction.

1.4 Key Considerations when Interpreting Suicide-Related Risk Factors

A critical consideration when studying suicide is the terminology itself. Within the field of suicide research, the term "suicide" is often used broadly and may encompasses distinct phenomena including passive and active SI, suicide plans and preparatory behaviour, as well as

aborted, interrupted, non-fatal and fatal SA. Clarity in language is essential, particularly when identifying and interpreting risk factors, as predictors of SI may differ from those associated with progression to SA.

In an attempt to dismantle the complexities of suicide, many frameworks have been formulated. One influential model is the ideation-to-action framework (summarized in Figure 2), which stipulates that there is a progression from SI to SA, and, as mentioned in the previous section, these are distinct phenomena with distinct explanations and predictors (Klonsky, May and Saffer, 2016). Building from this framework, the three-step theory to suicide proposes that SI develops when an individual experiences any form of pain (e.g., physical suffering, social isolation, burdensomeness, low belongingness, etc.), and hopelessness regarding alleviation of suffering (step 1). These thoughts remain low-to-moderate in intensity when an individual experiences a high degree of connectedness, which can be connectedness to people, interests, roles, a project, or any sense of purpose or meaning (step 2). SI escalates in intensity when the person's pain and hopelessness overwhelm the feeling of connectedness. SI progresses to an SA only once a person has the capacity to do so (step 3). Numerous factors contribute to an individual's capacity, including ones' ability to overcome the fear of death, dispositional traits such as innate pain sensitivity, acquired habituations to pain, and knowledge and access to lethal means.

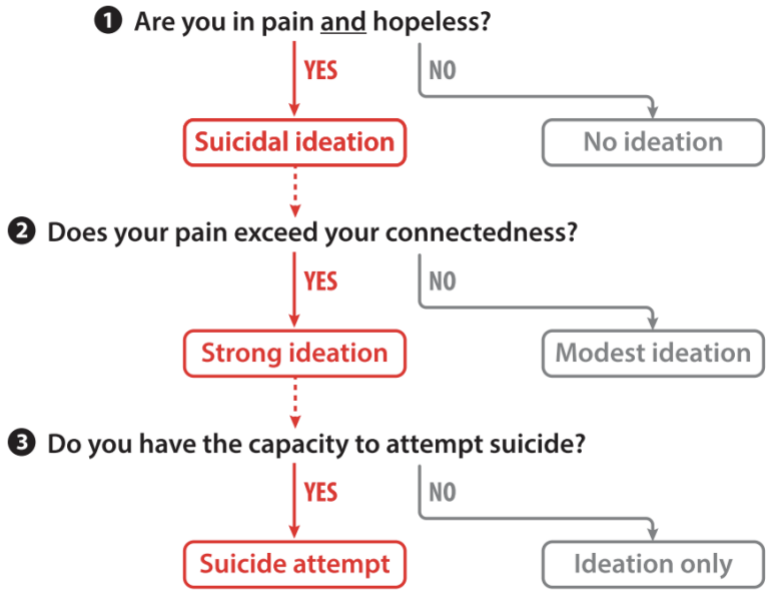

Figure 2. The three-step theory of suicide (Klonsky, May and Saffer, 2016).

This framework provides a comprehensive stepwise understanding to suicide, although is not without limitations. Few studies have investigated the predictive nature of this model, and the risk factors associated with each step. The key message here is to acknowledge that when assessing risk factors, it is imperative to recognize that risk factors may differ within the context of where an individual may lie on the suicide continuum. Additionally, clear distinctions in suicide-related terminology must be maintained to accurately interpret risk.

1.5 Beyond Risk: Understanding the Reasons for Dying

As reflected above, the field of suicide research has developed a solid understanding of psychosocial risk factors associated with suicide. Many studies, whether psychological, social, or biological, have focused on identifying those at risk, and more recently, on leveraging these factors to predict future suicidal behaviour. These approaches offer valuable insight that are imperative to understanding and preventing suicide, however, it is important to note that they primarily tell us

who might be at risk, and do not tell us why someone comes to see suicide as the best or only option.

At times, truths lie in simplicity. Rather than relying solely on complex theories to explain suicidal behaviour, a direct open-ended question such as "*Why did you attempt suicide?*" can yield profound insight. Exploring the explicit reasons and motives behind suicide helps move us closer to a deeper, more complete understanding. While the reasons behind suicidal thoughts and behaviours may seem deeply individualistic, and to some degree they are, qualitative research has shown common themes that often emerge. In a study by Van Orden et al. (2015), older patients were directly asked why they attempted suicide. Reponses revealed that reasons for suicide could be attributed to seven themes, with the first three being the most commonly reported (Van Orden *et al.*, 2015):

1) escapism (e.g. "*I wanted to get away from life*"),

2) functioning and autonomy ("*Can no longer do the things I used to*"),

3) psychological problems ("*I had a panic attack, and didn't want to have that again*"),

4) somatic problems and pain ("*I wanted to get away from the pain, I decided, I've had enough*"),

5) burden to others ("*I wanted to release my granddaughter from the burden I cause her*"),

6) social problems ("*I don't belong anywhere*"), and

7) lack of meaning in life ("*I thought life was meaningless*").

Earlier work similarly points to themes of escapism and/or general attitude of giving up, self-deprecating statements beliefs, and social problems (Jobes and Mann, 1999).

The unifying factor between these reasons lies not in the content of the reasons themselves, but a shared sense that the experience is unbearable. Neurobiological influences may shape how

this suffering is experienced, processed and endured, ultimately impacting the threshold at which suicide becomes a plausible option. Furthermore, neurobiology can impact the expression of traits, such as impulsivity, aggression, and hopelessness, which can influence one's likelihood of overcoming certain 'barriers' to suicide such as fear of death and or consideration of deterrents, thereby influencing the transition from thoughts to action. In this way, neurobiology plays a role in shaping the serious consideration or enactment of suicidal behaviour. Furthermore, it may help explain why individuals with similar reasons for suicide and comparable protectives may diverge, some developing passive or active suicidal thoughts, some acting on such thoughts, while others do not. The section below delves into the relationship between neurobiology and suicide-related thoughts and behaviours.

1.6 Suicide as a Neurobiological Phenomenon

Suicide, unlike almost all other behaviours, acts directly against the instinctive, evolutionary-driven tendency observed across nearly all organisms to promote survival. The very fact that a person can override such deeply rooted human instincts to reach a conclusion that ending life is the best course of action, speaks to the degree of biopsychosocial disruption that results in life becoming unbearable. Suicide is not merely a decision that just anyone might come to. Early stress models of suicidal behaviour proposed that negative life events, if severe enough, can precipitate suicidal behaviour even in the absence of predisposing psychological or biological risk factors (Van Herringen, 2012). These models are too narrowly focused, and do not explain the observations that even extreme stress does not lead to suicidal behaviours in all exposed individuals (Mann *et al.*, 1999; Van Herringen, 2012). Instead, suicidal behaviour is thought to involve pre-existing vulnerabilities, or diatheses, as distal risk factors, that predisposes some individuals to contemplate suicide, while others may render the consideration unfathomable,

regardless of the stressors they encounter. This concept can be understood within the *stress-diathesis model of suicidal behaviour*, which proposes that the risk of suicidal acts is determined not merely by stressors, but by their interaction with a diathesis, or trait-like predispositions (Rubinstein, 1986; Mann *et al.*, 1999; John Mann and Rizk, 2020). A diathesis is a biological, social or cognitive pre-disposing factor, or set of factors, that make a person vulnerable to a disorder. In suicide, the diathesis may be due to genetic and epigenetic effects or early life adversities, which are reflected by distinct biological, psychological or clinical profiles (Van Heeringen and Mann, 2014; Kaminsky *et al.*, 2015). A diathesis alone is not sufficient to produce a disorder but requires a potentiating factor (i.e. stress) to become problematic. The stress may constitute psychosocial stresses, such as poverty, unemployment and social isolation, and psychiatric disorders such as depression. Furthermore, a diathesis is not necessarily static or dichotomous, but often rather continuous. Repeated stress can cause neuronal changes, thereby altering the diathesis and modifying sensitivity and reactivity stress. Thus, examining underlying vulnerabilities that may shape how one responds to stressful life events is essential to truly understand why certain individuals progress from thoughts of suicide to behaviours and attempts.

This doctoral thesis will use the stress-diathesis model as a framework of reference, focusing specifically on the diathesis component of the model. Among the many potential diathesis factors, neurobiology stands out as a particularly valuable one to investigate. Neuroanatomical, neurofunctional and neurochemical alterations in the brain can reflect the cumulative influence of genetic, epigenetic, neurotransmission, and glial factor changes, offering a meso-level signature of micro-level disruptions. In other words, genetic, epigenetic, and environmental perturbations can alter the expression of gene products such as transcription factors, receptors, and intracellular signaling proteins that regulate synaptic plasticity and neuronal functioning. As a result, neuronal

connections may be altered, existing synapses strengthened or weakened, and brain structure and electrophysiological properties of the neuronal networks controlling higher-order brain functions can be affected, ultimately leading to observable neural phenotypic (Coda and Gräff, 2020). These neuronal changes can influence behavioural or clinical profiles, such as trait impulsivity, aggression, and mitigation of negative feelings, representing a macro-level disruption that can be observed clinically. Neuroimaging allows us to probe these phenotypic changes in brain structure, function and chemistry, and to measure how they relate to suicide risk.

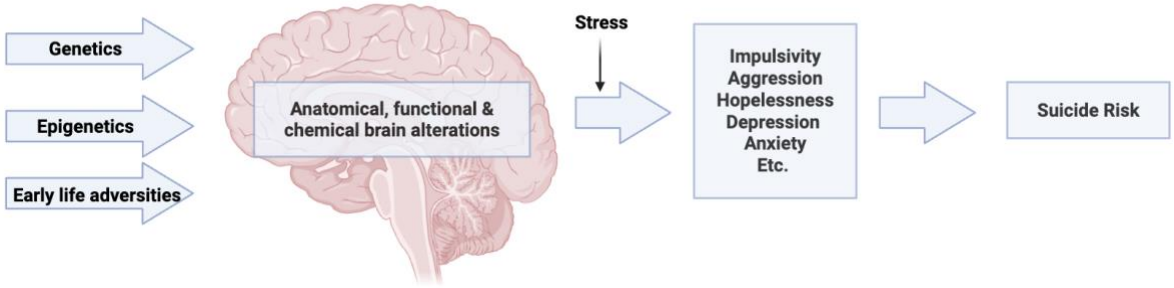

Figure 3. An Adapted Stress-Diathesis Model Highlighting Neurobiological Pathway of Suicide Risk

1.6.1 Neuroimaging Findings in Suicide Research: Overview of Existing Literature

Most studies on the neurobiology of suicide employ comparative study designs, typically comparing patients with a history of SA to patients without such a history and/or a healthy comparison (HC) group. Fewer studies focus specifically on SI, with those that do often comparing individuals with SI to non-ideators and/or healthy controls. Synthesizing this body of literature reveals extensive and widespread neural alterations associated with suicidal thoughts and behaviours in the context of depression. This broad neural involvement, often in differing degrees, diverging directions and without consistent replication, makes it challenging to integrate findings into unified conclusions about underlying mechanisms. To facilitate comprehension, the following

sections will take an anatomical approach, providing an overview of the entire brain organized by lobe (excluding the cerebellum), describing the anatomical orientation and core functions of each as they relate to depression and suicide (Figure 4). This section aims to synthesize localized brain abnormalities reported in existing comparative studies involved in suicide (reviewed studies are displayed in Table 2). While this doctoral thesis focuses on TRD, the limited number of studies investigating this population necessitates a broader examination. Therefore, studies comprising either MDD or TRD populations will be reported to provide a comprehensive understanding of the current literature and to better delineate how suicide-related outcomes in TRD may differ.

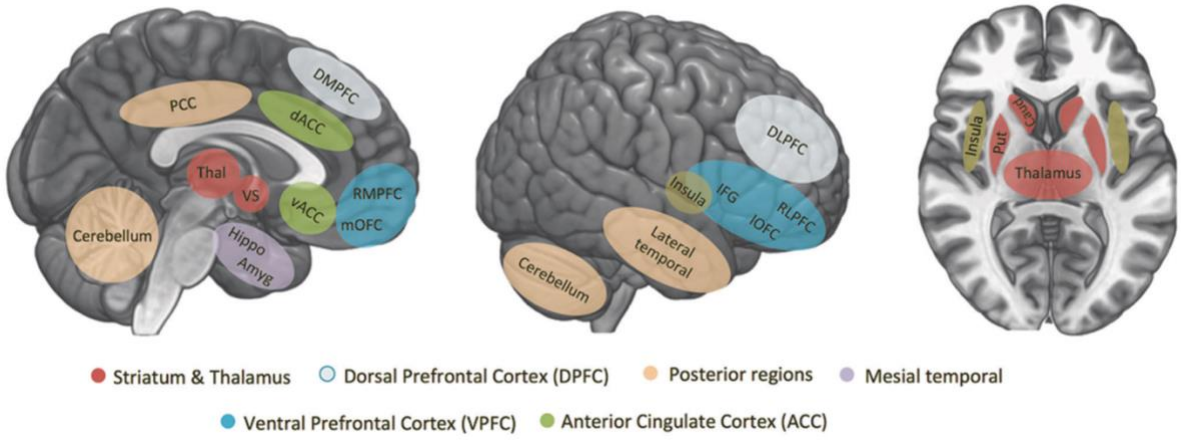

Image derived from Schmaal et al. Molecular Psychiatry (2020) 25:408-27

Figure 4. Overview of brain regions most reported in neuroimaging studies investigating structural, functional, and molecular brain alterations associated with suicidal thoughts and behaviors across psychiatric diagnoses. Image derived from (Schmaal *et al.*, 2020a). All regions depicted have shown involvement in the context of depression and suicide.

1.6.1.1 Prefrontal cortex

Anatomically, the frontal lobes are limited posteriorly by the central sulcus and divided into motor, premotor, and prefrontal regions. The anterior cingulate, classically a part of the limbic system, can also be considered an important subdivision of the frontal lobe (Chayer and Freedman, 2001). The frontal lobe, specifically the prefrontal cortex (PFC), plays a significant role in the pathophysiology of MDD and suicide, given its involvement in the generation and regulation of emotions. The PFC is comprised of the anterior cingulate cortex (ACC; subgenual, pregenual, anterior-middle), orbitofrontal cortex (OFC; lateral, medial), medial PFC (rostral, dorsal) and lateral PFC (rostral, ventral, dorsal) (Dixon *et al.*, 2017).

Neuroimaging studies have shown notable changes in gray matter volume across various regions of the PFC in relation to MDD and suicidal behaviours. Among individuals diagnosed with MDD, decreased gray matter volume has been observed in the right inferior orbital gyrus in those with a SA history compared to diagnostic controls, i.e., individuals with MDD and no history of SA (Yang *et al.*, 2020), a gyrus located within the OFC, and the ventral, medial and dorsal PFC (Wang et al., 2020). In contrast, increased gray matter volume has been noted in specific and broader orbitofrontal regions, including the left lateral OFC (Kang et al., 2020) and the whole OFC, as well as in the dorsolateral PFC and the insula in participants with MDD and a history of SA compared to diagnostic controls (Rizk *et al.*, 2019; Kang *et al.*, 2020b). Suicide state markers, such as lethality of attempt, may help explain some of the variations in reported literature. One study reported individuals with a history of more lethal SA have shown greater gray matter volume in the OFC, insula and both the rostral and caudal ACC compared to those with lower lethality attempts (Rizk *et al.*, 2019).

In addition to structural involvement, ^{1}H-MRS findings provide neurochemical insights into prefrontal regions implicated in suicide. To our knowledge, only two studies have used ^{1}H-MRS to study suicide-related outcomes in the context of depression; in which only one is specific to MDD, and the ACC and PFC were the sole regions examined. Lower Glx (composite measure of glutamine/glutamate) and lower N-acetylaspartate (NAA)/Glx ratios have been reported in the ACC of adolescents with depressive symptoms and current SI compared to those without (Lewis *et al.*, 2020). Similarly, reduced NAA concentrations in the medial PFC among patient participants with a history of SA compared to HC participants has also been reported (Jollant *et al.*, 2017). Although limited, these findings suggest that disruptions in glutamatergic neurotransmission and neuronal integrity in the PFC may contribute to the neurobiology of suicide.

1.6.1.2 Parietal Cortex

The parietal lobe is bounded anteriorly by the central sulcus, posteriorly by the parieto-occipital sulcus, and inferiorly by the lateral sulcus. Anatomically, the parietal lobe can be divided into the postcentral gyrus, inferior parietal lobe (comprising the supramarginal and angular gyri), superior parietal lobe and on the medial surface, the precuneus (Wild *et al.*, 2017; Dziedzic, Bala and Marchel, 2021). The parietal lobe can also be distinguished by two functional landmarks: the primary somatosensory cortex (anterior zone, comprising the postcentral gyrus and the parietal operculum) and the posterior parietal cortex (comprising the remaining areas) (Tuite and Konczak, 2010). Regarding depression and suicide, the posterior parietal cortex is most relevant in depression and suicide given its involvement in decision making, working memory and perseverance thinking (Whitlock, 2017a; Sheehan *et al.*, 2022). Neuroimaging studies have reported decreased gray matter volume in the left angular gyrus in participants with MDD and a SA history compared to diagnostic controls (Lee *et al.*, 2016). While direct studies pertaining to

the role of the posterior parietal cortex in suicide are limited, its function in attention allocation may be relevant to understanding suicidal thoughts. Individuals with severe SI often exhibit excessive negative thought patterns, difficulties disengaging from suicidal thoughts, and challenges shifting attention to positive stimuli, characteristics that may be partially explained by impaired posterior parietal cortex function (Cha *et al.*, 2010).

1.6.1.3 Temporal Gyri

The temporal lobe is bordered superiorly by the lateral sulcus, and the lateral surface is indented by the superior and inferior temporal sulci, delineating the superior, middle and inferior temporal gyri (Kiernan, 2012). There is also the lateral occipitotemporal gyrus which extends posteriorly into the occipital lobe.

Two studies found decreased gray matter volume among adolescents with SA history in the right superior temporal gyrus (STG) in an adolescent population (Pan *et al.*, 2015; McLellan *et al.*, 2018). Conversely, larger gray matter volume in the right STG has been observed among individuals with MDD and SA compared to those with SI (Deng *et al.*, 2025). Resting-state fMRI studies further support these structural findings. Individuals with SA history have exhibited stronger functional connectivity (defined in Chapter 2) between the superior middle temporal gyrus (MTG) and the superior medial frontal gyrus compared to those with SI history only (Deng *et al.*, 2025). The STG and MTG involvement are in line with an earlier transdiagnostic meta-analysis that revealed increased activation in the bilateral STG and left MTG in patients with a psychiatric diagnosis and suicide-related thoughts and/or attempts (Chen, Chen and Zhang, 2022). Notably, the STG emerged as the most robust finding and was proposed as a potential marker of suicide. Functionally, the MTG is a key node of the default mode network (DMN) involved in self-

referential thoughts and rumination and thus, could foster negative core beliefs about the self and a suicidal belief system, eventually leading to SI (Jagger-Rickels *et al.*, 2023; Deng *et al.*, 2025).

1.6.1.4 Lateral occipital cortex

The occipital lobe is the smallest of the four lobes and is divided into the into superior, middle and inferior occipital gyri by the lateral occipital sulcus (Rehman and Al Khalili, 2023). The medial surface contains the parieto-occipital sulcus, cuneus, calcarine sulcus, lingual gyrus, collateral sulcus and fusiform gyrus. The anatomical delineation of the lateral occipital cortex is vague, and inconsistently described in the literature as it is bordered anteriorly by an arbitrary line that connects the lateral extension of the parieto-occipital sulcus to the preoccipital notch (Koutsarnakis *et al.*, 2019). The occipital lobe is primarily responsible for visual processing and less recognized for its involvement in memory formation (Rehman and Al Khalili, 2023). Despite this, studies have reported decreased gray matter volume in occipital lobe regions, including the left calcarine fissure (Yang *et al.*, 2020), the inferior occipital gyrus (Deng *et al.*, 2025) and another found larger surface area in the left lateral occipital lobe (Kang *et al.*, 2020a) in suicide attempters compared to non-attempers. Functionally, patients with MDD and SI have exhibited decreased functional connectivity between the right middle frontal gyrus and the left middle occipital gyrus relative to patient participants without SI (Deng *et al.*, 2025).

1.6.1.5 Limbic System

The limbic system is a highly complex and intricate network of brain regions, containing all the major cortical and cortical-like structures known to be especially important for emotional and motivational functions (Heimer and Van Hoesen, 2006). Components of the limbic system comprise the limbic cortex (cingulate gyrus and parahippocampal gyrus), hippocampal formation (dentate gyrus, hippocampus and subicular complex), amygdala, septal area and the hypothalamus

(Kaushal *et al.*, 2024). Functions attributed to the limbic system are vast, including but not limited to, cognitive, attentional, and emotional processing (cingulate gyrus), spatial memory (parahippocampal gyrus), long-term memory (hippocampus), and fear, anxiety, aggression, emotional memory, and social cognition (amygdala) (Kaushal *et al.*, 2024).

Neurobiological alterations within the limbic system have been extensively studied in the context of suicide. Individuals with MDD and a history of SA have shown to exhibit reduced gray matter volumes in several subcortical regions, including the putamen and hippocampus (Colle *et al.*, 2015), amygdala (Wang *et al.*, 2020), pallidum (Campos *et al.*, 2021), caudate (Yang *et al.*, 2020) and thalamus (Campos *et al.*, 2021), when compared to diagnostic controls. Conversely, studies have also reported no differences between individuals with MDD, regardless of SA history (Jia *et al.*, 2010; Jollant *et al.*, 2018). Notably, Jollant et al. were unable to identify robust and consistent structural neuroimaging markers of suicidal behaviour in two independent samples nor in a meta-analysis of twelve different neuroimaging studies with nearly 700 participants (Jollant *et al.*, 2018). The authors suggest morphometric differences may not emerge when individuals with SA history are considered as a single, homogenous group. However, authors did report associations between structural differences and factors such as family history of suicide and use of violent suicidal means, suggesting that group differences may not be driven by structure, but instead indicate the potential existence of distinct suicide phenotypes with specific biological underpinnings.

A substantial body of evidence highlights functional connectivity alterations involving limbic regions among individuals with MDD and suicide-related thoughts and behaviours. A recent review by Vieira et al. summarizes existing literature, reporting decreased functional connectivity between the amygdala and multiple cortical and subcortical regions, including the

pre- and post-central gyri, STG, MTG, right angular gyrus, inferior parietal lobule, precuneus, frontal gyri, and caudate nuclei in patients with SI (Vieira *et al.*, 2023a). Conversely, increased connectivity between the amygdala and the insula has also been observed. The amygdala frequently emerges in this literature, likely due to its extensive integration within widely distributed cortical–subcortical–limbic circuits. Resting-state functional connectivity between the right amygdala and the right MTG has even been identified as a "dysfunctional hub", distinguishing individuals with and without a history of suicide attempt (Stumps & Deng, 2025). The insula has similarly been implicated in the neurobiology of SI, with studies reporting reduced cortical thickness in individuals with MDD and SI and insular dysfunction potentially contributing to SI through its altered connectivity with the amygdala and cingulate cortex. Functionally, the insula is involved in a range of cognitive, affective, and regulatory processes. Dysregulation in this region has been linked to components of the acquired capability for suicide, including altered pain perception, disrupted self-awareness, and heightened negative affect, all of which may contribute to the emergence of SI.

Table 2. Main findings from structural, resting-state functional and proton magnetic resonance spectroscopy suicide studies in the context of MDD

Author	Imaging Analysis Approaches	Relevant main findings (patient groups only)	Population
Structural MRI studies			
Deng et al., (2025)	VBM	SI vs NSA: ↓ GMV in left insula and right cerebellum posterior lobe SA vs SI: ↑ GMV in right superior temporal gyrus SA vs NSI: ↓ GMV in left superior and inferior occipital gyrus, superior temporal gyrus and right cuneus ↑ SI severity ~ ↓ GMV in left insula, right cerebellum posterior lobe and superior medial frontal gyrus ↑ depression severity ~ ↓ GMV in left insula and right cerebellum posterior lobe	MDD+SI, MDD+SA, MDD-SI, HC
Jia et al. (2010)	VBM	SA vs NSA/HC: No difference in GMV	MDD+SA, MDD-SA, HC
Jollant et al. (2018)	VBM	No corrected group differences in GMV Secondary analyses results: SA with violent means vs SA without: ↑GMV in bilateral caudate nuclei Family history of suicide vs no family history of suicide: ↓ GMV in the bilateral temporal gyri, left temporal gyrus extending to fusiform gyrus, right dm PFC, and left putamen	MDD+SA, MDD–SA. HC
Lee et al. (2016)	VBM	SA vs NSA: ↓ GMV in the left angular gyrus and right cerebellum	MDD+SA, MDD-SA

Peng et al. (2014)	VBM	SA vs NSA: ↓ GMV in the left limbic cingulate gyrus	MDD+SA, MDD-SA, HC
Yang et al. (2020)	VBM	SA vs NSA: ↓ GMV in the right inferior frontal orbital gyrus, left caudate nucleus, and ↑ GMV in the left calcarine fissure	MDD+SA, MDD-SA, HC
Kang et al. (2020)	FreeSurfer	SA vs NSA: ↑ cortical surface areas of the left postcentral and left lateral occipital areas and ↓ cortical surface areas of the left superior frontal areas; ↑cortical volumes of the left postcentral and the left lateral OFC. No differences in cortical thickness.	MDD+SA, MDD-SA
Pan et al. (2015)	FreeSurfer	SA vs NSA: ↓ GMV in right superior temporal gyrus	Adolescent sample. MDD+SA, MDD–SA, HC
McLellan, (2018)	FreeSurfer	SA vs NSA: ↓ GMV in right superior temporal gyrus	Adolescent sample. TRD+SA, TRD–SA, HC
Campos et al (2021)	FreeSurfer	SA vs NSA: ↓ GMV in bilateral thalamus and right pallidum, ↓ left inferior parietal surface area. Cortical thickness did not survive corrections.	MDD+SA, MDD–SA, HC
Wang et al. (2019)	VBM	SA vs NSA: ↓ GMV in bilateral amygdala and in the ventral, medial and dorsal prefrontal cortex.	MDD+SA, MDD-SA, HC
Rizk et al. (2019)	VBM	SA (high lethality) vs SA (low lethality) ↑ GMV in OFC, rostral ACC, caudal ACC and insula SA (high lethality) vs NSA: ↑ GMV in dorsal lateral PFC, OFC and insula SA (lethal) vs SA (nonlethal)/NSA: ↑ GMV in right prefrontal lobe	MDD+SA (high lethality), MDD+SA (low lethality), MDD-SA

Colle et al., (2015)	SACHA	SA vs NSA: ↓ hippocampal volume	MDD+SA, MDD+NSA Acute vs remote SA
Resting-state functional connectivity fMRI studies			
Deng et al., (2025)	DPABI, seed-based	SI vs NSI: ↓ left insula with left superior frontal gyrus and bilaterial middle frontal orbital gyrus FC ↓ right superior middle frontal gyrus and left middle occipital gyrus FC ↑ right cerebellum posterior lobe with left precentral gyrus and right parahippocampal gyrus FC SA vs SI: ↓ right and left cerebellum posterior lobes FC ↓ right cerebellum posterior lobe and right lingual gyrus FC ↑ right superior middle gyrus with left middle temporal gyrus and right inferior parietal lobule FC	MDD+SA, MDD+SI (no attempt history), MDD+NSI
Qiu et al., (2020)	DPABI, seed-based	SA vs NSA: FC differences between 1. ACC subregions (pregenual ACC (↓), anterior (↑) and posterior (↑) subgenual ACC) and left superior frontal gyrus 2. Pregenual ACC and the left insula (↓) 3. Anterior subgenual ACC and right caudate (↓) SA group:↑ SI = ↑ pregenual ACC and superior frontal gyrus FC NSA group:↑ SI = ↑ pregenual ACC and superior frontal gyrus FC & ↓ subgenual ACC-superior frontal gyrus FC	MDD+SA, MDD–SA. HC
Du et al., (2017)	DPARSF, seed-based	SI vs NSI: ↓ right rostral ACC and orbital and medial prefrontal cortex FC & ↓ right rostral ACC and right middle temporal gyrus FC SI group: ↑ SI = ↑ right rostral ACC and middle temporal pole FC	MDD+SI, MDD– SI, HC
Yang et al., (2020)	DPARSF, seed-based	SA vs NSA: weaker negative FC between right inferior frontal orbital gyrus and left rectus gyrus and weaker positive FC right inferior frontal orbital gyrus and left inferior parietal lobule	MDD + SA, MDD – SA, HC

		SA group: ↑right inferior frontal orbital gyrus and left inferior parietal lobule FC ~ ↓ cognitive factor scores	
Magnetic resonance spectroscopy studies			
Jollant et al., 2017	Localized, right dorsal PFC	SA vs NSA: ↑ glutamine & ↑myo-inositol (did not survive correction). ↓ NAA when limited to individuals with no post exposure to medication and covariation with age. MDD: positive association between NAA levels and psychological pain, and between choline levels and current SI	MDD+SA, MDD-SA, HC
Lewis et a., 2020	Localized, ACC	SI vs NSI: ↑Glx and ↓ NAA/Glx ↑SI severity ~ ↓NAA/Glx ↑SI intensity ~ ↓NAA/Glx ↑SI intensity ~ ↑Glx	Adolescent sample. MDD + SI, MDD+ NSI, HC

Note: This table serves as a general summary, and is not a comprehensive review of existing literature
Abbreviations: DPARSF; data processing assistant for resting-state fMRI, DPABI; data processing & analysis for brain imaging, GMV; gray matter volume, HC; healthy controls, FC; functional connectivity, MDD; major depressive disorder; NSA; no suicide attempt; NSI; suicide ideation; VBM; voxel based morphometry

1.7 Focusing on Suicidal Ideation: Significance, Challenges and Neurobiology

Understanding the nature of human thought, let alone thoughts pertaining to suicide, has perplexed philosophers and scientists for centuries. The human mind has a natural tendency of drifting from one thought to another, a phenomenon termed as self-generated thought (SGT), which accounts for 30-50% of our wakeful thinking (Killingsworth and Gilbert, 2010; Andrews-Hanna, Smallwood and Spreng, 2014). SGT patterns, or "mind-wandering" occurs independently from external stimuli and appears to be the mind's default mode of operation. This default mode has a neurological signature known as the default mode network (DMN), a network of brain regions that are more active during relaxed, or passive states. Given the pervasive nature of mind wandering, and the consistent presence of the DMN among humans, its involvement is undeniably inherent to the human experience. Yet, its omnipresence does not exempt it from being maladaptive and has been shown to have an emotional cost (Killingsworth and Gilbert, 2010). While the mechanism of thought generation remains elusive, it is evident that excessive mind wandering has been associated with negative mood states, irrespective of the thought content (Killingsworth and Gilbert, 2010). Maladaptive SGT often manifests as rumination, which can perpetuate a vicious cycle, wherein negative thoughts and emotions reinforce each other, leading to a heightened sense of hopelessness, perceived burdensomeness, and a diminished ability to identify reasons for living (Orden *et al.*, 2010). This role may explain in part why the DMN has been so consistently implicated in mood disorders and suicide research. Patients may experience heightened rumination and reinforced negative emotions, contributing to the onset and escalation of suicidal thoughts. Moreover, the DMN is comprised of regions distributed across the ventromedial and lateral

prefrontal, posteromedial and inferior parietal, as well as the lateral and medial temporal cortices (Alves *et al.*, 2019), areas known to be involved in emotional regulation, decision making, self-referential processing and to be aberrant in mood disorders and suicide.

Resting-state neuroimaging studies have provided valuable insights into the neural correlates of spontaneous thought processes, although this technique cannot directly measure the influence of specific thoughts on neural activity. This approach relies heavily on reverse inference, using established knowledge about the functions of specific brain regions and networks, to extrapolate and infer their potential involvement in suicide-related phenomena. Few studies have focused their investigation directly on the neurobiological underpinnings of SI in patients with depression using functional neuroimaging. Among those that have, the DMN has emerged as reported network of interest in patients with MDD and SI, although results lack alignment. Unfortunately, methodological heterogeneity is a strong culprit contributing to the lack of converging findings. Studies vary drastically in terms of the clinical populations examined, depression and suicidal ideation severity status, and whether patients are being treated pharmacologically or are treatment naïve. As a result, study findings vary as well. For instance, Fatt et al. (2021) found that higher SI severity was associated with higher connectivity between DMN and striatal regions, as well as lower connectivity of the DMN and other limbic networks in participants aged 10-26 with unipolar or bipolar depression (Fatt *et al.*, 2021). Notably in this study, patients reported only mild depressive symptoms, and the statistical analyses were uncorrected. Similarly, Du et al. (2017) observed lower intrinsic functional connectivity between regions anchored in the DMN, particularly the right anterior cingulate cortex, orbitofrontal cortex, and right middle temporal pole, in patients with MDD with and without SI (Du *et al.*, 2017a). Markedly, these patients were drug-naïve with a single depressive episode, suggesting a less severe

clinical presentation. Ordaz et al. (2018) found lower levels of anterior subdivision of the DMN coherence was associated with greater lifetime severity of suicidal ideation, and completed a sophisticated analysis controlling for age, depression onset, and severity of depressive and anxiety symptoms within patients 14-17 years of age with MDD (Ordaz *et al.*, 2018). Notably, patients were mixed between treatment taking and treatment naïve. Although these findings show clear DMN involvement in suicidal ideation among patients with MDD, many studies have investigated the neurocircuitry of patients with relatively mild depression severity who are not in need of pharmacological treatment. While these studies still provide valuable insight, they may not be representative of the vulnerable individuals most at risk of suicide. Studying TRD has the potential to yield more clinically relevant and impactful findings that can inform suicide prevention and intervention strategies for those at highest risk.

Investigating brain function in isolation limits to our ability to elucidate the pathophysiology of suicide and depression. A concomitant understanding of brain structure is essential, as anatomical aberrations in brain structure may underlie alterations in brain network functioning. Unfortunately, few studies have explored the structural underpinnings of suicidal ideation. One study has reported a rare finding of reduced cortical thickness in frontoparietal regions and the insula (Taylor *et al.*, 2015a), while another found lower VLPFC thickness, but not volume, related to SI severity in adults with moderate MDD (Taylor *et al.*, 2015a). To our knowledge, those are the only two studies that have investigated the structural underpinnings of SI in MDD. Studying SI enhances our knowledge of the precursors of suicide attempt and has the potential to inform the development of effective treatments, interventions, and risk assessment tools. This information can allow us to intervene early, preventing individuals from advancing from SI to behaviours and attempts.

1.8 Study Rationale, Research Objectives and Hypothesis

This doctoral thesis will focus primarily on neurobiological alterations associated with suicidal thoughts and non-fatal SA history. Before delving into the neurobiological underpinnings, it is essential to accurately place the work of this thesis within the broader context on how it contributes to our understanding of suicide. Exploring the underlying neurobiology of suicide, particularly from a cross-sectional observational design perspective as conducted in our work, helps identify biological vulnerabilities that may be associated with increased suicide risk. In isolation and at present, neurobiological findings have limited clinical significance. Their true potential emerges when they are investigated alongside the exploration of how they influence traits or symptoms that heighten one's risk of suicide.

The question of whether neurobiological factors precede suicidal thoughts and behaviours, or result from them, cannot be resolved given the cross-sectional study design employed in this thesis. Addressing this question requires large-scale longitudinal studies with neuroimaging data collected prior to the emergence of any suicidal thoughts or behaviours, which do not yet exist. Instead, our work focuses on a single time point, offering insights into neural patterns associated with suicide risk.

1.8.1 Statement of research objectives and hypotheses

Research objective 1: To examine structural and resting-state functional MRI correlates of SI severity (Chapter 3).

Hypothesis: It was hypothesized that greater past-week SI severity would be associated with reduced cortical thickness and volumetric reductions in fronto-limbic regions, and aberrant functional connectivity among regions within the default mode, salience, frontoparietal and limbic networks.

Research objective 2: (A) To examine resting-state functional connectivity differences between healthy controls (HC), participants with TRD and lifetime history of SI but no history of SA (SI group), and participants with TRD and lifetime history of both SI and SA (SA group), and (B) to examine associations between functional connectivity and clinical features that differentiate SI and SA groups (Chapter 4).

Hypothesis: It was hypothesized that both the SI and SA groups would demonstrate comparable alterations in functional connectivity relative to the HC group. Additionally, it was expected that the SA and SI groups would show functional connectivity differences between regions involved in emotional regulation, memory, attention and rumination, specifically within the default mode, salience, frontoparietal, attention and limbic networks. It was further hypothesized that clinical measures associated with suicide risk would correlate with functional connectivity findings.

Research objective 3: (A) To compare neurometabolite concentrations, specifically glutamate (Glu), Glx (combined glutamine/glutamate), myo-inositol (mI), N-acetylasparatate (NAA), and creatine (Cr), in the dorsal ACC in participants with TRD compared to HC, and (B) to investigate associations between neurometabolite concentrations and suicide-related symptoms and behavioural traits including depression severity, SI severity, impulsivity and aggression (Chapter 5).

Hypothesis: It was hypothesized that in comparison to HC, participants with TRD would show lower Glu and Glx, and higher mI, NAA, and Cr concentrations. It was further hypothesized that clinical measures associated with suicide risk would correlate with neurometabolite findings.

Chapter 2: Methodological Approaches

2.1 Overview

The articles comprising this doctoral thesis are derived from a single cross-sectional multimodal neuroimaging study. A sample of individuals with TRD and age- and sex- matched HCs underwent clinical interviews, completed self-reported questionnaires, provided whole blood samples, and underwent a single MRI session to acquire structural, resting-state functional, diffusion-weighted, and ^{1}H-MRS imaging data. This section provides an overview of the study design and methodological approaches employed to acquire and analyse the data included in the three articles that comprise the thesis.

2.2 Participants

Participants diagnosed with MDD (age range, 18-65 years) were recruited from outpatient physician referrals to the University of Ottawa Institute of Mental Health Research Mood Disorders Research Unit, and the Royal Ottawa Mental Health Centre Mood and Anxiety Program between July 2017 and December 2022. Participants met the Diagnostic and Statistical Manual for Mental Disorders (DSM)-5 criteria for MDD with a current major depressive episode length of at least 6 months (American Psychiatric Association, 2013a). TRD was defined as lack of response following at least two trials of medication to treat depression from different drug classes at adequate dose and duration (Sackeim, 2001), as determined by the referring physician and confirmed by study investigators. Inclusion criteria included a score of ≥ 25 on the Montgomery-Åsberg Depression Rating Scale (MADRS; Montgomery and Asberg, 1979) and a score of ≥ 1 on the lifetime SI severity item of the Columbia Scale of Suicide Severity Rating Scale (C-SSRS; Posner et al., 2011). An age (± 2 years)- and sex- matched HC group was recruited via community advertisement and social media. HC participants had no lifetime DSM-5 axis 1 disorder diagnosis

assessed using the Research Version of the Structured Clinical Interview for DSM-5 (SCID-5-RV; First et al., 2015), nor a history of suicidal thoughts, behaviours or attempts as per the C-SSRS. Exclusion criteria for all study participants included a positive urine toxicology test for non-prescribed substances, pregnancy, a history of head injury with self-reported loss of consciousness, or a clinically relevant medical condition as deemed by study physician and investigators. Female participants of childbearing potential were scanned within the first 10 days of the menstrual cycle to minimize effects of endogenous ovarian hormone fluctuations (Dubol *et al.*, 2021). Informed written consent was obtained from all participants, and the study was approved by the Royal Ottawa Mental Health Centre Research Ethics Board.

2.3 Study Procedures

Eligibility Assessment. Once a patient referral was received in the Mood Disorder Research Unit, or a potential HC contacted the research team, participants were pre-screened by telephone and assessed for eligibility. Individuals not excluded through the phone screening were invited to attend a formal screening visit to determine eligibility.

Screening visit. Potentially eligible individuals attended a formal screening visit to evaluate study eligibility by assessing inclusion and exclusion criteria. Individuals first provided written informed consent. Participants then completed demographic and medical history questionnaires and provided a urine sample to screen for substance use and pregnancy. Individuals underwent a clinical interview where three scales were administered: 1) Structured Clinical Interview for DSM-5 Research Version (SCID-5-RV) to assess Axis 1 psychiatric diagnoses; 2) MADRS to assess severity of depressive symptoms, and 3) C-SSRS to assess lifetime, past month and past week history of suicidal thoughts, behaviours and attempt history. Individuals were invited to undergo an MRI simulator (or mock scanner) session to screen participants for claustrophobia or anxiety.

Study visit. Eligible participants were enrolled in the study following screening and they attended a study visit within approximately two weeks of screening. During this visit, participants underwent a clinical interview (which included administration of MADRS and past-week C-SSRS administered), completed self-report questionnaires (for detailed list of clinical and behavioural scales see section 2.5), underwent an MRI scan, and provided a blood sample (to measure peripheral inflammatory markers, such as interleukin-6, tumor necrosis factor-α and c-reactive protein). Exploration of blood-based biomarkers are beyond the scope of this thesis.

2.4 Magnetic Resonance Imaging

During the MRI session, participants underwent a brain scan in a 3T Siemens Biograph mMR PET-MR system (Magnetom Symphony Systems, Siemens, Erlangen, Germany). Acquisitions included T1-weighted structural data to quantify grey matter volumes and cortical thickness, fMRI to measure blood oxygen level dependent (BOLD) signal change during the resting state to assess functional connectivity, diffusion weighted imaging (DWI) data to assess white matter microstructure, and proton magnetic resonance spectroscopy (^{1}H-MRS) data to assess neurometabolite alterations. As mentioned above, the articles included in this doctoral thesis derive from analysis of structural, functional and MR spectroscopy data. DWI data from this study has been published (Annex A1, Vandeloo et al., 2023b).

2.4.1 MRI Basic Principles

As this thesis uses MRI technology, a brief overview of basic MR principles is presented within this section to provide readers with the foundational context necessary for interpreting subsequent methods and results.

MRI uses nuclear magnetic resonance coupled with gradients in strong magnetic fields to create images of biological tissue (Huettel, Song and McCarthy, 2014). The MR hardware has several principal components essential for image formation, including the magnet, gradient coils, radiofrequency (RF) coils, and computer system (Serai *et al.*, 2021). The magnet is responsible for the generation of a uniform magnetic field, with field strength measured in Teslas (T). The gradient coils generate spatially varying magnetic fields, with a magnetic field gradient in each direction (X, Y and Z). The RF coils are used to send RF pulses and receive the signal back from the patient's body. There are two main types of RF coils: the transmitter and receiver RF coils, and there is also sometimes a combined transmitter-receiver coil. The transmitter coil transmits a RF magnetic field to the imaging object, and the receiver RF coil detects the oscillation in magnetic field emerging from within the imaging object. The computer system controls the RF and gradient pulses, collects the data, and processes and displays the generated image. While comprehensive details on MRI physics are beyond the scope of this thesis, the following overview is informed by details described from works in MR physics literature (Lerch *et al.*, 2017; Martinez, 2018; Minas and Oliver, 2021).

During a typical MRI scan, the individual lies on the scanner table positioned within the bore of the MR machine, which is surrounded by a strong magnet. The magnet is responsible for the generation of a uniform magnetic field. Imaging formation in MRI relies heavily on the behaviours of hydrogen nuclei (^{1}H) in the human body and how they respond within a magnetic field. ^{1}H, or protons, are in constant motion, rotating about their axis like a spinning top, known as angular momentum or spin and each generate a small magnetic field. In the absence of an external magnetic field, the protons spin in random directions. Once an individual is placed within the MR scanner, the applied external magnetic field cause the protons spins to behave like bar magnets, with a net magnetization aligned with the direction of the magnetic field and begin to

precess (i.e., rotate around the axis of the external magnetic field). To acquire an image, the scanner captures information regarding changes in proton energy states. This is achieved through the RF coils, which transmit a RF pulse that excites the protons. This in turn shifts the net magnetization into from the longitudinal plane to the transverse plane, and causes the spins to precess in phase coherence, also known as resonance. The RF signal is next turned off, the protons revert to their original state, releasing energy in the process, which is detected using a RF receiving coil. The time constant for the ^{1}H to return to equilibrium is referred to as T1. The time accounting for the process by which spins are taken out of alignment with each other due to variations in the local tissue environment is referred to as T2. Different tissue types (e.g., white matter, gray matter, cerebrospinal fluid) emit different signal properties and intensities and this tissue-specific signal variations underlie the contrast observed in MRI which allow tissue identification.

2.4.2 Structural Magnetic Resonance Imaging

In contrast to the common metaphor of '*taking a picture of the brain'*, structural MRI is not a direct image of underlying neuroanatomy. Instead, it reflects signal contrasts from each voxel (a three-dimensional pixel), which are dependent on the density of protons within the voxel and the local environment (Lerch *et al.*, 2017). Derived measures such as neuroanatomical volumes or cortical thickness are sensitive to pulse sequence selections and MR strength, and exact measures may result in slight under- or over- estimates compared to postmortem truths. Advances in MRI technology have yielded anatomical imaging data that show remarkable similarities to postmortem brain tissue (Bigler, 2015).

2.4.2.1 FreeSurfer

FreeSurfer imaging analysis suite is a freely available software developed by the Laboratory of Computational Neuroimaging at the Athinoula A. Martinos Center for Biomedical Imaging (Fischl, 2012a). FreeSurfer provides an array of algorithms to quantify functional, connectional and structural properties of the human brain. Among the available functions, FreeSurfer conducts volumetric segmentation of most macroscopically visible brain structures, mapping of the thickness of cortical gray matter and the construction of surface models of the human cerebral cortex, all of which were used in this thesis. Whole brain group averaging of cortical thickness, cortical volume and pial surface can be calculated within FreeSurfer's Query, Design, Estimate, Contrast (QDEC) function (FreeSurfer, 2017).

Cortical thickness. The human cerebral cortex is a highly folded sheet of neurons, with thickness ranging from 1 and 4.5 mm and averaging 2.5 mm (Fischl, Dale and Raichle, 2000a). Cortical thickness alterations are often regionally specific, and provide insights into normal aging, neurodegeneration and psychiatric disorders. FreeSurfer enables automated measurements of cortical thickness by generating highly precise models of gray/white matter boundaries and pial surfaces, with calculated distances between these two surfaces defining cortical thickness (Fischl, Dale and Raichle, 2000a). Multiple validation studies, including direct comparisons against histological measurements, manual segmentation, and assessments of reliability with respect to scanner and sequence differences, have together provided strong evidence that cortical thickness output measures are accurate, stable, neurobiologically meaningful and clinically relevant (Fischl, 2012a).

Subcortical volume. Observed morphometric changes in psychiatric disorders often include variations in brain volume. While surface-based analyses can provide accurate information on the

cortex, volumetric techniques are required to detect changes in subcortical structures, such as the hippocampus, amygdala, thalamus, caudate and putamen (Fischl *et al.*, 2004a). FreeSurfer combines MR intensities and spatial information from a probabilistic atlas to calculate subcortical volume. The combined approach is necessary because tissue intensity of many subcortical structures overlap (gray matter and white matter have shown overlaps of over 12%), and therefore FreeSurfer incorporates spatial information, such as characteristic spatial patterns relative to one another (e.g., the amygdala is anterior and superior to the hippocampus) to identify subcortical structures and calculate volume (Fischl *et al.*, 2002a).

2.4.3 Resting State Magnetic Resonance Imaging

fMRI is a neuroimaging technique used to measure brain activity. Notably, fMRI does not provide a direct measure of brain activity but rather serves as an indirect proxy to neural activity, using inferences grounded in brain hemodynamic principles. The underlying concept is that when a brain region or network is activated, neural activity increases (i.e., neural firing, signaling processes) and local energy demand increases (Glover, 2011). To respond to this demand, vasodilation occurs, increasing local cerebral blood flow and delivering more oxygen and glucose to the area, a sequence of processes described as the hemodynamic response (Glover, 2011). Interestingly, more oxygen is delivered to the tissue than consumed, resulting in an increase in oxygenated hemoglobin and decreases in deoxygenated hemoglobin in the adjacent capillaries supplying the brain region. The change in oxygenation concentration is termed the BOLD contrast (Glover, 2011). fMRI techniques capitalize on the fact that oxygenated and deoxygenated blood have opposing magnetic properties. Oxygenated hemoglobin is diamagnetic, and magnetically indistinguishable from brain tissue. Deoxygenated hemoglobin, on the other hand, is paramagnetic and disrupts the local magnetic field, allowing detectable signal differences inferred as an indirect

measure of neural activity. There are several ways to acquire fMRI data, one of which being resting-state fMRI. This technique examines spontaneous brain function by using BOLD contrast in the absence of a task (Barkhof, Haller and Rombouts, 2014). Spatially distributed networks of temporal synchronization can be detected that can characterize resting state networks, such as the default mode, salience, visual, executive, dorsal attention and auditory networks. These networks are consistently observed across individuals, and alterations in their connectivity have been linked to a wide array and neurological and psychiatric disorders.

2.4.3.1 CONN Functional Connectivity Toolbox

The CONN functional connectivity toolbox is a free open-source software for the computation, display, and analysis of functional connectivity in fMRI. Developed by the Computational Neuroscience Research Lab, CONN offers an interactive graphic user interface (GUI) to preprocess functional and anatomical images, control for physiological and motion artifacts, quality controls and a wide array of connectivity analyses (Alfonso Nieto-Castanon, 2020). A series of default pre-defined regions from the HPC-ICA networks and the Harvard-Oxford atlas are available in the CONN toolbox and can be selected as region-of-interest (ROI) for analysis (Desikan *et al.*, 2006; Nieto-Castanon and Whitfield-Gabrieli, 2022).

Functional connectivity. In the context of resting-state fMRI, functional connectivity reflects the statistical interdependence of the BOLD signal of two or more brain regions during rest (Roell *et al.*, 2025). Simply put, functional connectivity refers to the degree of similarity of neural activation between different brain regions. The higher the statistical similarity between the neural activity of different brain regions is, the stronger both regions are assumed to be functionally connected.

2.4.4 Magnetic Resonance Spectroscopy

^{1}H-MRS is a non-invasive imaging technique used to quantify in vivo regional neurometabolite concentrations. Unlike conventional MRI, which detects signals from hydrogen nuclei predominantly from water, ^{1}H-MRS detects signals from hydrogen nuclei atoms from endogenous brain metabolites involved in key neurobiological processes such as glutamine (Gln), Glu, choline, gamma-aminobutyric (GABA), mI and NAA. In contrast to conventional MRI's whole-brain approach, a commonly used MRS technique is single voxel spectroscopy, which selects a specific ROI based on the research question, and acquires spectra from that localized region. The use of relatively large voxel size (2-8 cm^3) is required to achieve high-quality spectra, as the metabolites measured in ^{1}H-MRS are present at much lower concentrations (millimolar range, typically in concentrations of 0.5-10 mM) compared to water, resulting in lower signal-to-noise ratio (SNR) (Van Der Graaf, 2010; Currie *et al.*, 2013; Buonocore and Maddock, 2015). This larger voxel size also enables sufficient SNR to be achieved within a relatively short acquisition time, at the cost of reduced spatial resolution.

^{1}H-MRS output consists of an MR spectrum, a graphical display of signals arising from hydrogen protons as a function of frequency (see Figure 5). As outlined in section 2.4.1, when the RF pulse is switched off, proton nuclei realign with the external magnetic field. Relevant to ^{1}H-MRS, this realignment generates a decaying current known as the free induction decay (FID). Applying a Fourier transform, a mathematical technique that converts the raw signal, which changes over time, into a spectrum showing the different frequencies present and their intensities, transforms the FID and produces the MR spectrum (Burlina *et al.*, 2000). Of note, ^{1}H-MRS only detects protons, yet can distinguish different molecules. This is achieved because the nuclei are surrounded by electrons, which shield protons from the applied magnetic field in a way that affects

the local magnetic field, a phenomenon known as *electron shielding* (Burlina *et al.*, 2000). These subtle differences give rise to different peak frequencies in the MR spectrum, and this shift in frequency is referred to as the chemical shift (reported in parts per million). In addition to the influence of surrounding electrons, adjacent proton spins affect one another through bonding electrons, and cause resonance peaks to "*split*", a phenomenon known as *J-coupling* (or spin-spin coupling) (Buonocore and Maddock, 2015). This coupling introduces a distinct set of changes in frequencies that are identifiable on the spectrum. Together, chemical shifts, J-couple, among other influencing factors, generate characteristic spectral patterns that enable the identification of small molecules, i.e. neurometabolites, involved in neuronal metabolism and function.

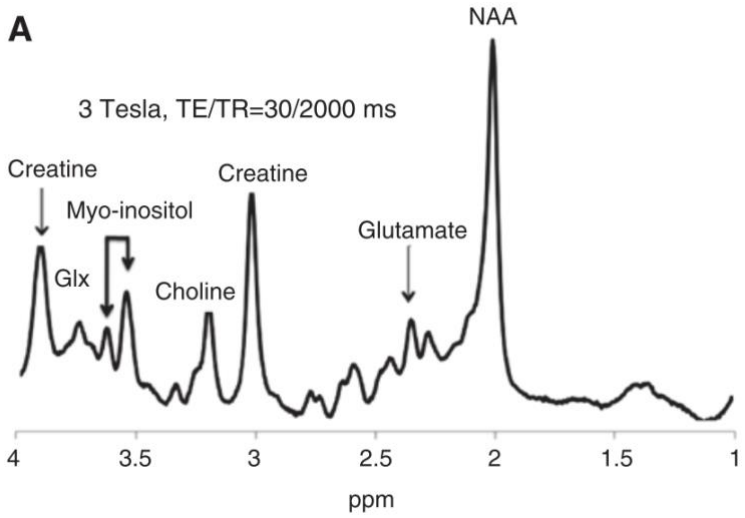

Image derived from Buonocore & Maddock. Reviews in the neurosciences journal (2015) 26(6):609-632

Figure 5. Sample ^{1}H-MRS spectra shown from the ACC at 3T. Image derived from (Buonocore and Maddock, 2015).

2.4.4.1 LC Model

Linear combination of model spectra (LCModel) is a widely used software package for the automatic quantification of in vivo MR spectrum, in which spectra are fitted to a model spectrum in a database resulting in intensity estimates of each measured metabolite (Provencher, 1993; Van Der Graaf, 2010). LCModel enables the reliable interpretation of complex, overlapping spectral patterns.

2.5 Clinical and Behavioural Measures

The following section describes the investigator- and self-rated questionnaires employed in this project.

2.5.1 Structured Clinical Interview for DSM-5 Research Version (SCID-5-RV)

The SCID-5-RV (First *et al.*, 2015b) is a semi structured clinical interview guide for making DSM-5 diagnoses. The scale is to be administered by a trained mental health professional and covers past and current psychiatric diagnoses including depressive disorders (persistent depressive disorder, major depressive disorder), psychotic disorders, substance use disorders, anxiety disorders, eating disorders and post-traumatic stress disorder.

2.5.2 Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS (Posner *et al.*, 2011a) is a semi-structured clinical interview designed to distinguish the domains of suicidal thoughts and behaviours. The scale is to be administered by a trained mental health professional and includes the '*Lifetime*' version, which assesses the most severe lifetime SI and lifetime history of suicidal behaviours and attempts, as well as the '*Since Last Visit*' version, which can be used to capture selected timeframes. In this study, the latter was used to assess SI severity over the past month and past week. A total of four constructs are

measured on the C-SSRS: 1) SI severity, rated on a 5-point ordinal scale (1=wish to be dead, 2=non-specific active suicidal thoughts, 3=active suicidal thoughts with methods (not plan) without intent to act, 4=active suicidal thoughts with methods and some intent to act, without specific plan, and 5=active suicidal thoughts with specific plan and intent), 2) SI intensity comprising five items, each rated on a 5-point ordinal scale: frequency, duration, controllability, deterrents, and reason for ideation, 3) behavioural subscale, rates on a nominal scale that includes actual, aborted, and interrupted attempts; preparatory behaviour; and non-suicidal self-injury, and 4) lethality, which assess actual attempts; actual lethality is rated on a 6-point ordinal scale, and if actual lethality is zero (indicating no or minimal medical damage), potential lethality associated with the attempt is rated on a 3-point ordinal scale. Potential lethality reflects the likelihood that the method used in the attempt could have caused serious harm or death, regardless of the actual medical outcome.

2.5.3 Montgomery-Åsberg Depression Rating Scale (MADRS)

The MADRS (Montgomery & Asberg 1979) is a 10-item structured clinical interview used to assess depressive symptom severity over the past week. The scale is to be administered by a trained mental health professional. The ten questions assess apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts and suicidal thoughts. Each question consists of a 6-point ordinal scale in which higher scores represent more elevated depressive symptoms. Raters followed the Structured Interview Guide for the MADRS (Williams and Kobak, 2008).

2.5.4 Beck Scale for Suicide Ideation (BSS)

The BSS (Beck, Kovacs and Weissman, 1979a) is a 21-item self-administered questionnaire to record SI severity over the past week. Each question consists of a 3-point ordinal scale with higher scores represent higher SI severity. The first 5 items serve as a screener for SI, specifically, if provides an answer of zero for items 4 and 5 (individuate no active SI), the participant can skip the subsequent 14 items and answer the final 2 regarding previous attempts (de Beurs *et al.*, 2015).

2.5.5 Beck Anxiety Inventory (BAI)

The BAI (Beck *et al.*, 1988) is a 21-item self-administered questionnaire to assess how specific situations had triggered anxiety. Each question consists of a 4-point ordinal scale with higher scores representing higher anxiety severity.

2.5.6 Beck Hopelessness Scale (BHS)

The BHS (Beck *et al.*, 1974) is a 20-item self-administered questionnaire utilized to assesses feelings about the future, motivation and expectations. Questions were measured through nominal true or false items, and higher total scores represent higher levels of experienced hopelessness.

2.5.7 Barratt Impulsiveness Scale (BIS-11)

The BIS-11 (Patton, Stanford and Barratt, 1995) is a 30-item self-administered questionnaire to assess trait impulsivity. This scale is arguably the most commonly administered self-report measure for the assessment of impulsiveness in both research and clinical settings (Stanford *et al.*, 2009). Each question consists of a 4-point ordinal scale with higher scores

representing higher impulsivity. The scale comprises 3 three main sub-traits: motor, cognitive, non-planning. The BIS-11 captures behavioural components of impulsivity across attentional (inability to focus attention or concentrate), motor (acting without thinking), and non-planning dimensions (lack of "*futuring*" or forethought) (Patton, Stanford and Barratt, 1995; Stanford *et al.*, 2009).

2.5.8 Buss Perry Aggression Questionnaire (BPAQ)

The BPAQ (Buss and Perry, 1992) is a 29-item self-administered to assess aggression in terms of physical aggression, verbal aggression, anger and hostility. Each question consists of a 5-point ordinal scale with higher scores representing higher aggression. Physical and verbal aggression measures the motor component of behaviour and involves harming others. Anger measures the emotional or affective component of behaviour involves physiological arousal and preparation for aggression. Hostility measures the cognitive component of behaviour and consists of feels of ill will and injustice (Buss and Perry, 1992).

2.5.9 Childhood Trauma Questionnaire – Short Form (CTQ-SF)

The CTQ-SF (Bernstein *et al.*, 2003) is a 28-item self-administered questionnaire to detect experiences of childhood abuse and neglect in adults and adolescents. Childhood trauma subscales include emotional abuse, physical abuse, sexual abuse, emotional neglect, physical neglect and minimization. Each question consists of a 5-point ordinal scale with higher scores in each subsection representing higher abuse and neglect severity.

Chapter 3: Structural and Functional Neuroimaging Correlates of Suicidal Ideation in Treatment-Resistant Major Depressive Disorder

3.1 Overview

This manuscript used structural MRI and resting-state fMRI techniques to study gray matter volume, cortical thickness, and functional connectivity correlates of SI in TRD.

3.2 Statement of author contribution

Patricia Burhunduli: Methodology, Software, Formal analysis, Investigation, Data Curation, Writing – Original draft, Writing – Review & Editing, Visualization, Project administration. **Katie Vandeloo**: Software, Investigation, Writing – Review & Editing, Project administration. **Zhuo Fang**: Software, Investigation, Writing – Review & Editing. **Pierre Blier**: Methodology, Resources, Writing – Review & Editing, Supervision. **Jennifer Phillips**: Conceptualization, Methodology, Resources, Writing – Review & Editing, Supervision, Project administration, Funding acquisition.

3.3 Title page

Structural and functional neuroimaging correlates of suicidal ideation in treatment-resistant major depressive disorder

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3.4 Significance Statement

Suicidal thoughts are widely recognized as a key indicator preceding to suicide attempts. Yet, despite substantial progress in the field, preventing suicide remains challenging. Investigating the relationship between the severity of suicidal thoughts and brain structure and function offers promise to enhance our understanding and reduce risk. Using structural and resting-state functional magnetic resonance imaging (MRI), we examined how suicidal ideation (SI) severity relates to cortical thickness, subcortical volume, and functional connectivity in individuals with treatment-resistant depression who had experienced SI. Our findings show that higher SI severity was associated with decreased cortical thickness in the right lateral occipital cortex, and lower functional connectivity between regions involved in emotional experience and cognitive processes. As SI can be amenable to treatment, identifying brain correlates of SI may provide insight on underlying neurobiological mechanisms and inform future treatment targets.

3.5 Abstract

Background: Treatment-resistant depression (TRD) is a severe form of major depressive disorder associated with elevated suicide risk. Identifying neurobiological markers of suicidal ideation (SI), a key modifiable risk factor, has important clinical implications. This study examined structural and functional magnetic resonance imaging (MRI) correlates of SI severity in individuals with TRD.

Methods: Structural and resting-state functional MRI data were collected from 41 participants with TRD and a history of SI. Investigator-rated past-week depression and SI severity was evaluated using the Montgomery-Åsberg Depression Rating Scale (MADRS) and the Columbia Scale of Suicide Severity Rating Scale (C-SSRS), respectively. Cortical thickness and subcortical gray matter volumes were measured using FreeSurfer, and resting-state functional connectivity measures were determined using the CONN functional connectivity toolbox. Associations between SI severity and cortical thickness, subcortical gray matter volume, and resting-state functional connectivity were assessed.

Results: Whole-brain vertex-wise surface-based structural analyses revealed a significant negative correlation between right lateral occipital cortical thickness and past-week SI severity, covaried for age, sex and depression severity ($p=0.03$, cluster-corrected). Network-based statistics analyses among 58 preselected regions of interest revealed a significant association between SI severity and resting-state functional connectivity between the right posterior parietal cortex and the left anterior insula, bilateral temporooccipital middle temporal gyrus and left frontal orbital cortex ($pFDR=0.017$), covaried for depression severity. Post-hoc analyses further characterized effects, revealing negative associations between SI and functional connectivity measures ($pFDR<0.0001$).

Conclusions: This multimodal imaging study identified distinct structural and functional

correlates of SI severity in TRD. These findings highlight the need to further investigate neurobiological markers of SI to better inform suicide risk assessments and intervention strategies in this high-risk population.

Keywords: Structural magnetic resonance imaging; Functional magnetic resonance imaging; Resting-state functional connectivity; Suicidal ideation; Treatment-resistant depression

3.6 Introduction

Suicide has long been recognized as a critical public health concern. Over the past two decades, an estimated 15.7 million individuals died by suicide globally (Ilic and Ilic, 2022). With over 720,000 recorded annual global deaths, suicide surpasses mortality rates of malaria, human immunodeficient virus/acquired immune deficiency syndrome (HIV/AIDS), breast cancer, war and homicide (World Health Organization, 2021c, 2025c). Despite extensive research in the field, understanding suicide remains difficult, in part due to its complex, multifactorial nature.

One of the clearest starting points for preventing suicide attempts is to mitigate suicidal thoughts, which are widely recognized as a precursor to suicide attempts and deaths (Klonsky, May and Saffer, 2016). Several theoretical models have aimed to explain the emergence and progression of suicidal ideation (SI). The interpersonal theory of suicide proposes that perceived burdensomeness and low belongingness, coupled with hopelessness about these perceptions, create a desire for suicide (Van Orden *et al.*, 2010). The integrated motivational-volitional theory proposes that feelings of defeat and entrapment are central to the onset of SI (O'Connor and Kirtley, 2018). While the theories and contributing mechanisms underlying thoughts of suicide may vary, the presence of SI itself represents a key modifiable risk factor for suicidal behaviours.

SI is a frequent and clinically significant symptom of a major depressive episode and is included among the diagnostic criteria for Major Depressive Disorder (MDD). Notably, treatment-resistant depression (TRD), typically defined as the failure to respond to at least two consecutive, mechanistically distinct treatments for depression, represents a severe form of MDD associated with higher rates of both SI and suicide attempts compared to non-resistant depression (Rush et al., 2006; Bergfeld et al., 2018; Orsini et al., 2022). While a significant proportion of patients with TRD experience suicidal thoughts to varying degrees, fewer progress toward making a suicide

attempt. This complicates risk prediction efforts, as nearly all individuals with depression who attempt suicide report SI, and predictors of ideation often mask as predictors of attempt and vice versa (Klonsky, May and Saffer, 2016; May and Klonsky, 2016).

To parse through these differences, the ideation-to-action framework of suicide proposes that the severity of SI is key to predicting suicide risk, suggesting that only severe SI confers meaningful risk of suicide attempt, whereas individuals with mild to moderate thoughts of suicide are less likely to progress to an attempt (Klonsky, May and Saffer, 2016; May and Klonsky, 2016). Supporting this framework, a recent longitudinal study found that among patients with mood disorders experiencing current SI, the most predictive risk factor for suicide attempt, regardless of prior attempt history, was higher SI severity (Nobile *et al.*, 2025b). These findings underscore the importance of clinical interventions that directly aim to target and reduce SI severity and intensity as an essential suicide prevention strategy (Nobile et al., 2025b).

Pharmacological treatment studies highlight the potential to mitigate SI and provide an opportunity to better understand its underlying neurobiological mechanisms. Suicide-related thoughts are fluid in nature, and subject to marked influence in response to pharmacological interventions. Intravenous ketamine, a rapid-acting treatment for depression, has demonstrated anti-SI effects at least partially independent of general depressive symptoms (Wilkinson *et al.*, 2018a; Phillips *et al.*, 2020; Hochschild, Grunebaum and Mann, 2021). Clozapine, lithium, and electroconvulsive therapy have also demonstrated transdiagnostic anti-SI effects, (Kellner *et al.*, 2005, 2016; Khan *et al.*, 2011; Sienaert *et al.*, 2022) as have several psychotherapy interventions, as depicted in a recent systematic review and meta-analysis (Van Ballegooijen *et al.*, 2025). Collectively, these findings provide indirect evidence that SI may, in part, arise from dysregulation within broader neural circuits involved in emotional regulation, cognitive control, and self-

referential processing. As such, targeted treatment of these underlying neurobiological mechanisms may offer a promising approach to reducing suicide risk, particularly in individuals with TRD.

Neuroimaging studies have begun to elucidate the neurobiological underpinnings of SI in MDD. While relatively few structural magnetic resonance imaging (sMRI) studies have been conducted in this field to date, existing findings report lower gray matter volume in the prefrontal cortex (PFC) and lower cortical thickness in the frontoparietal and insular regions among individuals with MDD and SI compared to individuals with MDD and no SI (Taylor *et al.*, 2015b; Schmaal *et al.*, 2020b; Zhang *et al.*, 2020; Vieira *et al.*, 2023b). Resting-state functional magnetic resonance imaging (fMRI) studies have been more extensively conducted, revealing functional connectivity differences between frontolimbic and temporal regions among individuals diagnosed with MDD experiencing SI compared to those without SI (Vieira *et al.*, 2023b). Specifically, resting-state functional connectivity aberrations have been reported between the amygdala and frontal and precentral gyri, as well as parietal regions (Li *et al.*, 2022). Furthermore, decreased resting-state functional connectivity has been reported between the right anterior cingulate cortex (ACC), orbitomedial prefrontal cortex (PFC), and the right middle temporal pole among individuals with MDD and SI compared to individuals with MDD and no SI (Du *et al.*, 2017b). Structural and functional neural disruptions may be central to the neurobiological alterations contributing to SI in MDD. Converging structural and functional findings across distinct and overlapping brain regions underscore the importance of using multimodal neuroimaging approaches to investigate the neurobiology of SI.

Most studies investigate SI through group comparisons, overlooking the nuances related to thoughts of suicide. Moving beyond traditional categorical comparisons (e.g., presence of SI vs.

no SI), a dimensional approach to studying SI severity may offer greater sensitivity in identifying neural correlates of symptom burden and thereby inform the development of mechanism-targeted interventions. TRD, a clinically complex and understudied subgroup of MDD, stands out as a critical population that may particularly benefit from such interventions; yet, limited research has been conducted in this patient population. In this study, we used sMRI and resting-state fMRI techniques to study cortical thickness, gray matter volume, and functional connectivity correlates of SI severity in the context of TRD. We hypothesized that higher SI severity would be associated with cortical thinning, volumetric reductions, and lower functional connectivity among brain regions implicated SI, such as those within the default mode, salience, frontoparietal, attention and limbic networks.

3.7 Materials and Methods

3.7.1 Participants

Participants (age range, 18-65 years) were recruited from outpatient physician referrals to the University of Ottawa Institute of Mental Health Research Mood Disorders Research Unit, and the Royal Ottawa Mental Health Centre Mood and Anxiety Program between July 2017 and December 2022. Participants met the Diagnostic and Statistical Manual for Mental Disorders (DSM)-5 criteria for MDD with a current major depressive episode length of at least 6 months (American Psychiatric Association, 2013a). TRD was defined an inadequate response following at least two trials of medication to treat depression from different drug classes at adequate dose and duration, (H. a Sackeim, 2001) as determined by the referring physician and confirmed by study investigators. Inclusion criteria included a score of ≥ 25 on the Montgomery-Åsberg Depression Rating Scale (MADRS;Montgomery and Asberg, 1979) and a score of ≥ 1 on the lifetime SI severity item of the Columbia Scale of Suicide Severity Rating Scale (C-SSRS; Posner et al.,

2011a). Exclusion criteria included a positive urine toxicology test for non-prescribed substances, pregnancy, a history of head injury with self-reported loss of consciousness, or a clinically relevant medical condition as deemed by study physician and investigators. Female participants of childbearing potential were scanned within the first 10 days of the menstrual cycle to minimize effects of endogenous ovarian hormone fluctuations (Dubol *et al.*, 2021). Informed written consent was obtained from all participants, and the study was approved by the Royal Ottawa Mental Health Centre Research Ethics Board.

3.7.2 Clinical Measures

DSM-5 Axis 1 diagnoses were assessed using the Research Version of the Structured Clinical Interview for DSM-5 (SCID-5-RV; First et al., 2015a). Depression severity was measured using the MADRS (Montgomery and Asberg, 1979). SI severity was evaluated using the investigator-rated C-SSRS (lifetime and past-week) and the self-reported Beck Scale for Suicide Ideation (BSS) (Beck, Kovacs and Weissman, 1979b; Posner *et al.*, 2011a). The C-SSRS SI severity item was used as the primary measure of SI, as it offers a structured, behaviourally anchored scale reflecting escalating SI severity, supporting clear interpretation of dimensional associations with neuroimaging measures. Suicide attempt history was assessed using the lifetime version of the C-SSRS, with suicide attempt defined as a potentially self-injurious act enacted with at least some wish to die. All scales had a Cronbach's alpha score of > 0.8.

Demographic, family history, and general medical information were obtained through self-report. The Antidepressant Treatment History Form (Sackeim *et al.*, 2019) was used to record and assess the medication trials in the current major depressive episode. Handedness was determined using the Edinburg Handedness Inventory (Oldfield, 1971a).

3.7.3 MRI Acquisition

A single scanning session was conducted for each participant on a 3T Siemens Biograph mMR PET-MR system (Magnetom Symphony Systems, Siemens, Erlangen, Germany) using a 32-channel receiving coil. T1-weighted sagittal sMRI images were acquired using a multi-echo magnetization-prepared rapid gradient echo (ME-MPRAGE) sequence (van der Kouwe *et al.*, 2008a) with the following parameters: TR=2530 ms, TE1=1.69 ms, TE2=3.55 ms, TE3=5.41 ms, TE4=7.27 ms, flip angle=7°, field of view= 256 mm2, number of slices=192, slice thickness=1 mm and voxel size=1.0 mm3. Resting-state fMRI data were acquired using a gradient echo echo-planar imaging (EPI) sequence with the following parameters: TE=34 ms, TR=2580 ms, flip angle=90°, field of view=192 mm x 192 mm, number of slices=42, slice thickness=3.0 mm and voxel size=3.0 mm3. Participants were instructed to focus on a fixation cross throughout the 7 min 52 sec resting-state fMRI acquisition.

3.7.4 Data Processing

3.7.4.1 Anatomical image processing

Raw images were converted from Digital Imaging and Communications in Medicine (DICOM) format to compressed Neuroimaging Informatics Technology Initiative (NIFTI) format using an open-source software (Li *et al.*, 2016a) and organized according to the Brain Imaging Data Structure (Gorgolewski *et al.*, 2016; Li *et al.*, 2016b). Images were then centered and aligned to a standardized position. Each output was inspected visually by a single rater (K.L.V.) for quality in 3D slicer (Fedorov *et al.*, 2012). Brain masks were created using an Advanced Normalization Tools (ANTs)-based script to delineate the boundaries of brain tissue versus skull (Billah, Bouix

and Rathi, 2019). Masks were manually inspected and corrected as needed using 3DSlicer, to eliminate instances of under- and/or over-segmentation.

Automated cortical reconstruction and volumetric segmentation was processed using the FreeSurfer imaging analysis suite (v.7.4.0) (Fischl, 2012b). The standard processing pipeline included motion correction and averaging, removal of non-brain tissue, automated Talairach transformation, segmentation of subcortical white matter and deep gray matter volumetric structures, intensity normalization, tessellation of the gray matter-white matter boundary, automated topology correction, and surface deformation following intensity gradients to optimally place gray matter-white matter and gray matter-cerebrospinal borders (Dale and Sereno, 1993; Sled, Zijdenbos and Evans, 1998; Dale, Fischl and Sereno, 1999; Fischl, Dale and Raichle, 2000b; Fischl, Liu and Dale, 2001; Fischl *et al.*, 2002b, 2004b; Ségonne, Pacheco and Fischl, 2007; Reuter, Rosas and Fischl, 2010). Individual reconstructed surfaces were then resampled onto Freesurfer's fsaverage standard space and smoothed at 5 mm full-width/half-max (FWHM) to prepare the data for group analysis. Images were automatically processed with the FreeSurfer longitudinal stream, with technical details published in prior publications (Reuter, Rosas and Fischl, 2010; Reuter *et al.*, 2012).

After structural preprocessing, quality control procedures were executed using automated and subjective visual inspection. The VisualQC medical imaging software library was used to identify outliers, poor-quality scans and assess anatomical accuracy of FreeSurfer parcellations (Raamana, 2022; Reddy Raamana et al., 2023). Skull stripping, delineation of gray matter-white matter boundaries and white matter intensity normalization were performed, and inaccuracies were visually inspected and manually corrected as necessary by a single rater (P.B.), blind to subject identity.

3.7.4.2 Functional image processing

FMRI processing was performed using the CONN functional connectivity toolbox (release 22.a) and the Statistical Parametric Mapping (SPM, release 12.7771) software (Friston *et al.*, 2007; Whitfield-Gabrieli and Nieto-Castanon, 2012; Nieto-Castanon and Whitfield-Gabrieli, 2022). The preprocessing pipeline included realignment with correction of susceptibility distortion interactions, SPM slice timing correction (interleaved top down slide order), outlier detection using Artifact Detection Tools thresholded at the 95th percentile, direct segmentation and MNI-space direct normalization using the default Tissue Probability Map, and smoothing using spatial convolution with a Gaussian kernel of 8 mm FWHM (Alfonso Nieto-Castanon, 2020). Additionally, a standard denoising pipeline was utilized (Alfonso Nieto-Castanon, 2020).

3.7.5 Statistical Analysis

3.7.5.1 Demographics and clinical variables

Descriptive statistical analyses of demographic and clinical variables were conducted using IBM SPSS version 29.0 (IBM Corp., Armonk, NY, USA).

3.7.5.2 Structural neuroimaging

Structural whole brain vertex-wise cortical thickness and regional subcortical volume correlational analyses were performed for SI severity measures. Whole-brain analyses were executed using FreeSurfer's suite of commands for preprocessing, general linear modeling (GLM) and multiple comparison correction (Jahn, 2009; Lamballais and Muetzel, 2021). Structural maps were resampled onto the standard fsaverage template, smoothed to 10 mm FWHM, analyzed using the Different Offset, Different Slope (DODS) method, (Greve, 2018) and cluster corrected at a vertex-wise threshold of 3.0 (corresponding to $p<0.001$).

Whole-brain techniques were limited to cortical surface measures, and subcortical volumetric analyses were conducted using a region-of-interest (ROI) approach. Subcortical ROIs included the bilateral hippocampus, amygdala, thalamus and caudate, and were selected based on known relevance to suicide (Schmaal *et al.*, 2020a; Vieira *et al.*, 2023a). Associations between subcortical volume and C-SSRS SI severity were measured using Pearson partial correlations. Bonferroni correction for multiple comparisons was implemented with a significance level of $p<0.0125$ ($p<0.05/4$ for each hemisphere). All analyses were bootstrapped with 1000 samples and bias corrected accelerated for confidence intervals, and missing values were excluded pairwise.

Right and left hemispheres were tested separately across all structural analyses. To account for confounding factors, whole-brain cortical thickness analyses included age, sex and MADRS total score as covariates, and regional subcortical volume analyses included total intracranial volume and MADRS total score as covariates.

3.7.5.3 Functional neuroimaging

For first-level analysis, ROI-to-ROI connectivity matrices were estimated to characterize the patterns of functional connectivity between each pair of regions among 58 ROIs. The ROIs selected included regions of the default mode network, salience network, dorsal attention network, frontoparietal network, language network, limbic network, visual network and additional relevant atlas regions (see Supplementary Material, Table S5). ROIs were selected among a series of default pre-defined regions from the HPC-ICA networks and the Harvard-Oxford atlas, available in the CONN toolbox (Desikan *et al.*, 2006; Nieto-Castanon and Whitfield-Gabrieli, 2022).

Linear regression analyses were performed in the CONN toolbox to examine the relationship between C-SSRS SI severity and functional connectivity among all preselected ROIs, with MADRS total scores included as a covariate. To account for multiple comparisons, network-based

statistics (NBS) inferential analyses were applied. Results were thresholded at p-uncorrected < 0.001 at the connection level, with a false discovery rate (FDR)-corrected p-value < 0.05 at the network mass/intensity level (Benjamini and Hochberg, 1995; Nieto-Castanon, 2020). A post-hoc analysis, restricted to regions comprising significant networks, were conducted to further characterize connections associated with C-SSRS SI severity, with depression severity (MADRS) as a covariate. To visualize the correlation scatter plots, functional connectivity values were extracted, and a linear regression was performed in SPSS to further assess the association between functional connectivity

3.8 Results

3.8.1 Participant Characteristics

A total of 46 participants with TRD and lifetime SI were enrolled in the study. Five participants were excluded from both sMRI and fMRI analyses: two did not undergo neuroimaging, two had incidental findings, and one had a coil-related artifact. An additional participant was excluded from the sMRI analysis but retained for the fMRI component due to a failed structural quality control check. The final dataset comprised 41 individuals with TRD (age range=18-65 years, M=45.6 years, SD=14.1, 46.3% female). All patients endorsed a lifetime history of SI and 36 (87.8%) reported presence of SI within the past-week (C-SSRS ≥ 1). Most study participants were White (n=35, 92.1%) and had a post-secondary education (n=33, 84.6%). Mean depression severity on the MADRS was marked-to-severe (M=34.5, SD=4.6), and most participants had experienced recurrent major depressive episodes (n=29, 78.4%). Mean past-week SI severity scores (M=2.1, SD=1.5), corresponding to non-specific active suicidal thoughts, and nearly half of participants endorsed a lifetime history of suicide attempt (n=20, 48.8%). Both rater-administered and self-reported past-week SI severity scores were positively correlated with

depression severity (total MADRS scores; CSSRS: r = 77, p<0.001, BCa 95% CI [0.69, 0.86]; BSS: r=0.89, p<0.001, BCa 95% CI [0.81, 0.96]). Detailed demographic and clinical characteristics of the sample are shown in Table 7. Participants' psychopharmacological treatments at the time of imaging are summarized in Supplementary Material, Table S6.

Table 7. Demographic and clinical characteristics of study participants.

Variables[a]	TRD (n=41)
Demographics	
Age, years, mean (SD)	45.6 (14.1)
Biological sex, n (%)	
Female	19 (46.3)
Male	22 (53.7)
Ethnicity, n (%)[b]	
BIPOC	3 (7.9)
White	35 (92.1)
Handedness, n (%)[c]	
Right/Left/Ambidextrous	32/1/6
Education status, n (%)[c]	
Post-secondary education	33 (84.6)
No post-secondary education	6 (15.4)
Employment status, n (%)[d]	
Employed or student	19 (47.5)
Seeking work or disability	21 (52.5)
Marital status, n (%)[d]	
Married or Common law	22 (55.0)
Single	18 (45.0)
Living arrangement[d]	
Living with others	32 (80.0)
Living alone	8 (20.0)
Depression	
MADRS, mean (SD)	34.5 (4.6)
Age of MDD onset, years, range, mean (SD)e	12-60, 28.8 (13.1)
Depressive episodes e	
Single	8 (21.6)
Recurrent	29 (78.4)
Length of current depressive episode, years, mean (SD)f	5.0 (5.8)

Suicide	
C-SSRS Suicide ideation severity past-week, mean (SD)	2.1 (1.5)
C-SSRS Suicide ideation severity past-week, item distribution, n (%)	
No SI	5 (12.2)
Wish to be dead	15 (36.6)
Non-specific active SI	5 (12.2)
Active SI with methods, without intent	9 (22.0)
Active SI with some intent, without specific plan	3 (7.3)
Active SI with plan and intent	4 (9.8)
BSS Suicide ideation severity, mean (SD)[d]	12.8 (8.2)
Suicide attempt, lifetime, n (%)	
Actual	20 (48.8)
Interrupted	2 (4.9)
Aborted	4 (9.8)
Suicide behaviour, lifetime, n (%)	28 (68.3)

Abbreviations: BIPOC, Black, Indigenous and People of Colour; MADRS, Montgomery Åsberg Depression Rating Scale; MDD, Major Depressive Disorder; C-SSRS, Columbia-Suicide Severity Rating Scale; SI, Suicidal Ideation; BSS, Beck Scale for Suicide Ideation.

[a] All participants were included in the fMRI dataset. One participant was excluded from the sMRI dataset due to failed quality control check
[b] BIPOC participants included Black (n=1), Latin American/Hispanic (n=1) and South Asian (n=1). Data missing for 3 participants
[c] Data missing for 2 participants
[d] Data missing for 1 participant
[e] Missing for 4 participants
[f] Missing for 5 participants

3.8.2 Neuroimaging

3.8.2.1 Neuroimaging correlates of SI severity

sMRI. Whole-brain vertex-wise surface-based analysis revealed a significant negative correlation between cortical thickness in the right lateral occipital cortex and past-week SI severity as measured by the C-SSRS, after controlling for age, sex and depression severity ($p=0.03$, cluster-wise correction for multiple comparisons; Figure 12). No significant correlations were found between subcortical volume in predefined ROIs (bilateral hippocampus, amygdala, thalamus and caudate) and C-SSRS scores (p-Bonferroni corrected > 0.0125, data not shown).

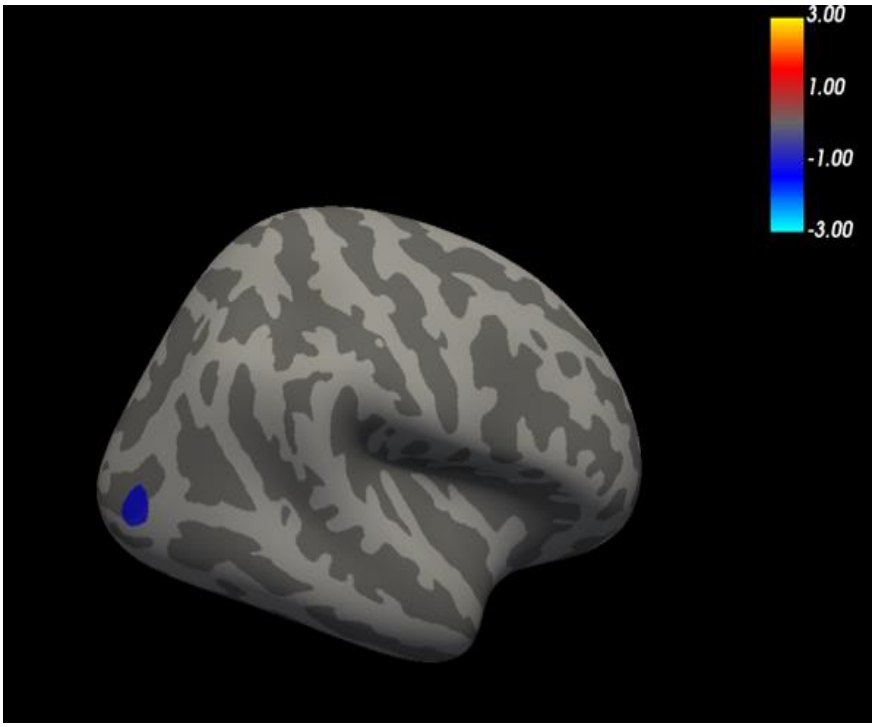


Figure 12. Right lateral view indicating the cluster in the lateral occipital cortex where cortical thickness was significantly negatively correlated with past-week SI severity, as measured by the C-SSRS, in participants with TRD. The blue cluster represents the significant region (cluster size: 180.0 mm2, MNI coordinates: 36.6, -81.2, 2.2, peak z-value: -4.6, p=0.03 cluster-wise correction for multiple comparisons).

fMRI. Functional connectivity analyses within the preselected 58 ROIs examined associations with past-week C-SSRS SI severity among patients in 1653 connections. NBS analyses revealed a significant association between C-SSRS SI severity scores and functional connectivity between the right posterior parietal cortex and four regions: the left anterior insula, bilateral temporooccipital middle temporal gyrus, and left frontal orbital cortex, after controlling for depression severity (Mass=137.12, pFDR=0.017; Figure 13). Post-hoc analyses further characterized these effects, revealing significant negative correlations between C-SSRS SI and functional connectivity between right PCC and the four identified regions (left anterior insula, bilateral temporooccipital middle temporal gyrus and left frontal orbital cortex; Figure 13, Table 8).

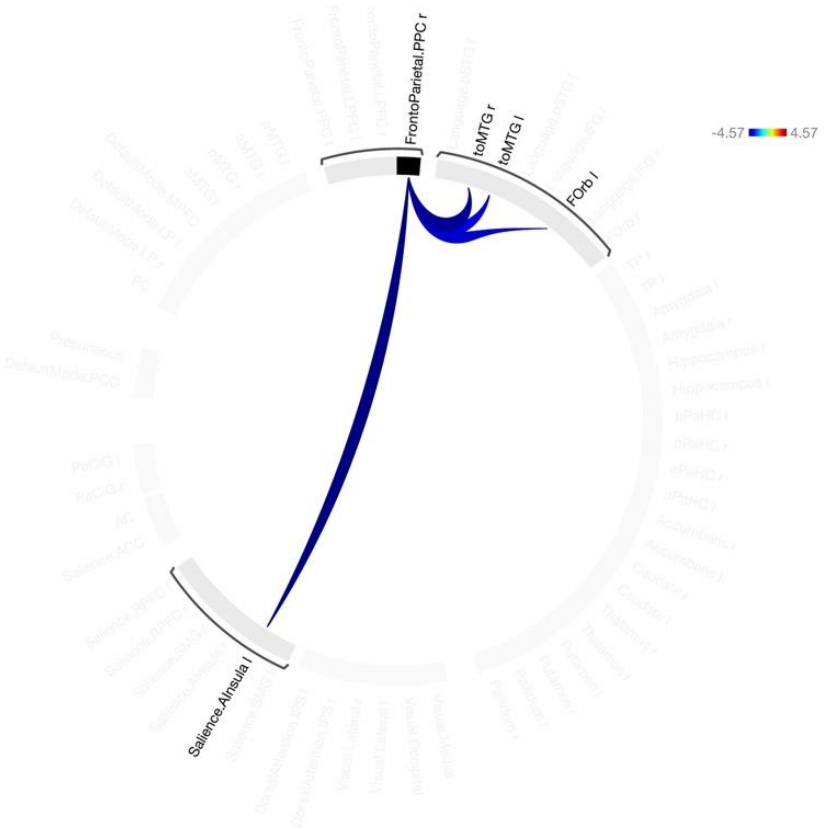


Figure 13. Connectome ring diagram of functional connectivity correlations with C-SSRS SI severity among participants with TRD. Legend represents resting-state functional connectivity strength and direction. Blue lines represent connections with significantly lower resting-state functional connectivity with higher C-SSRS SI severity (Mass=137.12, pFDR=0.017). Findings survived connection threshold of p-uncorrected < 0.001 and cluster threshold p-FDR < 0.05 network-level (NBS mass/intensity).

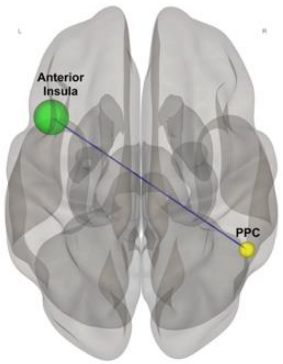
Abbreviations: l,left hemisphere; r,right hemisphere; FOrb, frontal orbital cortex; PPC, posterior parietal cortex; toMTG, temporooccipital middle temporal gyrus

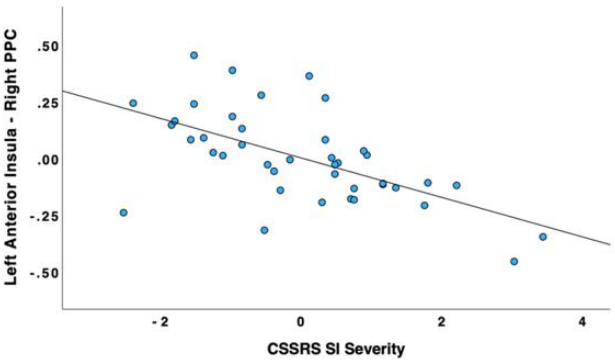
Table 8. Network and connection level functional connectivity associations with C-SSRS SI severity

Network	Statistics*	p-FDR	Connections	β	T (38)	p-uncorrected	p-FDR
1	137.12	0.017	Right posterior parietal cortex - Left anterior insula	-0.09	-4.57	0.000050	0.00018
			Right posterior parietal cortex - Left frontal orbital cortex	-0.07	-3.85	0.00044	0.00059
			Right posterior parietal cortex – Right temporooccipital middle temporal gyrus	-0.12	-4.37	0.000093	0.00018
			Right posterior parietal cortex – Left temporooccipital middle temporal gyrus	-0.08	-3.71	0.00067	0.00067

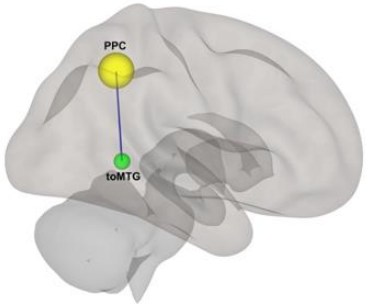
* Mass: sum of T-test statistics over all connections within the network

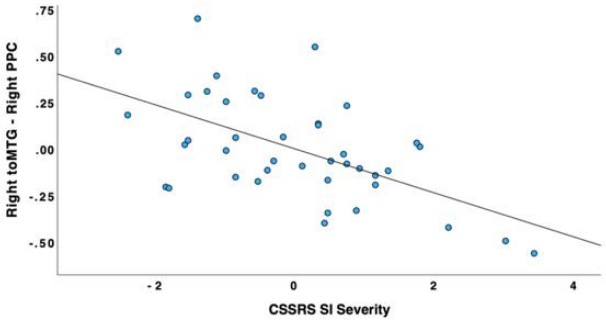
A


Anterior Insula
PPC

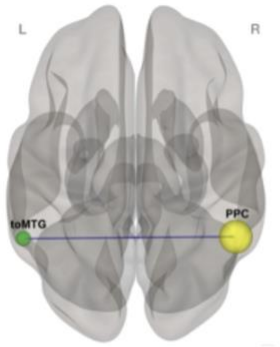

Left Anterior Insula - Right PPC
.50
.25
.00
-.25
-.50
-2
0
2
4
CSSRS SI Severity

B


PPC
toMTG


Right toMTG - Right PPC
.75
.50
.25
.00
-.25
-.50
-2
0
2
4
CSSRS SI Severity

C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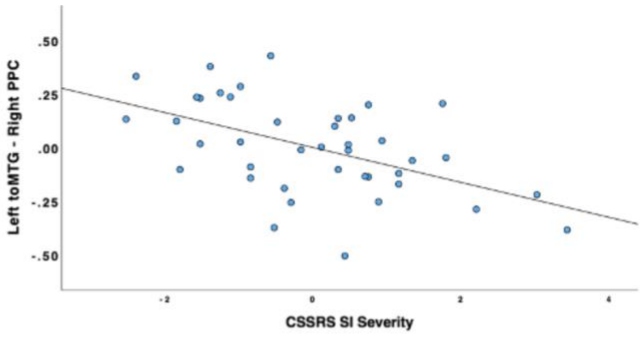
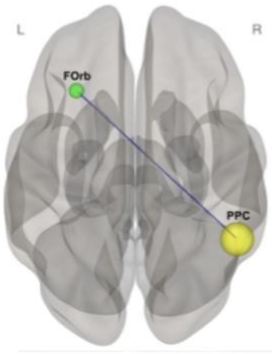
toMTG
PPC


Left toMTG - Right PPC
.50
.25
.00
-.25
-.50
CSSRS SI Severity

D


L
R
FOrb
PPC

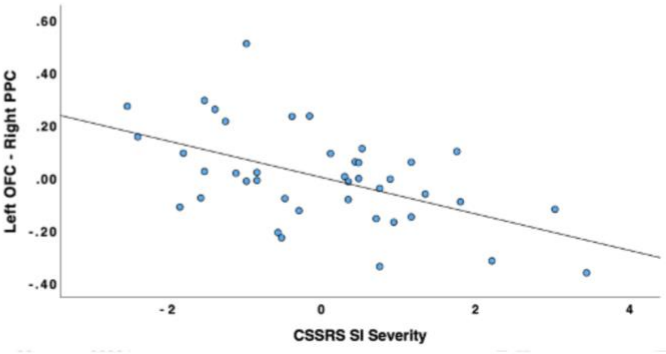

Left OFC - Right PPC
.60
.40
.20
.00
-.20
-.40
-2
0
2
4
CSSRS SI Severity

Figure 14. Relationship between functional connectivity residuals and CSSRS SI severity residual scores covaried for MADRS total score. Regression analyses revealed negative associations between SI severity (C-SSRS scores) and functional connectivity (FC) values in the following region pairs: (A) Left anterior insula and right posterior parietal cortex (PPC) (β=-0.09, p-FDR=0.0018); (B) Left temporooccipital middle temporal gyrus (toMTG) and right PPC (β=-0.08, p-FDR=0.00067); (C) Right toMTG and right PPC (β =-0.12, p-FDR=0.00018); (D) Left frontal orbital cortex (FOrb) and right PPC (β=-0.07, p-FDR=0.00059).

3.9 Discussion

This study examined structural and functional correlates of SI severity in a rigorously characterized sample of individuals with TRD. Unlike most prior research, which has relied on binary classifications of suicide-related outcomes (e.g., presence vs. absence of suicide attempt history), we assessed SI along a dimensional spectrum, capturing its varying degrees of severity. This approach more closely reflects the clinical reality of SI and its relevance to identifying individuals at elevated risk for suicide attempts. Furthermore, by focusing specifically on individuals with TRD, a subgroup often underrepresented in neuroimaging literature, this study directly addresses a common limitation of previous work, which often fails to account for the clinical heterogeneity of MDD.

Structural neuroimaging findings showed increased past-week SI severity was associated with reduced cortical thickness in the left lateral occipital cortex. Functional neuroimaging findings revealed resting-state functional connectivity was negatively associated with C-SSRS SI severity between the right posterior parietal cortex and the left anterior insula, the left frontal orbital cortex and the bilateral temporooccipital middle temporal gyrus. All associations remained significant after controlling for concurrent depression severity (MADRS total scores), a valuable distinction given the ongoing challenge of isolating suicide-specific neural correlates from those of depression more broadly.

With respect to the relationship between thoughts of suicide and brain anatomy, our structural findings were limited to reduced cortical thickness in the lateral occipital cortex. Although this region has not been directly linked to SI in individuals with MDD, previous studies have reported structural and functional alterations in parieto-occipito-temporal regions in individuals with suicide attempt history across various psychiatric diagnoses (van Heeringen,

Bijttebier and Godfrin, 2011; Kang *et al.*, 2020c). In addition, a recent resting-state functional connectivity study in adolescents with MDD identified the lateral occipital cortex as being associated with suicidal thoughts and behaviours (Schreiner, Klimes-Dougan and Cullen, 2019). While lateral occipital cortex involvement may seem unexpected given its primary role in visual processing, there is emerging evidence of visual cortex dysfunction in depression reported in both clinical and preclinical studies (Wu *et al.*, 2023). Its potential relevance to mood disorders is further supported by findings that repetitive transcranial magnetic stimulation targeting the occipital cortex can produce antidepressant effects (Guan *et al.*, 2021; Zhang *et al.*, 2021). Although further research is needed to delineate how occipital cortex alterations relate to mood disorders and suicide, (Wu *et al.*, 2023) our findings suggest this region warrants further investigation.

Functional connectivity analyses provide unique and complementary insights into the neural underpinnings of SI. In our sample, higher past-week SI severity, as measured by the C-SSRS, was associated with lower resting-state functional connectivity between the right posterior parietal cortex and the left anterior insula, bilateral temporooccipital middle temporal gyrus, and left frontal orbital cortex. In essence, the right posterior parietal cortex emerged as a core seed region exhibiting dispersed functional connectivity differences across a wide array of regions. This widespread involvement is unsurprising considering its role as an integration hub for many motor and sensory brain regions (Whitlock, 2017a) The right posterior parietal cortex, a key region of the frontoparietal network, is involved in selective attention, emotional processing and executive control (Whitlock, 2017b). In MDD, reduced function of the right posterior parietal cortex may contribute to selective attention bias towards negative stimuli, a clinical feature observed in some patients (Guo *et al.*, 2024). While direct studies on the role of the posterior parietal cortex in suicide are limited, its function in attention allocation may be relevant to understanding suicidal thoughts.

Individuals with severe SI often exhibit persistent negative thought patterns, difficulties disengaging from suicidal thoughts, and challenges shifting attention toward positive stimuli, characteristics that may be partially mediated by impaired posterior parietal cortex function (Cha *et al.*, 2010).

Lower functional connectivity between the posterior parietal cortex and the anterior insula in association with increased SI severity may reflect alterations in self-referential processing. The anterior insula plays a crucial role in emotional experiences, subjective feelings, social affect, empathy, self-relatedness, and a sense of agency (Northoff *et al.*, 2006; Jollant, Lemogne and Fossati, 2017). The clinical relevance of functional connections between the posterior parietal cortex and the insula with respect to suicide is not fully understood; however, disrupted connections may impact the balance between higher order cognitive and emotional processes. This disruption may help explain altered self-perceptions implicated in suicide, potentially mediating feelings of thwarted belongingness and perceived burdensomeness (Jollant, Lemogne and Fossati, 2017). Furthermore, such disruption may bias attention toward persistent negative self-referential thoughts and rumination related to suicide. Finally, decreased functional connectivity between the posterior parietal cortex and the frontal orbital cortex further highlights the complex interplay of cognitive and emotional processes in SI. These two regions work in concert, contributing to a broad range of cognitive functions including reward processing and attention (Olsen *et al.*, 2019; Reiten *et al.*, 2023). This finding complements our previous work in the same sample showing altered white matter microstructure and elevated free water in the inferior fronto-occipital fasciculus (IFOF), a white matter tract connecting the posterior parietal and frontal orbital cortices, which differentiated individuals with suicide attempt history from those with SI only (Vandeloo *et al.*, 2023a). The IFOF tract is a large association bundle that connects occipital, temporal and

parietal regions to the frontal lobe, with reported connections to the lateral occipital lobe, areas implicated in the present study through cortical thinning and reduced functional connectivity associations with SI severity (Wu, Sun, Wang and Wang, 2016; Palejwala *et al.*, 2020). While the relevance of these cross-modal observations remains correlational and speculative, alterations in structural connectivity may contribute to the observed disruptions in functional connectivity. These findings suggest a possible convergence across modalities, though this remains preliminary and requires further investigation (Fjell et al., 2017).

In line with prior studies investigating neural correlates of SI, the present work reveals limited structural but widespread functional associations. This pattern may reflect the differing susceptibilities for change between neural anatomy and function. The brain is a highly dynamic system, with functional patterns fluctuating alongside momentary changes in mental and emotional states, which are readily captured by functional neuroimaging measures (Yang *et al.*, 2022). In contrast, neuroanatomical features, which are also subject to time-dependent changes, typically occur at a much slower rate (Storsve *et al.*, 2014). Neuroanatomical alterations may only manifest following prolonged, sustained periods at a particular level of SI severity, rather than momentary fluctuations. Future research should therefore consider longitudinal designs that track structural and functional changes alongside SI severity changes over time.

Notwithstanding its strengths, the present study poses limitations to be considered. First, the sample size was modest. Despite recruitment challenges associated with attaining a clinically robust treatment-resistant sample, significant findings emerged after controlling for multiple comparisons, indicating robust results even with a modest sample size. Notably, participants with major psychiatric comorbidities, including posttraumatic stress disorder, obsessive compulsive disorder, eating disorders, substance use disorders, and psychosis were excluded, resulting in a

more homogenous sample that reduces confounding effects but may limit generalizability to more clinically diverse populations. Second, the cross-sectional study design limits causal and temporal inferences regarding the relationship between neuroimaging correlates and SI. Third, the relatively short duration of the resting-state fMRI acquisition may affect the reliability of the functional connectivity estimates (Birn *et al.*, 2013). Fourth, current medication regimen and illness chronicity (duration and number of major depressive episodes) varied significantly between participants, with illness chronicity ranging from weeks to years. These confounding factors could not be considered due to a lack of statistical power. Fifth, selection bias was apparent, as most participants were White and completed post-secondary education, failing to depict a representative population. Finally, this study did not include a control group, as the primary aim was to examine dimensional associations of SI severity within a TRD sample.

To conclude, our findings reveal widespread neural involvement in the pathophysiology of SI severity in TRD. Since SI may be amenable to treatment, examining the full spectrum of suicidal thoughts and behaviours, alongside retrospective suicide attempt history, can provide unique insights critical to the characterization of suicide neurobiology. Multimodal approaches are warranted, and multi-site collaborative studies may help overcome sample size limitations.

3.10 Supplementary Material

Table S5. Resting-state functional connectivity regions of interest.

	Regions of Interest
Default mode network	Medial prefrontal cortex (1, 55, -3)
	Left lateral parietal (-39, -77, 33)
	Right lateral parietal (47, -67, 29)
	Posterior cingulate cortex (1, -61, 38)
	Precuneus
Salience network	Anterior cingulate cortex (0, 22, 35)
	Left anterior insula (-44, 13, 1)
	Right anterior insula (47, 14, 0)
	Left rostral prefrontal cortex (-32, 45, 27)
	Right rostral prefrontal cortex (32, 46, 27)
	Left supramarginal gyrus (-60, -39, 31)
	Right supramarginal gyrus (62, -35, 32)
Dorsal Attention Network	Left intraparietal sulcus (-39, -43, 52)
	Right intraparietal sulcus (39, -42, 54)
Frontoparietal Network	Left lateral prefrontal cortex (-43, 33, 28)
	Right lateral prefrontal cortex (41, 38, 30)
	Left posterior parietal cortex (-46, 58, 49)
	Right posterior parietal cortex (52, -52, 45)
Language network	Left inferior frontal gyrus (-51, 26, 2)
	Right inferior frontal gyrus (54, 28, 1)
	Left posterior superior temporal gyrus (-57, -47, 15)
	Right posterior superior temporal gyrus (59, -42, 15)
Limbic network	Left parahippocampus anterior division
	Right parahippocampus anterior division
	Left parahippocampus posterior division
	Right parahippocampus posterior division
	Left thalamus
	Right thalamus
	Left amygdala
	Right amygdala
	Left hippocampus
	Right hippocampus
	Left caudate
	Right caudate
	Left putamen
	Right putamen
Visual network	Medial (2, -79, 12)
	Occipital (0, -93, -4)
	Left Lateral (-37, -79, 10)

	Right Lateral (38, -72, 13)
Additional regions	Left paracingulate gyrus
	Right paracingulate gyrus
	Anterior cingulate gyrus
	Posterior cingulate gyrus
	Left pallidum
	Right pallidum
	Left accumbens
	Right accumbens
	Left frontal orbital cortex
	Right frontal orbital cortex
	Left anterior middle temporal gyrus
	Right anterior middle temporal gyrus
	Left posterior middle temporal gyrus
	Right posterior middle temporal gyrus
	Left temporooccipital middle temporal gyrus
	Right temporooccipital middle temporal gyrus
	Left temporal pole
	Right temporal pole

Table S6. Psychopharmacological treatment regimen of participants with treatment-resistant depression.

Medication Drug Class	**n (%)**
Selective serotonin reuptake inhibitors[a]	15 (41.7)
Serotonin norepinephrine reuptake inhibitors[b]	16 (44.4)
Moclobemide	2 (5.6)
Bupropion	6 (16.7)
Mirtazapine	6 (16.7)
Vortioxetine	3 (8.3)
Dopamine/serotonin antagonists[c]	4 (11.1)
Brexpiprazole	8 (22.2)
Pramipexole	0 (0.0)
Buspirone	1 (2.8)
Lithium	1 (2.8)
Modafinil	0 (0.0)
Lamotrigine	8 (22.9)
Methylphenidate/lisdexamfetamine	2 (5.6)
Gamma-aminobutyric acid positive allosteric modulator	4 (11.4)
Ion channel blocker[d]	1 (2.8)

[a]Includes citalopram, esciptalopram, fluoxetine, sertraline
[b]Includes desvenlafaxine, duloxetine, levomilnacipran, venlafaxine
[c]Includes asenapine, lurasidone, olanzapine, quetiapine, risperidone
[d]Includes gabapentin

Chapter 4: Differentiation Suicide Risk in Treatment-Resistant Depression: Clinical and Functional Imaging Correlates of Suicidal Ideation and Attempt

4.1 Overview

In the present study, we used resting-state fMRI to identify functional connectivity differences between HCs, and TRD participants with a lifetime history of SI only (SI group), and those with a lifetime history of both SI and suicide attempt (SA group). While neuroimaging approaches have been used to identify potential biomarkers of suicide risk, such findings often lack clear clinical relevance without understanding their relationship with clinical and behavioural profiles. To address this gap, we extended our analysis beyond group-level functional connectivity comparisons to examine associations between functional connectivity alterations and clinical features that may differentiate SI and SA groups, exploring hopelessness, anxiety, depression, aggression, impulsivity, and childhood trauma. We hypothesized that both the SI and SA groups would demonstrate alterations in functional connectivity relative to healthy controls. Additionally, we expected that the SA and SI groups would show functional connectivity differences between regions involved in emotional regulation, memory, attention and rumination, specifically within the default mode, salience, frontoparietal, attention and limbic networks. Finally, we hypothesized that clinical measures associated with suicide risk would correlate with these functional connectivity alterations.

4.2 Statement of author contribution

Patricia Burhunduli: Methodology, Software, Formal analysis, Investigation, Data Curation, Writing – Original draft, Writing – Review & Editing, Visualization, Project administration. **Zhuo Fang**: Software, Formal analysis, Investigation, Writing – Review & Editing. **Katie Vandeloo**: Software, Investigation, Writing – Review & Editing, Project administration. **Fariba Sharmin**: Formal analysis, Writing – Review & Editing. **Pierre Blier**: Methodology, Resources, Writing – Review & Editing, Supervision. **Jennifer Phillips**: Conceptualization, Methodology, Resources, Writing – Review & Editing, Supervision, Project administration, Funding acquisition.

4.3 Title Page

Differentiating Suicide Risk in Treatment-Resistant Depression: Clinical and Functional Imaging Correlates of Suicidal Ideation and Attempt

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(ID: NICL-25-847).

4.4 Abstract

Background: Treatment-resistant depression (TRD) is associated with elevated suicide risk. While many individuals with TRD experience suicidal ideation (SI), only a subset progress to suicide attempts (SA). This study identifies resting-state functional connectivity (FC) differences between individuals with TRD who experience SI only and those with SA history, and examines how these neural differences relate to clinical and trait-level suicide risk factors.

Methods: Resting-state functional MRI data were acquired from 41 individuals with TRD and lifetime SI, including 21 with no SA history (SI group) and 20 with a lifetime SA (SA group), alongside 47 age- and sex-matched healthy controls. FC was measured using the CONN FC toolbox. Associations between clinical features and connectivity markers explored the clinical relevance of neural differences.

Results: Group-level network-based statistics analyses identified FC differences among 11 ROIs and 9 connections (p-FDR < 0.05). The SA group exhibited lower FC than the SI group between the right anterior insula and bilateral anterior parahippocampal gyri (right: pFDR=0.02; left: pFDR=0.04), the left anterior middle temporal gyrus (pFDR=0.04), and higher FC between the right anterior parahippocampal gyrus and the left amygdala (pFDR=0.01). Within the SA group, SI severity (p=0.005), anxiety severity (p < 0.001), and childhood sexual abuse scores (p <0.001) were independent predictors of FC between the left amygdala and right anterior parahippocampal gyrus.

Conclusion: This study highlights distinct neural signatures associated with SI and SA in individuals with TRD in regions implicated in emotional memory and self-referential processing.

These neural markers meaningfully relate to clinical features and may differentiate SI and SA in TRD, advancing our understanding of suicide risk.

Keywords: Functional magnetic resonance imaging; Resting-state functional connectivity; Suicidal ideation; Suicide Attempt, Clinical Symptoms, Treatment-resistant depression; Major depressive disorder

4.5 Highlights

- Functional neuroimaging distinguishes suicidal ideation from attempts in depression
- Functional connectivity broadly higher in suicide ideator compared to attempt group
- Amygdala-parahippocampal connection positively linked to suicidal ideation severity
- Amygdala-parahippocampal connectivity inversely linked to anxiety and sexual abuse
- Connectivity-clinical symptom link seen only in those with suicide attempt history

4.6 Introduction

We are in urgent need of more effective tools and strategies to better understand, prevent and predict suicide. Every year, over 720,000 individuals lose their lives to suicide worldwide (World Health Organization, 2024). Depression is of particular concern with respect to suicide risk, as major depressive disorder (MDD) is the most prevalent psychiatric condition among those who die by suicide (Dong *et al.*, 2019; Cai *et al.*, 2021; McQuaid *et al.*, 2022). Individuals with difficult-to-treat depression, commonly known as treatment-resistant depression (TRD), face an even higher risk, as approximately one-third of individuals with TRD attempt suicide at least once in their lifetime (Bergfeld et al., 2018).

Despite decades of effort, suicide risk assessment remains challenging. Current approaches rely primarily on subjective self-report and clinical judgement, which, while informative, often fall short. This is underscored by the fact that a large proportion of individuals who die by suicide seek care from health professionals in the time leading up to their death (Luoma, Martin and Pearson, 2002; Stene-Larsen and Reneflot, 2019). While many individuals with depression experience suicidal ideation (SI), significantly fewer go on to make a suicide attempt (SA) (Klonsky, May and Saffer, 2016; Porras-Segovia *et al.*, 2023). The challenge in discerning who is at risk of an attempt among those experiencing suicidal thoughts lies, in part, in the inherently complex and nuanced nature of suicide. Suicidal behaviour exists along a spectrum, ranging from thoughts of ending one's life to plans, preparatory behaviours, and attempts; with each representing distinct phenomena that may involve unique predictors and underlying mechanisms (Klonsky, May and Saffer, 2016). Characterizing differences between individuals with a history of SI only and those with both a history of SI and SA, through integration of biological, clinical, and trait-

level factors, may enhance our understanding of suicide and complement traditional risk assessment strategies.

In recent years, empirically driven neurobiological research has contributed significantly to our understanding of heuristic biological models of suicidal behaviour (Sudol and Mann, 2017). A promising approach has been resting-state functional connectivity, which provides a window into the intrinsic functional organization of the brain at rest and has been used to reveal associations between neural connectivity patterns and suicidal thoughts and behaviours. Evidence suggests that the most relevant neural networks associated with suicide (attempt and/or ideation) are the default mode, salience and frontoparietal networks, with relevant contributions from the cognitive control network (Dobbertin *et al.*, 2023). More specifically, decreased internetwork connectivity between the default mode, salience, fronto-parietal and insula networks have been reported in patients with depression and suicidal behaviours compared to those without, potentially reflecting psychological processes related to suicidal vulnerability (Cao *et al.*, 2019; Jung *et al.*, 2020; Ishikawa *et al.*, 2022). Regions within language, visual and limbic networks have also been implicated in both SA history and SI severity (Olié *et al.*, 2024; Averill *et al.*, 2025; V. C. H. Chen *et al.*, 2025).

To date, only one review has specifically examined brain correlates of SI and SA as distinct phenomena, a notable strength given that most studies aggregate SI and SA, a common practice that likely obscures meaningful differences and contributes to ongoing limitations in suicide prediction (Vieira et al., 2023). The review identified frontal, limbic and temporal alterations associated with SI and, comparatively, frontal, limbic, parietal and basal ganglia alterations associated with suicidal behaviours. However, these findings are largely drawn from MDD patient populations with few studies making direct comparisons between individuals with SI only and those with a history of SI and SA within the same TRD population.

In the present study, we used resting-state functional magnetic resonance imaging (fMRI) to examine functional connectivity differences among healthy controls and TRD participants with a lifetime history of SI only (SI group), and those with a lifetime history of both SI and SA (SA group). While neuroimaging has been used to identify potential biomarkers of suicide risk, such findings often lack clear clinical utility without understanding their relationship with clinical and behavioural profiles. To address this gap, we extended our analysis beyond group-level functional connectivity comparisons to examine associations between functional connectivity alterations and clinical features that may differentiate SI and SA groups, exploring hopelessness, anxiety, depression, aggression, impulsivity, and childhood trauma. We hypothesized that both the SI and SA groups would demonstrate comparable alterations in functional connectivity relative to healthy controls. Additionally, we expected that the SA and SI groups would show functional connectivity differences between regions involved in emotional regulation, memory, attention and rumination, specifically within the default mode, salience, frontoparietal, attention and limbic networks. Finally, we hypothesized that clinical measures associated with suicide risk would correlate with these functional connectivity findings.

4.7 Methods

4.7.1 Participants

Participants diagnosed with MDD (age range 18-65 years) were recruited from outpatient physician referrals to the University of Ottawa Institute of Mental Health Research Mood Disorders Research Unit and the Royal Ottawa Mental Health Centre Mood and Anxiety Program between July 2017 and December 2022. Participants met the Diagnostic and Statistical Manual for Mental Disorders (DSM)-5 criteria for MDD (American Psychiatric Association, 2013b) with a current major depressive episode lasting at least 6 months. TRD was defined as a lack of response

following at least two trials of medication to treat depression from different drug classes at adequate dose and duration (Sackeim, 2001), as determined by the referring physician and confirmed by study investigators. Inclusion criteria included a score of ≥ 25 on the Montgomery-Åsberg Depression Rating Scale (MADRS; (Montgomery and Asberg, 1979), a score of ≥ 1 on the lifetime SI severity item of the Columbia Scale of Suicide Severity Rating Scale (C-SSRS; Posner et al., 2011). Exclusion criteria included all DSM-5 Axis 1 comorbid disorders apart from unipolar depressive disorders and generalized anxiety disorder, as well as receipt of electroconvulsive therapy or ketamine within the 6 weeks preceding the study.

An age (± 2 years)- and sex- matched healthy comparison (HC) group had no lifetime DSM-5 Axis 1 disorder diagnosis assessed using the Research Version of the Structured Clinical Interview for DSM-5 (SCID-5-RV; First et al., 2015), nor any history of suicidal thoughts, behaviours or attempts as per the C-SSRS. Exclusion criteria for all study participants included a positive test for non-prescribed substances, pregnancy, a history of head injury with self-reported loss of consciousness, or a clinically relevant medical condition as deemed by the study physician and investigators. Female participants of childbearing potential were scanned within the first 10 days of the menstrual cycle, estimated from the self-reported date of last menstrual period, to minimize the effects of endogenous ovarian hormone fluctuations (Dubol *et al.*, 2021). Informed written consent was obtained from all participants, and the study was approved by the Royal Ottawa Mental Health Centre Research Ethics Board.

4.7.2 Clinical Measures

DSM-5 Axis 1 diagnoses were assessed using the SCID-5-RV (First et al., 2015). Depression severity was measured using the MADRS (Montgomery and Asberg, 1979). SA history was

assessed using the investigator-rated C-SSRS, with SA defined as a potentially self-injurious act enacted with at least some wish to die (Posner et al., 2011). SI severity was evaluated using the C-SSRS (lifetime and past-week; Posner et al., 2011) and the self-rated Beck Scale for Suicide Ideation (past-week, BSS; Beck, Kovacs and Weissman, 1979). Additional clinical and trait assessments included the Beck Anxiety Inventory (BAI; Beck et al., 1988), Beck Hopelessness Scale (BHS; Beck et al., 1974), Barratt Impulsivity Scale (BIS-11; Patton, Stanford and Barratt, 1995), Buss-Perry Aggression Questionnaire (BPAQ; Buss and Perry, 1992) and Childhood Trauma Questionnaire (CTQ; Bernstein et al., 2003). All scales had a Cronbach's alpha score of > 0.8. Demographic, family history, and general medical information were obtained through self-report. The Antidepressant Treatment History Form (Sackeim *et al.*, 2019) was used to record and assess medication trials during the current major depressive episode. Handedness was determined using the Edinburgh Handedness Inventory (Oldfield, 1971).

4.7.3 MRI Acquisition

A single scanning session was conducted for each participant on a 3T Siemens Biograph mMR PET-MR system (Magnetom Symphony Systems, Siemens, Erlangen, Germany) using a 32-channel receiving coil. T1-weighted sagittal sMRI images were acquired using a multi-echo magnetization-prepared rapid gradient echo (ME-MPRAGE) sequence (van der Kouwe *et al.*, 2008a) with the following parameters: TR=2530 ms, TE^1=1.69 ms, TE^2=3.55 ms, TE^3=5.41 ms, TE^4=7.27 ms, flip angle=7°, field of view=256 mm^2, number of slices=192 and slice thickness=1 mm. Resting-state fMRI data were acquired using a gradient echo echo-planar imaging (EPI) sequence with the following parameters: TE=34 ms, TR=2580 ms, flip angle=90°, field of view=192 mm x 192 mm, number of slices=42, slice thickness=3.0 mm. Participants were instructed to focus on a fixation cross during the resting-state acquisition, which lasted 7 minutes

52 seconds. Diffusion-weighted images (DWI) and MR spectroscopy data were also acquired during the imaging session, with DWI findings published separately (Vandeloo et al., 2023).

4.7.4 Functional Image Preprocessing

Resting-state fMRI processing was performed using the CONN functional connectivity toolbox (release 22.a) and Statistical Parametric Mapping (SPM, release 12.7771) software (Friston *et al.*, 2007; Whitfield-Gabrieli and Nieto-Castanon, 2012; Nieto-Castanon and Whitfield-Gabrieli, 2022). T1-weighted structural images were used for anatomical segmentation, normalization and co-registration steps within the CONN pipeline. The preprocessing pipeline included realignment with correction of susceptibility distortion interactions, SPM slice timing correction (interleaved top-down slice order), outlier detection using Artifact Detection Tools thresholded at the 95th percentile, direct segmentation and MNI-space direct normalization using the default Tissue Probability Map and smoothing using spatial convolution with a Gaussian kernel of 8 mm full-width at half-maximum (FWHM) (Alfonso Nieto-Castanon, 2020). Additionally, a standard denoising pipeline was utilized (Alfonso Nieto-Castanon, 2020).

4.7.5 Statistical Analysis

4.7.5.1 Demographics and clinical variables

Statistical analyses were conducted using IBM SPSS version 29.0 (SPSS Science, Chicago, IL, USA). Demographic and clinical variables were compared across SI, SA and HC groups using one-way ANOVAs for continuous variables and chi-square tests for categorical variables. Pairwise comparisons were conducted using independent samples t-tests or chi-square tests as appropriate.

4.7.5.2 Resting-state functional connectivity

For first-level analysis, ROI-to-ROI connectivity matrices were estimated to characterize the patterns of functional connectivity between each pair of regions among 58 ROIs. The ROIs selected included regions of the default mode network, salience network, dorsal attention network, frontoparietal network, language network, limbic network, visual network and additional relevant atlas regions (see Table S5 in Chapter 3). ROIs were selected among a series of pre-defined regions from the HPC-ICA networks and the Harvard-Oxford atlas, available in the CONN toolbox (Desikan et al., 2006; Nieto-Castanon and Whitfield-Gabrieli, 2022).

Group-level analyses were performed using GLMs in the CONN functional connectivity toolbox. A one-way ANOVA was conducted to examine functional connectivity differences across all predefined ROIs between SI, SA, and HC groups. To identify ROI-to-ROI connection differences, we employed Network Based Statistics (NBS). Results were thresholded using a combination of cluster-forming p-uncorrected < 0.001 at the connection-level threshold and p-false discovery rate (FDR) < 0.05 at the network-mass level (Benjamini and Hochberg, 1995; A Nieto-Castanon, 2020). Functional connectivity pairs showing significant group effects from the ANOVA were selected for post-hoc pairwise group comparisons. Bonferroni correction for multiple comparisons was implemented, with a significance level of pFDR ≤ 0.0167 (0.05/3 pairwise comparisons). A subsequent covariate-adjusted analysis was conducted to compare the SA and SI groups, with depression severity (MADRS total score) included as a covariate at a significance level of pFDR < 0.05.

To assess associations between functional connectivity and clinical features of suicide risk among patient participants, linear regression analyses were performed. Functional connectivity values showing significant SI- and SA-group differences in the covariate-adjusted analysis were

entered as dependent variables. Independent variables included clinical and trait features that differed significantly between the SI and SA groups. Specifically, these included self-rated suicidal ideation severity (BSS scores), anxiety severity (BAI scores), physical aggression (BPAQ physical aggression subscale) and childhood sexual abuse (CTQ sexual abuse subscale). Depression severity (MADRS total scores) was included in the model as a covariate of no interest to statistically control for its potential confounding effect. These models were corrected for multiple comparisons using a Bonferroni-adjusted significance level of $p \leq 0.0125$ ($p<0.05/4$ identified functional connectivity pairs).

4.8 Results

4.8.1 Participant Characteristics

The final sample included 88 individuals comprising 41 individuals with TRD and a lifetime history of SI (n=21 with no attempt history [SI group], and n=20 with a lifetime suicide attempt history [SA group]), and 47 age- and sex- matched control participants (HC group) (Figure S1). All participants with TRD endorsed a lifetime history of SI and 35 (88%) reported presence of SI within the past-week (C-SSRS ≥ 1). Detailed demographic and clinical characteristics are shown in Table 9. Age and sex distributions were comparable across groups ($p>0.05$). Most study participants were White (n=64, 83%) and had completed post-secondary education (n=79, 92%). There were no significant between-group differences for handedness, ethnicity, marital status, or living alone versus with others (all $p>0.05$).

Among TRD participants, mean depression severity on the MADRS was marked to severe in the SI group (M=33.10, SD=4.9) and severe in the SA group (M=36.05, SD=3.9), and most patient participants experienced recurrent major depressive episodes (n=29, 78.4%). Both TRD groups had an average past-week SI severity score corresponding to non-specific active suicidal

thoughts (SI group: M=1.8, SD=1.6, SA-group: M=2.35, SD=1.5). On clinical scales, the SA group had significantly higher anxiety severity (p=0.003), depression severity (p=0.04), sexual abuse scores (p=0.003), and physical aggression (p=0.02) compared to the SI group. Bonferroni correction were applied for multiple comparisons involving subscales, specifically those assessing childhood trauma and aggression. Participants' psychopharmacological treatments at the time of imaging are summarized in Supplementary Material Table S6 (see Chapter 3).

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Table 9. Demographic and clinical characteristics of study participants

Variables	SA Group (n=20)	SI Group (n=21)	HC (n=47)	Statistics	SA vs SI	SA vs HC	SI vs HC
Demographics							
Age, years, mean (SD)	46.6 (15.6)	44.6 (12.9)	44.3 (14.2)	$F(2, 85)= 0.185$, $p=0.83$	$t_{39}=0.46$, p = 0.65	$t_{65}=0.58$, p = 0.57	$t_{66}=0.064$, p = 0.95
Biological sex, n (%)							
Female	12 (33.3)	7 (33.3)	21 (44.7)	$X^2_2= 2.96$,	$X^2_1=2.93$, p	$X^2_1=1.32$, p	$X^2_1=0.77$,
Male	8 (40.0)	14 (66.7)	26 (55.3)	p= 0.23	= 0.087	= 0.25	p= 0.38
Ethnicity, n (%) [a]							
BIPOC	1 (5.0)	2 (9.5)	11 (23.4)	$X^2_2= 5.21$,	$X^2_1= 0.26$,	$X^2_1=3.64$, p	$X^2_1=2.41$,
White	17 (85.0)	18 (85.7)	29 (61.7)	p= 0.07	p= 0.61	= 0.06	p= 0.12
Handedness, n (%) [b]							
Right/Left/Ambidextrous	17/0/2 (85.0/0.0/10.0)	15/1/4 (71.4/4.8/19.0)	38/4/5 (80.9/8.5/10.6)	$X^2_4= 3.03$, p= 0.55	$X^2_2= 1.77$, p= 0.41	$X^2_2= 1.74$, p= 0.42	$X^2_2= 1.21$, p= 0.55
Education status, n (%) [c]							
Post-secondary education	15 (75.0)	18 (85.7)	46 (97.9)	$X^2_2= 5.08$,	$X^2_1=0.42$, p	**$X^2_1=4.76$, p**	$X^2_1=3.88$,
No post-secondary education	3 (15.0)	3 (14.3)	1 (2.1)	p= 0.08	= 0.84	**= 0.03**	p = 0.05
Employment status, n (%) [d]							
Employed or student	11 (55.0)	8 (38.1)	46 (97.9)	**$X^2_2=31.1$, p<0.001**	$X^2_1=1.57$, p	**$X^2_1=18.36$,**	**$X^2_1=31.72$**
Seeking work or disability	8 (40.0)	13 (61.9)	1 (2.1)		= 0.21	**p<0.001**	**, p<0.001**
Marital status, n (%) [d]							
Married or Common law	8 (40.0)	14 (66.7)	30 (63.8)	$X^2_2=3.20$,	$X^2_1=2.43$, p	$X^2_1=2.61$, p	$X^2_1=0.05$,
Single	11 (55.0)	7 (33.3)	17 (36.2)	p = 0.20	= 0.12	= 0.11	p = 0.82
Living arrangement, n (%) [d]							
Living with others	13 (65.0)	19 (90.5)	41(87.2)	$X^2_2=4.43$,	$X^2_1=3.03$, p	$X^2_1=3.22$, p	$X^2_1=0.15$,
Living alone	6 (30.0)	2 (9.5)	6 (12.8)	p = 0.11	= 0.08	= 0.07	p = 0.70
Depression							
MADRS, mean (SD)	36.05 (3.9)	33.10 (4.9)	0.43 (0.8)	**$F(2, 85)= 1357.92, p<0.001$**	**$t_{39}=2.13$, p=0.04**	**$t_{65}=60.10$, p<0.001**	**$t_{66}=44.72$, p<0.001**

Age of MDD onset, years, range, mean (SD) [e]	12-51, 25.9 (12.1)	14-60, 30.9 (13.6)	-	-	t_{35}=1.15, p=0.26	-	-
Depressive episodes [e] Single Recurrent	 3 13	 5 16	-	-	X^2_1=0.14, p = 0.71	-	-
Length of current depressive episode, years, mean (SD) [f]	5.8 (7.8)	4.4 (3.7)	-	-	t_{34}=0.75, p=0.46	-	-
Suicide							
C-SSRS Suicide Ideation Severity past-week, mean (SD)	2.35 (1.5)	1.8 (1.6)	-	-	t_{39}=1.25, p=0.22	-	-
Suicide Ideation Severity (BSS), mean (SD) [d]	16.05 (7.5)	9.9 (7.8)	0.04 (0.3)	***F*(2, 84)=73.47,*p*<0.001**	**t_{38}=2.56, p=0.015**	**t_{64}=14.80, p<0.001**	**t_{66}=8.69, p<0.001**
Suicide attempt, lifetime, n (%) Actual Interrupted Aborted	20 (100.0) 5 (25.0) 5 (25.0)	0 (0.0) 2 (9.5) 4 (19.0)	-	-	X^2_1=41.00, **p<0.001** X^2_1=1.73, p = 0.19 X^2_1=0.21, p = 0.645	-	-
Suicide behaviour, lifetime, n (%)	20 (100.0)	8 (38.1)	-	-	**X^2_1=18.1, p<0.001**	-	-
Clinical							
Comorbid Diagnosis Generalized Anxiety Disorder, current, n (%)	9 (45.0)	11 (52.4)	-	-	X^2_1=0.22, p=0.64	-	-
Hopelessness (BHS), mean (SD) [d]	17.0 (3.8)	15.9 (3.6)	1.7 (1.6)	***F*(2, 84)=307.86,*p*<0.001**	t_{38}=0.93, p=0.36	**t_{64}=23.20, p<0.001**	**t_{66}=22.37, p<0.001**

Anxiety Severity (BAI), mean (SD) [d]	23.5 (7.2)	17.4 (9.6)	1.8 (1.9)	**$F(2, 84)=110.83, p<0.001$**	**$t_{38}=2.26$, p=0.03**	**$t_{64}=19.29$, p<0.001**	**$t_{66}=10.76$, p<0.001**
Childhood Trauma (CTQ), mean (SD) * [d]	12.8 (5.5)	11.6 (5.0)	6.6 (2.9)	**$F(2, 84)=19.91, p<0.001$**	p=1.00	**p<0.001**	**p<0.001**
Emotional Abuse, mean (SD)	7.1 (2.7)	7.1 (2.4)	6.0 (1.9)	$F(2, 84)=2.78, p=0.07$	p=1.00	p=0.22	p=0.15
Physical Abuse, mean (SD)	9.3 (6.5)	5.6 (1.6)	5.5 (2.0)	**$F(2, 84)=8.69, p<0.001$**	**p=0.003**	**p<0.001**	p=1.00
Sexual Abuse, mean (SD)	15.05 (5.4)	17.6 (4.7)	7.9 (3.5)	**$F(2, 84)=43.80, p<0.001$**	p=0.20	**p<0.001**	**p<0.001**
Emotional Neglect, mean (SD)	8.4 (3.3)	7.05 (2.5)	5.7 (1.7)	**$F(2, 84)=8.97, p<0.001$**	p=0.23	**p<0.001**	p=0.11
Physical Neglect, mean (SD)							
Aggression (BPAQ), mean (SD) *							
Physical Aggression, mean (SD) [d]	19.00 (7.4)	14.6 (3.4)	13.8 (4.3)	**$F(2, 82)=7.23, p=0.001$**	**p=0.02**	**p<0.001**	p=1.00
Hostility, mean (SD) [d]	25.5 (9.6)	22.95 (6.4)	13.0 (3.5)	**$F(2, 82)=37.95, p<0.001$**	p=0.58	**p<0.001**	**p<0.001**
Verbal Aggression, mean (SD) [c]	13.4 (4.3)	11.1 (5.5)	11.4 (3.4)	$F(2, 82)=1.79, p=0.17$	p=0.28	p=0.27	p=1.00
Anger, mean (SD) [c]	17.9 (6.2)	14.8 (5.4)	11.0 (3.7)	**$F(2, 82)=14.41, p<0.001$**	p=0.13	**p<0.001**	**p=0.01**
Impulsivity (BIS), mean (SD)*							
Attention, mean (SD) [d]	21.2 (4.9)	20.3 (4.2)	13.4 (3.3)	**$F(2, 82)=37.88, p<0.001$**	p=1.00	**p<0.001**	**p<0.001**
Motor, mean (SD) [c]	23.2 (4.3)	21.8 (4.4)	20.4 (3.3)	**$F(2, 82)=3.76, p=0.03$**	p=0.75	**p=0.03**	p=0.48
Non-planning, mean (SD) [c]	27.4 (6.6)	28.4 (4.7)	18.8 (3.6)	**$F(2, 82)=41.26, p<0.001$**	p=1.00	**p<0.001**	**p<0.001**

Abbreviations: BIPOC, Black, Indigenous and People of Colour; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, Major Depressive Disorder; C-SSRS, Columbia-Suicide Severity Rating Scale; BSS, Beck Scale for Suicide Ideation; BHS, Beck Hopelessness

Scale; BAI, Beck Anxiety Inventory; CTQ, Childhood Trauma Questionnaire, BPAQ, Buss-Perry Aggression Questionnaire; BIS, Barrett Impulsivity Scale.

*post-hoc tests with Bonferroni correction for multiple comparisons

[a] BIPOC SA participants included and South Asian (n=1). BIPOC SI participants included Black (n=1) and Latin American/Hispanic (n=1). BIPOC HC participants included Arab (n=1), Black (n=5), Chinese (n=1), Latin American/Hispanic (n=1), Southeast Asian (n=1), West Asian (n=1), Other (n=1). Data missing for 7 participants
[b] Data missing for 2 participants (n=1 SA-group and n=1 SI-group)
[c] Data missing for 2 participants (n=2 SA-group)
[d] Data missing for 1 participant (n=1 SA group)
[e] Missing for 4 participants (n=4 SA group)
[f] Missing for 5 participants (n=4 SA group, n=1 SI group)

4.8.2 Neuroimaging

4.8.2.1 Between-group neuroimaging comparisons

Functional connectivity analyses within the 58 preselected ROIs examined 1653 connections between the SI, SA and matched HC groups. NBS identified two networks of interconnected regions, one comprising five connections and the other comprising four, that showed significant group differences in functional connectivity. Findings are summarized in Figure 15 and Table S9.

Post hoc analysis findings are summarized in Figure 16 and Table S8. To further investigate connectivity differences specifically between patient participant groups, covariate-adjusted analyses comparing the SA and SI groups were conducted in four functional connectivity pairs, with depression severity (MADRS total score) included as a covariate. Findings revealed significantly lower functional connectivity in the SA group compared to the SI group between the right anterior insula and three target regions: bilateral anterior parahippocampal gyri (right: T(38)=3.3, pFDR=0.02; left: T(38)=2.8, pFDR=0.04) and the left anterior middle temporal gyrus (T(38)=2.60, pFDR=0.04). Higher functional connectivity was observed between the right anterior parahippocampal gyrus and the left amygdala (T(38)=3.45, pFDR=0.01). Findings are summarized in Figure 17 and Table 10.

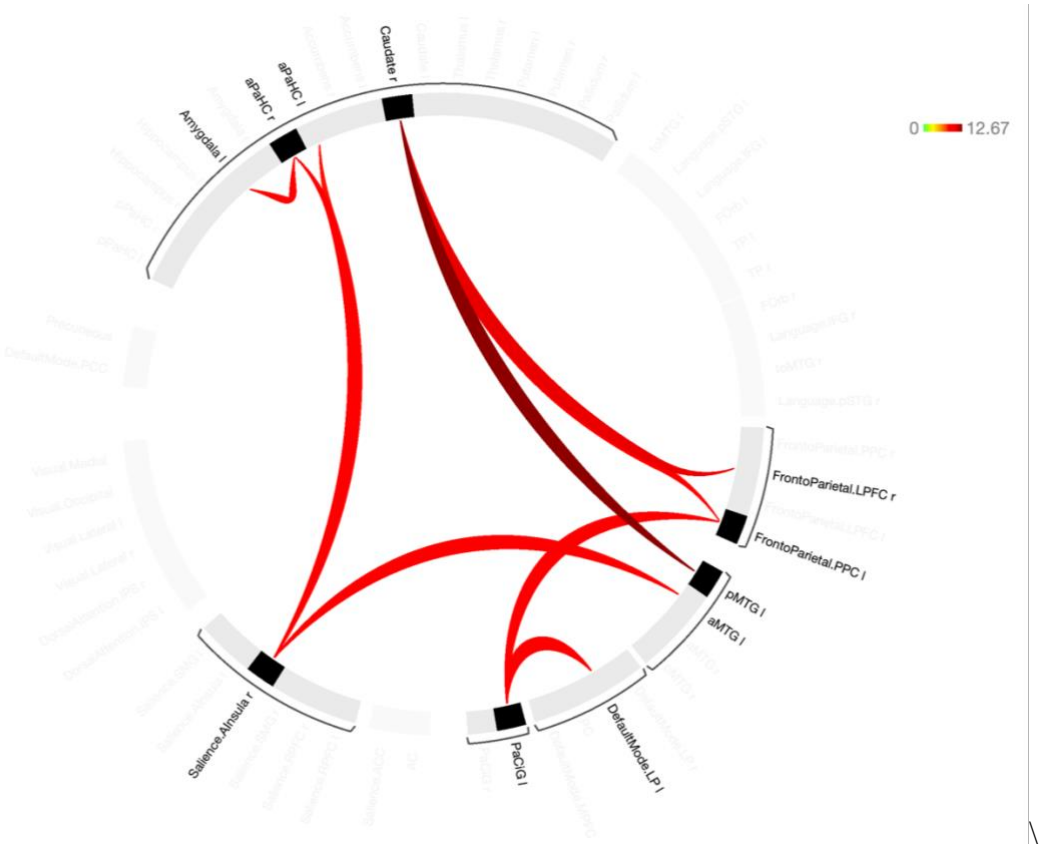

Figure 15. Connectome ring diagram of functional connectivity differences between three groups (SI, SA and HC groups). Legend represents resting-state functional connectivity strength. Findings survived connection threshold of p-uncorrected < 0.001 and cluster threshold p-FDR < 0.05 network-level (NBS mass/intensity).

Abbreviations*: l, left hemisphere; r, right hemisphere; aInsula, anterior insula; aMTG, anterior middle temporal gyrus; aPaHC, anterior parahippocampus; LP, lateral parietal; LPFC, lateral prefrontal cortex; PaCiG, paracingulate gyrus; pMTG, posterior middle temporal gyrus; PPC, posterior parietal cortex*

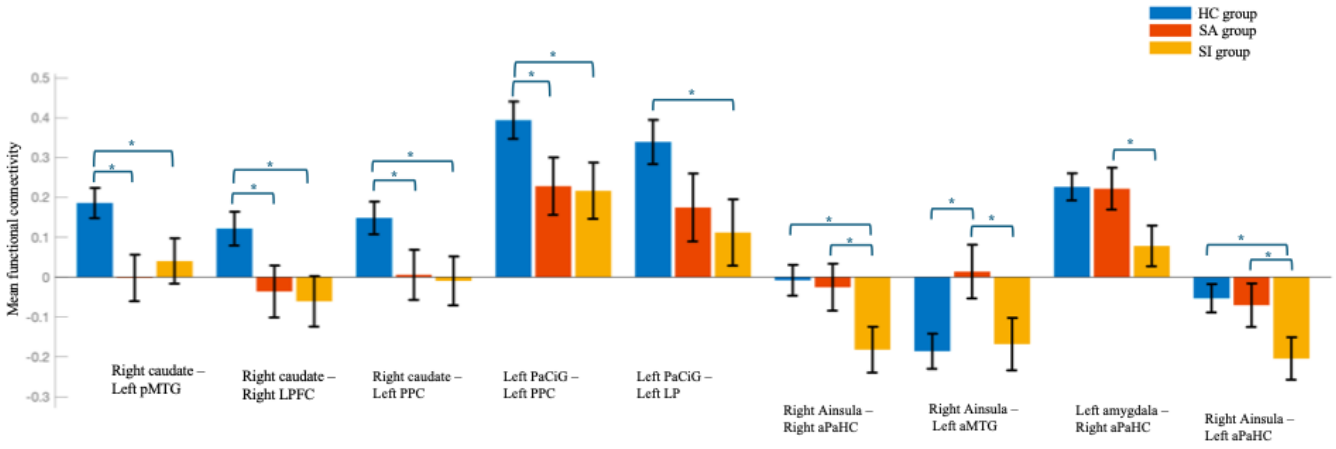

Figure 16. Resting-state functional connectivity differences between SI, SA and HC groups. Post-hoc comparisons were corrected for three group comparisons. * indicates group differences that survived correction for multiple comparisons (pFDR≤0.017).

Abbreviations*: Ainsula; anterior insula, aMTG; anterior middle temporal gyrus, aPaHc; anterior parahippoccampal gyus, HC; healthy controls, LPFC; lateral prefrontal cortex, PaCiG; paracingulate gyrus, pMTG; posterior middle temporal gyrus, PPC; posterior parietal cortex, SA; suicide attempt, SI; suicidal ideation.*

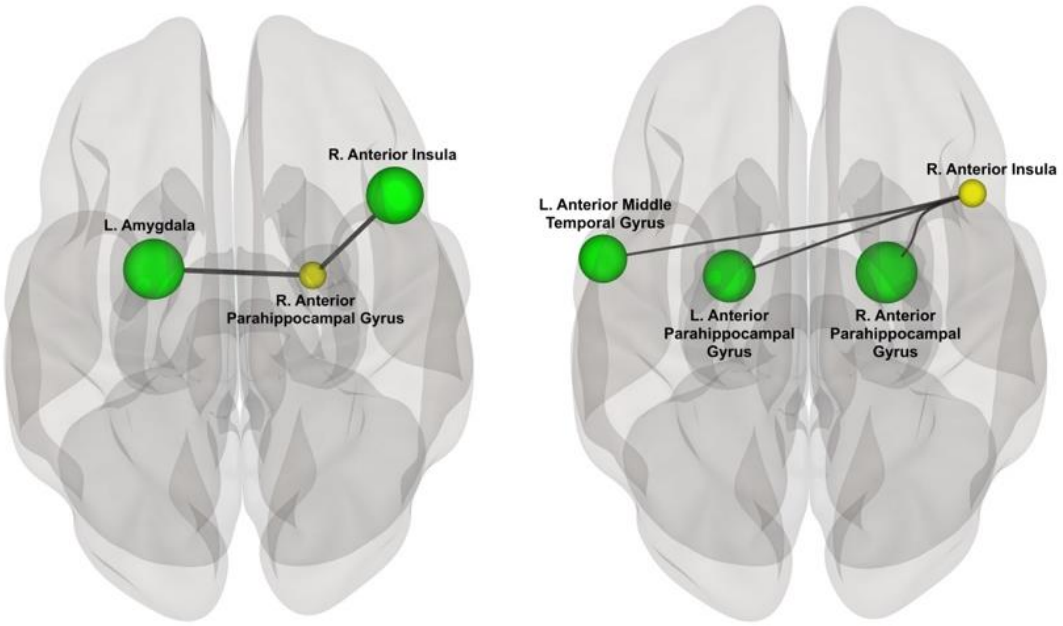

Figure 17. Functional connectivity differences between SA and SI groups, covaried for depression severity. Lower functional connectivity in the SA group compared to the SI group was observed between the right anterior insula and the left anterior middle temporal gyrus as well as bilateral middle temporal gyrus, and higher functional connectivity between the right parahippocampal gyrus and the left amygdala.

Table 10. ROI-to-ROI significant resting-state functional connectivity differences between SA and SI groups, adjusting for depression severity (MADRS total score).

Functional connectivity pair	β	T (38)	p-uncorrected	p-FDR
r.Ainsula-r.aPaHc	0.16	3.28	0.0022	0.022
r.Ainsula-l.aPaHc	0.13	2.82	0.0075	0.038
r.Ainsula-l.aMTG	0.18	2.60	0.013	0.043
r.aPaHc-l.amygdala	0.17	3.45	0.0014	0.011

Abbreviations: Ainsula; anterior insula, aMTG; anterior middle temporal gyrus, aPaHc; anterior parahippoccampal gyrus, l; left, r; right

4.8.2.2 Correlations between functional connectivity and clinical features

To explore the clinical relevance of the functional connectivity differences observed between the SA and SI groups, we conducted within-group linear regression analyses in each patient group separately. Specifically, we examined the relationship between the functional connectivity showing group differences (i.e., reported in Table 10) and the clinical features/subscales showing group differences (i.e., physical aggression, anxiety, history of childhood sexual abuse, and self-reported SI; reported in Table 9). Depressive symptoms (MADRS) were included in the model as a covariate of no interest.

In the SA group, the association between functional connectivity of the left amygdala and right anterior parahippocampal gyrus and clinical variables was significant ($F(5,13)=7.92$, $p=0.001$, adjusted $R^2=0.66$). Past-week suicidal ideation severity (BSS: $\beta = 0.10$, $t = 3.39$, $p=0.005$), anxiety severity (BAI:$\beta = –0.016$, $t = –4.52$, $p < 0.001$), and childhood sexual abuse scores (CTQ-SA: $\beta = -0.018$, $t = 1.79$, $p <0.001$) were significant independent predictors of FC between the left amygdala and the right anterior parahippocampal gyrus (see Figure 18). In the SI group, none of the examined connections showed significant associations with the clinical variables examined.

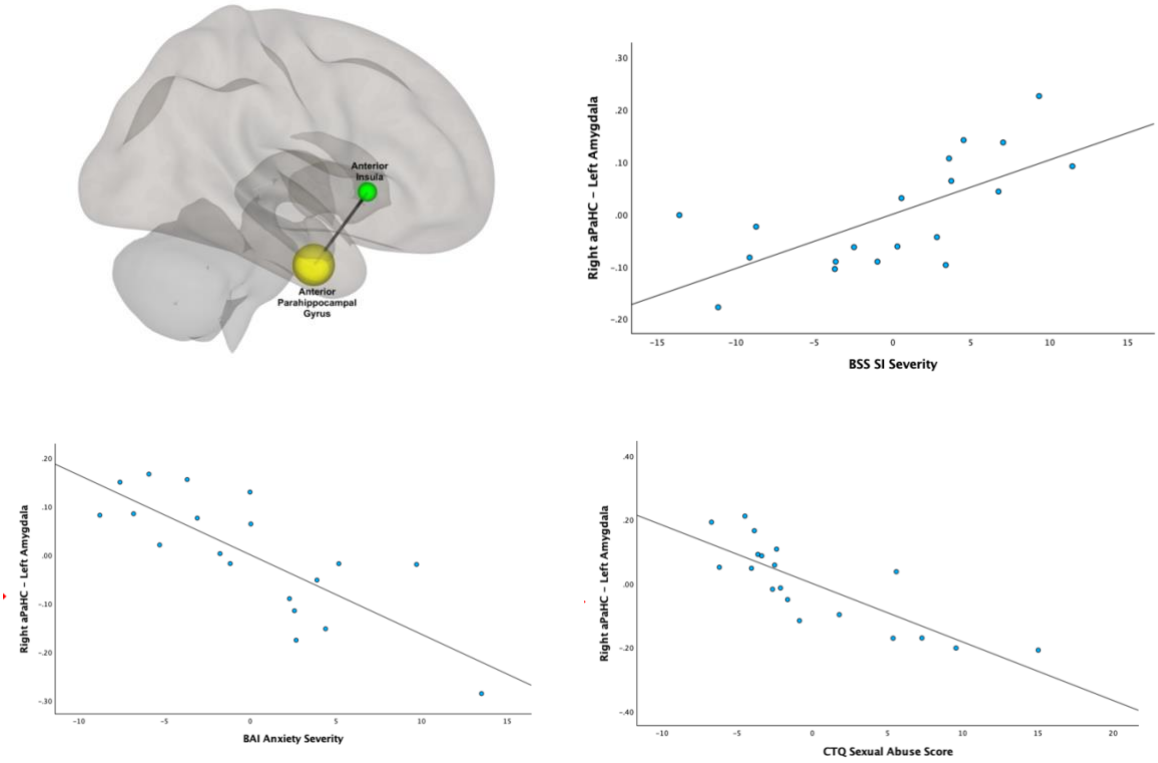

Figure 18. Correlations between functional connectivity residual values and clinical residual scores among participants with SA history. Functional connectivity residual values of the left amygdala and the right anterior parahippocampal gyrus were positively associated with BSS suicidal ideation scores ($p=0.005$),and negatively associated with BAI anxiety symptoms ($p<0.001$) and CTQ sexual abuse scores ($p<0.001$).

4.9 Discussion

This study identified distinct patterns of resting-state functional connectivity that differentiate individuals with TRD who have experienced SI only from those with a history of both SI and SA. By directly comparing these two clinically relevant groups within a rigorously characterized TRD cohort, this work advances a more nuanced neurobiological model of suicide risk, one that goes beyond the conventional binary categorization based solely on the presence or absence of suicide-related outcomes. Instead, this work acknowledges the reality that most patients with TRD have endorsed SI, but not all progress to an SA. Understanding what differentiates these groups at the neurobiological and clinical levels is critical for improving risk stratification. To this end, our approach integrates both resting-state functional connectivity with clinical symptoms and trait-level factors to explore whether individual differences in suicidal behaviour were reflected in neural connectivity. By focusing specifically on TRD, this study also addresses a common limitation in prior research, which often overlooks the clinical and neurobiological heterogeneity of MDD.

Compared to the matched HC group, both SI and SA groups exhibited significant and partially overlapping functional connectivity differences. Among the five relevant connections in the SA vs HC comparison showing significant differences, four also appeared in the SI vs HC comparison (see Figure 16 and Table S8). These findings highlight the shared neural alterations in individuals with TRD relative to HC (regardless of suicidal behaviour history). This underscores the need to directly compare SI and SA groups to identify connectivity patterns specifically associated with progression to SA.

In line with this stratified approach to suicide risk, our findings revealed distinct functional connectivity patterns among fronto-temporo-limbic regions that differentiate SI and SA groups.

More specifically, individuals with a history of SA had lower functional connectivity between the right anterior insula and both the left anterior middle temporal gyrus and the bilateral anterior parahippocampal gyrus compared to the SI-group, as well as higher functional connectivity between the right anterior parahippocampal gyrus and the left amygdala. These neuroimaging findings emerged while controlling for concurrent past-week depression severity (MADRS total scores), a valuable distinction given the common challenge of isolating suicide-specific neural correlates from depression overall. Our findings suggest a gradation of neurobiological disruption consistent with a dimensional model of suicide risk in TRD, where a history of SA marks distinct neural profiles beyond ideation alone. The functional connectivity differences invite closer examination of the known roles of these regions, which may help elucidate their contribution to suicide risk.

The anterior insula, a core region of the salience network, plays a crucial role in emotional experiences, subjective feelings, social affect, empathy, self-relatedness, and a sense of agency (Northoff *et al.*, 2006; Jollant, Lemogne and Fossati, 2017). Additionally, the insula is a key node in the pain matrix, a neural network responsible for processing physical pain, and has shown aberrant functional activity in individuals with SA history, potentially reflecting increased pain tolerance in this population (Jiang *et al.*, 2024). This is consistent with recent evidence linking suicide capability (a construct linked to fearlessness of death and pain tolerance) and pain intensity to altered insula functional connectivity in individuals with MDD and suicide risk (Wang *et al.*, 2023). The parahippocampal gyrus, in contrast, is involved in episodic memory, processing emotional stimuli, navigation, scene processing, and contextual processing (Aminoff, Kveraga and Bar, 2013). The anterior parahippocampal gyrus has known direct structural connectivity with the insula (Ghaziri *et al.*, 2017), which may underlie the functional coupling observed. Despite a lack

of prior studies reporting anterior insula–anterior parahippocampal functional connectivity patterns with respect to suicide, both regions have independently shown involvement in suicide-related endophenotypes. Altered functional connectivity may reflect the integration of emotionally salient experiences with memory systems, potentially contributing to how past adverse events are encoded, re-experienced, or cognitively appraised in individuals with a history of SA. Our findings also showed altered functional connectivity between the anterior insula and the anterior middle temporal gyrus, which is involved in social cognition and theory of mind, which is the ability to understand other's thoughts, feelings, and intentions (Xu *et al.*, 2019). In addition to the anterior insula, the parahippocampus also showed altered connectivity with the amygdala in the SA group compared to the SI group. Given their direct structural connections (Aminoff, Kveraga and Bar, 2013) and mutual involvement in affective memory, parahippocampal-amygdala coupling may reflect emotion-laden memory processes relevant to suicide behaviour.

SA and SI groups differed on several clinical variables with the SA group reporting significantly higher past-week SI severity, anxiety severity, physical aggression, and childhood sexual abuse scores. In the SA group, fronto-limbic connectivity was also associated with key clinical features: greater connectivity between the right anterior parahippocampal gyrus and the left amygdala correlated positively with higher past-week SI severity. Greater connectivity between these areas were also inversely correlated with anxiety symptoms and childhood sexual abuse scores. These associations may reflect the involvement of limbic circuits in processing emotionally salient or autobiographical material influencing suicidal thinking (Miller *et al.*, 2018). Alternatively, altered limbic connectivity may signify disruptions in emotion regulation that contribute to difficulties in managing distressing thoughts or memories related to SI (Schmaal et al., 2020). The inverse relationships with anxiety and trauma history may reflect individual

variability in how these factors influence neural circuits implicated in suicide risk. No comparable associations were observed in the SI group, suggesting that connectivity-behaviour links may be specific to those with a history of SA. Together, these findings highlight specific fronto-limbic circuits that may serve as candidate biomarkers for distinguishing suicide risk phenotypes in TRD, with potential implications for targeted intervention and prevention strategies.

This study had several notable strengths, including a well-characterized clinical cohort with rigorously defined TRD, detailed clinical phenotyping, and integration of resting-state functional connectivity with both symptom and trait-level measures relevant to suicide risk. These features strengthen the interpretability and relevance of the findings. The inclusion of a matched healthy control group provided a valuable normative baseline, contextualizing both the imaging and clinical/trait differences observed between TRD subgroups, as well as deviations from healthy patterns observed in patient–control comparisons. However, the lack of a psychiatric control group limits our ability to determine whether the observed connectivity alterations are specific to SA history or reflect more general features of TRD. Notwithstanding its strengths, the present study poses limitations to be considered. First, the sample size was relatively small. However, despite recruitment challenges associated with attaining a clinically well-characterised TRD sample, significant findings emerged after controlling for multiple comparisons, indicating robust results despite the modest sample size. Second, current medication regimen and illness chronicity (duration and number of major depressive episodes) varied significantly between participants. These potentially confounding factors could not be fully examined due to limited statistical power. Third, the sample may have been subject to selection bias, as most participants were White, completed post-secondary education, and were employed or students. Fourth, the resting-state fMRI scan duration was relatively short, which may reduce the reliability of functional

connectivity estimates and limit detection of more subtle connectivity differences (Birn *et al.*, 2013).

To conclude, this study highlights distinct neural signatures associated with SI and SA in individuals with TRD. Our findings underscore the importance of examining the trajectory of suicidal thoughts, in relation to clinical and behavioural factors and underlying brain function. As SI can be responsive to treatment, clarifying these neurobiological distinctions is critical for advancing targeted interventions and risk stratification. Moving forward, multimodal imaging approaches and large-scale, multi-site collaborative studies will be essential to improve generalizability and address current sample size limitations.

4.10 Supplementary Material

See Table S5 in Chapter 3 listing the resting-state functional connectivity regions of interest.

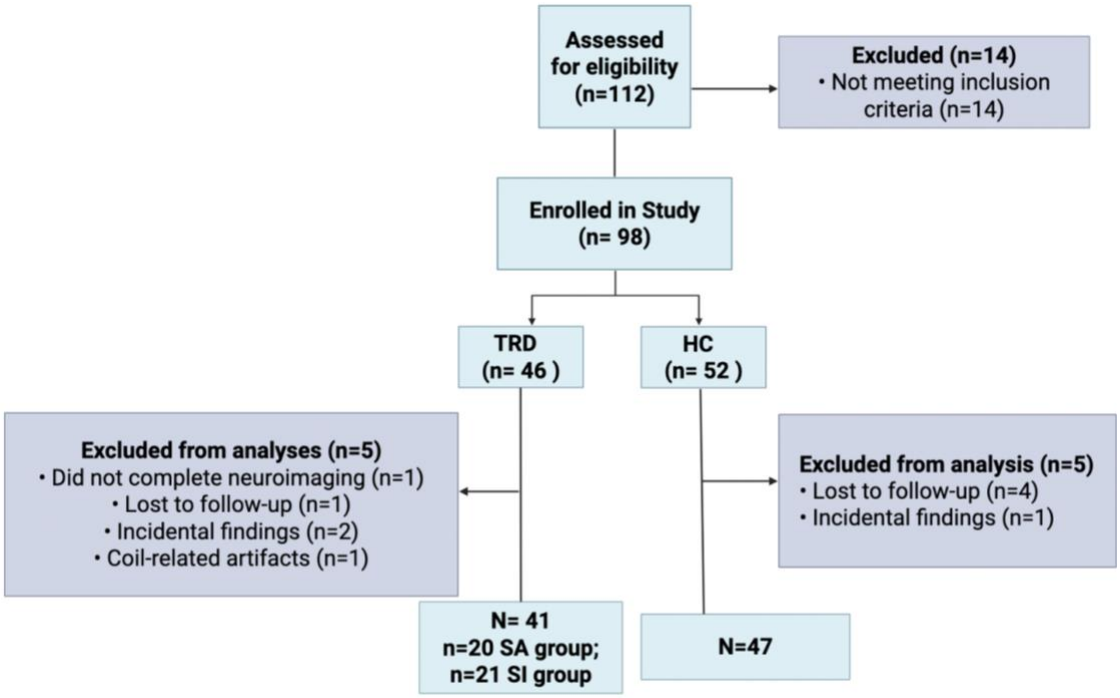

Figure S1. Participant Flow Chart

Abbreviations*: HC; healthy controls, SA; suicide attempt, SI; suicidal ideation; TRD; treatment-resistant depression.*

See **Table S6 in Chapter 3** listing the psychopharmacological treatment regimen for study participants with treatment-resistant depression.

Table S7. Individual ROI-to-ROI statistics for connections that showed significant group differences in resting-state functional connectivity based on ANOVA (SI, SA & HC).

Network	Statistics*	p-FDR	Connections	β	F (2,85)	p-uncorrected	p-FDR
1	97.80	0.021	Right Caudate - Left posterior middle temporal gyrus	0.19	12.67	0.000015	0.00015
			Right Caudate - Right lateral prefrontal cortex	0.16	10.54	0.000082	0.00041
			Right Caudate - Left posterior parietal cortex	0.14	8.70	0.000365	0.0012
			Left paracingulate gyrus - Left posterior parietal cortex	0.17	8.56	0.00041	0.0023
			Left paracingulate gyrus - Left lateral parietal	0.18	8.43	0.00046	0.0023
2	69.65	0.035	Right anterior insula - Right anterior parahippocampal gyrus	0.16	9.15	0.00025	0.0015
			Right anterior insula - Left anterior parahippocampal gyrus	0.13	8.03	0.00064	0.0021
			Right anterior insula - Left anterior middle temporal gyrus	0.27	8.96	0.00030	0.0015
			Right anterior parahippocampal gyrus - Left amygdala	0.14	8.69	0.00037	0.0018

* Mass: sum of F-test statistics over all connections within the network

Table S8. Post-hoc ANOVA results showing ROI-to-ROI connections with significantly different resting-state functional connectivity values between SA, SI and matched HC groups.

Seed	Target	β	T*	p-uncorrected	p-FDR
SA group > HC group					
Right caudate	Left posterior middle temporal gyrus	-0.19	-4.27	0.000065	**0.00065**
	Right lateral prefrontal cortex	-0.16	-3.45	0.0010	**0.0050**
	Left posterior parietal cortex	-0.14	-3.27	0.0017	**0.0058**
Right anterior insula	Left anterior middle temporal gyrus	0.20	4.20	0.000082	**0.00083**
Left paracingulate gyrus	Left posterior parietal cortex	-0.17	-3.36	0.0013	**0.013**
SI group > HC group					
Right caudate	Left posterior middle temporal gyrus	-0.15	-3.74	0.00039	**0.0020**
	Right lateral prefrontal cortex	-0.18	-3.98	0.00017	**0.0017**
	Left posterior parietal cortex	-0.16	-3.50	0.00084	**0.0021**
Right anterior insula	Left anterior parahippocampal gyrus	-0.15	-3.70	0.00044	**0.0022**
	Right anterior parahippocampal gyrus	-0.17	-4.01	0.00016	**0.0016**
Left paracingulate gyrus	Left lateral parietal	-0.23	-3.73	0.00040	**0.0040**
	Left posterior parietal cortex	-0.18	-3.28	0.0017	**0.0056**
SA group > SI group					
Right anterior insula	Right anterior parahippocampal gyrus	0.16	3.42	0.0015	**0.015**
	Left anterior parahippocampal gyrus	0.13	3.03	0.0043	0.021
	Left anterior middle temporal gyrus	0.18	2.79	0.0081	0.027
Right anterior parahippocampal gyrus	Left amygdala	0.14	2.93	0.0057	0.023

*SA > HC group: T(65), SI > HC group: T(66), SA > SI group: T(39).

Note: ROI-to-ROI connectivity is symmetrical (i.e., non-directional) and minor differences in p-values can arise depending on which ROI is designated as the seed. All reported connections were statistically significant regardless of direction. Bolded p-FDR values survived multiple

comparisons testing. Connections surviving correction for multiple comparisons (pFDR ≤ 0.017) are reported.

Chapter 5: Brain Metabolite Signatures of Suicide Risk in Treatment-Resistant Depression: A Proton Magnetic Resonance Spectroscopy Study

5.1 Overview

In the present study, we used ^{1}H-MRS to compare levels of glutamate (Glu), Glx (combined glutamine/glutamate), myo-inositol, N-aceylaspartate (NAA), and creatine (Cr) in the dorsal anterior cingulate cortex (dACC) in participants with TRD and a lifetime history of SI to a healthy control (HC) group. Furthermore, we investigated associations between neurometabolite concentrations and suicide-related symptoms and traits including depression, suicidal ideation severity, impulsivity and aggression.

5.2 Statement of author contribution

Patricia Burhunduli: Methodology, Software, Formal analysis, Investigation, Data Curation, Writing – Original draft, Writing – Review & Editing, Visualization, Project administration. **Reggie Taylor**: Methodology, Software, Investigation, Data Curation, Writing – Review & Editing, Supervision. **Katie Vandeloo**: Writing – Review & Editing, Project administration. **Jennifer Cuda**: Data Curation. **Sara Tremblay:** Resources, Writing – Review & Editing. **Pierre Blier**: Methodology, Resources, Writing – Review & Editing, Supervision. **Jennifer Phillips**: Conceptualization, Methodology, Resources, Writing – Review & Editing, Supervision, Project administration, Funding acquisition.

5.3 Title page

Brain Metabolite Signatures of Suicide Risk in Treatment-Resistant Depression: A Proton Magnetic Resonance Spectroscopy Study

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5.4 Abstract

Background: Treatment-resistant depression (TRD) is a severe form of major depressive disorder associated with elevated suicide risk. While structural and functional neural correlates of depression and suicide have been extensively explored, much less is known about their neurometabolic underpinnings. Addressing this gap is particularly relevant, as disruptions in neurometabolites may underlie observed anatomical and functional disruptions. In the present study, we used proton magnetic resonance spectroscopy (^{1}H-MRS) to investigate neurometabolite alterations in the dorsal anterior cingulate cortex (ACC) in a high suicide-risk cohort of participants with TRD and a lifetime history of suicidal ideation (SI). We further examined associations between neurometabolite concentrations and suicide-related symptoms and traits, including SI severity, depression severity, anxiety symptoms, hopelessness, impulsivity and aggression.

Methods: ^{1}H-MRS data were obtained from 21 participants with TRD and a lifetime history of SI, and 43 age- and sex-matched healthy controls (HC). Measured neurometabolites included glutamate (Glu), Glx (combined Glu and glutamine), myo-inositol, N-acetylaspartate, and creatine (Cr) within the dorsal ACC. All metabolite concentrations were expressed as ratios to creatine (Cr). Metabolites showing significant between-group differences were examined for associations with suicide-related clinical and behavioral risk factors within the TRD group. Analyses were controlled for age and sex, with significance thresholded at $p<0.05$.

Results: ANCOVA revealed that TRD participants had significantly lower Glu/Cr and Glx/Cr ratios compared to the HC group, controlling for age and sex (Glu/Cr: p-Bonferroni corrected=0.004, partial eta squared (η^2p)=0.13; Glx/Cr: p-Bonferroni corrected=0.043, η^2p =0.067). Group-stratified linear regression analysis showed that within the TRD group, both Glu/Cr and Glx/Cr ratios were positively associated with total impulsivity scores (Glu/Cr:

beta=0.44, p=0.028; Glx/Cr: beta=0.48, p=0.045), adjusting for age and sex. Additionally, Glx/Cr was positively associated with past-week SI severity (beta=0.54, p=0.013). No significant associations were observed between Glu/Cr or Glx/Cr and aggression, depression severity, hopelessness, or anxiety symptoms. Tissue correction for gray matter, white matter, and cerebrospinal fluid fractions was explored, with no emerging significant findings.

Conclusions: ^{1}H-MRS is currently the only non-invasive neuroimaging method capable of directly detecting and quantifying brain metabolites in vivo, yet it remains among the least utilized modalities in suicide research. This study identifies glutamatergic deficits in individuals with TRD and a history of SI in the dorsal ACC, a region implicated in emotional self-regulation and appraisal of negative experiences. Preliminary findings linking Glu/Cr and Glx/Cr ratios to impulsivity and SI highlight a potential neurochemical target for suicide risk stratification and intervention.

Keywords: Proton magnetic resonance spectroscopy, treatment-resistant depression, suicide risk factors, impulsivity, anterior cingulate cortex

5.5 Introduction

Suicide is among the leading causes of preventable mortality across the globe, with over 720,000 deaths recorded annually (World Health Organization, 2025d). Among psychiatric conditions, major depressive disorder (MDD) is especially relevant to suicide research, as it is one of the most common diagnoses among individuals experiencing suicide-related thoughts and behaviours, with treatment-resistant depression (TRD) associated with particularly elevated suicide risk (Reutfors *et al.*, 2018; Kern *et al.*, 2023). The multifactorial biopsychosocial features characterizing suicide risk render it challenging to understand the underlying mechanisms. Clinical risk factors alone have demonstrated low predictive value in identifying suicide risk, prompting growing interest in biomarkers that capture objective measures of suicide-related thoughts and behaviours (Sudol and Mann, 2017a).

Neuroimaging studies have advanced our understanding of the neurobiology underlying suicide risk. Across modalities and psychiatric populations, converging evidence highlights abnormalities in frontal-limbic circuitry, including regions involved in emotion regulation, impulsivity, and decision making, such as the prefrontal cortex (PFC), orbitofrontal cortex (OFC), insula, dorsal anterior cingulate cortex (ACC), and subcortical limbic regions (Schmaal *et al.*, 2020a). Notably, impulsivity and aggression are key transdiagnostic behavioural traits that have been consistently associated with increased suicide risk (Dumais *et al.*, 2005; Perroud *et al.*, 2011), potentially reflecting dysregulation within these neural circuits and contributing to the heterogeneity of suicidal behavior. Despite extensive research identifying structural and functional brain abnormalities associated with suicide in the context of depression, much less is known about neurometabolic correlates. This gap is particularly relevant, as disruptions in neurometabolite

concentrations may underlie these observed macro-level anatomical and functional disruptions (Luykx *et al.*, 2012; Moriguchi *et al.*, 2019).

Proton magnetic resonance spectroscopy (^{1}H-MRS) is a non-invasive imaging technique used to quantify in vivo regional neurometabolite concentrations. Of particular interest are neurometabolites with key biological roles relevant to both depression and suicide risk. These include glutamate (Glu) and Glx (a composite of glutamine and glutamate), involved in excitatory neurotransmission; N-acetylaspartate (NAA), a marker of neuronal viability and mitochondrial function; and myo-inositol (mI), a glial marker linked to neuroinflammation (Stork and Renshaw, 2005; Shirayama *et al.*, 2017). Previous ^{1}H-MRS studies have revealed glutamatergic involvement in the pathophysiology of depression, showing altered regional concentration differences in patients compared to controls, as well as changes in response to subanaesthetic ketamine treatment and associations with its antidepressant effects (Moriguchi *et al.*, 2018; Milak *et al.*, 2020; Boucherie *et al.*, 2023; Saccaro *et al.*, 2024; Godfrey *et al.*, 2025). NAA has also been linked to depression (Yildiz-Yesiloglu and Ankerst, 2006).

To date, few studies have examined ^{1}H-MRS correlates of suicide-related outcomes in the context of depression. One study reported lower Glx and lower NAA/Glx ratios in the ACC of adolescents with depressive symptoms and current suicidal ideation (SI) compared to those without (Lewis *et al.*, 2020). Another study investigating unmedicated adults with MDD and a history of suicide attempt (SA), reported reduced NAA concentrations in the medial PFC relative to healthy control (HC) participants, although these findings did not survive correction for multiple comparisons (Jollant *et al.*, 2017). Beyond group differences, the above-mentioned studies also reported associations between neurometabolite concentrations and SI severity, specifically

reporting increased Glx and Cho, and decreased NAA/Glx ratios linked to higher current SI severity (Jollant *et al.*, 2017; Lewis *et al.*, 2020).

The present study used ^{1}H-MRS to investigate neurometabolite alterations in the dorsal ACC in a high-risk sample of individuals with TRD and a lifetime history of SI, compared to a matched healthy control (HC) group serving as a normative reference. Beyond group-level comparisons, variations in suicide-related traits, including SI severity, impulsivity, and aggression, were explored in relation to metabolite concentrations. The dorsal ACC was selected as the region of interest due to its established role in both depression and suicide risk. We measured in vivo concentrations of Glu, Glx, mI, NAA, and creatine (Cr). Metabolite-to-creatine ratios are commonly reported in ^{1}H-MRS studies in psychiatry because Cr is a relatively stable point of reference for signal normalization (Maddock and Buonocore, 2012). However, since water concentration and relaxation properties differ between gray matter, white matter, and cerebrospinal fluid, the proportion of each tissue type within the measured voxel also requires consideration (Gussew *et al.*, 2012). In this study, the primary analyses used metabolite-to-Cr ratios to align with prior literature. Secondary analyses used voxel tissue composition-corrected values (gray matter, white matter, and cerebral spinal fluid). Based on prior evidence, it was hypothesized that participants with TRD would exhibit lower ratios/concentrations of Glu, Glx, mI and NAA, and that these alterations would be associated with suicide-related clinical symptoms and behavioural traits. This work aligns with growing initiatives in psychiatric neuroimaging aiming to develop objective biomarkers of suicide risk, addressing a critical gap in identifying mechanistic targets in individuals with TRD and suicide risk.

5.6 Methods

5.6.1 Population

Participants diagnosed with MDD (age range, 18-65 years) were recruited from outpatient physician referrals to the University of Ottawa Institute of Mental Health Research Mood Disorders Research Unit, and the Royal Ottawa Mental Health Centre Mood and Anxiety Program between July 2017 and December 2022. Patient participants met the Diagnostic and Statistical Manual for Mental Disorders (DSM)-5 criteria for MDD with a current major depressive episode length of at least 6 months (American Psychiatric Association, 2013a). TRD was defined as an inadequate response following at least two trials of medication to treat depression from different medication classes at adequate dose and duration (Sackeim, 2001), as determined by the referring physician and confirmed by study investigators. All TRD participants were receiving pharmacological treatment at the time of scanning. Due to ethical considerations, medication washout was not feasible. Medications were recorded and are summarized in Table S9. Inclusion criteria included a score of ≥ 25 on the Montgomery-Åsberg Depression Rating Scale (MADRS; Montgomery and Asberg, 1979) corresponding to moderate depression, and a score of ≥ 1 on the lifetime SI severity item of the Columbia Scale of Suicide Severity Rating Scale (C-SSRS; Posner et al., 2011). HC participants served as a normative reference group, allowing identification of neurometabolic deviations potentially linked to suicide vulnerability in the TRD group. The HC participants had no lifetime DSM-5 axis 1 disorder diagnosis assessed using the Research Version of the Structured Clinical Interview for DSM-5 (SCID-5-RV; First et al., 2015), nor a history of suicidal thoughts, behaviours or attempts as per the C-SSRS. Exclusion criteria for all study participants included a positive urine toxicology for non-prescribed substances, pregnancy, a self-reported history of head injury with self-reported loss of consciousness, or a clinically relevant

medical condition as deemed by study physician and investigators. Female participants of childbearing potential were scanned within the first 10 days of the menstrual cycle to minimize effects of endogenous ovarian hormone fluctuations (Dubol *et al.*, 2021). Informed written consent was obtained from all participants, and the study was approved by the Royal Ottawa Mental Health Centre Research Ethics Board.

5.6.2 Clinical Measures

DSM-5 axis 1 diagnoses were assessed using the SCID-5-RV (First et al., 2015). Current depression severity was measured using the MADRS (Montgomery and Asberg, 1979). Lifetime SA history was assessed using the investigator-rated C-SSRS, with SA defined as a potentially self-injurious act enacted with at least some wish to die (Posner *et al.*, 2011a). Past-week SI severity was evaluated using the C-SSRS and the self-rated Beck Scale for Suicide Ideation (BSS; Beck et al., 1979; Posner et al., 2011). Behavioural traits were assessed using self-report measures including the Barratt Impulsivity Scale (BIS-11; Patton et al., 1995) and Buss Perry Aggression Questionnaire (BPAQ; Buss & Perry, 1992). Demographic and general medical information were obtained through self-report. The Antidepressant Treatment History Form was used to record and assess the medication trials in the current major depressive episode (Sackeim *et al.*, 2019). Handedness was determined using the Edinburg Handedness Inventory (Oldfield, 1971b).

5.6.3 ^{1}H-MRS Acquisition

A single MRI scanning session was conducted for each participant using a 3T Siemens Biograph mMR PET-MR system (Magnetom Symphony Systems, Siemens, Erlangen, Germany) using a 32-channel head coil. A T1-weighted multi-echo magnetization-prepared rapid gradient echo (MEMPRAGE) sequence (FOV = 256 mm, 256x256 matrix, 192 slices, TR = 2500 ms, TE

= 1.67, TI=1100 ms, FA = 7°) was acquired and used for voxel localization (van der Kouwe *et al.*, 2008b). Spectra were acquired using a Point RESolved Spectroscopy (PRESS) sequence (TR=2000ms, TE=30ms, 128 averages) (Kaiser et al., 2007) with VAPOR water suppression (Tká *et al.*, 2001). A 16 average water-unsuppressed spectrum was also acquired for lineshape correction and quantification. The ^{1}H-MRS voxel was 40x20x15 mm^{3} and placed at the dorsal anterior cingulate cortex (ACC, see Figure 19).

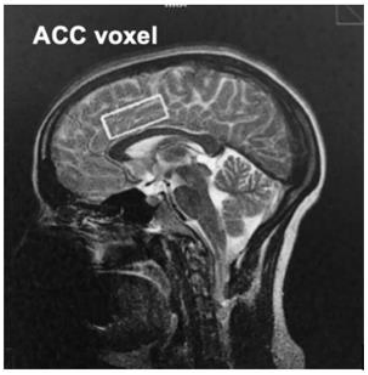

Figure 19. ^{1}H-MRS voxel placement over dorsal anterior cingulate cortex (ACC)

Spectra were individually frequency and phase corrected using in-house software before being averaged together. All spectra were visual inspected for quality. Spectra were analyzed using LCModel software (Provencher, 1993) using basis sets that were simulated using FID-A (Simpson *et al.*, 2017).

5.6.4 Tissue Composition Effects Correction

LCModel metabolite estimates were corrected for partial volume effects by applying a tissue specific correction to raw concentration values that accounted for voxel fractions of gray matter, white matter, and cerebral spinal fluid. Tissue information was segmented using SPM-4 T1-weighted images and co-registered with the MRS voxel by two study investigators (P. Bu & J.C).

5.7 Statistical Analysis

Demographic and clinical variables were compared between TRD and HC groups using independent-samples t-tests for continuous variables and chi-square tests for categorical variables in IBM SPSS Statistics, version 29.0. Quantification of ^{1}H-MRS peaks were completed using LC Model® software. An ANCOVA was performed to compare metabolite concentrations between the TRD and HC groups, covarying for age and sex. Metabolites that demonstrated significant between-group differences were subsequently examined in relation to suicide-related clinical and behavioural risk factors. Specifically, linear regression analyses were conducted to examine the relationships between Glu/Cr and Glx/Cr with self-reported SI severity (BSS), current depression severity (MADRS), impulsivity (BIS-11), and aggression (BPAQ) in the TRD group, controlling age and sex. To account for multiple comparisons, Bonferroni correction was applied for each individual analysis.

5.8 Results

5.8.1 Participant Characteristics

The final sample included 21 individuals with TRD (age range 20-65 years, M=46.5 years, SD=15.6, 33% female). All participants with TRD endorsed a lifetime history of SI, 19 (86%) reported presence of SI within the past-week (C-SSRS ≥ 1), and over half had a lifetime history of SA (n=13, 62%). The healthy comparison (HC) group included 43 participants (age range=18-64 years, M=44.1 years, SD=14.4, 46.5% female). TRD and HC groups did not differ significantly in terms of age (t_{62}=0.60, p=0.55) or sex (X^2_1=1.01, p=0.32). Most study participants were White (n=43, 67%) and had a post-secondary education (n=59, 92%). Compared to the HC group, a

significantly higher proportion of individuals with TRD lived alone (29% vs 9%) and were unemployed (43% vs 2%). No between-group differences were found for education and marital status ($p>0.05$). On clinical scales, the TRD group had significantly higher aggression and impulsivity scores compared to the HC group ($p<0.001$). On average, TRD participants had severe depression (M=35.5, SD=4.0) and most experienced recurrent major depressive episodes (77%). Past-week SI severity ranged from no suicidal thoughts (CSSRS=0, n=3), to passive SI (CSSRS=1, n=7), and active SI (CSSRS=2-4, n=11). Detailed demographic and clinical characteristics are shown in Table 11. Participant psychopharmacological treatments at the time of imaging are summarized in Supplementary Material Table S9.

Table 11. Demographic and clinical characteristics of study participants.

Variables	TRD (n=21)	HC (n=43)	Statistics
Demographics			
Age, years, mean (SD)	46.5 (15.6)	44.1 (14.4)	t_{62}=0.60, p = 0.55
Biological sex, n (%)			
Female	7 (33.3)	20 (46.5)	X^2_1=1.01, p = 0.32
Male	14 (66.7)	23 (53.5)	
Ethnicity, n (%) [a]			
BIPOC	2 (9.1)	10 (22.2)	X^2_1= 2.17, p= 0.14
White	17 (77.3)	26 (60.0)	
Handedness, n [b]			
Right/Left/Ambidextrous	16/0/4	34/4/5	X^2_1= 2.53, p= 0.28
Education status, n (%) [c]			
Post-secondary education	17 (81.0)	42 (97.7)	X^2_1=1.93, p = 0.17
No post-secondary education	2 (9.5)	1 (2.3)	
Employment status, n (%) [b]			
Employed or student	11 (52.4)	42 (97.7)	**X^2_1=18.62, p < 0.001**
Seeking work or disability	9 (42.9)	1 (2.3)	
Marital status, n (%) [b]			
Married or Common law	9 (42.9)	28 (65.1)	X^2_1=2.28, p = 0.131
Single	11 (52.4)	15 (34.9)	
Living arrangement [b]			
Living with others	14 (66.7)	39 (90.7)	**X^2_1=4.38, p = 0.036**
Living alone	6 (28.6)	4 (9.3)	
Depression			
MADRS, mean (SD)	35.5 (4.0)	0.5 (0.9)	t_{62}=55.51, p=<0.001
Age of MDD onset, years, range, mean (SD) [d]	14-60, 30.06 (14.5)	-	-
Depressive episodes, n (%) [d]			
Single	4 (23.5)	-	-
Recurrent	13 (76.5)		
Length of current depressive episode, years, mean (SD) [d]	6.33 (7.8)	-	-
Suicide			
C-SSRS SI Severity past-week, mean (SD)	1.91 (1.4)	-	-

SA, lifetime, n (%) Actual Interrupted Aborted	13 (61.9) 0 (0.0) 1 (4.8)	-	-
Behavioral Traits			
Aggression, mean (SD) [c]	68.6 (18.5)	49.5 (11.7)	t_{59}=4.84, p=<0.001
Impulsivity, mean (SD) [c]	68.6 (12.7)	52.7 (8.1)	t_{59}=5.87, p=<0.001

Abbreviations: BIPOC, Black, Indigenous and People of Colour; MDD, Major Depressive Disorder; C-SSRS, Columbia-Suicide Severity Rating Scale; BSS, Beck Scale for Suicide Ideation; SA, suicide attempt; SI, suicidal ideation

[a] BIPOC TRD participants included Black (n=1) and South Asian (n=1). BIPOC HC participants included Arab (n=1), Black (n=4), Chinese (n=1), Latin American/Hispanic (n=1), Southeast Asian (n=1), West Asian (n=1), Other (n=1). Data missing for 9 participants
[b] Data missing for n=1 in TRD group
[c] Data missing for n=2 in TRD group
[d] Data missing for n=4 TRD group

5.8.2 Metabolite Concentration Differences Between TRD and HC

Participants with TRD and a history of lifetime SI had significantly lower Glu/Cr and Glx/Cr ratios in the dorsal ACC compared to HC, after adjusting for age and sex and controlling for multiple comparisons using the Bonferroni method (Table 12). In a separate analysis of tissue composition-adjusted metabolite concentrations, no significant associations were found (Table 12).

Table 12. Metabolite concentration differences in the dorsal ACC between TRD and HC.

Metabolites	TRD Mean (SD)	HC Mean (SD)	F(1,60)	p-value	partial η^2
Metabolite/Cr ratio					
Glu/Cr	1.11 (0.11)	1.19 (0.10)	9.09	**0.004**	0.13
Glx/Cr	1.34 (0.15)	1.41 (0.13)	4.28	**0.043**	0.07
mI/Cr	0.84 (0.10)	0.84 (0.06)	0.06	0.81	0.001
NAA/Cr	1.24 (0.13)	1.12 (0.08)	0.002	0.97	0.000
Tissue composition adjustment					
Glu	8.85 (1.72)	9.37 (1.61))	1.56	0.22	0.025
Glx	10.68 (2.30)	11.09 (1.84)	0.87	0.35	0.014
mI	6.71 (1.55)	6.66 (1.09)	0.00	0.99	0.000
NAA	9.82 (1.69)	9.70 (1.75)	0.02	0.89	0.000

Abbreviations: Cr, creatine; Glu, glutamate; Glx, glutamate + glutamine; mI, myo-inositol; NAA, N-acetylaspartate

Note. Mean values represent estimated marginal means (± standard deviation) after adjusting for age and sex. Bonferroni correction for multiple comparisons were applied.

5.8.3 Associations Between Suicide-Related Risk Factors and Metabolite Concentrations

In group-stratified linear aggression analyses, within the TRD group, both Glu/Cr and Glx/Cr ratios were positively associated with total impulsivity scores (Glu/Cr: beta=0.44, p=0.028; Glx/Cr: beta=0.48, p=0.045), suggesting that higher glutamatergic metabolite/Cr ratios are associated with greater impulsivity among participants with TRD. Glx/Cr ratios were also positively associated with past-week C-SSRS SI severity (beta=0.54, p=0.013). No significant associations were seen between any of the measured neurometabolite/Cr ratios and depression severity or aggression scores. Furthermore, no significant associations were observed in the HC group between neurometabolite ratios and trait variables (aggression and impulsivity).

5.9 Discussion

^{1}H-MRS remains the only imaging technique capable of directly detecting and quantifying in vivo brain metabolites non-invasively, yet it remains among the least utilized neuroimaging modalities in suicide research. The main findings from this cross-sectional study on individuals at elevated suicide risk experiencing longstanding, treatment-resistant major depressive episodes demonstrated lower Glx/Cr and Glu/Cr ratios in the dorsal ACC compared to HC. While group-level comparisons provide valuable insight, integrating symptom- and trait-level influences can further elucidate mechanisms and factors that contextualize the observed neurobiological differences. In this line, we observed positive correlations between both Glu/Cr and Glx/Cr ratios and impulsivity scores within the TRD group. In addition, Glx/Cr ratios were also positively associated with past-week SI severity. While these findings support the limited previous work in this field and suggest that trait-level impulsivity may influence glutamatergic neurochemistry in

TRD, it is important to note that significant group differences and correlations with clinical features were not replicated when using tissue composition-corrected metabolite concentrations, indicating that caution is warranted when interpreting the results.

Our focus on the dorsal ACC was informed by its well-known implication in emotional self-regulation and appraisal of negative experiences, including those pertaining to fear, anxiety and emotional conflict (Phan *et al.*, 2005; Etkin, Egner and Kalisch, 2010). While the ACC is a commonly indicated region of interest in depression and suicide, and our findings show decreased Glu/Cr and Glx/Cr ratios in the ACC in TRD compared to HC, previous reports on neurometabolite alterations in the ACC have been variable. A recent systematic analysis of 180 MRS studies retrieved from the Metabolite Network of Depression Database (MENDA) reported that within the ACC, neurometabolite alterations were limited to reductions in NAA, while whole brain findings revealed a more widespread downregulation of glutamatergic metabolites in patients with unipolar depression (Xie *et al.*, 2023). In contrast, another systematic review and meta-analysis comprising 49 studies reported decreased Glx in the medial PFC in medicated, but not unmedicated patients with MDD compared to HCs (Moriguchi *et al.*, 2019). As the ACC and mPFC anatomically overlap, these regions are combined in many MRS studies, therefore reported findings likely reflect, at least in part, alterations in the ACC as well. An earlier meta-analysis of 16 studies involving 281 medicated and unmedicated patients with MDD and 301 controls similarly revealed lower Glu and Glx concentrations in patients with depression compared to HCs (Luykx *et al.*, 2012). Notably however, a secondary analysis of baseline data from a randomized controlled ketamine trial reported elevated Glx and Glu in the ventromedial PFC/ACC in medication-free patients with MDD relative to HCs at baseline, with metabolite levels positively correlated with depression severity (Milak *et al.*, 2020; Kantrowitz *et al.*, 2021).

Given that emerging evidence has provided insight into the involvement of glutamate in depression, a closer examination of glutamatergic metabolites is warranted. Glutamate is the major excitatory neurotransmitter in the brain and is critically involved in learning and memory (Pal, 2021). Among the clinical symptoms and behavioural traits investigated in this study, impulsivity emerged as particularly relevant. There is substantial clinical and preclinical evidence highlighting the link between glutamatergic dysfunction and impulsivity (Yates, 2024). Impulsivity, however, is a broad multidimensional construct encompassing subtypes including motor, attentional and non-planning impulsivity (Patton, Stanford and Barratt, 1995; Stanford *et al.*, 2009). Collapsing across these subtypes may mask important neurobiological distinctions. Nonetheless, studies on psychiatric conditions characterized, at least partially, by impulsive behaviours, such as attention deficit hyperactivity disorder and borderline personality disorder have reported that increased glutamate in the ACC drives impulsive behaviours (Chaibi *et al.*, 2023; Yates, 2024). To our knowledge, there are no previous studies directly examining neurochemical measures with impulsivity in MDD cohorts.

Our work adds to the scarce literature suggesting a potential role for glutamatergic involvement in SI. As previously mentioned, the investigation of suicide using MRS has been limited, with only two studies published to date (Jollant *et al.*, 2017; Lewis *et al.*, 2020). While preliminary, our findings support the growing body of preclinical and clinical work implicating glutamate involvement in suicide-related behaviours (Jimenez-Trevino *et al.*, 2020; Can *et al.*, 2023) The glutamatergic system has emerged as a promising target for anti-suicidal interventions. Meta-analytic evidence demonstrates rapid reduction in suicidal ideation in patients with TRD following a single subanaesthetic dose of ketamine, often with moderate to large effect sizes

(Wilkinson *et al.*, 2018b; Shen *et al.*, 2024). Further research is necessary to delineate mechanisms, and assess longer-term outcomes.

This study highlights an important methodological consideration regarding ^{1}H-MRS data analysis. Referencing neurometabolite concentrations to creatine is a common normalization strategy, and the approach used by the only other work to be published thus far in this field. However, while neurometabolite/Cr ratios yielded significant group differences and associations with clinical features in this study, these findings did not persist when corrected for tissue composition effects. This emphasizes the need to consider tissue composition in ^{1}H-MRS studies to minimize underestimation of metabolic concentrations caused by partial volume effects, as failing to do so may result in misinterpretation of findings (Gussew *et al.*, 2012). In our case, the discrepancy between results obtained using neurometabolite/Cr ratios and tissue composition-correction suggests that the observed glutamatergic group differences may at least partially reflect differences in voxel tissue composition rather than true neurochemical alterations. Accordingly, future work should incorporate tissue composition to better distinguish true metabolite differences from those driven by structural variability.

This study holds notable strengths, including its novel focus on neurochemical signatures in a cohort of participants with TRD, specifically in relation to suicide-related clinical and behavioural factors. Nonetheless, this study has a few limitations. First, patient participants were on psychotropic medication at the time of scanning. Although this reflects the clinical reality of patients with TRD and offers insights into neurochemical alterations in a naturalistic cohort of patients with treatment-resistant depression, there are known influences of medications used to treat depression on neurometabolite concentrations, which could not be considered (Boucherie *et al.*, 2023; Godfrey *et al.*, 2025). Second, the sample size was relatively small and may have reduced

statistical power to detect the involvement of other examined metabolites and associations with clinical symptoms and behavioural traits. Third, our sample may have been subject to selection bias due to recruitment strategies used for the control group. Although the HC control group was recruited through social media, hospital advertisement and word of mouth, similar to approaches used in other studies, best practice involves selecting a random sample of individuals from the same source as the clinical group (Wachokjer *et al.*, 1992). Future studies could consider a control group comprising treatment-seeking patients without MDD or suicide risk. Fourth, our voxel placement was limited to the dorsal ACC, preventing detection of relevant neurometabolite alterations in additional brain regions implicated in depression and suicide. Additionally, as anatomically landmarks may differ slightly between participants when identifying the ACC, there may be minor variability in voxel placement. Finally, as this was a cross-sectional study, it does not allow for conclusions about the directionality or causality of the observed relationships between glutamatergic metabolites and suicide-related features.

5.10 Conclusion

To conclude, this study provides preliminary evidence that glutamatergic dysfunction in the dorsal ACC may be associated with trait-level impulsivity in individuals with TRD and SI. While these findings align with emerging evidence of glutamatergic involvement in suicide risk, the absence of significant results in tissue composition-corrected analyses highlights the need for cautious interpretation. These results further emphasize the importance of examining metabolites in relation to both state and trait-level factors in the context of suicide risk. Future work should include larger samples and employ methodological rigour through tissue composition correction to more accurately identify neurochemical biomarkers of suicide in TRD. Understanding these

mechanisms is important given the growing interest in treating SI in depression using glutamatergic-targeting agents.

5.11 Supplementary Material

Table S9. Psychopharmacological treatment regimen of participants with treatment-resistant depression with available ^{1}H-MRS data.

Medication Drug Class	n (%)
Selective serotonin reuptake inhibitors[a]	5 (22.7)
Serotonin norepinephrine reuptake inhibitors[b]	10 (45.5)
Bupropion	4 (18.2)
Mirtazapine	3 (13.6)
Vortioxetine	3 (13.6)
Dopamine/serotonin antagonists[c]	2 (9.1)
Brexpiprazole	4 (18.2)
Lamotrigine	2 (9.1)
Methylphenidate/lisdexamfetamine	1 (4.5)
Ion channel blocker[d]	1 (4.5)

[a]Includes citalopram, esciptalopram, fluoxetine, sertraline
[b]Includes desvenlafaxine, duloxetine, levomilnacipran, venlafaxine
[c]Includes asenapine, lurasidone, olanzapine, quetiapine, risperidone
[d]Includes gabapentin

Chapter 6: General Discussion

6.1 Overview

Prior to delving into the neurobiological details that structure this discussion, this subsection serves to refocus and concisely reiterate what this work truly represents and situate it within its proper context in the broader landscape of suicide neurobiology research. Broadly speaking, the overarching research questions investigated in this doctoral thesis are three-fold: 1) *Do varying degrees of current SI severity have a biological signature that can be captured using neuroimaging?*, 2) *Irrespective of current SI characterization (present or absent; passive or active), are there neurobiological markers that differentiate individuals who have acted on suicidal thoughts (those with a lifetime history of SA) from those whose SI has never progressed to an attempt?*, and 3) *How are suicide-related symptoms and behavioural traits related to these neurobiological findings*? As previously mentioned, while a cross-sectional study design cannot determine whether neurobiological differences contribute to the manifestation of suicide-related thoughts and behaviours, or conversely, whether SI or SA history itself alters neurobiology, this work explores important associations. Fundamentally, the importance of understanding the brain-suicide relationship lies in its potential for clinical translational. The more we can delineate neural correlates of suicide-related thoughts and behaviours, the more readily this knowledge can be integrated into clinical practice, selecting treatments targeting neural systems most in need of modulation. As articulated in a neuroimaging-focused review on precision psychiatry, once a foundation in the brain is established, we have a basis to specify the relationships between brain circuits, behaviours, and symptoms, thereby enabling the interpretation of clinical profiles with respect to underlying neurobiology (Williams and Whitfield Gabrieli, 2024).

6.2 Summary of Findings

Given that all participants with TRD in the overarching study had experienced SI at some point in their lives, the manuscripts comprising this thesis do not directly examine the emergence or onset of suicidal thoughts. Instead, the three manuscripts investigate how variations in SI severity and SA history are reflected in brain structure, function, and neurochemistry once SI has already emerged. The first manuscript (Chapter 3) uses a dimensional approach to explore the structural and functional neural correlates of past-week SI severity. The second manuscript (Chapter 4), shifts focus away from current SI severity to lifetime history of SA, exploring functional connectivity correlates differentiating SA and SI, and their associations with suicide-related symptoms and traits including SI severity, anxiety, hopelessness, impulsivity, aggression and childhood trauma. The final manuscript (Chapter 5) investigates neurochemical associations of suicide risk using ^{1}H-MRS, exploring differences between individuals with TRD and a normative control group, and associations between neurometabolites and variation in SI severity, impulsivity and aggression. The main findings and their relevance are summarized below.

In Manuscript 1, we report that higher SI severity (measured using the investigator-rated C-SSRS) was associated with lower cortical thickness in the right lateral occipital cortex while no significant associations were found between SI severity and subcortical volumes of the bilateral hippocampus, amygdala, thalamus and caudate. Resting-state fMRI analyses revealed that higher SI severity was associated with lower functional connectivity between the posterior parietal cortex and the left anterior insula, bilateral temporooccipital middle temporal gyrus and left frontal orbital cortex. As SI severity is potentially modifiable through treatment, identifying its neural correlates may offer valuable insight into the underlying neurobiological mechanisms and inform the identification of novel treatment targets.

Group comparisons in Manuscript 2 showed that distinct functional connectivity correlates were associated with SA history, which did not overlap with those reported with SI severity. Group-level analysis showed that, compared to patients with SI only (no history of SA), those with a history of SA exhibited lower functional connectivity between the right anterior insula and the bilateral anterior parahippocampal gyri and the left anterior middle temporal gyrus, and higher functional connectivity between the right anterior parahippocampal gyrus and left amygdala. Within-group analyses exploring the clinical relevance of the functional connectivity findings revealed that, in the SA group (with no associations observed in the SI only group), functional connectivity between the left amygdala and right anterior parahippocampal gyrus was positively associated with self-rated SI severity, and negatively associated with anxiety symptom severity and childhood sexual abuse scores. Identifying neural markers that not only differentiate between SI and SA in TRD, but also show meaningful associations with relevant clinical features, may enhance our understanding of the neurobiological mechanisms underlying the progression from SI to SA.

Neurometabolite investigations in Manuscript 3 revealed lower Glu/Cr and Glx/Cr ratios in the dorsal ACC in individuals with TRD and SI compared to a HC group. Further, within the TRD group, both Glu/Cr and Glx/Cr ratios were positively associated with total impulsivity scores, and Glx/Cr ratios were positively associated with past-week C-SSRS SI severity. While these associations were not significant with correction for gray matter, white matter and cerebrospinal fluid tissue composition partial volume effects within the examined voxel, the observed trends nevertheless provide preliminary evidence of glutamatergic involvement in suicide risk in TRD.

The sections below will not reiterate the discussions presented in the individual manuscripts but instead will explore proposed mechanisms underlying the main findings.

6.3 Proposed Mechanisms Underlying Reduced Cortical Thickness

Regional cortical thinning has frequently been reported in psychiatric populations, suggesting that the cortex is vulnerable to the influence of emotional states and psychiatric symptomatology (Schmaal *et al.*, 2020a; Vieira *et al.*, 2023a). Cortical thickness is determined by the architecture of the cerebral cortex, the 1-5 mm multilayered outer region of the cerebrum (i.e. gray matter) (Wagstyl and Lerch, 2018). On a cellular level, variations in cortical thickness primarily reflect changes in the neuropil, which constitutes approximately 84% of cortical volume and comprises unmyelinated axons, dendrites, and synapses (Wagstyl and Lerch, 2018). Specifically, cortical thickness changes observed in vivo are more likely to reflect volumetric modifications related to dendritic arborization or glial density, rather than changes in neuronal number (Wagstyl and Lerch, 2018). Neuronal number remains relatively stable across the lifespan, with neurogenesis largely restricted to the prenatal period (with the exception of the dentate gyrus) and therefore, unlikely to influence cortical thickness changes.

Characterization of the cellular determinants underlying morphometric changes related to SI severity are yet to be established. However, evidence from preclinical models of depression and human post-mortem studies provide indirect insight into potential mechanisms. Post-mortem studies have shown reduced dendritic arborization in the ACC in patients with depression and suicide attempt compared to matched sudden death controls (Hercher *et al.*, 2010). Animal models of depression have shown that chronic stress is a key driver of microstructural brain changes, with studies reporting dendritic atrophy and reduced dendrite complexity spine density in the hippocampus and PFC and increases in the basolateral amygdala and nucleus accumbens (Duman and Duman, 2014; Qiao *et al.*, 2016). These opposing directions of remodeling illustrate the complex and sometimes paradoxical nature of stress-related plasticity. Although the mechanisms

underlying these effects are unclear, the stress-induced alterations of dendrites and spines are thought to drive regional anatomical changes in brain regions related to depression (Qiao *et al.*, 2016).

A proposed mechanism underlying cortical thickness changes in depression is captured by the neurotrophic hypothesis, which suggests that stress, a major factor in depression and suicide, leads to decreased levels of brain-derived neurotrophic factor (BDNF), although the precise molecular and cellular mechanisms remain unclear (Dwivedi, 2009). BDNF is abundantly expressed in the central nervous system, with highest concentrations found in the hippocampus and cortex, and regulates neuroplasticity by regulating dendritic growth, synapse formation, synaptic strength, and neurotransmitter systems (Qiu *et al.*, 2025). Stress-related reductions in BDNF in MDD have been associated with regionally specific reductions in dendritic length in pyramidal neurons of the medial PFC, as well decreased number and function of spines (Duman and Duman, 2014), which may underlie observable anatomical changes in cortical thickness.

Pertaining to suicide, Khan et al., argue that the neurotrophic hypothesis of depression may need to be extended to include SI within MDD, as serum BDNF levels were found to be significantly lower in patients with MDD experiencing SI compared to those without (Khan *et al.*, 2019). Furthermore, a reduction in BDNF has been reported in post-mortem brain tissue of individuals who have died by suicide (Levy *et al.*, 2018). To further explore this relationship, studies have directly investigated the association between BDNF and cortical thickness. A pilot study in patients with minor depressive episode (defined in the DSM-IV as one to four depressive symptoms for at least two weeks) reported a positive association between serum BDNF and cortical thickness and volume in multiple regions involved in depression, such as the OFC, ACC and insula (Polyakova *et al.*, 2020). Notably, this study also reported lower cortical thickness in

the pericalcarine cortex, located in the occipital lobe. While this finding does not align precisely with our structural finding in the right lateral occipital cortex (and was not significant after FDR correction) in a design focused on symptom severity, it nonetheless raises the possibility that structural alterations in the visual cortex may be involved in depression and suicide.

Further evidence linking the occipital cortex to depression comes from a study reporting that higher BDNF methylation (which inhibits BDNF gene expression) may be associated with reduced cortical thickness in the occipital and prefrontal cortices in patients with recurrent MDD (Na *et al.*, 2016). Taken together, although speculative, our structural finding of lower right lateral occipital cortical thickness in association with higher SI severity may reflect broader stress-related neuroplastic changes, potentially involving neurotrophic mechanisms such as BDNF. However, while the BDNF-depression and suicide literature supports an association between BDNF and the presence of suicide-related thoughts and behaviours, evidence directly linking BDNF levels to SI severity is limited. Hence, interpreting our SI severity findings through a BDNF lens is therefore speculative. Nonetheless, this broader association with suicide underscores the need for further investigation. Moreover, most well-established BDNF-related structural changes are typically reported in the PFC, hippocampus, and other limbic regions. The occipital cortex (including the lateral occipital cortex) is not a region typically implicated in the BDNF-depression and suicide literature, therefore, the relevance of BDNF to occipital cortex changes and its specific relationship to SI are also speculative. Despite this, emerging evidence suggesting occipital cortex involvement highlights the need for further investigation into its potential role in suicide.

6.4 Proposed Mechanisms Underlying Functional Connectivity Findings

As described in Chapter 2, functional connectivity refers to the degree of similarity in neural activation between brain regions. More precisely, functional connectivity is an indirect measure of

inter-regional activity, quantified by temporally correlated BOLD signal fluctuations. Thus, when this activity (or BOLD signal) is temporally coherent across two populations, they are said to be 'functionally connected' (Honey *et al.*, 2009).

Determinants explaining how two distinct regions are functionally connected have not been fully elucidated, although several mechanisms have been proposed. The most straightforward mechanisms regard the correspondence between structural and functional connectivity, since brain regions communicate directly via signal propagation along white matter tracts. High resolution computational modeling has confirmed that structural connectivity, measured using diffusion spectrum imaging tractography, and resting state functional connectivity are strongly interrelated, with structurally connected cortical regions exhibiting stronger and more consistent resting state functional connectivity than unconnected regions (Honey *et al.*, 2009). Distance between brain regions has also shown to be an influencing factor, as resting state functional connectivity tends to decrease with greater regional distance between connected regions, further supporting that functional connectivity is reflective, at least in part, of anatomical involvement.

Structural connectivity, however, cannot fully explain BOLD signal functional connectivity patterns for numerous reasons. To begin, structural connectivity is essentially constant from day-to-day, but functional connectivity can change within a few hundred milliseconds, suggesting structure cannot fully determine functional connectivity (Honey *et al.*, 2009). Moreover, structurally distant regions, with no known white matter interconnections, have still shown high functional connectivity patterns. In a striking resting state functional connectivity case report study, a 6-year old boy who underwent a complete transection of the corpus callosum found a drastic post-operative loss of interhemispheric BOLD correlations with preserved intra-

hemisphere correlations, underscoring that structurally distant regions, even across hemispheres, still involve functional coupling (Johnston *et al.*, 2008).

Certain findings reported in this dissertation may be explained by the structural-functional connectivity coupling. In Manuscript 1, decreased functional connectivity between the right posterior parietal cortex and the right temporooccipital middle temporal gyrus was reported in correlation with increased past-week SI severity. Previous work has illustrated that these two regions are linked by the superior longitudinal fasciculus, which has been specifically shown to connect the posterior part of the middle and interior temporal gyri with the angular and supramarginal gyri of the posterior parietal cortex (Wu, Sun, Wang, Wang, *et al.*, 2016). These regions are unified at the temporo-parieto-occipital junction, and the structural interconnections may underlie functional communication (Wu, Sun, Wang, Wang, *et al.*, 2016). In Manuscript 2, we compared patients with a history of SI only (no SA history) to patients with history of SA. In this comparison, the SA group exhibited lower functional connectivity between the right anterior insula and right anterior parahippocampus, regions shown to be interconnected by white matter fibres (Ghaziri *et al.*, 2017). Similarly, many of our functional connectivity findings had interhemispheric involvement, which may arise from interactions via anatomical pathways, suggesting that indirect, rather than direct, mechanisms may be implicated. In a recently published optogenetic fMRI study, authors argued that interhemispheric functional connectivity may be attributed to polysynaptic pathways involved in propagating spontaneous neural activity, highlighting a key point that since resting state functional connectivity depends on the correlation of hemodynamic activities, it can emerge when brain regions receive strong common input, rather than direct interactions between each other (Moon *et al.*, 2025).

Suicide-related thoughts and behaviours appear to influence regional neural interconnectivity patterns in BOLD signal fluctuations. As previously highlighted in Chapter 1 (see section 'suicide as a neurobiological phenomenon'), these alterations may reflect genetic, epigenetic or early childhood adversity inducing lasting neurological changes. Section 6.6 will further explore how these neuroimaging findings intersect with clinical presentation.

6.5 Proposed Mechanisms Underlying Neurochemical Findings

^{1}H-MRS provides a non-invasive snapshot of the neurochemical environment within a defined brain region (Licata and Renshaw, 2010). The measurable signal reflects the combined intracellular and extracellular pool of neurometabolites in neurons and astrocytes (Sarawagi, Soni and Patel, 2021). Each neurometabolite provides a unique contribution to neuronal health and brain functioning, and imbalances have been liked to many neurological and psychiatric disorders, including depression and suicide. As Manuscript 3 identified possible glutamatergic alterations among individuals with TRD and SI, this section will focus on proposed mechanisms of glutamatergic involvement in depression and suicide.

To begin, a brief overview on glutamate to contextualize significance. Glutamate is the most abundant free amino acid in the brain and serves as a major excitatory neurotransmitter in nearly every brain region. Glutamate is incredibly ubiquitous, as most cells in the central nervous system express at least one type of glutamate receptor, whether ionotropic (NMDA, AMPA or kainite) or metabotropic (the eight glutamate receptor subtypes), which are distributed pre-, post- and extra-synaptically throughout the nervous system (Pal, 2021). Glutamate levels are also tightly regulated, as deficiencies can deplete energy metabolism, and excess levels can lead to cell death (Pal, 2021). In addition to glutamate, glutamine is also an important component to the glutamatergic system. Glutamate and glutamine function in a cycle; after synaptic release and

receptor activation, astrocytes take up synaptic glutamate to prevent excitotoxicity, convert it to glutamine and export it, where it is taken up by neurons to be converted back to glutamate to replenish the glutamate pool for subsequent neurotransmitter release (Andersen, 2025). Although glutamine is an important neurometabolite to investigate, at a magnetic field strength of 3T, separating glutamate and glutamine by conventional MRS methodologies is challenging due to the heavy overlap over all their resonance frequencies, therefore a combined Glx signal is most often reported (Zhang and Shen, 2015).

A proposed mechanism linking glutamatergic dysregulation to depression and suicide centers on neuroplasticity. Neuroplasticity is a broad term referring to a collection of events for neuronal adaptation and encompasses mechanisms such as long-term potentiation (LTP, the strengthening of synaptic connections as a result of increased activity), regulation of spine density, and synaptic reorganization (Reznikov, Fadel and Reagan, 2009). Glutamatergic-mediated synaptic plasticity involves strengthening synaptic connections utilizing NMDA and AMPA receptors, essential for learning, cognition, mood regulation and memory (Reznikov, Fadel and Reagan, 2009). Chronic stress, a key factor in the stress-diathesis model of suicide (see Chapter 1), can supress glutamate release, impair LTP, reduce dendritic spines and diminish attentional control, particularly observed in the PFC and may explain the glutamatergic decline observed in depression (Reznikov, Fadel and Reagan, 2009). Findings in Manuscript 3 provide preliminary support to the growing evidence of glutamatergic reduction in depression. As previously mentioned, ^{1}H-MRS studies of SI specifically are scarce, and future studies are warranted to further explore suicide-specific mechanisms.

To conclude, it is important to consider ^{1}H-MRS-specific methodological variations both in this doctoral thesis and the broader literature. ^{1}H-MRS studies reveal widespread glutamatergic

involvement in the brain, although concentrations are not uniform, as there exists regional and tissue-specific differences (Zhang and Shen, 2015). Cortical gray matter contains significantly higher Glu/Cr ratios compared to white matter, with higher levels in the ACC and the paracentral lobule (Goryawala, Sheriff and Maudsley, 2016). Considering these regional and tissue-composition effects, in Manuscript 3 the dorsal ACC was used as the ^{1}H-MRS voxel, a region with reportedly higher glutamatergic concentrations, enhancing the ability to acquire a reliable signal. Neurometabolite concentrations corrected for gray matter/white matter/cerebrospinal fluid partial volume effects were also reported in Manuscript 3, and, although these analyses yielded negative results, this approach remains important for accurate quantification. Finally, similar to many other studies, our work reported Glu and Glx ratios relative to Cr. Creatine is often used as an internal reference as it is relatively stable across normal and pathological states (Maddock and Buonocore, 2012). The rationale for the use of metabolite ratios is that they self-correct for regional variations and partial volume effects, although this strategy has been questioned and may introduce additional variability (Li, Wang and Gonen, 2003). Nonetheless, the use of this approach in our work enables comparison of our findings with the broader literature while highlighting the value of robust tissue composition-corrected effects.

6.6 Conclusion: Bridging clinical and neuroimaging findings

Deciphering how neural components intertwine and work in unison to produce coherent thoughts and behaviour is profoundly complex. Currently, rudimentary approaches are often applied to link brain function to clinically relevant differences in pathophysiology and behaviour (Insel *et al.*, 2010). In this thesis, we use similar frameworks to separately identify structural, functional, and neurochemical alterations associated with suicide-related thoughts and attempts in TRD. Ideally, a biomarker should integrate biochemical, neuronal, psychophysical and

psychopathological levels of a disorder (Insel *et al.*, 2010; Cuthbert and Insel, 2013). Nonetheless, as suicide biomarker research remains in its infancy, a classical neuroscience approach using a compartmentalized perspective is appropriate in order to form a foundation towards such integration. Herein, although we acknowledge our present study design does not directly investigate how brain structure, function and neurochemistry interrelate, findings nonetheless provide important preliminary insights.

In the overarching sample, participants with TRD and SI differed markedly from HC symptomatically, neurochemically, and neurofunctionally. Clinically, participants with TRD exhibited more severe depression, higher SI, and greater impulsive traits (see Chapter 5). Neurochemically, lower Glu/Cr and Glx/Cr ratios in the dorsal ACC were observed in the TRD group relative to controls, a preliminary finding aligning with reports of glutamatergic downregulation in the ACC among populations with MDD (Luykx *et al.*, 2012). Within the TRD group, higher glutamatergic ratios were also associated with higher impulsivity scores, supporting theories that aberrant glutamatergic involvement may promote behavioural disinhibition (Yates, 2024). Interestingly, there may be a mechanistic link between neurochemistry and neuroanatomy through the glutamate system. As previously mentioned, glutamate plays an important role in regulating spine density which in turn contributes to cortical thickness and volume (Reznikov, Fadel and Reagan, 2009; Wagstyl and Lerch, 2018). Although our neurometabolite measures were acquired in the dorsal ACC and did not coincide with observable structural alterations, this neuroanatomical-neurochemical relationship may warrant further investigation to directly investigate potential multimodal interactions. Further, lack of significant findings in MRS analyses employing tissue composition correction suggests potential underlying differences in the structural

composition of the voxel in each group driving observed differences in glutamatergic metabolite ratios to creatine.

Within the TRD group, higher past-week SI severity was related to lower cortical thickness in the right lateral occipital cortex (Chapter 3), higher functional connectivity between the left amygdala and right anterior parahippocampal gyrus (Chapter 4), and lower Glx/Cr ratios in the ACC (Chapter 5). The sMRI findings, although unexpected, support previous preclinical and clinical work illustrating visual cortex dysfunction in depression, where disruptions in visual processing linked to possible maladaptive cognitions (Wu *et al.*, 2023). Altered limbic connectivity may reflect disruptions in emotional regulation that contribute to difficulties in managing distress thoughts or memories to SI (Schmaal *et al.*, 2020a). Finally, reduced glutamatergic involvement points to compromises in neuroplasticity, which may influence neural states involved in depression symptomatology (Pal, 2021). Together, this converging multimodal evidence reveals a widespread neurobiological dampening across neurochemistry and neuroanatomical domains with increasing severity in thoughts of suicide across regions involved in mood, fear, emotional regulation, memory, and interestingly, vision.

In addition to examining SI severity at the time of the scan, individuals with a lifetime history of SA (SA group) were studied both clinically and neuro-functionally. Compared to the SI group, the SA group exhibited higher clinical symptoms severity, with greater depression severity, higher current self-reported SI severity, higher anxiety, childhood sexual abuse history and heightened aggressive traits. These clinical differences were associated with disrupted functional connectivity between left amygdala and right anterior parahippocampal gyrus. Together, these findings underscore the possibility of fronto-limbic circuits serving as candidate biomarkers for distinguishing suicide risk phenotypes (SA from SI) in TRD.

In summary, this thesis characterizes neural correlates of SI and SA in TRD, illustrating heterogeneous alterations in cortical thickness, functional connectivity and neurometabolite concentrations. Suicide is a complex, multifactorial phenomenon and integrating clinical profiles and biomarkers provides an opportunity to better understanding underlying mechanisms. As SI can be responsive to treatment, clarifying these neurobiological distinctions is critical for advancing targeted interventions and risk stratification to prevent suicide-related behaviours and deaths.

6.7 Strengths and limitations

This cross-sectional multi-modal MRI study had several notable strengths, including a well-characterized clinical cohort with rigorously defined TRD, detailed clinical phenotyping, and integration of multimodal neuroimaging metrics with both symptom and trait-level measures relevant to suicide risk. This study adopted a more nuanced approach by focusing specifically on suicide-related outcomes in TRD, directly addressing a common limitation among similar studies, which fail to account for the clinically heterogeneous nature of MDD.

Each individual manuscript included herein fills a distinct gap in the literature. Manuscript 1 represents one of the few studies to move beyond the binary framework of suicide neurobiology, which typically characterizes individuals based on the presence or absence of suicide-related outcomes (such as suicide attempt history). Instead, SI was characterized along its dynamic spectrum, encompassing varying degrees of severity. Manuscript 2 acknowledges the reality that most patients with TRD have endorsed SI, but not all progress to an SA, enabling a more clinically informative comparison differentiating suicidal thoughts and actions. This work further incorporates clinical and behavioural dimensions, strengthening the interpretability and relevance of the findings. Manuscript 3 contributes to a particularly scarce body of literature by examining neurometabolic features associated with suicide risk more broadly. Furthermore, it explores

associations between neurometabolites concentrations and transdiagnostic behavioural traits linked with suicide risk.

Despite its strengths, the overarching study has several limitations that should be considered. To begin, all three manuscripts included the same participant cohort, limiting generalizability. Second, this study did not have a psychiatric control group. The inclusion of a participant group with TRD and no history of SI or SA would have strengthened the ability to distinguish neurobiological correlates of suicide risk separate from those of depression more generally. Nevertheless, the inclusion of a matched HC group provided a valuable normative baseline, contextualizing both the imaging and clinical/trait differences observed between TRD subgroups, as well as deviations from healthy patterns observed in patient–control comparisons. Third, the study is limited by its sample size. While the use of a well-characterized clinical sample with minimal psychiatric comorbidity is a notable strength, it also posed significant recruitment challenges. Small sample sizes are known to increase the risk of statistically underpowered studies, inflate effect sizes, and result in poor reproductivity, and brain-wide association studies reveal that in order to robustly identify associations between inter-individual differences in brain correlates and mental health phenotypes, sample sizes in the thousands are required (Marek *et al.*, 2022). Nonetheless, smaller-sample sizes still hold value, as many fundamental links between the human brain and behaviour have been uncovered and replicated in small neuroimaging samples (Marek *et al.*, 2022). Fourth, the cross-sectional study design prevents causal and temporal inferences, limiting associations to a particular moment in time. Fifth, among the SA group, the time elapsed between the SA and the study visit varied widely, and brain alterations immediately following a SA may differ over time. Future studies should more carefully consider the recency of SAs in

relation to potential dynamic biomarker changes. Lastly, clinical variables were obtained through self-report or clinical interviewing, making clinical data susceptible to recall bias.

6.8 Future directions

Our work aligns with an important future direction highlighted by the Enhancing Neuro Imaging Genetics through Meta Analysis (ENIGMA) group (https://enigma.ini.usc.edu/), who emphasize that "*Future studies should also further investigate the more elusive subjective aspects of suicide risk, such as SI, as well as implicated psychological constructs such as hopelessness, rumination, and anhedonia*" (Schmaal *et al.*, 2020a). Neuroimaging effect sizes are small, and large samples are often necessary to identify such effects, therefore future studies should aim to collaborate with international consortiums, such as ENIGMA, to combine data to achieve large samples necessary to detect modest, yet important, effects.

As of the fifth edition of the DSM, suicidal behaviour disorder has been included in Section III, which pertains to recognizing emerging diagnoses for future studies, providing strategies to enhance clinical practice and propose new criteria to stimulate future research (American Psychiatric Association, 2013b). The suggested inclusion of suicidal behaviour disorder underscores the value of considering suicide as an independent diagnosis. Currently, suicidal thoughts or behaviour has been included as a symptom or potential negative consequence of several disorders including mood disorders, borderline personality disorder, and schizophrenia according to the DSM-5 (American Psychiatric Association, 2013b). Consequently, many neuroimaging studies have investigated suicide-related outcomes within specific psychiatric diagnoses to minimize confounding effects. Treating suicidal behaviour as an independent diagnosis may reveal transdiagnostic neural correlates of suicide-related outcomes, above and beyond any single diagnostic group. One key feature of the proposed suicidal behaviour disorder

criteria is that a SA must occur within the last 24 months. This temporal constraint is particularly relevant for neuroimaging, where neural metrics, especially fMRI, are sensitive to changes over time. Narrowing the timeframe reduces heterogeneity and additional confounding effects pertaining to uncaptured life events over time. In line with Schmaal et al., neuroimaging studies would benefit from examining suicide across diagnostic categories with large, multisite studies (Schmall *et al.*, 2020). This approach enhances statistical power and considers variability across individuals, while also allowing a transdiagnostic approach. Furthermore, it may be time to move beyond observational single site cross-sectional approaches and more toward the growing field of machine learning, which provides new opportunities to classify and predict relationships regarding neural correlates of suicide-related thoughts and behaviours using large, widespread datasets (Parsaei *et al.*, 2023). In the meantime, research studies such as those presented herein remain valuable for their contribution to uncovering neurobiological signatures of suicide. Advancing this understanding is integral to complementing current suicide prevention efforts and offers promise to identifying novel treatment targets and improve clinical interventions.

Annex A: Project Acknowledgements, Funding, Statement of Interest and Data Availability

A1. Acknowledgements

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A3. Statement of Interest

P. Blier has received consulting and speaking honoraria from AbbVie, Allergan, Eisai, Idorsia, Janssen, Lundbeck, Merck, Pfizer and Otsuka, research grants from CAN-BIND, CIHR, Janssen, Neurocrine, OBI and Otsuka, and expert testimonies for the Canadian Medical Protective Association and Intra-Cellular Therapies. All other authors report no potential conflicts of interest.

A4. Data Availability

The data that support the findings of all included articles are available from the corresponding author upon reasonable request.

Annex B: Relevant Additional Academic Contributions During MD/PhD Training Program

B1. Manuscripts

i. Kaminsky ZA, **Burhunduli P**, Sani M, Mar-Kaminsky S, McQuaid R, Phillips JL. A Maching Learning Clinical Decision Support Tool for Reduction of Post-Hospital Discharge Suicide Risk, FOCUS-S: Facilitated Optimization of Clinical Understanding for Suicide Safety – completed draft, preparing submission

ii. Vandeloo KL, **Burhunduli P**, Bouix S, Owsia K, Cho KIK, Fang Z, Van Geel A, Pasternak O, Blier P, Phillips JL. Free-Water Diffusion Magnetic Resonance Imaging Differentiates Suicidal Ideation From Suicide Attempt in Treatment-Resistant Depression. Biol Psychiatry Cogn Neurosci Neuroimaging. 2023 Apr;8(4):471-481. doi: 10.1016/j.bpsc.2022.12.007. Epub 2022 Dec 20. PMID: 36906445; PMCID: PMC11421579.

iii. Phillips JL, Van Geel A, **Burhunduli P**, Vasudev D, Batten LA, Norris S, Talbot J, Ortiz A, Owoeye O, Blier P. Assessment of Objective and Subjective Cognitive Function in Patients With Treatment-Resistant Depression Undergoing Repeated Ketamine Infusions. Int J Neuropsychopharmacol. 2022 Dec 12;25(12):992-1002. doi: 10.1093/ijnp/pyac045. PMID: 35931041; PMCID: PMC9743964.

iv. McQuaid RJ, Nikolitch K, Vandeloo KL, **Burhunduli P**, Phillips JL. Sex Differences in Determinants of Suicide Risk Preceding Psychiatric Admission: An Electronic Medical Record Study. Front Psychiatry. 2022 May 27;13:892225. doi: 10.3389/fpsyt.2022.892225. PMID: 35711595; PMCID: PMC9196272.

B2. International conferences

i. **Burhunduli P**, Fang Z, Vandeloo K, Sharmin, F, Blier P, Phillips, JL*. (2025). Exploring resting-state functional neuroimaging and clinical features of suicide risk differentiating suicidal ideation and suicide attempts in treatment-resistant depression. Accepted for oral presentation at the **International Summit on Suicide Research, Boston, Massachusetts, November 8-11, 2025**

ii. **Burhunduli P**, Fang Z, Vandeloo K, Sharmin, F, Blier P, Phillips, JL. (2025). Resting-state functional connectivity associations with suicidal ideation severity in treatment-resistant depression. Poster presentation at the **International College of Neuropsychopharmacology/Asian College of Neuropsychopharmacology Joint Congress, Melbourne, Australia, June 15-18, 2025**

iii. **Burhunduli P**, Fang Z, Vandeloo K, Sharmin, F, Blier P, Phillips, JL. (2025). Functional neuroimaging correlates of suicidal ideation severity in treatment-resistant major depressive disorder. Poster presentation at the **Society of Biological Psychiatry, Toronto, Ontario, April 24-26, 2025**

iv. **Burhunduli P**, Fang Z, Vandeloo K, Blier P, Phillips, JL. (2024). A preliminary investigation of resting state functional connectivity networks in patients with treatment-resistant depression and a history of suicide attempt. Poster presentation at the **International College of Neuropsychopharmacology 35th World Congress, Tokyo, Japan**. May 23-26, 2024

v. **Burhunduli P**, Vandeloo K, Ghanayem L, Blier P, Phillips JL. Relationship between hippocampal CA1 subfield volume and childhood trauma in depression with suicidal

ideation. Poster presentation at the **International College of Neuropsychopharmacology 34th World Congress, Montreal, Quebec**. May 7-10, 2023

vi. Cherinet A, **Burhunduli P**, Cassidy C, Jaworska N, McQuaid RJ, Shlik J, Kamisky Z, Robillard R, Phillips JL. Relationship between hippocampal subfield volumes and depressive symptoms in veterans with posttraumatic stress disorder. Poster presentation at the **International College of Neuropsychopharmacology 34th World Congress, Montreal, Quebec**. May 7-10, 2023

vii. **Burhunduli P**, Vandeloo K, Ghanayem L, Blier P, Phillips JL. Relationship between Hippocampal CA1 subfield volume and Childhood Trauma in Depression with Suicidal Ideation. Poster presentation at **Society of Biological Psychiatry. San Diego, California**. April 27-29 2023

viii. International Academic of Suicide Research/American Foundation for Suicide Prevention **International Summit on Suicide Research Barcelona, Spain**, October 2023. Attendance only

ix. **Burhunduli P**, Fang Z, Vandeloo K, Blier P, Phillips, JL. Examining resting state functional connectivity in suicidal ideation and attempts. Virtual oral presentation at **61st Annual Meeting of the American College of Neuropsychopharmacology, Phoenix, AR, USA**. December 4-7, 2022

B3. Awards and scholarships

i. **Title**: Doctoral admission scholarships, 2023-2025

Source: University of Ottawa

Total value: $27,000

ii. **Title**: Brain Health Research Day Clinical Poster Award, 2025

Source: University of Ottawa Brain and Mind research Institute/Brain-Heart Interconnectome

Total value: $300

iii. **Title**: Student Encouragement Award, 2024

Source: International College of Neuropsychopharmacology

Total value: $200

iv. **Title**: Graduate Student and Postdoctoral Award, 2024

Source: University of Ottawa Institute of Mental Health Research at The Royal

Total value: $1000

v. **Title**: Canada Graduate Doctoral Scholarship, 2023

Source: Canadian Institute of Health Research, 2023

Total value: $110,000

vi. **Title**: Ontario Graduate Scholarship, 2023

Source: University of Ottawa

Total value: $15,000 (refused offer)

vii. **Title**: Mental Health Trainee Research Award, 2023

Source: University of Ottawa Brain and Mind Research Institute

Total value: $10,000 (refused offer)

viii. **Title**: Best Clinical PhD Poster Award, 2022

Source: University of Ottawa Brain Health Research Day

Total value: $1000

ix. **Title**: Best MD/PhD Poster Award, 2022

Source: University of Ottawa Faculty of Medicine Research Day, 2022.

Total value: $300

x. **Title**: Best MD/PhD Poster Award, 2022

Source: University of Ottawa, Faculty of Medicine Research Day, 2022.

Total value: $300

xi. **Title**: Best Medical Student Poster Award, 2021

Source: University of Ottawa Institute of Mental Health Research at The Royal Brain Research Day

Total value: $300

B4. Research Grants

i. **Source**: The Royal's Brain Imaging Centre PET Development Funding, 2024-2025

Title: Assessing brain synaptic density in mood disorders using multimodal imaging

Principal Investigator: Dr. Gayatri Saraf; Dr. Lauri Touminen

Co-Principal Investigators: Dr. Jennifer L. Phillips, Dr. Sara Tremblay, Katie Dinelle, Dr. Synthia Guimond, Dr. John Anderson, Dr. Natalia Jaworska, **Patricia Burhunduli**, Cecelia Shvetz

Amount: $15,200

ii. **Source**: Canadian Institute of Health Research (CIHR), Meetings, Planning and Dissemination Grant, 2024-2025

Title: Ottawa Neuroimaging Scientific Retreat: Assembling Brain Researchers in the Nation's Capital

Principal investigator: Dr. Jennifer L. Phillips

Co- Investigators: Katie Dinelle, Dr. Tram Nguyen, **Patricia Burhunduli**

Amount: $6,067

iii. **Source**: Ontario Brain Institute (OBI) Event Funding, 2024-2025

Title: Ottawa Neuroimaging Scientific Retreat

Co-Principal Investigators: Dr. Jennifer L. Phillips, Katie Dinelle, Dr. Tram Nguyen, **Patricia Burhunduli**

Amount: $5,000

iv. **Source**: University of Ottawa Medical Research Fund, 2023-2026

Title: Neuroimaging biomarkers of treatment response for rapid acting interventions in depression

Principal Investigator: Dr. Jennifer. L Phillips, Dr. Pierre Blier

Co-Investigators: Dr. Natalia Jaworska, Dr. Jeanne Talbot, Dr. Lisa McMurray, Dr. Stefanie Hassel, Dr. Reggie Taylor, **Patricia Burhunduli**, Sophie Brunet

Amount: $100,000

v. **Source**: Canadian Institutes of Health Research (CIHR), Café Scientifique Program – Open Pool, 2023-2024

Title: Understanding the current status of brain imaging for diagnosis and treatment planning in mental illness - perspectives from clinical and research applications

Principal Investigator: Katie Dinelle, Kevin Patrick

Co-Principal Investigators: Dr. Jennifer L Phillips, Dr. Georg Northoff, Dr. Natalia Jaworska, Dr. Clifford Cassidy, **Patricia Burhunduli**

Amount: $7,006

vi. **Source**: University of Ottawa Brain and Mind Research Institute, ORACLE Brain-Heart Funding Opportunity, 2021-2023

Title: Impact of depression on the autonomic nervous system of the heart

Principal Investigator: Dr. Lauri Tuominen, Dr. Robert deKemp

Co-Principal Investigators: Dr. Jennifer L Phillips, Katie Dinelle, Dr. Jess Fiedorowicz, Rob Beanlands, Peter Winfield, **Patricia Burhunduli**, Zacharie Saint-Georges

Amount: $49,900

B5. Knowledge Translation Activities

i. Ottawa Neuroimaging Scientific Retreat – Assembling Brain Researchers in the Nation's Capital, presenter, 2024

ii. The Royal's Leader for Mental Health Breakfast, featured speaker, 2024

iii. Royal Ottawa Foundation Internation Women's Day Event, invited panelist, 2024

iv. World Suicide Prevention Video at The Royal, invited speaker, 2024

v. Mental Health Hygiene, invited speaker, 2024

vi. Café Scientific with the Institute of Mental Health Research at The Royal, grant co-applicant, 2024

vii. Canadian Biomarker Integration Network in Depression and Ontario Brain Institute Podcast, invited speaker, 2021

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