WHITE MATTER MICROSTRUCTURE IN SUICIDE AND TREATMENT-RESISTANT DEPRESSION

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AD	Axial Diffusivity
ADt	Free Water Corrected Axial Diffusivity
ALIC	Anterior Limb of the Internal Capsule
ATR	Anterior Thalamic Radiation
B_0	Main Magnetic Field
BAI	Beck Anxiety Inventory
BDI	Beck Depression Inventory
BDNF	Brain Derived Neurotropic Factor
BHS	Beck Hopelessness Scale
BIC	Brain Imaging Centre
BSS	Beck Scale for Suicide Ideation
CCHS	Canadian Community Health Survey
CGH	Cingulum Bundle Adjacent to the Hippocampus
CNN	Convolutional Neural Network
CR	Corona Radiata
CRP	C-Reactive Protein
C-SSRS	Columbia Suicide Severity Rating Scale
D	Diffusion Coefficient
DA	Dopamine
DICOM	Digital Imaging and Communications in Medicine
dlPFC	Dorsal-Lateral Prefrontal Cortex
dmPFC	Dorsal-Medial Prefrontal Cortex
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DTI	Diffusion Tensor Imaging
DWI	Diffusion Weighted Imaging
ENIGMA	Enhancing Neuroimaging Genetics Through Meta-Analysis
EPI	Echo Planar Imaging
FA	Fractional Anisotropy
FAt	Free Water Corrected Fractional Anisotropy
FDR	False Discovery Rate
fMRI	Functional Magnetic Resonance Imaging
FSL	FMRIB Software Library
FW	Fractional Volume of the Free Water Compartment
FWE	Family-Wise Error
GWAS	Genome-Wide Association Studies
HP	Healthy Participants
HPA	Hypothalamic-Pituitary-Adrenal
ICF	Informed Consent Form
ILF	Inferior Longitudinal Fasciculus

MAO	Monoamine Oxidase
MADRS	Montgomery Åsberg Depression Rating Scale
MD	Mean Diffusivity
MDt	Free Water Corrected Mean Diffusivity
MDD	Major Depressive Disorder
MDE	Major Depressive Episode
MEMPRAGE	Multi-Echo Magnetization Prepared Rapid Gradient Echo
mFO	Medial Fronto-Occipital
MRI	Magnetic Resonance Imaging
NE	Norepinephrine
NIFTI	Neuroimaging Informatics Technology Initiative
NMR	Nuclear Magnetic Resonance
nSA	Non-Suicide Attempter
nSI	Non-Suicide Ideator
OFC	Orbitofrontal Cortex
PE	Phase Encoding
PHQ-9	Patient Health Questionnaire 9
PLIC	Posterior Limb of the Internal Capsule
QC	Quality Checking
RD	Radial Diffusivity
RDt	Free Water Corrected Radial Diffusivity
RF	Radiofrequency
ROI	Region-of-Interest
rsfMRI	Resting-State Functional Magnetic Resonance Imaging
SCID-5-RV	Structured Clinical Interview for DSM-5, Research Version
SA	Suicide Attempt/Suicide Attempter
SD	Standard Deviation
SI	Suicidal Ideation/Suicide Ideator
SLF	Superior Longitudinal Fasciculus
sMRI	Structural Magnetic Resonance Imaging
SNR	Signal-to-Noise Ratio
SSRIs	Selective-Serotonin Reuptake Inhibitors
STAR*D	Sequenced Treatment Alternatives to Relieve Depression
TBSS	Tract-Based Spatial Statistics
TE	Echo Time
TNF-α	Tumor-Necrosis Factor - Alpha
TR	Repetition Time
TRD	Treatment-Resistant Depression
UF	Uncinate Fasciculus
^{1}H-MRS	Proton Magnetic Resonance Spectroscopy
5-HT	5-Hydroxytryptamine

ABSTRACT

Background. Major depressive disorder (MDD) is a leading cause of death and disability worldwide, and many individuals with MDD will experience treatment-resistant depression(TRD). TRD can lead to the development of suicidal ideation and behaviours, and up to 30% of people with refractory depression will attempt suicide at some point in their life. A neurobiological understanding of suicide is lacking, and neuroimaging markers of illness may elucidate the relationship between suicidal ideation and attempt. Diffusion tensor imaging (DTI) is a particularly sensitive neuroimaging modality that quantifies the microstructural integrity of white matter tracts, which may be useful in the investigation of psychiatric disease. The source of white matter changes may be further elucidated using free water imaging to isolate signal specific to the fibre tract and quantify the fractional volume of the free water compartment. Methodology. For this study, data were obtained from N=36 outpatients with TRD (n=20 suicide ideators and n=16 suicide attempters). Clinical characteristics of the patient sample were examined using clinician-rated and self-report questionnaires of depression and suicidal ideation severity. Whole-brain analysis of DTI data was conducted using tract-based spatial statistics (TBSS) via FMRIB Software Library (FSL) to identify between-group differences in white matter microstructure between suicide ideators and attempters. Free water imaging correction was applied through estimation of a constrained bi-tensor model via an in house MatLab-based script developed at Harvard University. Between-group differences of suicide ideators versus attempters were identified at a family-wise error (FWE) corrected significance threshold of $p \leq 0.05$. Subsequent exploratory analyses were performed at an uncorrected significance threshold of $p \leq 0.01$. Results. Suicide attempters had greater family history of suicide attempt, higher self-reported suicidal ideation severity, and were more likely to have received overnight treatment in a psychiatric facility in the past. TBSS revealed

elevated mean diffusivity (MD), axial diffusivity (AD) and free water (FW) in suicide attempters compared to suicide ideators (thresholded p=<0.05, family-wise error corrected). Subsequent exploratory analyses revealed reduced fractional anisotropy (FA) and elevated radial diffusivity (RD) in fronto-thalamo-limbic white matter tracts of suicide attempters (thresholded p=<0.01, uncorrected). Free water correction appeared to increase detection of FA changes and suppress spurious differences in axial and radial diffusivity. Conclusion. The identification of significantly altered diffusion metrics in suicide attempters compared to suicide ideators suggests white matter pathology in TRD and suicide attempt. The effect of free water correction on diffusion metrics and the elevation of free water itself provide evidence toward the source of anisotropic changes. Future investigations to explore the combined impact of these measures in suicide and depression are recommended.

Chapter I. Introduction

1.1. Major Depressive Disorder (MDD) and Treatment-Resistant Depression (TRD)

1.1.1. Diagnostic Criteria

Major depressive disorder (MDD) is clinically diagnosed from criteria reported in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) by the American Psychiatric Association (American Psychiatric Association, 2013). MDD involves at least five of the following symptoms for the same two-week period: 1) depressed mood, 2) diminished interest or pleasure (anhedonia), 3) significant weight loss or weight gain, 4) changes in appetite, 5) psychomotor agitation or retardation, 6) fatigue or loss of energy, 7) feelings of worthlessness, excessive or inappropriate guilt, 8) diminished ability to concentrate and/or trouble with decision making, and 9) recurrent thoughts of death or suicide. Individuals must experience depressed mood and/or anhedonia for a consecutive two-week period, and a combination of any five other symptoms.

Treatment-resistant depression (TRD), a refractory form of MDD, is loosely conceptualized as significant residual or unresolved symptoms following one, two, and/or multiple attempted pharmacotherapy trials for depression (Limandri, 2018). Although the criteria for TRD is not universally defined, the most common definition for TRD is lack of response to two or more mechanistically distinct treatments for depression in the same major depressive episode (MDE; Gaynes et al., 2020). The consequences of treatment-resistance are consistently reported, and a better understanding of the biological correlates of TRD is needed (Akil et al., 2018).

1.1.2. Epidemiology

MDD is the single greatest contributor to global disability, with over 300 million people currently experiencing major depression (World Health Organization, 2017). Annual and lifetime prevalence rates vary across nationalities and cultures (Gutiérrez-Rojas et al., 2020), such as China (1% annual, 2% lifetime), Germany (3% annual, 10% lifetime), the United States (7% annual, 16% lifetime), and France (6% annual, 21% lifetime). According to the Canadian Community Health Survey (CCHS), annual and lifetime prevalence of major depression was 4% and 11% in the early 2000s (Knoll and MacLennan, 2017). Depression rates have not greatly improved over subsequent years, with the most recent version of the CCHS reporting an annual and lifetime prevalence of 5% and 11%, respectively (Statistics Canada, 2013). Across the Canadian provinces, the prevalence of depression has been shown to vary significantly (for example, 7% in Manitoba, 5% in Ontario, and 3% in Prince Edward Island; Palay et al., 2019). Additionally, suicide rates in Canada are three times higher in First Nations, twice as high in Métis, and nine times higher in Inuit people than the general population (Kumar and Tjepkema, 2019). Both national and global rates of depression differ based on factors such as age and sex, with females reporting MDD at a rate twice that of males (Pandorakalom, 2018). However, whether sex-related differences are due to psychosocial and/or biological factors remains incompletely understood (Godlewska, 2019).

Due to lack of concrete definition, varying conceptualizations of TRD limit research translatability and accurate epidemiological reporting of treatment-resistance. Despite this, it is estimated that only 30% of individuals with MDD will transition into recovery following initial intervention (Gaynes et al., 2020), and less than half of individuals will respond adequately to a second pharmacotherapy trial (Pandarakalam, 2018). This statement is supported by the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, which is the largest and longest

trial to assess the efficacy of pharmacotherapies for depression to date (Trivedi et al., 2006). This study involved the assessment of treatment response to conventional medications for depression (such as selective-serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants), in which the pharmacological agent was switched or augmented by another strategy in the case of treatment non-response or intolerance (Trivedi et al., 2006). Various retrospective analyses of STAR*D data support the reciprocal relationship between remission rates and relapse as a function of the number of ineffective pharmacotherapy trials attempted (Wu et al., 2019). Generally, TRD is associated with poorer functional outcomes, such as greater symptom severity and comorbid psychiatric and physiological disorders, as well as a higher likelihood of suicidal ideation and behaviours (Wu et al., 2019).

1.1.3. Aetiology

MDD is a complex, multifactorial disorder with biological and psychosocial elements. Based on the diagnostic criteria from the DSM-5, and the unique experience of each item (such as bidirectional changes in weight, sleep, and activity levels), various symptom profiles may manifest between individuals (Demyttenaere and Duppen, 2019). For example, in an analysis of nearly 4,000 outpatients with depression, over 1,000 unique symptom combinations were discovered (Fried and Nesse, 2015). Based on the heterogeneity of major depression, a multifactorial etiopathogenesis is reasonable (Chiriţă et al., 2015), however, this complicates its treatment (Kraus et al., 2019). To understand the neurobiological underpinnings of MDD, it is necessary to consider aetiological factors, such as gene-environment interactions, inflammatory processes, neurotransmission, and growth factors, as well as their effect on neuroplastic brain changes. Importantly, a concrete understanding of MDD pathogenesis may lead to the development of

biologically based markers of depression emergence and treatment (Strawbridge, Young and Cleare, 2017).

Gene-Environment Interactions

Historical twin studies estimate the heritability of MDD to be approximately 30-40% (Kraus et al., 2019), with over one-third of MDD onset explained by genetic variability (Chiriţă et al., 2015). Related to this, individuals with an affected first-degree relative are 2-3 times more likely to develop MDD; this appears to predict a more severe course of illness, involving earlier disease onset and/or greater chance of relapse following remission (Saavedra et al., 2016). Large genome-wide association studies (GWAS) have identified genes associated with MDD, such as those involved in neurotransmission, medication response, hormone fluctuations, and neuroplasticity (Kraus et al., 2019; Lee et al., 2012; Hing, Sathyaputri and Potash, 2017). However, no robust genetic markers of depression have been established, and specific variants predictive of MDD and its course remain undiscovered.

The study of epigenetics, the process by which gene expression is modified through the influence of external factors (Akil et al., 2018), has highlighted the importance of gene-environment interactions in MDD emergence. For example, the impact of stressful or traumatic life events may interact with genetic mutations, leading to biological and psychological changes that trigger MDD (Saavedra et al., 2016). Epigenetic mechanisms such as deoxyribonucleic acid methylation and acetylation are known to influence transcription and have been associated with medication response and neuroplastic brain changes in MDD (McIntyre et al., 2014). Transcriptional modifications may occur through genetic polymorphisms (Kraus et al., 2019) or environmental influences (Maul et al., 2020), and are enhanced by the interactions between these factors (Caspi et al., 2003). Indeed, the most consistently reported associations between epigenetic

changes and depression involve the hypothalamic-pituitary-adrenal (HPA) axis, monoamine systems, growth factors, and inflammatory processes (Silva et al., 2021). These changes appear to have lasting effects on the brain and body, which may increase one's susceptibility to major depression and treatment-resistance over time.

Inflammatory & Endocrine Responses

In the context of psychiatric disease, normal physiological processes may become pathological (Dean and Keshavon, 2017). Depression has long been associated with elevations in pro-inflammatory cascades, involving the release of cytokines, C-reactive protein (CRP), and tumour necrosis factor alpha (TNF-α) into circulation (Price et al., 2018). Under chronic conditions, the over-activation of immune cells such as microglia, astrocytes and macrophage may impact mitochondrial function, leading to the production of radioactive oxygen species (Hasler, 2010). Oxidative stress may then influence the structure and function of the brain, through its impact on neurogenesis, dendritic arborization and synaptic pruning (Otte et al., 2016).

Clinically, the bidirectional relationship between pro-inflammatory responses and chronic stress have been associated with the development and course of MDD (Ruiz et al., 2018). During the stress response, cortisol is released by the adrenal gland via the HPA axis, which indirectly supports pro-inflammatory conditions through its effect on metabolism (Price et al., 2018). More specifically, dysregulation of the HPA axis through chronic stress may lead to unrestrained cortisol release and the promotion of chronic, low-grade inflammation (Price et al., 2018). As individuals with MDD appear to have higher circulating levels of cytokines and CRP, the study of systemic inflammation may have merit as a biosignature of depression (Ruiz et al., 2018). Nervous system inflammation may also perpetuate other biological mechanisms, such as neurotransmission and plasticity (Strawbridge, Young and Cleare, 2017).

Neurotransmission & Neurocircuitry

Serotonin (5-HT), dopamine (DA) and norepinephrine (NE) brainstem nuclei have widespread projections throughout the brain, influencing critical processes relevant to mood, cognition, reward, and sleep (Hasler, 2010). The role of monoamines in depression was first discovered through the study of iproniazid, a monoamine oxidase inhibitor (MAO) used for the treatment of tuberculosis (López-Muñoz and Alamo, 2009). Clinical trials involving iproniazid revealed significant mood elevations in participants alongside the enhancement of 5-HT and NE neurotransmission (Ruiz et al., 2018). Further evidence supporting the monoamine hypothesis of depression include tryptophan depletion (Moreno et al., 1999) and reserpine administration (Price, Charney and Heninger, 1987), which have been found to precipitate depression while simultaneously reducing concentrations of 5-HT, DA, and NE (Otte et al., 2016). Finally, reductions in monoamine metabolites in the synaptic cleft have been predictive of treatment response, suggesting an inverse relationship between neurotransmitter reuptake and mood (Ruiz et al., 2018).

Despite these findings, delayed onset of monoaminergic agents as well as their sub-optimal treatment efficacy suggest the involvement of other upstream pathological mechanisms in depression pathophysiology (Hasler, 2010), such as reductions in brain derived neurotrophic factor (BDNF; Gupta et al., 2017, Wilkinson et al., 2018). BDNF supports neurogenesis, neuronal growth, and differentiation, which promotes neuroplastic brain changes in response to physiological and environmental factors (Ruiz et al., 2018). In the context of depression, neuroplasticity may become dysregulated, favouring inefficient or inaccurate synaptic pruning, apoptosis, erroneous signalling cascades, and subtle neurodegeneration (Ruiz et al., 2018). Plasma and serum BDNF levels are consistently reduced in individuals with MDD, with lowest

concentrations in those displaying greater symptom severity and treatment-resistance (Ménard, Hodes and Russo, 2016). Moreover, pharmacotherapy treatment for depression has been shown to attenuate BDNF levels and recover adverse morphological brain changes alongside symptomatic improvement (Boku et al., 2018).

Volumetric fluctuations in brain regions relevant to depression including the hippocampus (Sheline, Gado and Kraemer, 2003), amygdala (Rubinow et al., 2016) and frontal lobes (Abe et al., 2010) may relate to disruptions in neurotransmission and plasticity (Price et al., 2018). Observed structural disparities may lead to functional brain changes and subsequent influence of affective processing and cognition, which have been associated with depression severity (Price et al., 2018). Functional magnetic resonance imaging (fMRI) studies have identified abnormal connectivity in MDD, including alterations in synchronous activation of the affective-salience network (Hamilton et al., 2016), fronto-parietal cognitive control circuit (Schultz et al., 2018), and default mode network (Coutinho et al., 2016). Therefore, the onset and progression of MDD may result from functional connectivity changes between limbic (emotional) and frontal (cognitive) centres, through the promotion of maladaptive cognitive biases and inappropriate responses to emotional stimuli (Dean and Keshavron, 2017). This neurocircuitry model of depression is thought to relate to other biological mechanisms underlying MDD, including inflammation (Piser, 2010), neurotransmission (Hamon and Blier, 2013), and neuroendocrine responses (Gold and Chrousos, 1999).

Interactions Among Biological Mechanisms

The origins of major depression have been historically studied as discrete entities as opposed to a unified model (Ruiz et al., 2018). According to Dean and Keshavan, densely interconnected biological pathways (such as epigenetics, inflammation, and neuroplasticity) are

hypothesized to represent a matrix, where disruptions in any one node may induce detrimental cascades throughout the entire system (Dean and Keshavan, 2017). For example, chronic stress may lead to prolonged cortisol secretion and over-activation of the HPA axis, pro-inflammatory cascades, free radical production, and subsequent morphological brain changes under chronic conditions (Ruiz et al., 2018). A prolonged state of crisis may then disrupt monoaminergic transmission, through tyrosine hydroxylase overactivity and metabolism of 5-HT, DA and NE (Dean and Keshavan, 2017). Systemic inflammation may also promote a neurotoxic environment favouring reductions in dendritic complexity, synaptic plasticity, and functional connectivity changes among neuronal circuits (Price et al., 2018). As supported by these findings, a reductionistic approach to the study of MDD and treatment-resistance hinders our understanding of its heterogeneity. Although the feasibility of multi-modal trials assessing various biological and psychological markers of MDD is low, the magnitude of factors underlying structural and functional brain changes in depression must be recognized.

1.2. Suicide

1.2.1. Suicide in the Context of MDD

Suicide, as defined by intentional death through self-injurious behaviour(s), results in over 800,000 deaths annually (World Health Organization, 2017). This translates to approximately one death every 40 seconds, making suicide a leading cause of mortality worldwide (World Health Organization, 2017). Suicide attempts are predicted to occur at a multiple of 10-30 per suicide death (Bachmann, 2018), and previous suicide attempt is the single greatest predictor of future suicide death (Bostwick et al., 2016). Interestingly, females attempt suicide at a higher rate than males, however, males die by suicide more often than females (Deshpande et al., 2016). This sex

difference in suicide rates is thought to result from the use of more lethal methods by males (Turecki and Brent, 2016).

Among individuals who die by suicide, approximately 90% meet criteria for a psychological illness (Klonsky, May and Saffer, 2016), and over 60% are experiencing a MDE at the time of their death (Park et al., 2017). Suicidal ideation, defined by self-reported visualization, consideration, or mental planning of suicide-related behaviour (O'Carroll et al., 1996), is a core symptom of MDD outlined in the DSM-5 (American Psychiatric Association, 2013). Suicidal ideation may range in severity from passive suicidal thoughts (such as a wish to be dead), to thoughts of engaging in suicide with specific plan and intent to act, which may vary in intensity, frequency, and controllability (Posner et al., 2011). Suicidal ideation is incredibly prevalent in major depression, with 55% of outpatients and 76% of inpatients reporting current suicidal ideation to a clinician (Vuorilento et al., 2020). TRD is of particular concern, as up to 30% of individuals with refractory depression attempt suicide at some point in their life (Bergfeld et al., 2018). This rate is twice as high as that observed in non-refractory depression, and 15 times higher than that of the general population (Bergfeld et al., 2018). Indeed, suicidal ideation and attempts are closely related, and worst-point lifetime ideation may contribute to the emergence of suicidal behaviours (Park et al., 2017).

1.2.2. Suicidal Ideation, Behaviours and Attempts: A Progression

Suicide prediction has not improved significantly over the past 50 years (O'Connor and Kirtley, 2018), and robust clinical markers of suicide attempt have yet to be established (Park et al., 2017). Many vulnerability factors for suicide are strongly predictive of suicidal ideation, yet may fail to anticipate the development of suicidal behaviours (Kessler, Borges and Walters, 1999; Klonsky and May, 2014). For example, while the presence of a MDE, hopelessness, and/or

impulsivity is highly predictive of suicidal ideation, their severity does not appear to differ between suicide ideators and attempters (Klonsky, May and Saffer, 2016). The improvement of suicide prevention requires an understanding of the independent roles of suicidal thoughts, behaviours and attempts in conjunction with MDD (DiazGrandos et al., 2010), and the progression from passive suicidal thoughts to highly lethal suicide attempts (Klonsky and May, 2014). For this reason, it may be important to conceptualize the emergence of suicidal ideation and one's progression toward attempts as independent processes.

Various psychological theories relating to the progression from suicidal ideation to behaviours and attempts have been proposed (Baumeister, 1990; Schneidman, 1993; Joiner, 2005; O'Connor, 2011; Klonsky and May, 2015). According to the escape theory of suicide, anindividual develops suicidal ideation following the adaptation and internalization of cognitive biasin response to external events (Baumeister, 1990). This individual would then develop a negativeview of the world and self, in which they may resort to suicide to escape from psychological unrest(Baumeister, 1990). A subsequent theory proposed by Schneidman highlights psychological painor 'psychache' to be the core of suicidal ideation, from which suicide behaviours and/or attemptsmay emerge when one's threshold for pain is surpassed (Schneidman, 1993). More recent theories of this progression include the interpersonal theory of suicide (Joiner, 2005), the integrated motivated-volitional model of suicide (O'Connor, 2011), and the three-step theory of suicide (Klonsky and May, 2015). According to the interpersonal theory of suicide, a desire for death (acquired through the combination of high perceived burdensomeness and low sense of belonging,as well as feelings of hopelessness regarding these factors) must be accompanied by a high capability to act on these desires (Joiner, 2005). The integrated-motivational theory of suicide relates to Joiner's work, as it suggests that one develops suicidal ideation through defeat and

entrapment (rather than high burdensomeness and non-belonging), followed by the emergence of suicidal behaviours and/or attempts after a capability for suicide has been reached (O'Connor, 2011). As suggested by this theory, the development of suicidal ideation leads to a sense of defeat and humiliation, which may combine with the impact of negative life events to lower one's threshold for suicide (O'Connor, 2011). According to the three-step theory of suicide, an individual develops suicidal ideation through an overwhelming combination of psychological pain and hopelessness (Klonsky and May, 2015). When this psychological load overcomes a sense of connectedness to others and their external world, one's capacity for suicidal behaviours and attempts is increased (Klonsky and May, 2015). Capability for suicide can be dispositional (e.g., high trait impulsivity combined with genetic factors that lead to a greater pain threshold and low fear of dying) or acquired (e.g., habituation to painful or provocative events, influencing one's perspective on self-inflicted injury and death), which may have meaningful clinical implications during risk assessment (Klonsky and May, 2015).

1.2.3. Limitations in Suicide Prevention

While psychological theories of suicide have been widely reviewed, robust clinical correlates remain elusive (Park et al., 2017). The neurobiology of suicide is understudied, and a greater understanding of the progression from suicidal ideation to behaviours may have significant implications for the prevention of suicide attempts (Klonsky and May, 2014). Furthermore, the ability to recognize suicidal individuals using clinical risk assessments is limited, and up to 78% of psychiatric inpatients who go on to die from suicide will deny the presence of ideation in their last exchange with a clinician (Price et al., 2014). Implicating a neurobiological marker for suicide risk may limit biased reporting from individuals most at risk of a highly lethal suicide attempt, who may avoid disclosure to prevent interference with suicide plans (Sudol and Mann, 2017).

Altogether, the likelihood of a suicide attempt in a depressed cohort may be reduced through adequate identification and recognition of this progression using more objective assessment techniques (Miret et al., 2013).

In comparison to other fields of medicine, the development of clinical tests for the early detection and treatment of psychiatric illness is severely lacking (Scarr et al., 2015). In the context of heterogeneous disorders like MDD, unique etiological factors may precede the development of suicidal ideation and behaviours between individuals (Scarr et al., 2015), highlighting the significance of clinical subtypes in treatment. Current interventions for major depression and suicide are often one-size-fits-all, in which pharmacotherapies are attempted in a trial-and-error fashion to alleviate symptoms (Williams and Hack, 2020). This approach likely contributes to treatment-resistance, as well as residual symptoms including suicidal ideation following treatment (Akil et al., 2018). Furthermore, suicidal ideation and behaviour are not targeted directly, and their treatment is typically a side effect of MDD intervention (Griffiths, Zarate and Rasimas, 2014). Many hypothesized biological mechanisms of suicide overlap with depression, making it especially challenging to differentiate between the effects of MDD and suicide (Lee, Seol and Kim, 2017). Limitations in suicide prevention and the unwavering prevalence of suicide deaths across Canada and the world highlight the need for a biopsychosocial approach to mental health and disease (Fernandes et al., 2017), in which psychological risk factors and clinical correlates may be combined with unique biosignatures of illness.

1.3. Neuroimaging for the Study of Depression and Suicide

Biomarkers, defined as an objectively measured characteristic of normal or pathogenic function (Biomarkers Definitions Working Group, 2001), may have merit in the context of depression and suicide. For example, structural and functional neuroimaging markers of illness

may contribute to the understanding of the relationship between suicidal ideation and behaviours, to identify who is most at risk for suicide attempt (Schmaal et al., 2020). More specifically, the combination of spatially and temporally specific neuroimaging modalities may illustrate circuit-level dysfunction in psychiatric disease, in networks relevant to emotional and cognitive centres (Williams, 2016). While these methods have not yet been optimized for clinical use (Scarr et al., 2015), the study of microstructural neuronal networks in the context of depression and suicide may highlight dysfunctional pathways to be targeted through treatment (Williams and Hack, 2020).

1.3.1. Introduction to Magnetic Resonance Imaging (MRI)

The concept of nuclear magnetic resonance (NMR) was first demonstrated in 1938 through observed radiowave emissions upon the introduction of molecules to a magnetic field (Rabi et al., 1938). The discovery of NMR led to the translational work of Raymond Damadian, who proposed the utilization of magnetic resonance properties such as spin-spin and spin-lattice relaxation to investigate tissue malignancy (Damadian, 1999). Through the development of hardware and acquisition methods, optimized medical imaging systems have since become common in clinical research environments (Edelman, 2014). An advantage of magnetic resonance imaging (MRI) is the ability to adjust acquisition parameters of imaging sequences to optimize signal-to-noise ratio (SNR) among different tissue types (McManon, Cowin and Galloway, 2011). Repetition time (TR; the time between subsequent radiofrequency (RF) pulses) and echo time (TE; the time between proton excitation and reception of magnetic resonance signal) are influential as their values have a direct effect on image contrast (Yousaf, Dervenoulas and Politis, 2018). More specifically, TR and TE values impact longitudinal and transverse relaxation; the former representing the time required for excited protons to return to alignment with the main magnetic field (B_0) following an RF pulse, and the latter quantifying the dephasing of precessing protons and subsequent decline of

magnetic resonance signal strength (Lerch et al., 2016). Short TE and TR times are typically associated with T1-weighted images, whereas long TE and TR values are characteristic of T2-weighted contrasts (McManon, Cowin and Galloway, 2011). By definition, T1 is the time it takes for longitudinal magnetization to recover by 63%, whereas T2 is the time it takes for the transverse magnetization to decay by 37% (Pooley, 2005). Other significant modifiable imaging parameters include the flip angle (the degree to which net magnetization rotates in the transverse direction following an RF pulse), matrix size (in which voxel dimensions directly impact spatial resolution), field of view (the size of the spatially defined 2- or 3-dimensional imaging space), bandwidth (the frequency of signal acquisition), and slice thickness (Yousaf, Dervenoulas and Politis, 2018).

1.3.2. Study of White Matter using Diffusion Tensor Imaging (DTI)

Neuronal tissue is uniquely organized into axonal fibre bundles of varying orientations (Hagman et al., 2006). The directionality of these fibres, as well as their integrity (meaning their coherence in any given direction, density, degree of myelination and/or structural quality (Jones, Knösche and Turner, 2012)), impact the degree of water diffusion throughout the microstructural network of white matter (Yousaf, Dervenoulas and Politis, 2018). Brownian motion, the uncontrolled movement of particles in an open medium (Le Bihan et al., 2001), was first linked to the diffusion coefficient by Albert Einstein (Einstein, 1956). The concept of a theoretical diffusion coefficient was then understood (Hahn, 1950; Carr and Purcell, 1954), leading to the measurement of water diffusion in biological tissue (Stejskal and Tanner, 1965), and the first diffusion-weighted imaging (DWI) acquisition in humans in 1985 (Le Bihan et al., 1986). DWI utilizes this concept of Brownian motion through biological tissue to quantify metrics of diffusion and thus white matter architecture (Baliyan et al., 2016).

As water diffuses preferentially through axonal fibres in a principal direction, and is influenced by tissue integrity, the presence of physical barriers and membrane boundaries (Hagman et al., 2006), it is possible to make inferences about tissue microstructure based on the degree of isotropic diffusion through fibre tracts (Yousaf, Dervenoulas and Politis, 2018). Diffusion tensor imaging (DTI) quantifies the anisotropy of white matter through the application of diffusion-weighted signal in varying directions and compilation of a three-by-three diffusion tensor (Roberts and Schwortz, 2007). The diffusion tensor (which may also be conceptualized as an ellipsoid), mathematically represents the three-dimensional shape of water diffusion through axonal fibres (Lima and Le Bihan, 2016). From this theoretical ellipsoid (or diffusion tensor) three eigenvectors (ε_1, ε_2, ε_3) and three corresponding eigenvalues (λ_1, λ_2, λ_3), form the diffusion coefficient (D) in six non-collinear directions (D_{xx}, D_{yy}, D_{zz}, D_{xy}, D_{xz}, D_{yz}; Kingsley, 2006). From the diffusion tensor, metrics of tissue integrity can be mathematically derived, such as fractional anisotropy (FA; the directional preference of water diffusion, or the difference of the ellipsoid's shape from that of a perfect sphere), mean diffusivity (MD; the overall mobility of water molecules in each voxel), axial diffusivity (AD; the rate of diffusion parallel to the primary diffusion direction), and radial diffusivity (RD; the rate of diffusion perpendicular to the primary diffusion direction; Soares et al., 2013). Additional modifiable imaging parameters must be considered for diffusion imaging acquisition sequences, such as the number of diffusion directions (Ni et al., 2006), the echo planar imaging (EPI) factor (number of k-space lines acquired per excitation; Jeong, Gore and Anderson, 2013), and b-value (strength of diffusion weighting; Oida, Nagahara and Kobayashi, 2011).

DWIs are particularly susceptible to head motion, as well as artifacts caused by eddy currents, respiration, and heart rate (Soares et al., 2013). Quality control and preprocessing are

thus crucial to the optimization of SNR and the removal of artifacts, which is followed by estimation of the diffusion tensor at each voxel and subsequent statistical analyses (Nucifora et al., 2007). To extract diffusion metrics such as FA, region-of-interest (ROI) based approaches may be utilized, in which brain areas are selected for analysis based on an *a priori* hypothesis (Abe et al., 2010). Using this method, ROIs are traced manually using an imaging visualization software such as *3DSlicer* or *TrackVis*; however, this method has significant limitations. For example, there is no robust method for the co-registration of subject images to a common registration space, increasing the potential for human error (Soares et al., 2013). A second possible approach, voxel-based analysis, involves repeated measurements of diffusion in a single voxel and its comparison to all other voxels across the whole brain, which may be particularly useful in the context of exploratory analyses (Abe et al., 2010). However, voxel-based approaches are limited by inconsistencies in spatial smoothing, and care must be taken to eliminate cumulative error arising from multiple comparisons (Winston, 2012). A third approach, tract-based spatial statistics (TBSS), attempts to circumvent these issues through estimation of a group FA map, and projection of individual FA maps onto the white matter skeleton (Winston, 2012). This technique successfully eliminates the need for spatial smoothing and reduces the number of statistical comparisons across the whole brain (Soares et al., 2013). This method is thought to combine the strengths of both ROI and voxel-based analysis (Smith et al., 2006), and is the most conventionally used method for voxel-wise analysis (Bach et al., 2014).

Despite the benefits of TBSS, fundamental limitations are present. For example, TBSS assumes that each voxel in the brain contains diffusion information exclusively from white matter. However, it is likely that many voxels are contaminated with signal from other structural compartments, including extracellular free water (Bergamino et al., 2015). Free water, defined as

unrestricted water molecules accumulating in ventricles and the surrounding brain parenchyma, may limit the delineation of white matter fibre tracts during statistical analysis (Pasternak et al., 2009). More specifically, free water contamination such as that caused by the accumulation of cerebrospinal fluid may lead to reductions in FA and apparent diffusion coefficient values (Pasternak et al., 2009). Free water imaging correction using a constrained bi-tensor model appears successful in restricting signal contamination and provides a voxel-wise map of FW, which may be a useful clinical marker of extracellular status (Lyall et al., 2009). Therefore, the application of free water imaging correction to TBSS may improve the detection and characterization of white matter microstructure.

1.3.3. Previous DTI Findings in Depression and Suicide

To date, neuroimaging markers of depression and suicide have not yet been identified as a predictor of disease course and/or pharmacotherapy response (Schmaal et al., 2020; Price et al., 2018). An advantage of DTI is its sensitivity to microstructural brain changes invisible to the naked eye, and identification of a connectivity blueprint in this context could prove crucial in separating those most at risk for suicide attempt (Abe et al., 2010). Previous applications of DTI have been successful in identifying abnormalities in white matter structure associated with developmental abnormalities (Kimpton et al., 2021), neurodegeneration and aging (Kantarci et al., 2014), epilepsy (Widjaja et al., 2011), and schizophrenia (Hoptman et al., 2004). Clinically, DTI has been utilized in the context of ischemia to investigate post-stroke degeneration (Fragata et al., 2017), as white matter changes appear to predict the evolution of disease following infarct (Sotak, 2002).

DTI investigations in MDD and TRD are scarce, and the relationship between white matter and suicide is widely understudied; to date, only four published studies have investigated the role of white matter abnormalities in suicide using neuroimaging (Jia et al., 2014; Olvet et al., 2014;

Taylor et al., 2015; Myung et al., 2016; Table 1). In 2014, Jia and colleagues used DTI-based deterministic tractography to investigate fibre tracts in individuals with MDD and suicide attempt history, compared to non-attempters with MDD; this study identified greater white matter aberrations in the left orbitofrontal cortex (OFC) and thalamus of suicide attempters (Jia et al., 2014). Olvet and colleagues further investigated white matter in suicide attempters with MDD, compared to those with MDD and no suicide attempt, as well as healthy volunteers. This study reported lower FA in suicide attempters in the dorsomedial prefrontal cortex (dmPFC) using ROI-based analysis and TBSS (Olvet et al., 2014). Using voxel-wise analysis, Taylor and colleagues identified white matter abnormalities in fibre tracts of the salience network, default mode network and thalamocortical circuits in individuals with MDD and suicidal thoughts; this study did not investigate suicidal behaviour or attempts (Taylor et al., 2015). Finally, using a network-based statistics approach, Myung and colleagues identified a neuronal subnetwork with reduced structural integrity in individuals with MDD and suicidal thoughts, involving fronto-subcortical circuits and other regions known to be associated with executive function (such as the caudate, putamen and thalamus; Myung et al., 2016). As indicated by these preliminary investigations, white matter tracts in frontolimbic networks appear to be significantly implicated in MDD and suicide (Schmaal et al., 2020), however, further DTI investigations using more clearly defined criteria for suicidal ideation, behaviours and attempts are necessary (Cox Lippard, Johnston and Blumberg, 2014).

Table 1. Published DTI literature in suicide and MDD.

Study	Population	Methodology	Results
Jia et al., 2014	n=63MDD (n=23SA, n=40nSA), n=46 HP	-Probabilistic tractography using ALIC as a seed region -Age, sex, and illness duration included as covariates -Bonferroni correction for multiple comparisons	-Reduced mean % fibre projections through ALIC to the left mFO, OFC and thalamus in MDD -Reduced mean % fibres in left OFC and thalamus in SA
Olvet et al., 2014	n=52MDD (n=13SA, n=39nSA), n=46HP	-ROI based analysis including age as a covariate -TBSS of whole brain including age, BDI score, length of current MDE, and number of MDEs as covariates -Data uncorrected for multiple comparisons	-ROI analysis: SA group had lower FA than nSA and HP in the dmPFC -TBSS: significantly reduced FA in right dmPFC cluster in SA group compared to nSA group
Taylor et al., 2015	n=74MDD (n=21SI, n=53nSI), n=91HP	-TBSS of *a priori* ROIs including age and sex as covariates -FDR correction for multiple comparisons	-Higher RD and lower FA in the CGH, ATR, PLIC, posterior and superior CR in SI group
Myung et al., 2016	n=49MDD (n=24SI, n=25nSI), n=31 HP	-NBS and graph theoretical analysis covarying for age, gender, and level of education -FDR correction for multiple comparisons	-NBS: reduced structural integrity of fronto-subcortical circuits -Graph theory: reduced edge weights of fronto-subcortical network

MDD, major depressive disorder; SA, suicide attempters; nSA, non-suicide attempters; SI, suicide ideators; nSI, non-suicide ideators; HP, healthy participants; BDI, the Beck Depression Inventory; MDE, major depressive episode; ROI, region-of-interest; TBSS, tract-based spatial statistics; FDR, false discovery rate; NBS, network-based statistics; ALIC, anterior limb of the internal capsule; mFO, medial fronto-occipital; OFC, orbitofrontal cortex; dmPFC, dorsal medial prefrontal cortex; CGH, cingulum bundle adjacent to the hippocampus; ATR, anterior thalamic radiation; PLIC, posterior limb of the internal capsule, CR, corona radiata.

Chapter II. Project Objectives and Hypotheses

2.1. Study Rationale

MDD is a leading cause of death and disability worldwide, and a significant proportion of individuals with TRD go on to attempt suicide at some point in their life. Suicidal ideation and attempts are closely related, however, many vulnerability factors for suicide are most strongly predictive of suicidal ideation and fail to identify who is most at risk of suicide attempt. An unmet need in suicide prevention is the neurobiological understanding of suicide, and neuroimaging markers may elucidate the relationship between suicidal ideation and behaviours to identify who is most at risk of suicide attempt.

DTI is a highly sensitive neuroimaging technique that quantifies white matter microstructure. Using TBSS, metrics of the diffusion tensor may be extracted and compiled to make inferences about neuronal tract quality and degeneration. Through free water imaging, it is possible to derive highly specific diffusion metrics and quantify the fractional volume of the free water compartment, which may provide valuable insight towards the extracellular conditions underlying white matter integrity changes. Previous DTI investigations in MDD and suicide have reported the involvement of frontolimbic networks relevant to cognitive control and emotional regulation associated with suicidal thoughts and behaviour. However, to date, investigations are limited. Furthermore, free water correction has never been applied in the context of suicide, and DTI investigations using more clearly defined criteria for suicidal ideation, behaviours and attempts are necessary.

2.2. Statement of Project Objectives

Objective 1. To explore clinical characteristics between suicide ideators and suicide attempters with TRD.

Objective 2. To investigate white matter microstructure in individuals with TRD and suicidal ideation versus suicide attempt history using TBSS.

Objective 3. To compare raw diffusion metrics obtained via TBSS to free water corrected values, obtained through a free water imaging pipeline.

2.3. Statement of Project Hypotheses

Hypothesis 1. Clinical characteristics are expected to differ between suicide ideators and suicide attempters, such that suicide attempters will have a more severe clinical profile with higher depressive symptom and suicidal ideation severity relative to suicide ideators.

Hypothesis 2. Microstructural white matter differences (such as changes in FA, RD, AD, and/or MD) are expected in individuals with suicide attempt history compared to suicide ideators in frontal-thalamo-limbic neuronal tracts.

Hypothesis 3. Free water corrected diffusion metrics are expected to differ from raw diffusion values, reflecting a more accurate proxy of white matter integrity. Extracellular free water (FW) is hypothesized to be elevated in suicide attempters relative to suicide ideators.

Chapter III. Methodology

3.1. Population of Interest

The data on this project is derived from an ongoing, cross-sectional, multi-modal neuroimaging study. The population of interest includes individuals with TRD and suicidal ideation and/or suicide attempt history. Data from N=36 participants (n=20 with lifetime history of suicidal ideation and n=16 with lifetime suicide attempt history) are included in this thesis. Participants were recruited through external referrals to the Mood Disorders Research Unit at the Royal's Institute of Mental Health Research, affiliated with the University of Ottawa, and the Consultation Clinic in the Mood and Anxiety Program at the Royal Ottawa Mental Health Centre.

3.2. Inclusion and Exclusion Criteria

Inclusion Criteria

For study eligibility, participants met the following criteria:

1. Age 18 to 65 years.
2. Diagnosis of MDD as per the DSM-5 (American Psychiatric Association, 2013) determined through the Structured Clinical Interview for the DSM-5 Research Version (SCID-5-RV) interview.
3. Current MDE with duration of at least 6 months in length.
4. Treatment-resistant, defined as a lack of response to at least two medications for depression with differing mechanisms of action.
5. Montgomery Åsberg Depression Rating Scale (MADRS) total score of ≥25 at the screening visit (corresponding to moderate to marked depression severity).

6. Ability to understand and comply with the requirements of the study, as judged by the investigator(s).

Exclusion Criteria.

Participants fulfilling any of the following criteria were excluded from participation:

1. Presence of comorbid post-traumatic stress disorder, obsessive-compulsive disorder, eating disorder(s), schizophrenia, or other psychiatric disorders (excluding anxiety disorders).
2. History of a manic, hypomanic, or mixed depressive episode.
3. Treatment with electroconvulsive therapy, intravenous and/or intranasal ketamine in the 6-weeks preceding study enrolment.
4. History of a substance-use disorder in the past 6 months.
5. A positive urine toxicology screen for non-prescribed substance use.
6. A positive pregnancy test at screening.
7. A history of major medical or neurological illness.
8. A history of traumatic brain injury, stroke, seizures, or previous brain surgery.
9. Contraindications to MRI scanning.

3.3. Study Procedures

The study protocol involved four parts: a pre-screening phone-call, a screening visit, a study visit, and a post-study treatment consultation. Upon reception of a referral, individuals were contacted by phone. The pre-screening phone-call involved discussion of the study and its procedures, as well as a series of basic eligibility questions. To qualify for study enrollment,

individuals had to be experiencing a MDE of at least 6 months in length, and be treatment-resistant, defined as a lack of response to at least two mechanistically unique pharmacotherapy trials for depression (Sackeim, 2001)[1]. The screening visit began with a comprehensive informed consent process, in which the purpose of the study, study procedures, potential risks and benefits, confidentiality, and privacy were verbally disclosed. Individuals were given the option to review the informed consent form (ICF) independently and ask questions. To proceed with the screening visit, individuals were required to provide written informed consent. Original ICFs were stored in a locked cabinet in a separate location from the subject's study binder containing clinical and demographic information, which was coded using an identification number to maintain confidentiality. A copy of the signed ICF was given to each participant to review at their own discretion. A urine sample was acquired to confirm lack of current substance use, and lack of pregnancy in biological females via a human chorionic gonadotrophin test. Height and weight measurements were obtained to calculate body-mass index, and individuals completed basic medical and demographic questionnaires. Previous research has indicated that menstrual cycle may influence brain structure and function (Dubol et al., 2021). To minimize the effects of hormonal fluctuations, the date of start of last menstrual cycle was recorded and used to scheduleMRI scans during the estimated follicular phase of the menstrual cycle (~days 1-10) for naturally-cycling females. During the screening visit, participants underwent a structured clinical interview conducted by a trained clinical rater using the Structured Clinical Interview for the DSM-5 Research Version (SCID-5-RV), the Montgomery Åsberg Depression Rating Scale (MADRS), and Columbia Suicide Severity Rating Scale (C-SSRS)[2]. Finally, participants completed an MRI pre-screening form and disclosed any potential contraindications to MRI scanning. This was

[1] For a comprehensive list of inclusion and exclusion criteria, review section *3.4*.

[2] For a comprehensive description of the self-report and clinician-rated scales administered, refer to section *3.3.*

followed by a brief test in the MRI simulator (mock scanner) intended to habituate individuals to the scanner environment.

Following the screening visit, eligible participants were scheduled for the study visit. This involved a clinical assessment, self-report questionnaires, a blood draw, and an MRI scan. The MRI scan was conducted at the Royal's Brain Imaging Centre (BIC). The scan included structural MRI (sMRI), DWI, resting state fMRI (rsfMRI) and proton magnetic resonance spectroscopy (^{1}H-MRS) data acquisition. Importantly, this thesis includes only clinical and DWI data; other multi-modal imaging and biomarker data are to be analyzed through independent projects. Following the completion of the research study, participants were offered a post-study treatment consultation with a physician from the Mood Disorders Research Unit at the Royal's Institute of Mental Health Research. Individual treatment recommendations were derived for each participant and sent to their referring physician.

3.4. Clinical Measures

3.4.1. Clinician-rated measures

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

The SCID-5-RV (First et al., 2015) is a validated interview for the diagnosis of psychiatric conditions based on the DSM-5. This semi-structured assessment tool is administered by a trained rater and allows for the diagnosis and assessment of major DSM-5 disorders. During this study, the SCID-5-RV was administered once at the screening visit to confirm a diagnosis of MDD and rule out excluding psychiatric comorbidities.

Columbia-Suicide Severity Rating Scale (C-SSRS)

A substantial limitation in suicide literature is the lack of concrete definitions of suicidal ideation, behaviours, and attempts (Klonsky, May and Saffer, 2016). The use of a properly structured, well-defined suicide risk assessment such as the C-SSRS (Posner et al., 2011) is essential for both research and clinical use (Baca-Garcia et al., 2011). The C-SSRS quantifies suicidal ideation severity (measured by a five-point ordinal scale, in which 1=wish to be dead, 2=non-specific active suicidal thoughts, 3=active suicidal thoughts with any methods and no intent to act, 4=active suicidal intent, with some intent to act and no specific plan, and 5=active suicidal thoughts with specific plan and intent to act), suicidal ideation intensity (including frequency, duration, controllability, deterrents, and reasons for ideation), suicidal behaviour (including actual, aborted, and interrupted attempts, preparatory behaviour and non-suicidal self-injury), and lethality of suicide attempt(s), rated on a six-point ordinal scale of severity. During the screening visit, the C-SSRS Lifetime/Recent version was used to assess lifetime and past month time frames; for the study visit, the C-SSRS Since Last Visit version was used to assess past week suicidal ideation and behaviours.

Montgomery Åsberg Rating Scale (MADRS)

The MADRS (Montgomery and Åsberg, 1979) is a standardized, clinician-rated questionnaire for the assessment of depression severity over the past week. The questionnaire's nine items mirror the core diagnostic criteria of MDD as described by the DSM-5. This includes apparent and reported sadness, inner tension, sleep and appetite changes, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal ideation. In this study, the MADRS was administered twice, at the screening visit (to ensure participants met eligibility criteria for severity of depression) and study visit (to assess depression severity at the time of the scan).

3.4.2. Self-Report Measures

Beck Scale for Suicide Ideation (BSS)

The Beck Scale for Suicide Ideation (BSS; Beck, Covacs and Weissman, 1979) is a 21-item self-report questionnaire assessing the severity of suicidal thoughts, plans, and behaviours. Initially, the scale consists of five items which identify the presence of suicidal ideation and/or intent to act. If passive or active suicidal ideation is reported, individuals complete the remaining 16 items measuring duration and frequency of ideation, deterrents for suicide, and preparatory suicidal behaviour. In this study, the BSS was completed once, during the study visit.

Patient Health Questionnaire 9 (PHQ-9)

The Patient Health Questionnaire (PHQ-9; Kroenke et al., 2001) is a 9-item self-report questionnaire assessing depression severity. Like the MADRS, the items of the PHQ-9 are based on the core characteristics of MDD as outlined by the DSM. These items include little interest or pleasure in doing things, feeling down, depressed, or hopeless; trouble falling asleep, staying asleep, or sleeping too much, feeling tired or having little energy, poor appetite (or over-eating), feeling bad about oneself, trouble concentrating, motor agitation or retardation, and thoughts of death or suicide. During this study, the PHQ-9 was completed once during the study visit.

Beck Hopelessness Scale (BHS)

The Beck Hopelessness Scale (BHS; Beck et al., 1974) is a 20-item self-report questionnaire measuring three core aspects of hopelessness: feelings about the future, loss of motivation, and expectations. In this study, the BHS was completed once during the study visit.

Beck Anxiety Inventory (BAI)

The Beck Anxiety Inventory (BAI; Beck et al., 1988) is a 21-item self-report questionnaire assessing the severity of physical and psychological anxiety experienced. Through the questionnaire, individuals rate how often they have been bothered by a variety of subjective, somatic, and/or panic-related symptoms. In this study, the BAI was completed once during the study visit.

Perceived Stress Scale (PSS)

The Perceived Stress Scale (PSS; Cohen, Kamarck and Mermelstein, 1983) is a self-report measure aiming to quantify one's subjective experience of stress over the past month. Through the questionnaire, individuals record how often they have rated situations as adverse, uncertain, or out of their control, allowing for the quantification of subjective discomfort and one's perception of their ability to handle stress. In this study, the perceived stress scale was completed once during the study visit.

Edinburgh Handedness Inventory

The importance of lateralization differences in the structure and function of the brain have long been recognized. The Edinburgh Handedness Inventory (Oldfield, 1971) is a 10-item self-report questionnaire used to identify hand dominance during everyday activities, in which individuals may be classified as right-handed, left-handed, or ambidextrous. This questionnaire was completed once during the study visit.

3.5. Ethical Considerations

3.5.1. Population Safety Considerations

The patient sample was drawn from a population of individuals with TRD, including those at risk of suicidal behaviour and attempt. Throughout the study, participants were asked about current and past suicidal ideation, behaviours, and attempts, as well as depression severity. Due to the sensitive nature of this process, individuals could have disclosed information regarding current suicide plans with intent to act. For this reason, a suicide risk safety protocol was developed prior to study initiation to ensure patient safety. According to the protocol, in the case of an identified imminent suicide risk, the study principal investigator notified a physician in the research unit of a patient's current suicidal thoughts, plans and/or intent to act, and access to carry out plans. As necessary, individuals were assessed by the physician, and subsequent treatment and/or safety precautions were determined based on clinical need. All clinical raters in the study completed Applied Suicide Intervention Skills Training, and/or had previous experience working with similar patient populations and administering the clinical measures employed in this study prior to commencement. A physician was present in the research unit for all screening and study visits.

3.5.2. Incidental Findings

During MRI scanning, there was a potential for unexpected discovery of previously undiagnosed medical conditions or anatomical abnormalities. In this study, no diagnostic and/or clinical imaging sequences were acquired, and the imaging data was not reviewed by individuals capable of diagnostic interpretation. Obvious incidental findings discovered during the scan by the MRI technologist were reported to study staff, and as necessary, the principal investigator and/or study physician consulted a neuroradiologist for interpretation. In such cases, participants were

advised to consult with their personal or referring physician and were informed of their options for further testing and follow-up. Prior to scanning, participants were briefed on the possibility of incidental findings through the ICF.

3.5.3. Risks and Benefits

There were no known risks associated with participation in this study. However, some individuals may have experienced discomfort during the MRI scan, through the effort required to remain motionless in the scanner, the experience of claustrophobia, or by loud noises of the MRI machine. The MRI involved no exposure to harmful radiation, nor were any injections required. During the blood draw, individuals may have experienced minor discomfort. Overall, participants did not receive any direct benefits from the research study. However, as previously mentioned, individuals were offered a one-time treatment consultation with a Mood Disorders Research Unit physician and were given $25 compensation for their involvement.

3.6 Research Interruptions

Due to the COVID-19 pandemic, recruitment and enrollment for this study was paused from March 2020-March 2021. During the period from December 2019 to March 2020, the study focus shifted toward recruiting a healthy comparison group as part of the larger study objectives. However, upon resumption of research operations during the COVID-19 pandemic, clinical populations were prioritized allowing completion of the patient sample for this thesis. As a direct result of suspension of research during the COVID-19 pandemic, the sample size is limited.

3.7. Neuroimaging Procedures

3.7.1. MRI Acquisition

Magnetic resonance images were collected on a 3T Siemens MR-PET system at the BIC, using a 32-channel head coil. Each MRI session consisted of four acquisition sequences, including sMRI, rsfMRI, DWI and ^{1}H-MRS. For structural acquisitions, T1-weighted images were obtained using a multi-echo magnetization-prepared rapid gradient echo (MEMPRAGE) protocol in the anterior-to-posterior direction. Imaging parameters included: TR=2530.0ms, TEs: TE_1=1.69ms, TE_2=3.55ms, TE_3=5.41ms, TE_4=7.27ms; flip angle=7.0^{o}, field of view=256mm, slice thickness=1.00mm, bandwidth=650Hz/Px, and a voxel size=1.0mm x 1.0mm x 1.0mm. DWI data was obtained using a single shot two-dimensional diffusion tensor EPI pulse sequence in the axial plane. At the expense of susceptibility-induced distortions (resulting in potential signal loss or signal pile up in the phase encoding (PE) direction), EPI allows for reduced scanning time (Poustchi-Amin et al., 2001). To correct for consequential distortions, diffusion images were acquired in two PE directions: anterior-to-posterior (b=1000 s/mm^2) and posterior-to-anterior (b=0s/mm^2). Diffusion imaging parameters included TR=10900ms, TE= 105.0ms, field of view=256mm, slice thickness=2.0mm, voxel size=2.0mm x 2.0mm x 2.0mm, bandwidth=1776Hz/Px, and EPI factor=128. Diffusion data was acquired in 64 directions (Table 2).

Table 2. Imaging Acquisition Parameters.

	T1w	DWI
Repetition Time (TR)	2530.0ms	10900ms
Echo Time (TE)	1.69ms, 3.55ms, 5.41ms, 7.27ms	105.0ms
Flip Angle	7.0º	-
Field of View	256mm	256mm
Slice Thickness	1.0mm	2.0mm
Bandwidth	650Hz/Px	1776Hz/Px
Voxel-Size	1.0mm x 1.0mm x 1.0mm	2.0mm x 2.0mm, 2.0mm
b-value (A-P, P-A)	-	1000 s/mm^2, 0 s/mm^2
Diffusion Directions, N	-	64
Echo Planar Factor	-	128

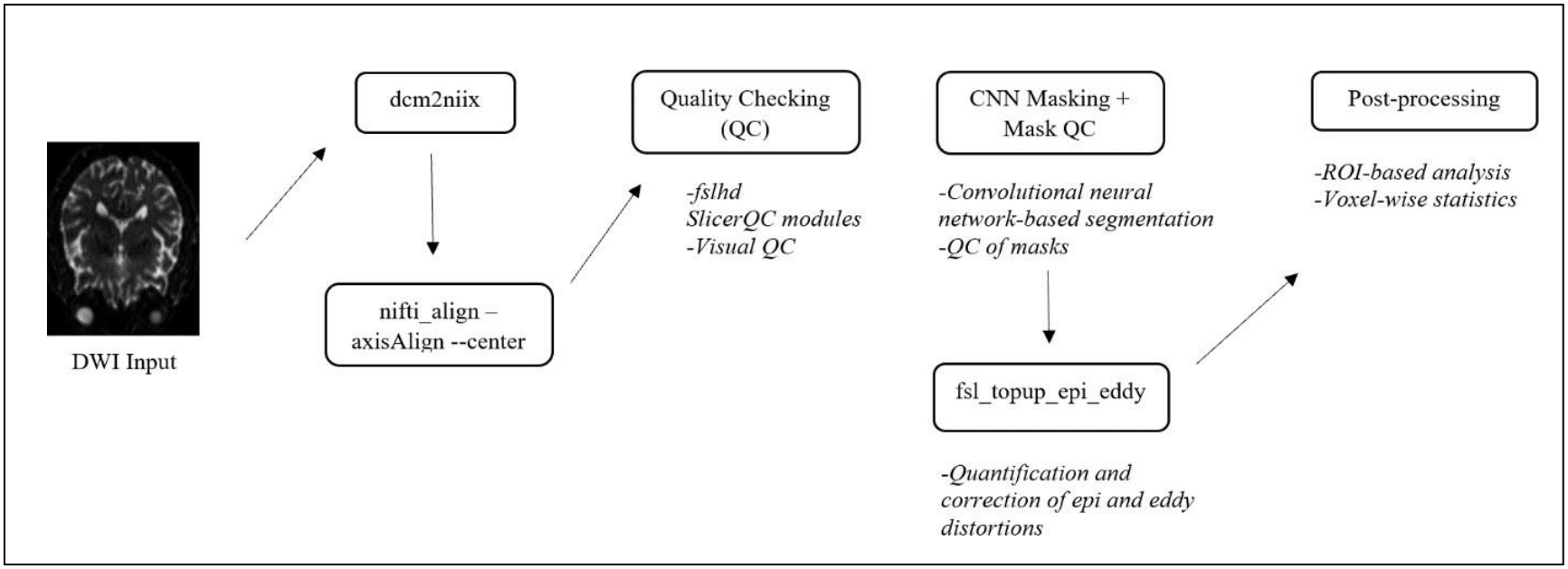
T1w, T1w imaging sequence; TR, Repetition Time; TE, Echo Time; DWI, diffusion weighted imaging sequence; A-P, anterior-to-posterior direction; P-A, posterior-to-anterior direction; N, number.

3.7.2. MRI Analysis

3.7.2.1. Preprocessing

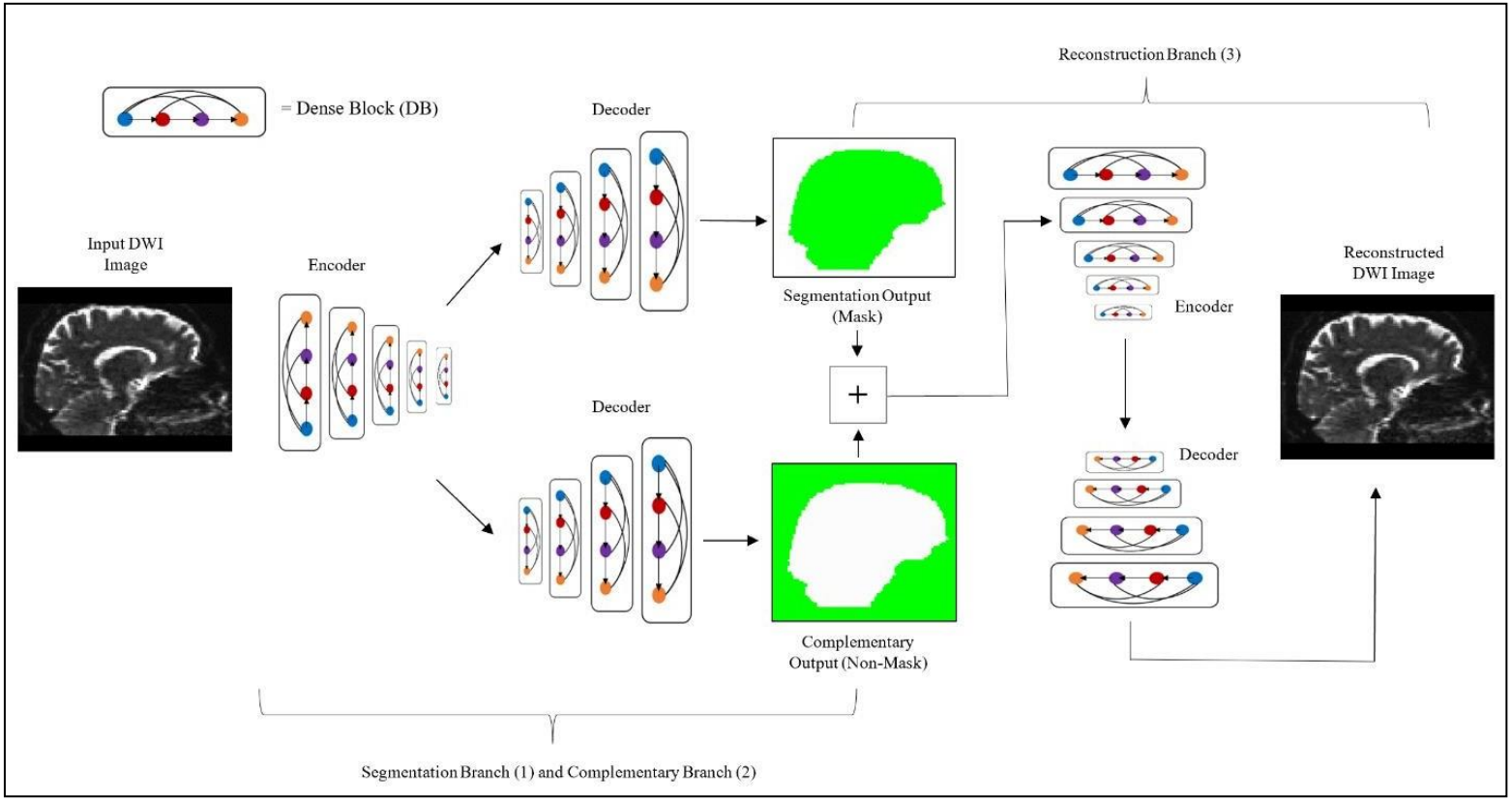
Raw images were downloaded from the BIC and converted from Digital Imaging and Communications in Medicine (DICOM) to Neuroimaging Informatics Technology Initiative (NIFTI) format (Figure 1); this file type was ideally compatible with analysis pipelines used in this project (Billah, Bouix and Rathi, 2019). Diffusion weighted images were checked for quality by manual inspection in *3DSlicer*, and were axis aligned and centered to ensure non-diagonal alignment in the affine transform. Diffusion masks were created using Convolutional Neural Network (CNN) based segmentation (Dey, 2018; Roy et al., 2019), which involves automated extraction of B_0 images, registration, normalization, and deep learning of neural networks in the sagittal, coronal, and axial planes (Palanivelu et al., 2020) according to a pre-existing dataset of over 1200 scans. This was followed by multi-view aggregation to compile probability maps from all three segmentations (Dey, 2018), and cleaning of aggregated data using a mask filter intended to remove remaining islands of non-neuronal tissue. CNN masking was applied to each stack of diffusion images in the anterior-to-posterior direction, and again separately for single B_0 images acquired in the posterior-to-anterior direction (Figure 2). Further correction was applied using an FSL-based script identifying diffusion directions, weighting, and off-resonance in each volume; eddy and epi current distortions were subsequently removed (Andersson, 2016a; https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/eddy), and a diffusion tensor was fit at each voxel.

Figure 1. Outline of DWI pre-processing pipeline.



Diffusion-weighted inputs were converted to Neuroimaging Informatics Technology Initiative (NIFTI) file format, followed by axis-align and centering. Both parameter (fslhd command) and visual quality checking (QC) was performed. Convolutional neural network (CNN) based segmentation was used to skull strip and create masks of neural vs. non-neural tissue. Epi and eddy distortions were corrected, followed by post-processing using voxel-wise statistics.

Figure 2. Convolutional neural network (CNN) masking.

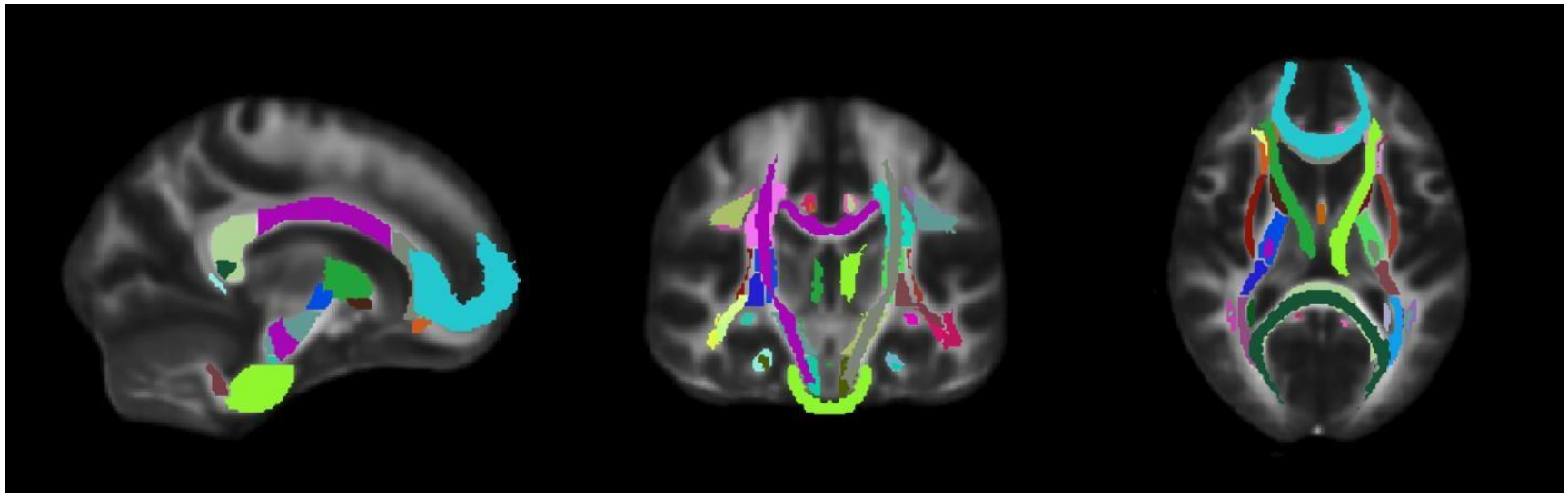


Overview of convolutional neural network (CNN) based segmentation used for the generation of diffusion masks. Briefly, the model architecture includes sets of encoder-decoder networks (separated by dense blocks) with three pathways: 1) segmentation, 2) complementary segmentation, and 3) reconstruction. Outputs included the primary segmentation (brain mask), the complementary segmentation (non-brain mask), and the original DWI image.

3.7.2.2. Imaging Data Analysis

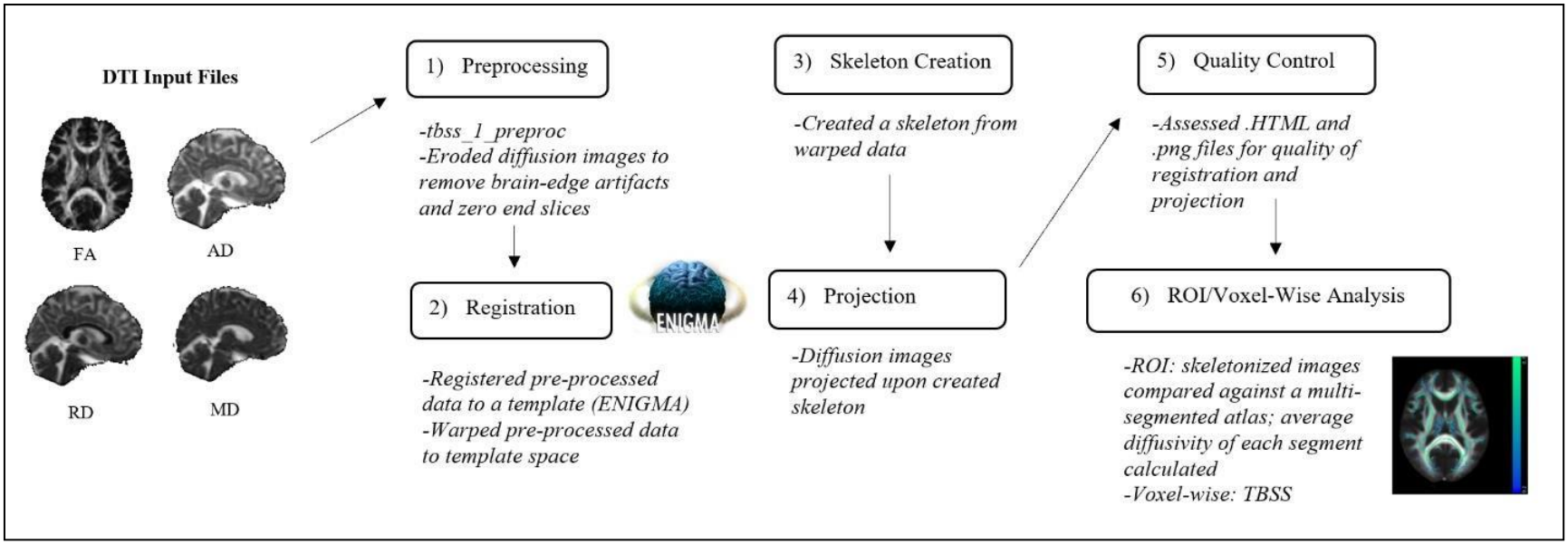
TBSS was performed post-processing through FSL (Smith, 2006; Billah, Bouix and Pasternak, 2019). Free water imaging correction was applied using an in-house MatLab-based script developed at Harvard University (Pasternak et al., 2009), from which raw and free water corrected values of FA, RD, MD, AD were extracted, as well as FW values. To perform TBSS, nonlinear registration of FA images to a 1x1x1mm standard space was conducted using a target image (FMRIB58_FA) available through FSL (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FMRIB58_FA). A group mean skeleton was created, on which diffusivity maps for each subject were projected. The general linear model was set to perform a non-parametric, two-sample t-test between suicide attempters and suicide ideators including mean-centered age and sex as covariates. Voxel-wise statistics were applied to each 4-dimensional output file containing projected, skeletonised diffusion data via nonparametric permutation (Winkler et al., 2014) using threshold-free cluster enhancement (Smith and Nichols, 2009) with the number of randomized permutations set to 5000. Other diffusion metrics including RD, AD and MD were derived using an additional post-processing script on corresponding skeletonised masks produced through TBSS. Correction for multiple comparisons was accomplished through family-wise error (FWE) and results were reported at a significance threshold of $p<0.05$. Voxel-wise results were subsequently visualized in FSLeyes (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLeyes) using the JHU White Matter Atlases (Mori et al., 2005) as a reference (Figure 3). Follow-up exploratory visualization of FA, FAt, RD, and RDt maps was carried out using an uncorrected significance threshold of $p<0.01$.

Figure 3. JHU white matter atlases.



White matter tract segmentation and labelling was accomplished using the JHU White Matter Atlases.

Figure 4. Outline of TBSS pipeline.



Overview of Tract-Based Spatial Statistics (TBSS) pipeline: Briefly, diffusivity files (including FA, AD, RD, MD, FW, FAt, MDt, RDt, and ADt) were fed through tbss_1_preproc, including erosion of images to remove artifacts and zero end slices. Files were registered to the Enhancing Neuroimaging Genetics Through Meta-Analysis (ENIGMA) template and warped to the template space. Diffusion skeletons were created for each metric, and individual participant data was projected upon the mean skeleton. Quality control involved visual inspection of skeletons for review of registration and projection. ROI-based analysis involved extraction of diffusion values for each tract in the atlas. Voxel-wise analysis was accomplished through TBSS.

Table 3. Design matrix for voxel-wise statistics.

	FSL Randomise Setup
Matrix type	Higher level/non-time series design
Model	Two groups, unpaired t-test
Thresholding	TFCE
Number of permutations	5000
Multiple comparisons correction	FWE
Covariates	Mean-centered age, sex

TFCE, Threshold-free cluster enhancement; FWE, family-wise error.

3.8. Clinical Data Analysis

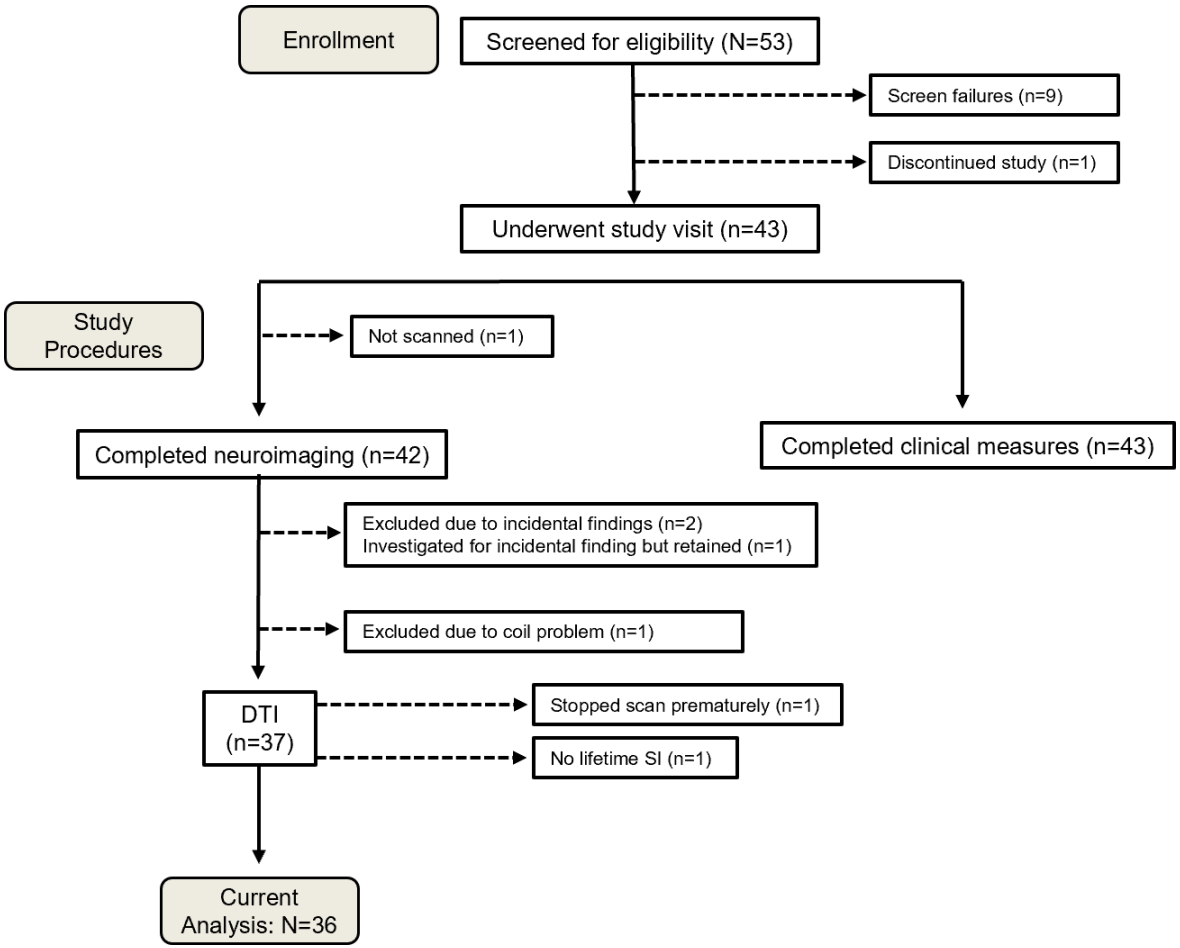
The analysis of clinical and demographic information was performed using IBM SPSS Statistical Software (v27). Participant data was divided into two groups using the C-SSRS: suicide ideators (lifetime history of suicidal ideation) and suicide attempters (lifetime history of suicide attempt). Chi-squared tests were used to identify significant differences in categorical variables between groups; this included sex, handedness, family history of depression and suicide attempt, and history of overnight treatment in a psychiatric facility. Independent samples t-tests were used to explore differences in continuous variables between groups; this included age, length of current depressive episode, MDD age of onset, number of lifetime MDEs, depression severity (as per the MADRS and PHQ-9), suicidal ideation severity (as per the C-SSRS and BSS), hopelessness (as per the BHS), perceived stress (as per the PSS), and anxiety (as per the BAI). Pearson bivariate correlations were subsequently performed to investigate potential associations between all clinical variables. Results were considered significant at $p \leq 0.05$.

Chapter IV. Results

4.1. Demographic and Clinical Results

Between July 2017 and June 2021, a total of 56 participants were consented, screened, and enrolled under this study protocol (Research Ethics Board #2017014). From this sample, n=43 had TRD, and n=13 were healthy volunteers. Imaging data from several TRD participants were unusable: two subjects were excluded due to incidental findings discovered during the MRI scan, two individuals did not undergo MRI scanning due to anxiety and participant dropout following screening, one subject was excluded due to significant artifact caused by a hardware (coil) issue, and one subject was excluded due to lack of lifetime suicidal ideation. Furthermore, the DWI sequence was not completed for one individual due to their inability to withstand the full scanning session. Data from healthy volunteer participants were not included in this thesis. Therefore, analyzable DTI data was available for n=36 TRD participants (n=20 males, n=16 females). Within the DTI sample, n=20 participants were suicide ideators, and n=16 were suicide attempters (Table 4; Figure 5).

Figure 5. Participants screened, enrolled, and included in the final analysis.



DTI, diffusion tensor imaging; SI; suicidal ideation.

The mean age of the whole sample was 46.6 (±14.2) years. In total, 29 participants were classified as right-handed, 1 was left-handed, and 6 were ambidextrous, as determined by the Edinburgh Handedness Inventory (Table 4). The mean MADRS total score was 32.0 (±4.3; Table 5), which is reflective of moderate depression (Montgomery and Åsberg, 1979; Table 6). The mean C-SSRS SI severity scores were 4.3 (±1.1) for lifetime SI, and 2.1 (±1.6) in the past-month (Table 4). These scores correspond to 'active suicidal ideation with some intent to act, without specific plan', and 'non-specific active suicidal thoughts', respectively (Posner et al., 2011; Table 6). Finally, the mean BSS score was 13.2 (±8.2), and mean PHQ-9 score was 20.8 (±3.9; Table 5), corresponding to severe depressive symptoms and significant self-reported suicidal ideation severity, respectively (Beck, Covacs and Weissman, 1979; Kroenke et al., 2001).

Independently, while the suicide ideator group had more males than females (n=13 males and n=7 females), and the suicide attempter group had more females than males (n=7 males, n=9 females), between group sex differences were not statistically significant (p=0.20, X^2=1.63). The groups did not differ on age (p=0.47, t=-0.73) or handedness (p=0.53, r=1.27). The average age of MDD onset for attempters (28.2 years) and ideators (30.5 years) was similar (p=0.63, t=0.48). The lifetime number of major depressive episodes was higher for attempters (5.4 episodes) relative to ideators (3.2 episodes), however, this difference was not statistically significant (p=0.19, t=-1.33). There was no significant difference in the length of current depressive episode between groups (p=0.98, t=0.03). More participants in the suicide attempter group reported a family history of suicide attempt than in the ideator group (p=0.04, X^2=6.26), however, there was no significant difference in family history of depression between groups (p=0.12, X^2=4.28). Finally, significantly more participants in the attempter group had previously received overnight treatment in a psychiatric hospital relative to ideators (p<0.001, X^2=13.9).

Regarding depression severity, the MADRS total score was 33.2 (±5.0) and 36.1 (±4.2) in the suicide ideator and attempter groups, respectively; these scores are reflective of moderate and severe depression severity (Montgomery and Åsberg, 1979; Table 6). Lifetime suicidal ideation severity as per the C-SSRS was 3.8 (±1.2) and 5.0 (±0.0) in the suicide ideator and attempter groups, respectively; this corresponds to 'active suicidal ideation with any methods (not plan) without intent to act' and 'active suicidal ideation with specific plan and intent' (Table 7). In the past week, suicidal ideation severity as per the C-SSRS was 1.9 (±1.5) and 2.5 (±1.5) for suicide ideators and suicide attempters, respectively. This corresponds to 'non-specific active suicidal thoughts' and midway between 'non-specific active suicidal thoughts' and 'active suicidal ideation with any methods (not plan) without intent to act' (Table 7). As per the BSS, self-reported suicidal ideation severity was higher in the suicide attempter group (p=0.03, t=-2.2), but there was no significant difference in self-reported depression severity between groups as per the PHQ-9 (p=0.97, t=-0.04). Using the BHS and PSS, self-reported hopelessness and perceived stress were higher in the suicide attempter group; however, these differences were not significant (p=0.47, t=-0.73; p=0.43, t=-0.80). As per the BAI, self-reported anxiety was higher in the suicide attempter group, which approached statistical significance (p=0.058; t=-2.0). Clinical information for the whole sample and each group appears in Table 5.

Within the sample as a whole, Pearson bivariate correlations revealed significant positive associations between lifetime and past week suicidal ideation severity on the C-SSRS (p=0.01, r=0.41), clinician and self-reported suicidal ideation severity (p=<0.001, r=0.72), depression and suicidal ideation severity (p=0.007, r=0.44), self-reported and clinician-rated depression severity (p=0.001, r=0.52), depression and anxiety severity (p=0.008, r=0.43), hopelessness and both clinician-rated (p=0.015, r=0.40) and self-reported suicidal ideation severity (p=0.001, r=0.54),

self-reported suicidal ideation and perceived stress (p=0.003, r=0.50), hopelessness and self-reported depression severity (p=0.009, r=0.44), hopelessness and anxiety (p=0.008, r=0.44), hopelessness and perceived stress (p=0.001, r=0.53), and anxiety and perceived stress (p=0.007, r=0.50). A full list of correlations and associated significance may be viewed in Table 8.

Table 4. Participant demographic information.

	Whole Group	SI	SA	*p*-value
Participants, N	36	20	16	-
Age (mean ± SD)	45.1 ± 14.1	43.6 ± 13.1	47.1 ± 16.4	0.47
Sex, N	18M, 16F	12M, 7F	7M, 9F	0.20
Handedness, N (R, L, A)	28, 1, 4	17, 1, 1	11, 0, 3	0.53
Age onset MDD (mean ± SD)	29.6 ± 13.2	30.5 ± 13.8	28.2 ± 12.5	0.63
Lifetime # MDE (mean ± SD)	4.0 ± 4.4	3.2 ± 2.2	5.4 ± 6.7	0.19
Current MDE length (mean ± SD)	4.4 ± 4.4	4.4 ± 3.8	4.3 ± 5.3	0.98
Family History MDD	66.7%	65.0%	68.8%	0.12
Family History SA	16.7%	5.0%	31.3%	**0.04**
Overnight Psychiatric Stay in Past Year (Y, N)	19, 17	5, 15	14, 2	< **0.001**

SI, suicide ideators; SA, suicide attempters; SD, standard deviation; N, number; R, right; L, left; A, ambidextrous; MDD, major depressive disorder; MDE, major depressive episode; Y, yes; N, no.

Table 5. Participant clinical information.

	Whole Group	SI	SA	*p*-value
MADRS Total (mean ± SD)	34.4 ± 4.9	33.2 ± 5.0	36.1 ± 4.2	0.76
C-SSRS Past-Week SI (mean ± SD)	2.0 ± 1.6	1.9 ± 1.5	2.5 ± 1.55	0.22
BSS Total (mean ± SD)	13.2 ± 8.2	10.5 ± 7.8	16.4 ± 7.7	**0.03**
PHQ-9 Total (mean ± SD)	20.8 ± 3.9	20.8 ± 3.3	20.8 ± 4.7	0.97
BHS Total (mean ± SD)	16.2 ± 3.8	15.6 ± 3.7	16.7 ± 4.0	0.47
BAI Total (mean ± SD)	20.1 ± 9.2	17.6 ± 9.8	23.4 ± 7.5	0.058
PSS Total (mean ± SD)	28.3 ± 5.8	27.6 ± 6.0	29.2 ± 5.7	0.43

SI, suicide ideators; SA, suicide attempters; MADRS, Montgomery Åsberg Depression Rating Scale; C-SSRS, Columbia Suicide Severity Rating Scale; BSS, Beck Scale for Suicide Ideation, PHQ-9, Patient Health Questionnaire 9; BHS, Beck Hopelessness Scale; BAI, Beck Anxiety Inventory; PSS, Perceived Stress Scale.

Table 6. Distribution of MADRS total scores.

MADRS Total	Depression Severity	Frequency in Sample (%)
0-8	Symptoms absent	0
9-17	Mild	0
18-34	Moderate	17 (47)
35-60	Severe	19 (53)

MADRS, Montgomery Åsberg Depression Rating Scale.

Table 7. Distribution of C-SSRS total scores.

Severity Score	SI Severity	Lifetime Frequency (%)	Past-Week Frequency (%)
0	None	0 (0.0)	4 (11.1)
1	Wish to be dead	1 (2.8)	13 (36.1)
2	Non-specific active suicidal thoughts	1 (2.8)	4 (11.1)
3	Active suicidal ideation with any methods (not plan) without intent to act	7 (19.4)	8 (22.2)
4	Active suicidal ideation with some intent to act, without specific plan	4 (11.1)	3 (8.3)
5	Active suicidal ideation with specific plan and intent	31 (63.9)	4 (11.1)

SI, suicidal ideation; C-SSRS, Columbia Suicide Severity Rating Scale.

Table 8. Clinical correlations across the whole sample (N=36).

	MADRS Total	C-SSRS Lifetime SI	C-SSRS Past-Week SI	BSS Total	PHQ-9 Total	BHS Total	BAI Total	PSS Total
MADRS Total	1							
C-SSRS Lifetime SI	p=0.52 r=0.11	1						
C-SSRS Past Week SI	p=0.007 r=0.44**	p=0.01 r=0.41**	1					
BSS Total	p=0.05 r=0.33	p=0.005 r=0.47**	p=<0.001 r=0.72**	1				
PHQ-9 Total	p=0.001 r=0.52**	p=0.53 r=-0.11	p=0.26 r=0.19	p=0.02 r=0.41*	1			
BHS Total	p=0.05 r=0.33	p=0.39 r=0.15	p=0.02 r=0.40*	p=0.001 r=0.54**	p=0.009 r=0.44**	1		
BAI Total	p=0.008 r=0.43**	p=0.34 r=0.16	p=0.08 r=0.30	p=0.07 r=0.31	p=0.05 r=0.34	p=0.008 r=0.44**	1	
PSS Total	p=0.67 r=0.07	p=0.95 r=-0.009	p=0.40 r=0.15	p=0.003 r=0.50**	p=0.11 r=0.28	p=0.001 r=0.53**	p=0.007 r=0.45**	1

SI, suicidal ideation; MADRS, Montgomery Åsberg Depression Rating Scale; C-SSRS, Columbia Suicide Severity Rating Scale; BSS, Beck Scale for Suicide Ideation; PHQ-9, Patient Health Questionnaire 9; BHS, Beck Hopelessness Scale; BAI, Beck Anxiety Inventory; PSS, Perceived Stress Scale.

4.2. Imaging Results

TBSS revealed altered diffusivity in several metrics. Primary investigations applied a FWE corrected significance threshold of $p<0.05$ to examine raw and free water corrected differences in FA, MD, AD, RD, and FW between suicide ideators and attempters. At this significance threshold, no differences in FA, FAt, RD, or RDt were identified between groups.

Examination of raw MD maps revealed significantly elevated MD in various white matter tracts in suicide attempters relative to ideators. Significant tracts included the bilateral cingulum (adjacent to the hippocampus), the bilateral inferior longitudinal fasciculus, the bilateral uncinate fasciculus, the bilateral inferior fronto-occipital fasciculus, the forceps major, the left anterior thalamic radiation and the left superior longitudinal fasciculus (Figure 6a). Following free water correction, altered MDt appeared more widespread in suicide attempters, with a greater quantity of significant voxels in widespread white matter areas[3] (Figure 6b).

Examination of AD maps revealed widespread alterations in diffusivity across many white matter tracts in suicide attempters, including the forceps minor, the forceps major, the bilateral posterior and anterior limb of the internal capsule, the bilateral corticospinal tract, the bilateral uncinate fasciculus, the bilateral inferior and superior longitudinal fasciculi, the bilateral inferior fronto-occipital fasciculus, the bilateral anterior thalamic radiation, the body of the corpus callosum, and the bilateral anterior and superior corona radiata (Figure 7a). Following free water correction, subtle differences in ADt were noted in the left anterior thalamic radiation and the bilateral anterior limb of the internal capsule of suicide attempters (Figure 7b).

[3] For an explanation of MDt differences, see section 5.2.3.

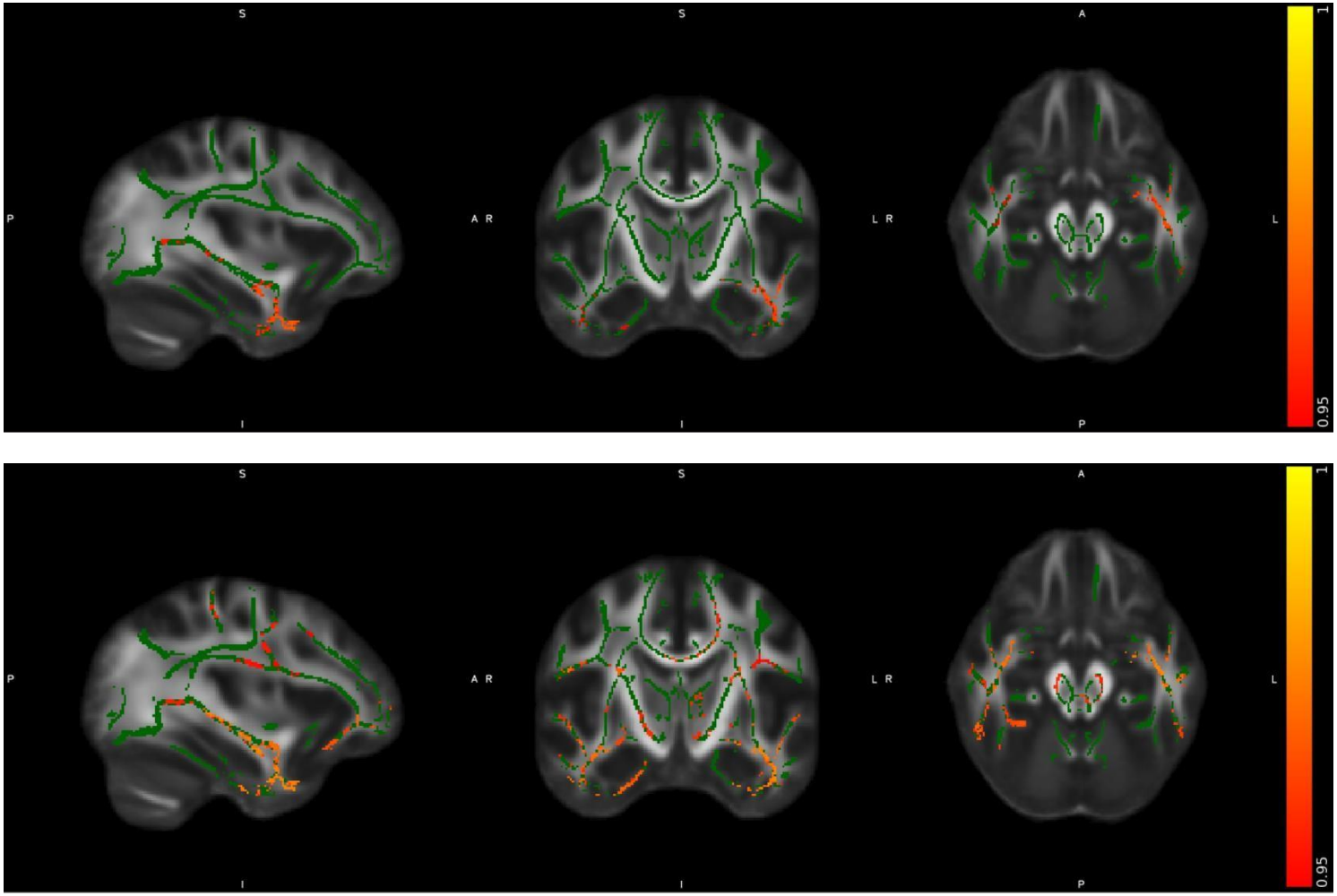
Focal elevations in FW were identified in the suicide attempter group, which appeared constrained to the left hemisphere. FW was elevated in the left inferior fronto-occipital fasciculus, the left inferior longitudinal fasciculus, the left anterior thalamic radiation, and the left uncinate fasciculus (Figure 8).

Following examination of diffusivity maps at an FWE corrected significance threshold of $p<0.05$, exploratory visualization of FA, FAt, RD, and RDt maps was performed at an uncorrected significance threshold of $p\leq0.01$. Exploratory analyses revealed significantly lower FA in the suicide attempter group in the right anterior thalamic radiation and the right superior longitudinal fasciculus (Figure 9a). Following free water correction, reductions in FAt in the suicide attempter group were identified in the bilateral superior longitudinal fasciculus, the bilateral anteriorthalamic radiation, the left inferior fronto-occipital fasciculus, the left inferior longitudinal fasciculus, and the left cingulum bundle adjacent to the hippocampus (Figure 9b). Examination of
RD maps revealed significantly elevated RD in the bilateral cingulum adjacent to the hippocampus, the bilateral inferior longitudinal fasciculus, the bilateral inferior fronto-occipital fasciculus, the bilateral corticospinal tract, and the bilateral anterior thalamic radiation (Figure 10a). Following free water correction, only slight significance was evident in the left cingulum adjacent to the hippocampus and the right superior longitudinal fasciculus (Figure 10b).

Figure 6. Elevated MD and MDt in suicide attempters.

a)

b)

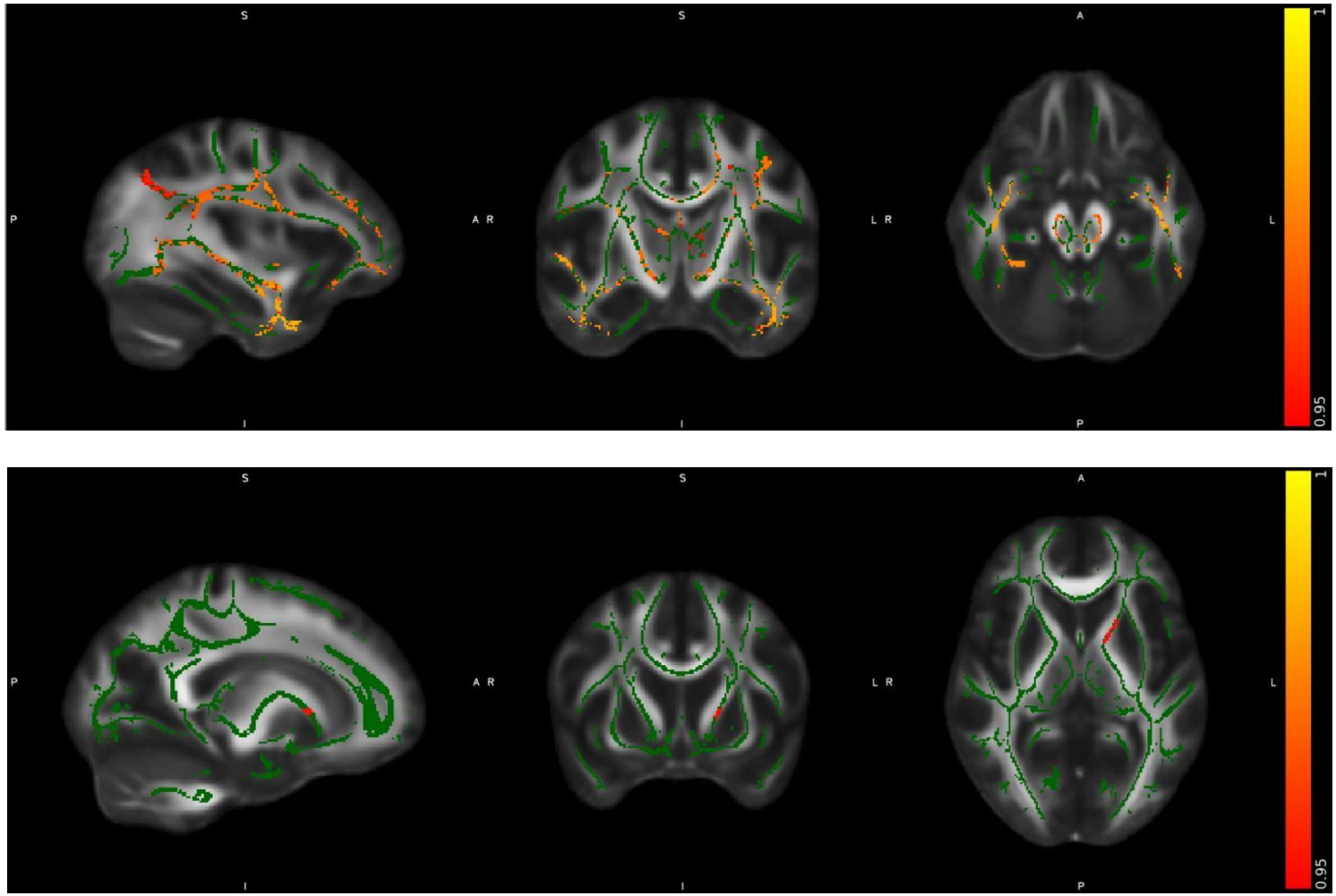


White matter tracts showing significant areas of elevated a) MD and b) MDt in suicide attempters compared to suicide ideators (pFWE < 0.05 corrected for multiple comparisons, warm colours). Statistical images were projected onto a mean skeleton (green) for visualization.

Figure 7. Elevated AD and ADt in suicide attempters.

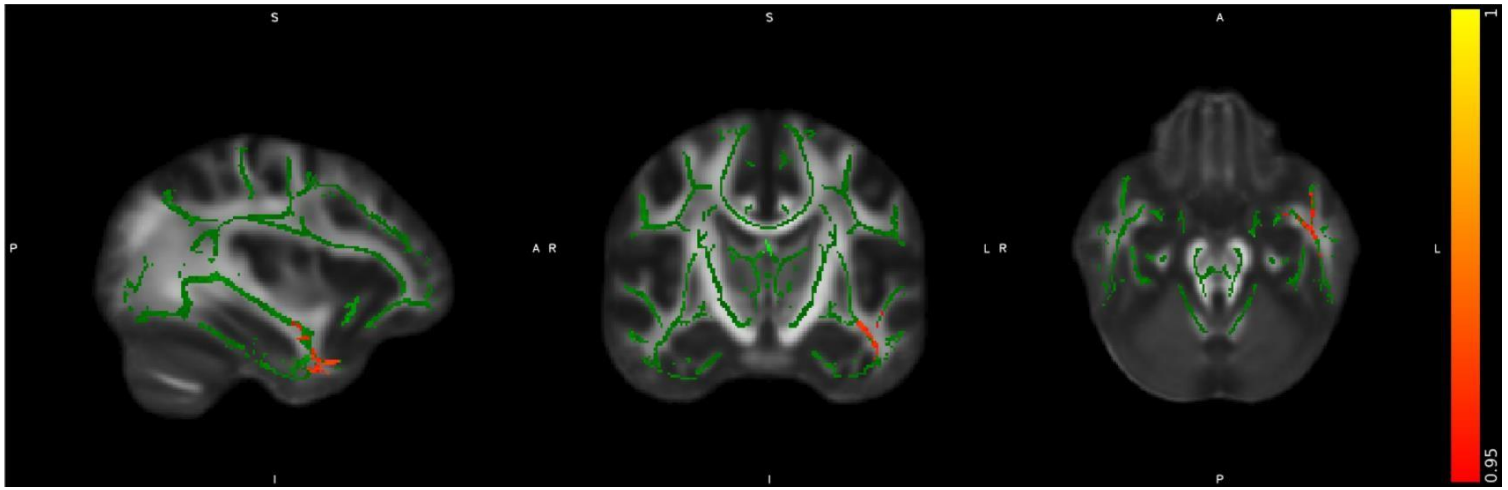
a)

b)



White matter tracts showing significant areas of elevated a) AD and b) ADt in suicide attempters compared to suicide ideators (pFWE < 0.05 corrected for multiple comparisons, warm colours). Statistical images were projected onto a mean skeleton (green) for visualization.

Figure 8. Elevated FW in suicide attempters.

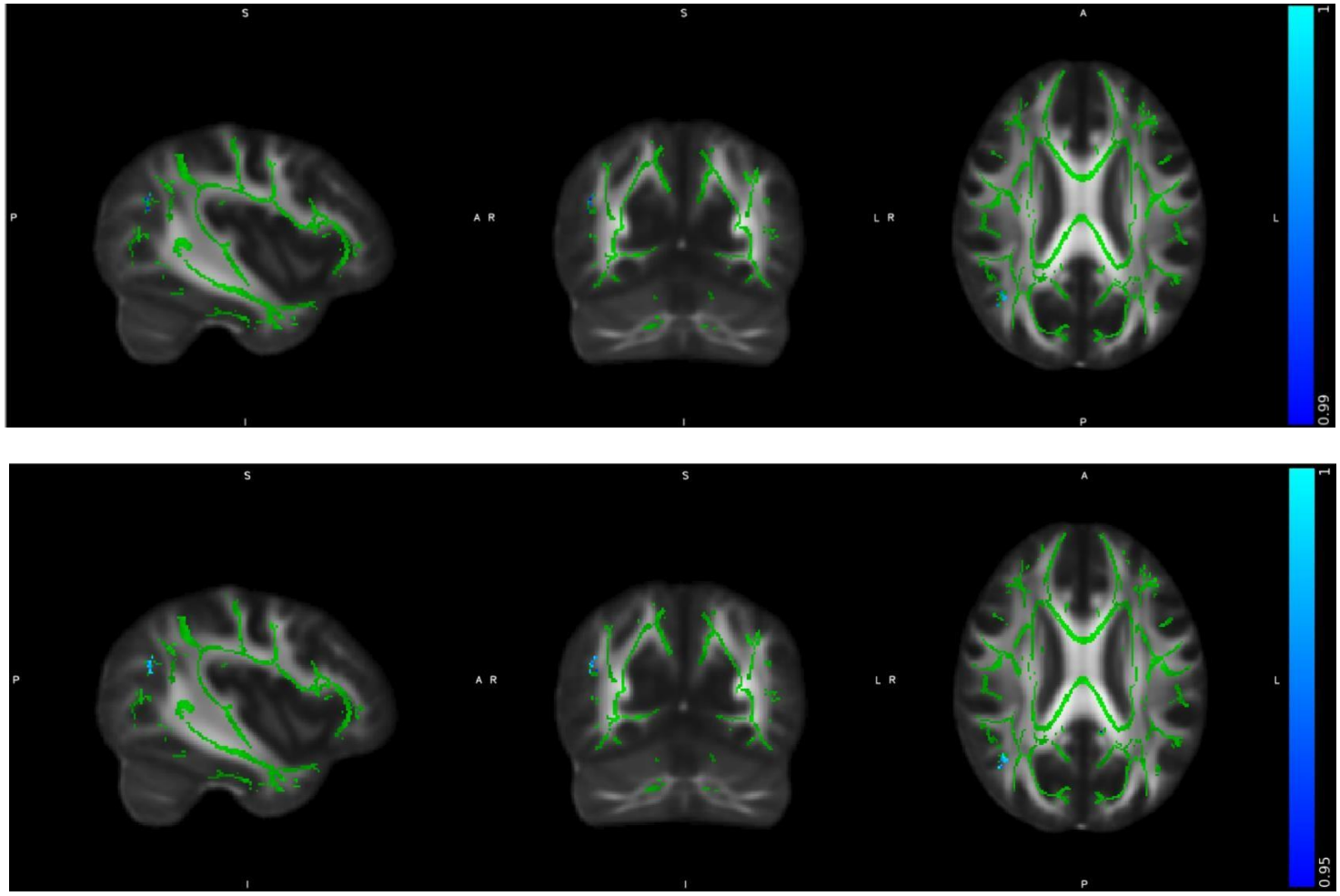


White matter tracts showing significant areas of elevated FW in suicide attempters compared to suicide ideators (pFWE < 0.05 corrected for multiple comparisons, warm colours). Statistical images were projected onto a mean skeleton (green) for visualization.

Figure 9. Reduced FA and FAt in suicide attempters.

a)

b)

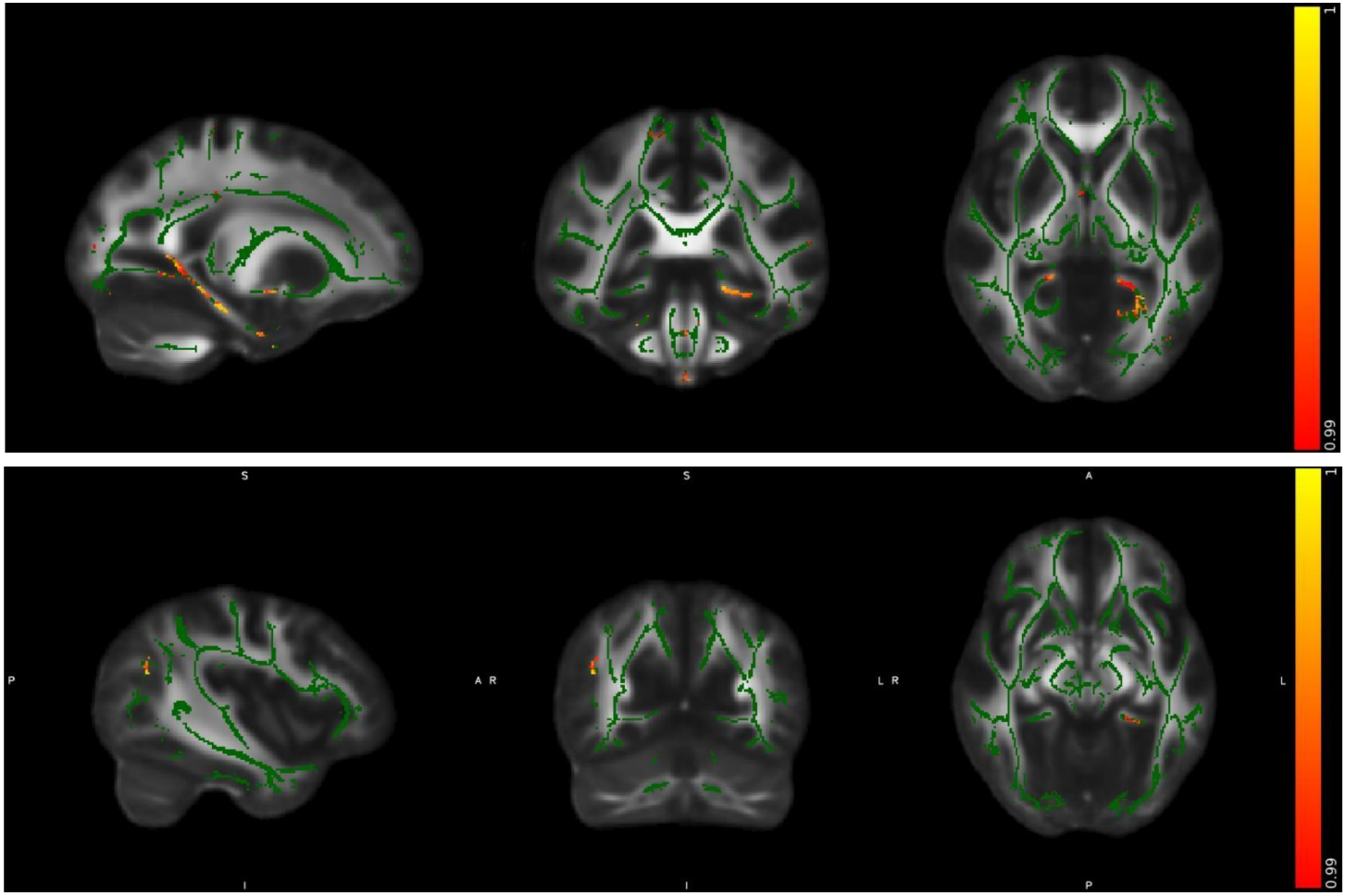


White matter tracts showing significant areas of reduced a) FA and b) FAt in suicide attempters compared to suicide ideators (uncorrected p< 0.01, blue). Statistical images were projected onto a mean skeleton (green) for visualization.

Figure 10. Elevated RD and RDt in suicide attempters.

a)

b)



White matter tracts showing significant areas of elevated (a) RD and (b) RDt in suicide attempters compared to suicide ideators (pFWE < 0.05 corrected for multiple comparisons, warm colours). Statistical images were projected onto a mean skeleton (green) for visualization.

Chapter V. Discussion

5.1. Study Summary

5.1.1. Rationale, Objectives and Hypotheses

MDD is a leading cause of death worldwide (World Health Organization, 2017), and TRD poses a significant risk for individual morbidity and mortality (Wu et al., 2019). More specifically, TRD is associated with a high risk of suicide attempt (Bergfeld et al., 2018). Biologically, the understanding of suicide in depression is incredibly limited (Miret et al., 2013), and brain-based definitions of the various facets of suicide could provide insight into the progression from passive suicidal ideation to highly lethal suicide attempts (Klonsky and May, 2014).

The evolution of neuroimaging for the study of health and disease has led to the emergence of a multitude of imaging analysis techniques and subsequent investigations across countless pathologies (Edelman, 2014). Despite this, no robust neuroimaging biomarkers of depression and suicide have been established (Schmaal et al., 2020; Price et al., 2018). In the current state of the field, a better understanding of the structural and functional manifestations of suicide in the context of depression may inform future studies with clinical implications in the identification and treatment of suicide risk (Schmaal et al., 2020). By combining spatially and temporally specific neuroimaging modalities and clinical markers of illness, it may be possible to identify dysfunctional neural networks related to modifiable risk factors for suicide in a more precise manner (Williams, 2016).

In many cases, the physiological impact of mental illness is not grossly evident to the naked eye, making the interpretation of structural brain scans inconsequential (Pasternak et al., 2018). DTI is advantageous due to its sensitivity to microscopic changes, allowing for the quantification

of neuronal white matter at the cellular level (Alexander et al., 2007). DTI has been used successfully to identify white matter abnormalities in specific neurological and psychiatric conditions (Kimpton et al., 2021; Kantarci et al., 2014; Widjaja et al., 2011; Hoptman et al., 2004), suggesting its utility for related disorders such as depression and suicide. Despite its advantages, DTI results are often inconsistent between studies (Bergamino et al., 2015), which may be related to the contamination of diffusion signal from additional tissue compartments (Pasternak et al., 2009). Extracellular free water accumulates in the ventricles and surrounding brain parenchyma and may impact the quantification of fibre tract delineation (Oesterich et al., 2017). In line with this, the optimization of DTI signal through the addition of free-water correction to DTI analysis may prove beneficial.

Previous DTI investigations of suicide in depression are scarce. The overarching objective of this study was to investigate clinical and imaging data of suicide ideators versus suicide attempters with TRD using DTI. It was hypothesized that suicide attempters would have a more severely characterized course of illness with respect to various clinical variables. Microstructural white matter differences including alterations in FA and/or MD, RD, AD and free water related measures (including free water corrected diffusion and FW) were expected in the suicide attempter group.

5.1.2. Summary of Results

Clinical and imaging data were analyzed for n=36 individuals (n=20 suicide ideators, n=16 suicide attempters). More suicide attempters reported a family history of suicide attempt and previous overnight treatment in a psychiatric facility, and as a group, attempters had more severe self-reported past-week suicidal ideation compared to ideators. There were no significant differences between groups for other clinical variables. Pearson bivariate correlations revealed

significant associations between clinician-rated and self-reported suicidal ideation severity, suicidal ideation severity and hopelessness, suicidal ideation and depression severity, and self-reported suicidal ideation severity and perceived stress.

Imaging analyses revealed significantly elevated MD, MDt, AD, ADt, and FW in white matter tracts of suicide attempters at an FWE corrected significance threshold of $p \leq 0.05$. At an uncorrected significance threshold of $p \leq 0.01$, reductions in FA and FAt in white matter tracts of the suicide attempter group were identified, as well as elevations in RD and RDt. Between group white matter differences were found across several fronto-thalamo-limbic tracts following free water correction, including the anterior thalamic radiation, anterior limb of the internal capsule, superior and inferior longitudinal fasciculi, cingulum bundle, and inferior fronto-occipital fasciculus. Elevations in FW were identified in overlapping white matter tracts in the suicide attempter group, with the addition of the uncinate fasciculus.

5.2. Interpretation of Results

5.2.1. Objective 1) Clinical Characteristics of Suicide Ideators versus Suicide Attempters

The prediction of suicide attempt on a clinical level remains challenging (O'Connor and Kirtley, 2018) and many theorized risk factors for suicide do not distinguish between suicidal ideation and attempt (Klonsky and May, 2014). For example, risk factors for suicide such as the presence of an affective disorder and hopelessness have been consistently associated with suicidality (Klonsky and May, 2014), however, these constructs do not appear to predict suicide attempt (Klonsky, Saffer and Bryan, 2018). Use of the ideation-to-action framework for the study of suicide could be helpful in this regard (May and Klonsky, 2016), as it allows for the independent conceptualization of suicidal ideation development, progression toward suicidal behaviours, and

suicide attempt (Bayliss et al., 2021). A lack of concrete definitions of the various facets of suicide also restricts the improvement of suicide prevention, as it does not allow for the distinction between those who think about suicide and those who are most at risk for an attempt (Klonsky, May and Saffer, 2016). Finally, suicide attempt is not often examined as an outcome measure, and individuals with acute suicide risk are often excluded from clinical studies which limits the understanding of these constructs (Wiebenga et al., 2021). This sample was thus unique in its clinical severity, as all participants were characterized as having moderate-to-severe TRD and approximately half of the sample had a history of suicide attempt. Furthermore, the various facets of suicide were well characterized using the C-SSRS (Posner et al., 2011), which allowed for the study of suicidal ideation, behaviours, and attempts as distinct entities and subsequent conceptualization of these constructs as a continuum of severity.

Previous literature highlights a complex relationship between depression and suicide (Vuorilento et al., 2020), and psychological autopsies indicate that approximately 60% of those that die by suicide are experiencing a MDE at the time of their death (Park et al., 2017). In this study, the majority of participants had experienced multiple MDEs. However, in accordance with the literature, depression severity does not appear to differ significantly between suicide ideators and attempters, which may hinder its use as a predictive variable (Keilp et al., 2012). In this study, depression and suicidal ideation severity were significantly correlated, which replicates the results of previous investigations (Brådvik, 2018).

The only significant sociodemographic differences between suicide ideators and attempters were a family history of suicide attempt, a history of overnight treatment in a psychiatric facility, and self-reported suicidal ideation severity. These findings are all in line with previous investigations (Qin and Nordentoft, 2005; Crawford, 2018; Lizardi et al., 2009; Simon et al., 2019).

For example, elevated suicide risk in those with a history of psychiatric hospital admission has been previously reported (Qin and Nordentoft, 2005), and appears most significant in the weeks following hospital discharge (Crawford, 2018). In this investigation, the cause of this finding is unclear; for example, a higher rate of overnight psychiatric treatment may increase suicide risk through a greater understanding of one's illness severity following discharge (Crawford, 2018). Alternatively, a greater rate of psychiatric admission may be a direct result of medical intervention following suicide attempt. Previous literature has also highlighted an association between the number of suicide attempts and history of suicidal behaviours in first- and second-degree relatives (Lizardi et al., 2009). This relationship is hypothesized to arise from higher trait aggression and impulsivity in suicide attempters, as well as faulty emotional regulation and coping strategies that may be passed on from parent to child (Lizardi et al., 2009). Finally, self-reported suicidal ideation has been previously identified as a significant predictor of suicide attempt in psychiatric outpatients in related disorders (Simon et al., 2019), however, self-reported suicidal ideation severity has not been specifically examined as a predictor of suicide attempt in the context of MDD. Given the limited predictive ability of clinicians to identify imminent suicide risk (Price et al., 2014), the necessity of self-report questionnaires in addition to clinician-rated assessment of suicide risk is significant.

Pearson bivariate correlations revealed associations between clinician-rated and self-reported suicidal ideation and variables such as hopelessness and perceived stress. To begin with, clinician-rated suicidal ideation as measured by the C-SSRS was significantly correlated with self-reported ideation via the BSS. Disagreement between clinician-rated and self-reported measures of depression and suicidal ideation severity are often evident (Gao et al., 2015), which may have a negative impact on suicide prediction and clinical characterization of illness severity. Although

clinician-rated assessments of suicide risk are considered gold standard, individuals often under-report or minimize their symptoms when compared to self-assessment (Gao et al., 2015). This may be related to patient discomfort in disclosing suicidal ideation, plans, and/or behaviours (Yigletu et al., 2004). Additionally, clinician-rated assessments may involve a certain degree of bias and are typically less standardized when compared to self-assessment tools (Yigletu et al., 2004). In this study, both the C-SSRS lifetime and past-week suicidal ideation severity assessment were highly correlated with BSS total scores, indicating high agreement between clinician and self-reported measures of suicidal ideation. Similarly, clinician-rated and self-reported depression severity were highly correlated, further supporting the accuracy of data collection between participants and clinical raters in this study.

In accordance with the literature, current suicidal ideation (as measured by the C-SSRS past-week and BSS) was associated with trait hopelessness as per the BHS. Hopelessness is one of the most commonly cited risk factors for suicide (Qiu, Klonsky and Klein, 2017), and it has been hypothesized to motivate depressed individuals to engage in suicidal behaviours as a way to escape prolonged psychological pain (Beck, 1967). Despite this, the relationship between depression, hopelessness and suicide appears complex, as current suicidal ideation may be a significant moderating factor (Qiu, Klonsky and Klein, 2017). The intricate relationship between these variables may explain inconsistencies in the literature, as previous studies have identified hopelessness as a predictor of suicide death (Ribeiro et al., 2018), while others could not differentiate the severity of hopelessness between suicide ideators and attempters (Qiu, Klonsky and Klein, 2017). In this study, hopelessness did not differ between groups. As all individuals had a lifetime history of suicidal ideation, it is reasonable to assume that hopelessness was predictive of ideation rather than attempt, as per previous literature (Klonsky, Saffer and Bryan, 2018).

Interestingly, self-reported but not clinician-rated depression severity was also significantly associated with the experience of hopelessness, further highlighting the importance of self-assessments in psychiatric populations.

Finally, a significant correlation was identified between self-reported suicidal ideation severity and perceived stress. This finding is in line with previous literature highlighting the impact of stress and faulty coping mechanisms on suicidal ideation (Cole et al., 2015). As a whole, stress appears to have a significant impact on cognition and biology (Lopez-Castroman, Olie and Courtet, 2014), and both short-term and chronic stress may interact with additional vulnerability factors to precipitate the development of suicidal ideation and behaviours (Cole et al., 2015). Importantly, the perception of one's stress and ability to cope may have a greater contribution to negative health outcomes than the objective number and/or impact of external stressors one experiences (Keller et al., 2012), highlighting the significance of this finding in the current sample. As one's perception of stress and subsequent coping mechanisms may be modified through psychotherapy (Enns et al., 2018), the identification and treatment of perceived stress could be a meaningful avenue for individuals with severe suicidal ideation.

5.2.2. Objective 2) White Matter Microstructure in Suicidal Ideation versus Suicide Attempt and TRD Using TBSS

As previously mentioned, the diffusion tensor is a three-by-three matrix representing the displacement of water diffusion across time and space (Alexander et al., 2007), allowing for quantification of fibre tracts on a microscopic level (Assaf and Pasternak, 2008). The degree of anisotropic diffusion in biological tissue is influenced by the structure of tract membranes and may change significantly in the presence of pathology such as demyelination or degradation of tissue architecture (Alexander et al., 2007). To indirectly summarize white matter tract quality, the degree

of intracellular anisotropic diffusion may be quantified using a summary metric such as fractional anisotropy (FA) or mean diffusivity (MD; Mukherjee et al., 2008). Reductions in FA represent a loss of fibre coherence in the dominant direction of water diffusion, leading to the assumption of hindered white matter integrity in the presence of FA reductions (Alexander et al., 2007). MD represents the directional average of water diffusion, and elevations in MD have been suggested to indicate damaged tissue or edema as evidenced by higher free diffusion in each individual voxel (Alexander et al., 2007). Quantification of additional diffusion metrics may provide insight toward the source of white matter changes indicated by FA and MD, including AD and RD, in which altered values are hypothesized to represent changes in the axon or myelin, respectively (Winklewski et al., 2018; Wheeler-Kingsholt and Cercignani, 2009).

Using whole brain analysis, hundreds of thousands of statistical comparisons are conducted across all voxels, which may lead to a significant increase in false positive results (Mirman et al., 2018). Through the use of a statistical correction such as FWE, it is possible to remove noise caused by multiple comparisons (Han, Glenn, and Dawson, 2019). However, there may be a significant trade-off between the removal of noise and remaining signal (Mirman et al., 2018). In similar DTI studies using TBSS, alterations in FA have been reported at uncorrected significance thresholds (Olvet et al., 2014; Liu et al., 2011), and large sample sizes are more likely to yield significant imaging results (Szucs and Loannidis, 2020). In this study, significant alterations in FA were not identified at a FWE corrected significance threshold of $p \leq 0.05$. Although FA results were below the threshold of FWE corrected significance in this study, their presence at a more stringent, uncorrected p-value suggests a trend of reduced white matter integrity associated with suicide attempt. Furthermore, although the literature on white matter in suicide and depression is limited,FA findings appear to align with previous investigations reporting associations between suicide

attempt and white matter integrity in fronto-thalamo-limbic tracts (Jia et al., 2014; Olvet et al., 2014).

Despite the favoured use of FA as a summary metric of diffusion in neuroimaging studies, its non-specificity may lead to a knowledge gap with regards to the source of white matter aberrations (Alexander et al., 2007). Each neuronal white matter tract encompasses thousands of axons, as well as a dense array of oligodendrocytes and myelin; it is therefore uncertain if reductions in white matter integrity represent a pathology of the neuronal fibres themselves, demyelination, or other factors including inflammation and/or edema (Assaf and Paskernak, 2008). Given the classic interpretations of additional diffusion metrics including MD, AD, and RD (Mukherjee et al., 2008), one may postulate the source of white matter alterations for any given pathology. More specifically, AD represents the diffusion coefficient parallel to the direction of the fibre tract, and reductions in AD are thought to indicate axonal damage (Winklewski et al., 2018). Finally, RD is a metric of water diffusion in the direction perpendicular to the fibre tract, and elevations in RD are hypothesized to indicate pathology of the myelin itself (Wheeler-Kingsholt and Cercignani, 2009). Therefore, by combining a summary metric such as FA with supplementary metrics such as MD, RD, and AD, one may obtain a more complete picture of white matter alterations associated with a particular disorder.

In this study, elevations in MD and AD in white matter tracts of the suicide attempter group were identified at FWE thresholded significance levels. Furthermore, elevated RD in the suicide attempter group was identified at an uncorrected significance threshold of $p<0.01$. Although elevations in AD alongside increased MD seem counterintuitive, previous investigations have identified similar findings in combination with elevated MD and reduced FA (Rose, Janke and Chalk, 2008; Ryan et al., 2013; Li et al., 2017; Della Nave et al., 2010). Elevations in AD in the

suicide attempter group may relate to increased extracellular space secondary to axonal degeneration (Wheeler-Kingsholt and Cercignani, 2009). Additionally, bilateral elevations in RD in several white matter tracts including the cingulum, inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, corticospinal tract, and anterior thalamic radiation may suggest altered patterns of myelination in suicide attempters (Winklewski et al., 2018). However, the association of AD and RD with axonal status and myelin may not be accurate depending on the white matter tracts examined and the pathological processes involved in a particular disorder (Alexander et al., 2007). In the context of diseases with multiple potential competing pathological processes (including inflammation, axonal damage, and demyelination) the interpretation of diffusionmetrics such as AD and RD become less specific (Winklewski et al., 2018). Furthermore, as AD and RD are incredibly sensitive to crossing fibres, noise and partial volume effects, a definitive interpretation of these findings should be avoided (Wheeler-Kingsholt and Cercignani, 2009), and results must be interpreted with caution. Further investigation of diffusion metrics in association with free water measures may provide additional information regarding the source of diffusion abnormalities[4] (Pasternak et al, 2009).

Several common white matter tracts were identified as significantly altered across different metrics in the suicide attempter group. These included the superior and inferior longitudinal fasciculi, the uncinate fasciculus, the inferior fronto-occipital fasciculus, the anterior thalamic radiation, the cingulum bundle, and the anterior limb of the internal capsule. Many of these tracts subserve connections between cognitive and emotional centres and have been highlighted in studies of related disorders.

[4] For an explanation of free water measures, see section 5.2.3.

To begin with, the superior longitudinal fasciculus (SLF) has been identified as significantly altered in several psychiatric conditions (Jenkins et al., 2016), including MDD (Murphy and Frodl, 2011), psychosis (Szeszko et al., 2018), bipolar disorder (Sprooten et al., 2016), and obsessive-compulsive disorder (Spalletta et al., 2014). Anatomically, the SLF is a major association tract facilitating communication between the frontal, parietal, and temporal cortices (Nakajima et al., 2020). Given its projections and prevalence in emotional disorders, the SLF is thought to play a significant role in the perception of emotional information, working memory, and social functioning (Jenkins et al., 2016; Nakajima et al., 2020; Szeszko et al., 2018), which may have significant implications for an individual contemplating suicide. Similarly, the inferior longitudinal fasciculus (ILF) extends from the occipital cortex to the anterior temporal lobe, indirectly connecting the uncinate fasciculus (UF) to orbito-frontal areas (Ashtari, 2012), allowing communication between the amygdala and visual system (Herbet, Zemmoura and Daffau, 2018). The ILF has been identified in association with related psychiatric disorders including MDD (Versace et al., 2010), bipolar disorder (Ren et al., 2020), and schizophrenia (Ashtari et al., 2007), and is thought to be involved in visual emotion and cognitive processes (Ashtari, 2012).

The UF is a bilateral association tract joining the anterior temporal lobes with the anterior prefrontal and lateral orbitofrontal cortices (Ocklenburg and Güntürkün, 2018), and appears highly connected to the limbic system (Von Der Heide et al., 2013). Previous studies have suggested the role of UF integrity in bipolar disorder (Li et al., 2021), schizophrenia (Kubicki et al., 2002), MDD (Wei et al., 2020), and overall emotional empathy (Oishi et al., 2015). Interestingly, the UF does not mature fully until the third decade of life, which may influence the relationship between adverse experiences during development and/or young adulthood and the development of psychiatric disease (Von Der Heide et al., 2013). Overlapping heavily with the ILF, SLF, arcuate

fasciculus and middle longitudinal fasciculus (Wu et al., 2016), the inferior fronto-occipital fasciculus (IFOF) is a major white matter association tract connecting the frontal lobe to the temporal, parietal, occipital, and insular cortices (Ramos-Fresnedo et al., 2019). The IFOF has previously been highlighted in association with MDD and bipolar disorder (Wei et al., 2020; Manelis et al., 2021), as well as obsessive-compulsive disorder (Gruner et al., 2012) and schizophrenia (Oestreich et al., 2017), suggesting a significant role of the IFOF in psychiatric disorder.

The anterior thalamic radiation (ATR) is a white matter tract connecting the dorsolateral prefrontal cortex (dlPFC) and the thalamus through the anterior limb of the internal capsule (ALIC) and is thought to be implicated in executive function and emotion regulation (Niida et al., 2018;Deng et al., 2018). In related disorders such as MDD (Deng et al., 2018), schizophrenia (Mamah et al., 2010), and bipolar disorder (Niida et al., 2018), FA in the ATR has been identified as abnormal. Related to this, the cingulum bundle is a major white matter association tract spanning the superior surface of the corpus callosum and extending to the ATR, prefrontal cortex, and insula (Jones et al., 2013). Dysfunction of the cingulum has been consistently identified in association with psychiatric disease including MDD (Taylor et al., 2014), obsessive-compulsive disorder (Versace et al., 2019), schizophrenia (Fitzsimmons et al., 2020), and post-traumatic stress disorder (Weis et al., 2018), which is hypothesized to relate to its dense connections with the limbic system (Bubb, Metzler-Baddeley and Aggleton, 2018). Finally, the internal capsule is a deep subcortical structure originating in the inferomedial portion of each hemisphere, consisting of afferent and efferent fibres that terminate in the cerebral cortex (Emos and Agarwal, 2020). The ALIC joins the thalamus with the prefrontal cortex and cingulum, and the posterior limb of the internal capsule (PLIC) consists of overlapping fibres from the corticospinal tract, thalamic radiation,

corticopontine and corticorubral tracts (Emos and Agarwal., 2020). Importantly, the ALIC has been heavily implicated in emotional disorders, including MDD and suicide (Jia et al., 2014), likely due to its intersecting fibres from the prefrontal and anterior cingulate cortices, amygdala, and thalamus (Mithani et al., 2020).

5.2.3. Objective 3) Comparison of raw diffusion metrics to free water corrected values

DTI is an incredibly sensitive neuroimaging method that allows for the quantification of tissue microstructure (Soares et al., 2013), making it ideally suited for the study of the brain in the context of psychiatric disease (Pasternak et al., 2018). Despite the benefits of DTI, there are some significant limitations, and studies across several related disorders including MDD (Bergamino et al., 2015), obsessive-compulsive disorder (Nakamae et al., 2011), and schizophrenia (Kannan et al., 2005) have published inconsistent results. A potential explanation for this may be lack of specificity in measurement due to partial volume effects of different tissue compartments, including free water (Bergamino et al., 2015). This may be particularly evident in the context of inflammation, as free water may accumulate in the presence of pathology such as axonal injury and degeneration (Bergamino et al., 2021).

In this study, diffusion measurements were affected by extracellular free water. This was evidenced by differences in the quantity and distribution of significantly altered white matter voxels in raw and free water corrected diffusion metrics, as well as overall elevations in extracellular free water in the suicide attempter group. In this study, there was considerable overlap between MD and FW maps, which is expected due to the mathematical relationship between these two metrics (Pasternak et al., 2009). Importantly, there appeared to be significant elevations in MDt following free water correction, however, this result was likely due to signal variability rather than biological differences between groups (Golub, Neto Henriques and Gouvela Nunes, 2021).

Prior to free water correction, widespread elevations in AD and RD were evident across several white matter tracts, however, this was not apparent following free water correction. This pattern suggests the ability of this technique to eliminate erroneous signal (Berlot et al., 2014), and highlights the impact of free water on diffusion results in this particular study. Finally, greater reductions in FA emerged following free water correction, with significant alterations in the left superior longitudinal fasciculus, the left inferior longitudinal fasciculus, the left cingulum adjacent to the hippocampus, and the left anterior thalamic radiation in suicide attempters. This is consistent with previous studies demonstrating the ability of free water correction to unmask significant results hidden by free water contamination (Berlot et al., 2014). Together, it appears that the free water correction model was successful in filtering signal caused by overlap in tissue compartments, and uncovering significance suppressed by signal contamination. These results thus align with previous work highlighting the utility of free water correction in the improvement of DTI signal accuracy, allowing for a more precise measurement of fibre tracts and removal of artifact caused by extracellular fluid (Albi et al., 2017).

Effective synaptic communication relies on the integrity of neuronal white matter, which is composed of tightly packed, myelinated axons (Bells et al., 2019). In this study, it appears that white matter integrity was compromised in individuals with TRD and a history of suicide attempt, however, the pathophysiological basis for this change is unknown. Importantly, the inclusion of free water correction allows for the quantification of the volume of the free-water compartment, providing a measurement of extracellular fluid accumulation (Pasternak et al., 2009). This allows for a greater understanding of the source of white matter aberrations, as elevations in extracellular free water have been hypothesized to indicate the presence of neuroinflammation, while the use of free water corrected metrics such as FAt, ADt, and RDt may more accurately reflect pathology of

the white matter fibre itself (Qian et al., 2021). In the context of neuroinflammation, pro-inflammatory cells such as microglia become active, leading to osmosis from the brain's vasculature and subsequent edema (Oestreich et al., 2017). In the context of chronic illness, pro-inflammatory responses may contribute to axonal damage and demyelination, which can be measured using conventional and free water corrected metrics of the diffusion tensor (Pasternak et al., 2012). Previously, chronic inflammation has been suggested as an etiological contributor to MDD pathophysiology (Ruiz et al., 2018), which may also play a role in the development of suicidal ideation and behaviours (Brundin, Bryleva and Thirtamara-Rajamani, 2017). However, an established link between depression, suicide, and inflammation is not realistic without the use of additional data, such as plasma cytokine levels alongside white matter and free water findings.If such an association can be consistently identified, the use of inflammation as a biomarker in depression and suicide may prove significant, as peripheral inflammation is generally simple to measure and may be treated through anti-inflammatory medication (Pasternak et al., 2012).

5.3. Limitations and Future Directions

5.3.1. Study Logistics

Marginalized groups are largely underrepresented in neuroimaging research, which hinders the neurobiological understanding of psychiatric disease across diverse populations (Brett, Schneider and Aggarwal, 2021). Biological differences in racial and ethnic minorities may result from discrimination, and both structural and functional differences in the brain have been identified as a result of psychosocial stress and adversity (Akdeniz et al., 2014). Previous studies have identified a significant link between ethnicity and the development of mental disorders including schizophrenia, depression, and anxiety (Berger and Sarnyai, 2015), which may be related to epigenetic influence on neural networks responsible for stress regulation (Tost, Champagne and

Meyer-Lindenberg, 2015). In relation to this, indigenous peoples have been shown to experience greater health problems and rates of suicide than the general population (Ketheesan et al., 2020), and the institutionalization of indigenous peoples has resulted in generational trauma rooted in discrimination and abuse (Pollock et al., 2018). Acute, chronic, and inter-generational effects of racism and discrimination may manifest as biological differences in the neural pathways that process physical pain, chronic stress, and the flight or fight response (Berger and Sarnyai, 2015). Due to the overlap between these constructs and psychiatric disease (Saavedra et al., 2016), it is reasonable to expect structural and functional differences associated with race, ethnicity, and aboriginal status. At the very least, it is critical to acknowledge potential neurobiological differences in these individuals, and to consider race, ethnicity, and aboriginal status during study recruitment to ensure that marginalized groups are properly represented in clinical and imaging research.

Another important consideration is the influence of sex and gender on neurobiology. From a young age, neurological differences are evident between sexes, including disparities in total brain weight, cortical thickness, and regional brain volumes (Savic, Garcia-Falgueras and Swaab, 2010). Clear sex differences exist with respect to the prevalence of depression and suicide between males and females (Deshpande et al., 2016), and gender has been highlighted as more influential than sex to this relationship (Zagni, Simoni and Colombo, 2016). Both sex (Savic, Garcia-Falgueras and Swaab, 2010) and gender (Fisher et al., 2018) appear to influence brain structure and function, highlighting a need for further study of these constructs. In this project, information on biological sex but not gender identity was considered, and due to the limited sample size, no meaningful sex-based analyses were realistic. However, sex-ratios between groups were similar, and care was

taken to account for menstrual cycle variation in biological females. Overall, it is critical for future studies to consider the implications of sex and gender on imaging results.

Although the use of the C-SSRS allowed for the documentation of suicidal ideation, behaviours and attempt history, a detailed account of suicide plans and complete information on the lethality and timing of suicide attempts was lacking. For example, although an individual may have reported 'active suicidal ideation with specific plan and intent to act' (Posner et al, 2011), there was no reliable way to quantify suicide plans in these individuals. Furthermore, greater detail on the timing of suicide attempt would have allowed for exploratory comparisons within the suicide attempter group, such as differences between those who attempted suicide in the last year, five years, or ten years and beyond. Intuitively, there may be structural or functional differences in the brain in individuals with a higher lethality of suicide plans as well as those with more recent suicide attempts (Rojas et al., 2019). Finally, the inclusion of additional participants such as healthy volunteers and individuals with a combination of TRD and no lifetime suicidal ideation would allow for a more thorough characterization of the progression toward suicide attempts in this population. Importantly, the overarching multimodal study from which this thesis derives is current recruiting a healthy volunteer population for statistical comparison.

Due to limited available literature on white matter analysis in suicide and depression, a power analysis was not calculated specifically for the DTI. Although this sample size aligns with that of similar publications in the literature (Myung et al., 2016; Xiao et al., 2015; Korgaonkar et al., 2011), neuroimaging studies including upwards of 100 participants would be conductive of more significant results accompanied by appropriate sex and gender-based analyses (Szucs and Ioannidis, 2020). Furthermore, a greater sample size may allow for inclusion of additional covariates in the general linear model, including anxiety and depression severity. Due to the

intricate relationship between these variables and their frequent co-occurrence in this population (Hirschfeld, 2001), covarying for depression and anxiety at a larger sample size would increase the detection of white matter differences in this sample without significantly compromising the diffusion signal. Additionally, a larger sample size may allow for more intricate statistical analyses including logistic regression in which predictor variables of suicide may be estimated in addition to simple group differences and correlations (Bujang et al., 2018).

Finally, as an inclusion criteria for this study was treatment-resistance, the majority of individuals had attempted several pharmacotherapies for depression, and many participants were currently taking one or more psychotropic medications. A number of studies have highlighted structural and functional implications of medications for depression, particularly involving affective and reward networks (Nord et al., 2021). More specific to this project, antidepressant treatment has been shown to attenuate white matter differences in individuals with MDD, however, this finding was correlated with treatment response (Zeng et al., 2012). As most participants in this study were severely depressed and/or acutely suicidal, it would not have been ethical to hold medications for the duration of the study. However, a detailed list of current medications was obtained for each participant, and the overarching multimodal investigation will characterize medication use through the Antidepressant Treatment History Form (Sackeim, 2001).

5.3.2. Imaging

Imaging data was collected on a 3T Siemens MR-PET system using a 32-channel head coil. Prior to the enrolment of the 11th subject, the scanner underwent a significant software upgrade from VB20 to VE11P. This resulted in a higher bandwidth in the diffusion weighted scans (1346 Hz/Px versus 1776 Hz/Px), which subsequently influenced echo spacing. To investigate the impact of the scanner upgrade on DTI data, a test analysis was performed with n=8 subjects pre-

upgrade, and n=8 subjects post-upgrade matched for age and sex. The test involved the same pre-processing pipeline of that completed for the main analysis, as well as TBSS using an independent samples t-test. This examination yielded no significant results between groups.

TBSS circumvents issues of spatial smoothing and groupwise registration, making it the most popular technique for voxel-wise analysis of white matter data (Bach et al., 2014). Despite this, previous studies have highlighted several limitations of this method. For example, the diffusion skeleton has been highlighted as 'rotationally variant', suggesting that issues of misalignment may not be completely ameliorated with this technique (Bach et al., 2014). Furthermore, use of the diffusion map may compromise anatomical accuracy in the case of overlapping white matter tracts, and exclude significance that does not fall within the restricted template (Wang et al., 2016). Alternative techniques such as tractography may be useful when combined with TBSS, as they may allow for the quantification of fibre bundle characteristics, such as the origin and termination of fibre bundles, the magnitude of individual fibres per bundle and the location of any given tract (Jbabdi and Johansen-Berg, 2011). In line with this, the use of additional complimentary white matter analyses including tractography may address inherent limitations in each individual technique to provide more detailed information on neuronal pathology (Wang et al., 2016).

Previous studies have highlighted the potential effect of total brain volume on neuroimaging findings (Whitwell et al., 2001). Total brain volume measurement may compliment voxel-wise analysis, as signal from cortical white matter may be underestimated through the use of skeletonization in TBSS (Carceller-Sindreu et al., 2019). More specific to depression, individuals with reoccurring MDE have been shown to exhibit alterations in total brain volume, which may contribute to white matter differences (Carceller-Sindreu et al., 2019). Furthermore,

total brain volume has been demonstrated to fluctuate with age, likely due to neuronal rewiring and changes in myelination patterns (Westlye et al., 2010). Therefore, it may be useful to measure and covary for total brain volume in future investigations of white matter microstructure, in addition to the use of additional complimentary methods of DTI analysis.

Chapter VI. Conclusion

Suicide is highly prevalent in the context of TRD, however, factors underlying the progression from suicidal ideation to suicide attempt are incompletely understood. Alongside clinical information, DTI allows for the characterization of white matter microstructural correlates associated with suicide attempt history. The source of white matter changes may be further explored using free water imaging to improve the accuracy of diffusion measures and quantify free water volume. In this study, the comparison of clinical and imaging data allowed for the differentiation of suicide ideators and attempters. Using TBSS, white matter alterations (including elevated AD, RD, and MD, as well as reduced FA) were identified in several white matter tracts in suicide attempters with TRD, suggesting reduced fibre tract integrity in fronto-thalamo-limbic areas. Free water correction appeared to increase detection of FA changes and suppress spurious differences in AD and RD. The effect of free water correction on all diffusion metrics and the elevation of FW itself provide evidence toward the source of anisotropic changes. To date, these results provide the first indication of free water alterations associated with history of suicide attempt, and future investigations should explore the combined impact of free water and white matter differences in suicide and depression. To conclude, preliminary DTI studies highlight the potential for neurobiological differentiation of suicide ideators and attempters, which may have significant implications for suicide prevention on a clinical level.

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