

Neuroanatomical Predictors of Suicidality in Women with Dissociative Identity Disorder

By

Lilly-beth Linnell

A Thesis

Submitted to the faculty of the

WORCESTER POLYTECHNIC INSTITUTE

In partial fulfillment of the requirements for the

Degree of Master of Science

In

Neuroscience

by

December 2022

APPROVED:

Dr. Benjamin Nephew, Advisor

Dr. Angela Rodriguez, Committee Member

Dr. Stacy Shaw, Committee Member



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This report represents work of WPI graduate students submitted to the faculty as evidence of a degree requirement. WPI routinely publishes these reports on its website without editorial or peer review. For more information about the projects program at WPI, see

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Acknowledgements

This thesis would not have been possible without the technical support and analysis pipelines created by Dr. Suhas Srinivasan and Senbao Lu, as well as the consent of McLean Psychiatric Hospital and their patient sample. Most of all, this would not have been possible without the guidance of Dr. Benjamin Nephew throughout this project.

Abstract

Dissociative Identity Disorder (DID) occurs when an individual has two or more separate identities (or personality states; DSM-5, 2013). While those who have DID are more likely to engage in self-harm, suicide attempts, and completed suicides (Kluft, 1995; Webermann et al., 2016; Foote et al., 2008; Galbraith & Neubauer, 2000; Tanner et al., 2017), much of the research on suicide has excluded individuals with DID (Foote, et al., 2008). One reason for this exclusion is that it becomes difficult to identify and treat suicidal ideations and behaviors when an individual has multiple, often competing, identities. Moreover, traditional methods of studying suicidality (e.g., self-report and diagnostic measures) are less reliable when an individual completes it with one identity and then another identity emerges (see Rifkin, et al., 1998 for more on this issue). Given the limited research, the current study seeks to examine suicidality with individuals with DID. To account for the complexities of understanding suicidality with individuals with DID, we rely on structural MRI images which can help us assess the current suicide risk as well as history of suicide attempts based on cortical thickness (width of the gray matter in the cortex) and subcortical volume of associated regions (width of white matter of subcortical regions) (Tahedl, 2020). We chose cortical thickness and subcortical volume because research has shown that as they are important neurological characteristics that are greatly influenced by genetic influences, psychiatric and mood disorders, etc. (Bas-Hoogendam et al., 2018; Xu et al., 2020; Zhao et al., 2017) and have significant associations to intellectual ability, social cognition, and other aspects of cognition including verbal recall and visuospatial functioning (Menary et al., 2013; Serra et al., 2020; Sowell et al., 2008). Thus, this study aims to develop a neuroanatomical foundation of suicidality in DID to be used towards achieving a better understanding of the neural mechanisms behind suicidality for those with DID.

Introduction

Dissociative disorders are defined by the dysfunction they cause with memory, behavior, identity, and one's sense of self (Kihlstrom et al., 1994). More specifically, those with these disorders often have gaps in memories ranging from their everyday memories to specific memories about traumatic events. Along with this, individuals experiencing a dissociative disorder often report feeling as if they are outside of their body and feel as if they are more of an observer of themselves than the person in control of their own actions, emotions, and thoughts. These feelings of not being in control of their own senses of selves usually stem from reports of hearing multiple voices all at once, as well as their own perceived sense of control over themselves alters with their current identity state (DSM-5, 2013).

In this study, we focus on Dissociative Identity Disorder (DID), which is a type of dissociative disorder that occurs when an individual has two or more separate identity states (DSM-5, 2013). Those with DID suffer from the symptoms usually associated with dissociative disorders. In addition to these dysfunctions and symptoms, those with DID tend to display high instances of self-harm and high rates of suicide (Kluft, 1995). Dissociative disorders also tend to affect women more than men at a 9 to 1 ratio (Spitzer et al., 2003), which is reflected in our patient sample being all women. Overall, dissociative disorders are rare disorders, with DID specifically affecting about 1% to 1.5% of the global population. DID also faces a lot of diagnostic aversion usually instead favoring PTSD, schizophrenia, bipolar disorder, etc., (Ashraf et al., 2016). This is for a myriad of reasons and is dependent on area, overall, even amongst professionals, beliefs about dissociative identity disorder are not always based on the scientific evidence (Loewenstein, 2018). Along with this, there is a cultural disconnect is how DID is

diagnoses and perceived on in Western civilization versus Eastern civilization. More specifically, Western civilization has now acknowledged DID in the DSM-5, however, Eastern civilizations tend to view DID as possession or a possessive disorder and believe that DID is a culture-bound syndrome that only exists in Euro-American cultures (Kim et al., 2016).

In addition to the diagnostic aversion and cultural differences, DID is particularly hard to understand because it's comorbidities, which will be discussed in the following sections.

Childhood Trauma, Dissociative Identity Disorder, and Post-traumatic Stress Disorder

In research involving DID, patients are often co-diagnosed with Post-traumatic Stress Disorder (PTSD). PTSD is a psychiatric disorder defined by intense distress and dysfunction in all aspects of life due to intrusive and involuntary symptoms following exposure to traumatic event(s) (DSM-5, 2013). These symptoms include distressing memories, dreams or nightmares, dissociative reactions (such as flashbacks, depersonalization, derealization), distress due to internal or external reminders or cues, avoidance of reminders, as well as negative changes in cognitions and mood - all in association with the traumatic event(s) (DSM-5, 2013).

Most studies using DID involve investigating populations with a dissociative subset of PTSD (PTSD-DS), or with both DID and PTSD (Rodewald et al., 2011). This is due to their overlapping symptomatology; specifically, their primary focus on dissociative tendencies caused by traumatic events and the emphasis on a dysfunction with memories. One main difference between the two is how they are affected by their own memories. Those with DID often experience gaps in memory — whether they be everyday memories or specific memories (Mitra & Jain, 2021) while those with PTSD may experience painful flashbacks to memories of trauma or may also have gaps in memory surrounding the traumatic events (DSM-5, 2013). Both those with PTSD (Bryan, 2016) and DID (Foote et al., 2008) exhibit high rates of suicidal behavior

and self-harm and should be included in suicidality research as separate disorders, unless co-diagnosed like in our population.

Suicidality and Dissociative Identity Disorder

Suicidality is defined by a combination of suicidal ideation, plans of suicide, as well as suicide attempts (VandenBos, 2007). According to the World Health Association, roughly 800,000 people die per year from suicide, globally, independent of any psychological factors (Sudol & Mann, 2017). One issue with global suicide statistics is that they often do not include those experiencing psychiatric disorders, including those with DID, where the suicide rates are even more drastic.

DID is often linked to past suicide attempts and physical self-harm (Webermann et al., 2016), noting that over 70% of those diagnosed with DID have attempted suicide at least once (Foote et al., 2008; Webermann et al., 2016). Overall, around 67% of those with DID have attempted suicide multiple times (Foote et al., 2008), and around 1 — 2% of those with DID complete their suicide attempts (Kluft, 1995, Galbraith & Neubauer, 2000). Along with this, an experiment conducted with outpatients at a psychiatric clinician Switzerland found that 23.5% of those with DID attempted suicide at least once during a 12-month observation period, while none of the outpatients without DID attempted during the same observational period (Tanner et al., 2017). In comparison to the average population, those with DID attempt suicide at least once 70 times more (Foote et al., 2008; Webermann et al., 2016). In our patient population for our study 77% of patients diagnosed with DID attempted suicide at least once.

Suicide and number of suicide attempts also differ between men and women. Specifically for suicidality independent of DID, men commit suicide at a higher rate, but women are more likely to attempt to commit suicide (O'Rourke et al., 2021; O'Loughlin & Sherwood,

2005). Though there are limited sex or gender statistics investigating suicide in DID patients, with these existing statistics we can infer that since dissociative disorders affect women more than men, most of the DID patients who attempt suicide are women.

In those diagnosed with DID it is difficult to investigate suicidality using normal therapeutic or existing qualitative methods due to the reliance on patient self-report and scale-based diagnostic techniques (Rifkin et al., 1998). In patients with DID, their dissociative symptoms force them to be considered an unreliable narrator (Gillig, 2009; Krause-Utz et al., 2017), thus making self-report ineffectual. More specifically, patients may not remember their past suicidal behaviors due to common amnesia and memory symptoms, and the patient's current or presenting identity state may not be the identity state that is responsible for suicidal tendencies and self-harm. By investigating the neural substrates of suicidality in those with DID, it will allow for clinicians to better treat and recognize suicide risk in DID affected populations because it will not rely on the own patient's memory or current identity state. Investigating neural substrates also will provide a neuroanatomical foundation that will allow for the enhancement of interventions by targeting specific regions and related functions. Neural substrates are ideal in those with DID for many reasons, but mainly because neural substrates are not often affected by current personality state (Tsai et al., 1999). The current personality state and every other possible personality state all share the brain of one individual, which means that each personality state should see and share identical neural substrates (Tsai et al., 1999), even if the patient's personality state has changed. This means that even if the patient is not in the suicidal identity state, clinicians and diagnostic professionals will be able to rely on similarities in brain regions when assessing overall risk of suicide and suicide behaviors. But, before clinicians can rely just on brain regions instead of self-report, we need to discuss the neural substrates of DID and

suicidality and then create methods able to simplify them. I discuss these substrates and methods below.

Neural Substrates for those with DID

To begin our investigation of neural substrates as predictors of suicidality risk in those with DID, we needed to understand the pre-existing neural substrates associated with DID already. Although there is a strong association between DID and suicidality (Kluft, 1995; Webermann et al., 2016; Foote et al., 2008; Galbraith & Neubauer, 2000; Tanner et al., 2017) there is a need for neuroanatomical research to better treat and diagnose those with DID who are at risk of attempting suicide. Abnormal cortical thickness is the width of the gray matter of the human cortex but excludes deeper subcortical regions. Subcortical volume includes the width of the white matter of subcortical regions such as the thalamus, caudate, putamen, pallidum, hippocampus, amygdala, nucleus accumbens, and is often commeasured with intracranial volume (ICV) (Wen et al., 2016).

From the research that exists so far, researchers have discovered that there is significant abnormal cortical thickness and subcortical volume involved with regions in patients with DID. More specifically, most research has found that these decreases are most prevalent in the insula, the anterior cingulate, the lateral occipital cortex, the temporal cortex, as well as parietal and frontal cortices, most likely due to their roles in memory, fear, and emotion (Reinders et al., 2018; Perez et al., 2018; Chalavi et al., 2015). Researchers believe these regions show abnormal cortical thickness/subcortical volume based on exposure to intense trauma, especially childhood trauma, and the experience of specific symptoms of dissociation such as feeling outside of one's body and depersonalization (Reinders et al., 2018; Perez et al., 2018; Chalavi et al., 2015). More

specifically, abnormal cortical thickness in the anterior cingulate was found to be associated with high levels of somatoform dissociation, which is a type of dissociation used to describe specific forms of dissociative symptoms experienced as somatic disturbances due to alterations in the functions of consciousness, memory or identity specifically related to stressful experiences (Perez et al., 2018; Bob et al., 2013).

Those with DID are known to suffer from high levels of somatoform dissociation (Nijenhuis, 2009), and research has shown that patients with higher levels of somatoform dissociation also show higher symptoms of traumatic stress, depression, anxiety, and alexithymia (a term used to define when a person has trouble identifying, describing, and distinguishing feelings in their body and cognitions) (Bob et al., 2013; Goerlich, 2018). When compared to the neuroanatomical evidence of suicidality, DID shares abnormal subcortical volume in the hippocampus, as well as abnormal cortical thickness in parietal and frontal structures - structures known to be associated with memory, emotions and emotional behavior, and cognition (Anand & Dhikav, 2012; Budson & Solomon, 2016; Jankovic et al., 2022; Fuster, 1999). An implication for shared abnormal cortical thickness and subcortical volume in both suicidality and DID could be correlated with the observation that many of those diagnosed with DID have past experiences with suicide attempts and/or suicidal ideation. Another implication of the shared cortical thickness and subcortical volume could relate to the comorbidity of depression symptoms and suicidality, given the correlation between high levels of somatoform dissociation and depression symptoms (Vandivort & Locke, 1979; Jeon, 2011; Wagner et al., 2012; Bob et al., 2013). Overall, using neural substrates to study suicidality can be difficult due to the possibility of causal relationships between neuroanatomical changes, and whether these changes cause

suicidality symptoms or if these changes are an effect of past suicide attempts and overall heightened levels of suicidality.

Neural Substrates Associated with Suicidality in All Populations

In addition to understanding the neural substrates behind DID, we also needed to investigate the established neural substrates involved with suicidality and how they may overlap with those diagnosed with DID. Investigating suicidality from a neurobiological standpoint provides clinicians with more specific tools to assist with the diagnosis and prevention of suicidal behavior, especially in vulnerable populations, such as those with DID (Balcioglu & Kose, 2018). Suicidality is linked to abnormal cortical thickness and subcortical volume in areas of the brain in many regions as described in Table 1, including regions associated with memory and emotional behavior such as the amygdala, the anterior cingulate cortex, the hippocampus, and the orbitofrontal cortex (Balcioglu & Kose, 2018; Wagner et al., 2012). Mainly, the problem with the existing neurobiological research on suicidality is that it tends to exclude those with dissociative disorders as part of their population, and instead choose to either use populations that have people with multiple disorders or illnesses (excluding dissociative disorders) - such as bipolar disorder (Lijffijt et al., 2014; Johnston et al., 2017), schizophrenia (Aguilar et al., 2008; Spoletini et al., 2011), and depression (Wagner et al., 2012; Colle et al., 2014). However, none of these studies focused on finding the neural substrates specific to those with dissociative disorders or disorders with high dissociative symptomatology.

Table 1

Neural substrates, and their functions

Brain area/neural substrate	Area function
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Suicidality

Gray matter of prefrontal cortex	Control of movement, memory, emotions
White matter of prefrontal cortex	Axonal signal transmission (myelin), cognitive function
Orbitofrontal cortex*	Taste, touch, reward/punishment behavior, emotional behavior, reversal of stimulus-reinforcement associations
Left Angular Gyrus	Word processing, semantic processing, reading comprehension, number processing
Right Cerebellum	Reflexive and planned motor coordination, emotion, and cognitive processes
Nucleus Raphe	Serotonin release
Nucleus lentiformis	Motoric coordination, executive function, attention, working memory, reward
Insula*	Sensory and affective processing, high-level cognition, sensorimotor processing
Hippocampus*	Learning, memory, spatial navigation, emotional behavior
Rectal gyrus	Language, memory recall, major depression
Superior temporal gyrus	Auditory and language processing, social cognition, autism
Caudate	Successful goal-directed action, effective behavior
Corpus Callosum	Abnormalities associated with early-life trauma

DID

Anterior Cingulate Cortex*	Affect-regulation (The ability to control and manage uncomfortable emotions)
Parietal Structures	Language perception, perception of spatial orientation, spatial function
Frontal Structures*	Skeletal and eye movement, speech, and logic reasoning,
Amygdala	Emotional learning, memory

Note. Areas that are associated with both DID and suicidality are marked by *. Gray matter information taken from (Mercadante, 2020). White matter information taken from (Filley & Fields, 2016; Bolandzadeh et al., 2012). Orbitofrontal cortex information taken from (Rolls, 2004). Left angular gyrus information taken from (Seghir, 2013). Right cerebellum information taken from (Witter & De Zeeuw, 2015). Nucleus raphe information taken from (Hornung, 2003). Nucleus lentiformis information taken from (Li et al., 2021). Insula information taken from (Uddin et al., 2017). Hippocampus information taken from (Anand & Dhikav, 2012). Rectal gyrus information taken from (Joo et al., 2016; Bremner et al., 2002). Superior temporal gyrus (Bigler et al., 2007). Caudate

information taken from (Grahn et al., 2008). Corpus Callosum information taken from (Harker, 2018). Anterior Cingulate Cortex taken from (Stevens et al., 2011). Parietal structures taken from (Budson & Solomon, 2016; Jankovic et al., 2022). Frontal structures taken from (Fuster, 1999). Amygdala information taken from (Balleine & Killcross, 2006).

Previous Work in this Cohort

A previous study using a part of the same cohort used Artificial Intelligence (AI) and Machine Learning (ML) to identify dissociative patients and to predict and prevent suicide with the addition of analyzing psychometric data (Srinivasan et al., 2022). Their population involved more than just those with DID as well as they did not incorporate neuroanatomical methods such as structural MRI. They found one of the AI/ML algorithms (the unsupervised machine learning algorithm) identified patients along a spectrum of dissociation. They also found that the supervised machine learning algorithm accurately predicted a history of suicide attempts with an accuracy of 83%. Overall, they found that those with DID as well as PTSD had the highest risk of suicide attempts, and distinct symptoms of dissociation, such as hearing voices and a lack of control over thoughts and actions, predicted suicide attempts in PTSD and DID (Srinivasan et al., 2022). They also found that when comparing the DID and PTSD/PTSD-DS groups, the odds of a patient attempting suicide was 140% higher in patients with DID and PTSD, and those with a DID diagnosis had a 40% increased risk of attempting suicide compared to those just with a PTSD diagnosis (Srinivasan et al., 2022). To go a step further, in addition to using this same AI method for suicide prediction, this study focused our patient group on those now defined as most at risk, (i.e., those with a primary diagnosis of DID, compared with controls), and wanted to use a neuroanatomical measure, structural MRI data, to predict suicidality. This is due to an issue using purely clinical characteristics such as qualitative assessments, for example the Beck Depression Inventory-II (BDI-II). The BDI-II has an item to predict suicide and is often relied on

in studies investigating suicidality but was found to be very poor at accurately predicting suicide in patients (Srinivasan et al., 2022). To combat this, we introduced the potential for using structural MRI to establish a foundation in DID research to understand the neural substrates involved with suicidality in this population, not currently available in research today.

Method

Participants

This study included 107 female participants (78 patients with DID, 29 individuals without DID/controls) who were recruited at a psychiatric hospital in the Northeastern United States. The participants were mainly White (87.9%), heterosexual (40.2%), and ranged between 18 to 62 years in age ($M = 34.6$), see Table 2 for a summary of the participants demographic and clinical characteristics. During the study, the 78 patients diagnosed with DID received varied levels of care including inpatient, residential, and outpatient care, depending on the individual's severity of symptoms. All 78 patients were co-diagnosed with PTSD and various levels of dissociation, including some with the dissociative subtype of PTSD (PTSD-DS), and some with dissociative identity disorder (DID) or a dissociative disorder not otherwise specified (DDNOS). Patients were excluded if they had a current alcohol or substance use disorder within the past month or a history of or current psychotic spectrum disorder through self-report methods provided by the psychiatric hospital. Control participants had no psychiatric diagnoses. The study was approved by the appropriate ethical institutional review boards. Informed consent was obtained from all research participants.

Table 2
Demographic Breakdown

Controls	PTSD	PTSD-DS	DID	DDNOS	Total
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Demographics	N	%	N	%	N	%	N	%	N	%	N	%
Female-assigned at birth	29	100	22	100	19	100	36	100	1	100	107	100
Race												
White	26	89.7	30	83.3	17	89.5	30	83.3	1	100	94	87.9
Black	2	6.9	2	5.6	0	0	3	8.3	0	0	5	4.7
Asian	1	3.4	3	8.3	1	5.3	2	5.6	0	0	6	5.6
American Indian	0	0	1	2.8	0	0	1	2.8	0	0	1	0.9
Other	0	0	0	0	1	5.3	0	0	0	0	1	0.9
Hispanic	4	66.7	1	16.7	0	0	1	16.7	0	0	6	5.6
Sexual Orientation												
Straight/heterosexual	15	51.7	13	59.1	8	42.1	6	16.7	1	100	43	40.2
Bisexual	0	0	3	13.6	3	15.8	7	19.4	0	0	13	12.1
Gay or lesbian	2	6.9	2	9.1	2	10.5	1	2.8	0	0	7	6.5
Pansexual	0	0	2	9.1	0	0	1	2.8	0	0	3	2.8
Queer	0	0	0	0	0	0	2	5.6	0	0	2	1.9
Did not report	12	41.4	2	9.1	6	31.6	19	52.8	0	0	39	36.4
Handedness												
Right-handed	20	69.0	19	86.4	16	84.2	26	72.2	1	100	82	76.6
Left-handed	3	10.3	1	4.5	1	5.3	3	8.3	0	0	8	7.5
Ambidextrous	0	0	0	0	0	0	2	5.6	0	0	2	1.9
Did not report	6	20.7	2	9.1	2	10.5	5	13.9	0	0	15	14.0
<hr/>												
	Controls		PTSD		PTSD-DS		DID		DDNOS		Total	
	N	%	N	%	N	%	N	%	N	%	N	%
Current level of care (patients)												
Inpatient	0	0	4	18.2	5	26.3	7	19.4	0	0	16	15.0
Outpatient	1	3.4	14	63.6	8	42.1	17	47.2	1	100	41	38.3
Residential	0	0	3	13.6	6	31.6	11	30.6	0	0	20	18.7
Other	0	0	1	4.5	0	0	1	2.8	0	0	2	1.9
None	28	96.6	0	0	0	0	0	0	0	0	28	26.2

Materials

The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5)

The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) is a 30-item structured diagnostic interview that assesses the diagnostic and symptom severity of PTSD (Weathers et al., 2018). The standardized questions assessed 20 defined PTSD symptoms according to the DSM-5, some examples include: “In the past month, have you had any unwanted memories of (insert the event) while you were awake, so not counting dreams?”, “How much do these memories bother you?”, “How often have you had these memories in the past month?”, etc. (Hamblen & Barnett, 2018). These are rated on a 5-point Likert-type scale from 0 to 4 by the clinicians themselves. This might look like, a clinician rating a patient as “0” or “absent” for a certain PTSD criterion; or “3” for “severe/markedly elevated” meaning that a patient struggles with this PTSD criterion about 2x a week but it isn’t completely debilitating (Weathers et al., 2018).

The Childhood Trauma Questionnaire (CTQ)

The Childhood Trauma Questionnaire (CTQ) is a 70-item self-report measure that uses a 5-point Likert-type scale (1 being “never true” and 5 being “very often true”) to assess experiences of abuse in childhood as well as childhood environment. Questions are organized based on four types of abuse: physical and emotional abuse, emotional neglect, sexual abuse, and physical neglect (Bernstein et al., 1998).

The Multidimensional Inventory of Dissociation (MID)

The Multidimensional Inventory of Dissociation (MID) is a 218-item self-report measure that uses a 11-point Likert-type scale (0 being “Never” and 10 being “Always”). One hundred and sixty-eight items are used to assess dissociation (i.e., self-confusion, amnesia, angry intrusions, etc.) and the remaining 50 items are used as validity checks to assess things like

defensiveness, emotional suffering, rare symptoms, attention-seeking behavior, factitious behavior, and a severe borderline personality disorder index. Some examples of the questions asked in this questionnaire include rating how often: “Things around you suddenly seem strange.” and “Feeling as if your body (or certain parts of it) are unreal” (Chu, 2011; Dell, 2006; Dell et al., 2017).

The Beck-Depression Inventory-II (BDI-II)

The Beck-Depression Inventory-II (BDI-II), is a 21-item self-report measure that uses a 4-point Likert-type scale (0 to 3), to assess the presence and severity of depressive symptoms. This is done through given items such as work inhibition or suicidal ideas. An example of the suicidal ideas item would be: 0 being “I don’t have any thoughts of killing myself”, 1 being “I have thoughts of killing myself, but I would not carry them out”, 2 being “I would like to kill myself”, and 3 being “I would kill myself if I had the chance” (Lee et al., 2017).

Magnetic Resonance Imaging (MRI)

After obtaining informed consent from each patient, patients were then placed into an MRI machine to acquire structural images of each patient’s brain (ie., patients were not given any task during the MRI process). MRI scanning was performed in a 3-T Tim Trio scanner (Siemens Healthcare, Erlangen, Germany) using the vendor supplied 12-channel phased-array head coil and standard T2*-weighted echo-planar imaging (TR = 3000ms, TE = 30ms, flip-angle = 85 degrees, 3x3x3mm voxels) (LeBois et al., 2021).

MRI Image Preprocessing

MRI data often needs to be preprocessed and cleaned of noise before being properly analyzed in a study (Esteban et al., 2019). We used fMRIPrep to correct for head movement,

susceptibility distortion (corrects whether there were any distortions of the images due to local signal change of the local magnetic field), and spatial normalization (normalizes a brain's shape, size, and weight) (Esteban et al., 2019). This allows us to map locations as approximately the same in all brains. Finally, we also used fMRIPrep to strip the skull to ensure patient anonymity by removing any recognizable aspect of their faces. After correcting for noise, we corrected for intensity nonuniformity (Belaroussi et al., 2006) then reconstructed the brain image in FreeSurfer using the morphometric features of the Desikan-Killiany Atlas. This allows us to have a brain image with uniform intensity, essentially so we can see each region equally clearly. Then we were able to complete our analysis via our ML approach.

Extracting Cortical Thickness and Subcortical Volume Values

Cortical thickness and subcortical volume values were extracted from the brain images using FMRIPrep and FreeSurfer to parcellate the brain into regions of interest (ROIs) according to the Desikan-Killiany atlas (Desikan et al., 2006) then cortical thickness and subcortical volume were computed for each ROI determined by the atlas. A matrix was constructed from our dataset with the subjects on the y-axis and the brain regions on the x-axis – then correlations were computed for each ROI the matrix of which is referred to as structural covariance (Saritepe, 2022).

Data Scaling

The range of data in the study varies a lot (cortical thickness ranges from 1.339 to 4.405, subcortical volume ranges from 0 to 1,624,666). To overcome the impact of large data range on the ML algorithm when we combine different modalities of data, we used a data scaler to

normalize our dataset. We utilized a min-max scaler (eqn.1), which is sensitive to outliers and response well for non-Gaussian distribution. Since we have a dataset with both control and patients, and we want to detect brain region changes between two groups, this scaler fulfills our need to preprocess the dataset.

$$X_{\text{new}} = (x - x_{\text{min}}) / (x_{\text{max}} - x_{\text{min}}) \text{ (eqn.1)}$$

Age Correction

Age is considered as a confounding variable when analyzing MRI data. To ensure that the differences in cortical thickness and subcortical volume we found were not due to age, we created an age correction pipeline based on a published paper on age correction on multivariate classification in Alzheimer's Disease (Falahati et al., 2016). We build generalized linear models (GLM) for each feature using data from the control group and apply the corresponding model to all data to eliminate any age-related effects. Specifically, for each GLM, we use control group data to fit in a linear regression model (eqn.1) and solve for coefficients k and b. Then we apply the model to all data to find the feature value caused by age. Finally, we subtract the original feature value by the amount caused by age to detrend age effects (eqn.2).

$$\text{feature} = k * \text{age} + b \text{ (eqn.1)}$$

$$\text{feature}_{\text{detrnd}} = \text{feature} - (k * \text{age} + b) \text{ (eqn.2)}$$

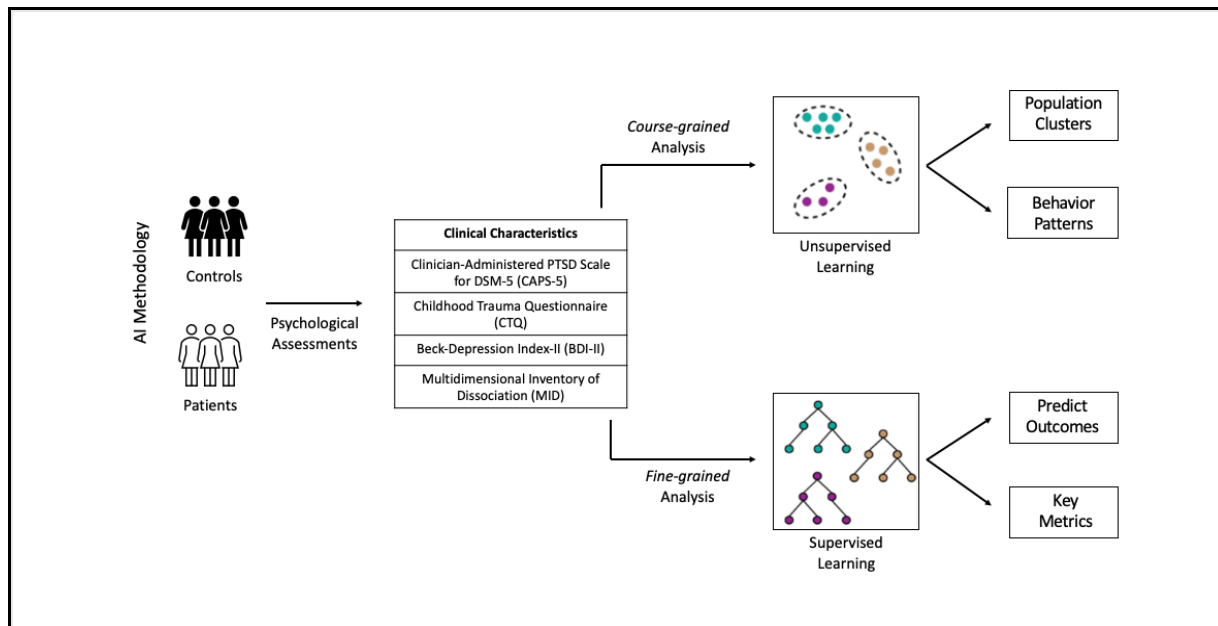
Artificial Intelligence and Machine Learning Algorithms

We implemented a developed integrated AI approach (Figure 1) and applied it to our clinical dataset of participants enrolled at a psychiatric hospital in the northeastern United States, where each patient's data is represented as a numeric feature (variable) vector consisting of self-report and clinical interview characteristics. We then apply two AI algorithms to apply this data

to cortical thickness and subcortical volume data found from our patient’s structural MRI images. The two algorithms were the unsupervised and supervised AI algorithm, which were utilized to study patterns, categorize the high-dimensional data, and to identify clinical characteristic signatures in the patient sample (e.g., the scores from the qualitative assessments). More specifically some of the signatures were based on the clinical assessments and included things such as history of suicide attempts and dissociative symptoms. We then took this data and applied it to cortical thickness and subcortical volume in our patient’s structural MRI images.

Figure 1

AI Methodology



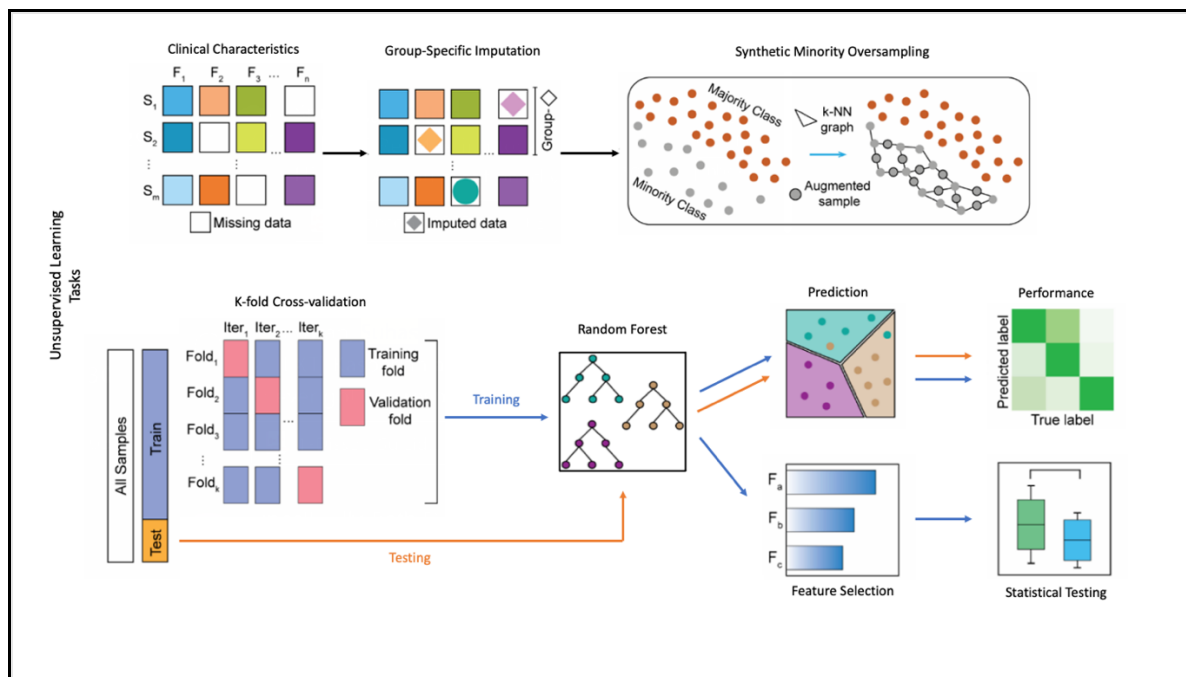
Machine Learning - Unsupervised Learning

Unsupervised learning algorithms allow for the identification of patterns in the data at a low, coarse-grained, resolution. Our unsupervised learning algorithm (Koutroumbas & Theodoridis, 2008) was used to mine for the presence of a complex intrinsic structure in the

dataset that was not discovered via a traditional statistical analysis of the patient clinical characteristics, thus expanding the basic delineation by diagnostic groups, and obtaining a coarse-grained knowledge of the entire cohort (Figure 2). For this approach, only the numeric features were used (such as Likert-type scale numbers taken from the clinical assessments): the goal was to identify clusters of data points sharing common patterns and then describe the relationships among the clusters to assess clinical behaviors and categories of interest, in our case previous suicide attempts.

Figure 2

AI Methodology, Unsupervised Learning Task Organization



To discern these patterns, we employed clustering (Jain et al., 1999) and dimensionality reduction techniques, to map and visualize high-dimensional data into two-dimensional (2D) spaces while preserving the similarity between the data points. Specifically, we applied t-distributed stochastic neighbor embedding (t-SNE; Van der Maaten & Hinton, 2008), a technique

commonly used to analyze biological data (Klein et al., 2015). We chose this technique because it is efficient in capturing critical parts of the local structure of high-dimensional data and mapping it into 2D space, as well as it can determine clusters without prior knowledge of cluster number or sizes. The 2D points were then annotated according to the categories of interest (e.g., categories that were initially excluded), revealing the pattern of correlation between data structures and clinical labels. Next, we used a more generalizable dimensionality reduction method with deep learning architecture, Denoising Autoencoder with Neuronal Approximator (DAWN; Srinivasan et al. 2020), to uncover additional high-dimensional relationships in the patient sample.

Machine Learning - Supervised Learning

For the higher resolution analysis, a different class of algorithms— supervised learning (Kotsiantis et al., 2007)—was required, where the distinction between the groups could be enhanced with the identification of important metrics. The algorithm first undergoes training on the paired input-output data, where the input corresponds to clinical characteristics and output corresponds to categories of interest, e.g., PTSD status, final diagnosis, risk of attempting suicide, etc.

We designed two types of classification tasks, but only used the second task in our study. The first type, models categorized individuals between the controls and entire patient sample, or between the controls and patient diagnostic groups. For the second type of classification task, the patient inter-group categorization, we developed models to identify inter-group predictors and attempted to model the risk of attempting suicide based on our predicted history of suicide attempt per patient.

A hybrid technique was developed for the supervised learning tasks to overcome challenges inherent in the study design and to obtain robust models with consistent predictions and predictors. The primary issue with using the original data was the class imbalance problem (Jankovic, 2022), where sample sizes of the control group and patient sub-groups were highly uneven, which could introduce classification bias in the supervised learning models. We used a data augmentation technique to add samples, known as synthetic minority over-sampling technique (SMOTE) (Chawla et al., 2002). Samples were added geometrically by creating intermediate points in the existing feature space of the k-nearest neighbors (i.e., k-NN graph, Figure 2) (Fukunaga & Narendra, 1975) of each control sample. These augmented and balanced data were used for all further steps.

Next, an ensemble supervised learning algorithm was implemented, the multi-class Random Forest (RF; Liaw & Wiener, 2002). This works by building many decision trees and avoids overfitting by randomly sampling the features. The final prediction is the consensus of the decision trees. Because the number of features were much greater than the overall sample size, a train/test split strategy was used to further avoid overfitting and rigorously evaluate the created model (Vabalas et al., 2019). Stratified random sampling was used to partition 80% of the samples for training and 20% for testing (Acharya et al., 2013). To simplify the pipeline, we used 10 subjects (9.26% of all subjects and 12.66 % of the patient group) as testing sets in all our models. Since the augmented data could make the model evaluation seem unrealistic or optimistic, the 20% test data contained only the original samples, and the augmented data were included only in the training set. Additionally, the 80% training data was used with a 5-fold cross-validation protocol (Kohavi, 1995) for the RF algorithm to reduce bias and variance in predictions. Cross-validation is a resampling procedure that randomly splits the data into k-folds,

$k = 5$, where 5 iterations were created to cover the entire training data, each with a complementary split of the data with 4-training folds and 1-validation fold. During the 5-fold cross-validation procedure, the prediction of each iteration is measured for accuracy, represented by F_1 score.

$$F_1 \text{ score} = \frac{TP}{TP + \frac{1}{2} (FP + FN)}$$

where FP is the number of false positives, FN is the number of false negatives, and TP is the number of true positives. Each iteration in the 5-fold cross-validation produces a F_1 score, which is averaged across the 5 iterations and reported with a standard deviation.

Furthermore, during the 5-fold cross-validation process, we implemented recursive feature elimination (RFE; Darst et al., 2018) to sequentially remove non-beneficial and highly correlated features. The combined 5-fold cross-validation and recursive feature elimination can lead to highly complex models with many features. Therefore, at the end of the cross-validation process, we analyzed changes in the F_1 score due to the consecutive reduction of the feature set, selecting a minimal number of features while preserving a high F_1 score. In addition to the feature selection, the RF model also provided a ranking of the features (Saeys et al., 2008).

To verify the fitness and generalizability of the selected features, a new model was retrained on the 80% training data using 5-fold cross-validation. This retrained model was then applied to the withheld test data to generate the final predictions. For predicting suicide attempt in the patients, we used the patient responses for the question “Have you ever attempted suicide?” with yes/no answers as the output labels, that would be predicted by our supervised

learning model. The unsupervised learning and supervised learning methods were implemented using scikitlearn (Pedregosa et al., 2011).

RESULTS

Model Performance

Among all models we obtained, we observed that the testing score was lower, if not significantly lower, than the training accuracy. This could be explained mainly by the small size of the dataset. We cannot afford to eliminate any outliers before training process, therefore while randomly selecting the independent testing samples, an outlier might be included and causing low testing score. The purpose of having independent testing group is to prevent overfitting in the models. Since we also have the 5-fold cross validation process to avoid overfitting, we choose to use the training accuracy to represent the model performance and select best-performing models.

Neuroanatomical Results

For our results we split how we analyzed the effectiveness of our predictive model into three sections because binary classification would make our analysis easier, as well as we had limited DDNOS and PTSDDS subjects. Those subgroups being the patient group versus to control group, the DID and DDNOS group versus the PTSD and PTSDDS group, and finally the suicide versus non-suicide group. We used a five-fold cross validation, where the predictive model fit is tested five times with 80% of the data, selected at random, which is used to train the model and 20% of the data is used for validation.

Table 3

Sample table showing the F-scores for specific data types, each subgroup, and both biomarkers.

Patient versus. Control			
Cortical Thickness			
Data type	<i>Original</i>	<i>Age Corrected</i>	<i>Scaled</i>
Features Selected	11	11	7
Training Accuracy	0.87	0.86	0.87
Training Std	0.05	0.07	0.08
Testing Score	0.8	0.64	0.7
Subcortical Volume			
Data type	<i>Original</i>	<i>Age Corrected</i>	<i>Scaled</i>
Features Selected	2	9	11
Training Accuracy	0.8	0.82	0.81
Training Std	0.03	0.07	0.06
Testing Score	0.7	0.7	0.74
Both			
Data type	<i>Scaled</i>		
Features Selected	12		
Training Accuracy	0.89		
Training Std	0.03		
Testing Score	0.6		
DID + DDNOS versus. PTSD + PTSDDS			
Cortical Thickness			
Data type	<i>Original</i>	<i>Age Corrected</i>	<i>Scaled</i>
Features Selected	8	6	6
Training Accuracy	0.73	0.7	0.75
Training Std	0.11	0.09	0.14
Testing Score	0.45	0.5	0.5
Subcortical Volume			
Data type	<i>Original</i>	<i>Age Corrected</i>	<i>Scaled</i>
Features Selected	5	2	5
Training Accuracy	0.72	0.76	0.8
Training Std	0.13	0.05	0.07
Testing Score	0.49	0.75	0.7
Both			
Data type	<i>Scaled</i>		

Features Selected			11
Training Accuracy			0.73
Training Std			0.12
Testing Score			0.64
Suicide versus. Non-suicide			
Cortical Thickness			
Data type	<i>Original</i>	<i>Age Corrected</i>	<i>Scaled</i>
Features Selected	5	6	2
Training Accuracy	0.78	0.73	0.78
Training Std	0.1	0.08	0.08
Testing Score	0.39	0.45	0.49
Subcortical Volume			
Data type	<i>Original</i>	<i>Age Corrected</i>	<i>Scaled</i>
Features Selected	2	8	5
Training Accuracy	0.78	0.66	0.73
Training Std	0.08	0.12	0.16
Testing Score	0.5	0.6	0.45
Both			
Data type			<i>Scaled</i>
Features Selected			7
Training Accuracy			0.75
Training Std			0.11
Testing Score			0.6

**Features used can be found in Appendix A.*

Focusing on the age-corrected data, our predictive model was able to tell the difference between the patient and control group 89.0% (F = 0.89) of the time when combining both cortical thickness and subcortical volume. When just relying on cortical thickness, the model was accurate 86.0% (F = 0.86) of the time versus subcortical volume which was accurate 82.0% (F = 0.82) of the time. There is a 4% difference between the two, but considering the predictive accuracy being over 80%, this can be considered almost negligible and may be due to the difference in features selected (11 versus 9). Moving on to subgroup specific differences, beginning with the DID + DDNOS versus PTSD + PTSDDS groups, our model was 73.0% (F = 0.73) accurate in determining the difference between the DID +DDNOS subgroup and the PTSD

+PTSDDS subgroup. However, our study mainly focused on our model’s ability to detect suicide versus non-suicide, as mentioned in the following paragraph.

Most importantly, our predictive model was able to detect those with a past suicide attempt versus those with no past suicide attempt (suicide versus non-suicide subgroup), 75.0% ($F = 0.75$) of the time when using both cortical thickness and subcortical volume features, a total of seven features (left isthmus thickness, left pars orbitalis thickness, left temporal pole thickness, left thalamus proper volume, left accumbens area volume, right hippocampus volume, and surface hole volume). In this case, our model was more accurate when using cortical thickness features when assessing past suicide attempt than subcortical thickness (73% ($F = 0.73$) versus 66% ($F = 0.66$)).

Table 4

Table showing the features used in the suicide versus non-suicide subgroup and their functions.

Suicide v. Non-suicide Group Features and Functions	
Feature	Function
Left isthmus cingulate thickness	Emotion regulation, sensing, acting, and reacting in response to emotional stimuli.
Left pars orbitalis thickness	Language processing of the production and comprehension of language.
Left temporal pole thickness	Language, visuospatial and audio-spatial functions (e.g., semantic processing, speech comprehension, and naming as well as assigning meaning to auditory cues).

Left thalamus proper volume	Arousal and pain regulation, regulation of sensory domains (except smell/olfaction), motor language function, cognitive functions, and mood and motivation.
Left accumbens area volume	Mediating motivational and emotional processes (preference, learning, avoidance, impulsivity, risk-taking, feeding, sexual motivation, unpredictable reward).
Right hippocampus volume	Spatial memory (i.e., navigating through a familiar city).
Surface hole volume	Lack of research.

Isthmus cingulate information taken from (Luu et al., 2003). Pars orbitalis information taken from (Novick, Trueswell, and Thompson-Schill, 2010). Temporal pole information taken from (Ardilla et al., 2014). Thalamus proper information taken from (Torricco, 2019). Accumbens area information taken from (Salgado & Kaplitt, 2015). Hippocampus information from (Ezzati et al., 2016; Mobley, 2019). Surface hole information not available in current research.

We also calculated graphs showing the feature importance per each of the 30 experiments we ran to achieve the above F-scores. Out of all 30 experiments, the most common features were the cortical thickness of the left isthmus cingulate, the subcortical volume of the right hippocampus, both being within the top important features of 12 of the 30 experiments. The cortical thickness of the left pars orbitalis was also common; being in eight out of the 30 experiments. None of the other features came close to these three in terms of commonality of

feature importance throughout all 30 experiments. According to the features in our calculated features of importance, 34 were cortical thickness and 32 were subcortical volume.

Discussion

This research provides a novel foundation of suicidality in DID, although our study had limitations, it still provided results that are new and important to DID research. More specifically, we found that although those with DID have an extremely high rate of suicidality, they are often excluded from studies investigating suicidality. While investigating the neuroanatomical biomarkers for suicidality in those with DID, we discovered a unique issue with how to research past suicide attempts in those with DID. This being that we cannot rely on patient self-report to provide the best care, given the common memory loss at identity switch. More specifically, the patient could have lost memories of important information for providers and researchers to identify any alarming thinking or behavior. To counteract this issue, we created our ML model to discover the decreased cortical thickness and subcortical volume in our found regions. This introduced the possibility that we can infer that a DID patient has attempted suicide before – without the need for them to remember or self-report it. Additionally, since those with DID are more likely to attempt suicide again (Foote et al., 2008), we can infer from them attempting once that they may attempt again and use this information to guide treatment. Our study still relied on self-reported past suicide attempt per patient, but, using the cortical thickness and subcortical volume in the regions we found, future research will be able to apply these regions towards research that will no longer rely on self-report.

Functionality Implications

There were seven main features found with decreased cortical thickness or subcortical volume in our suicide versus non-suicide subgroup. Those being: the left isthmus thickness, left pars orbitalis thickness, left temporal pole thickness, left thalamus proper volume, left accumbens area volume, right hippocampus volume, and surface hole volume. Each of these features have associated functions, and in theory, should correlate with various functional networks. As a whole, functional networks have been implied to be able to differentiate dissociative behaviors per certain regions, region sizes, as well as disorder such as PTSD. For example, previous research has shown that trauma-related dissociative symptoms distinct from PTSD can be estimated by network connectivity in a similar study cohort as ours (Lebois et al., 2021). This study mainly found that the connections that were involved with dissociation severity and symptom estimation scores on the MID were the frontoparietal control, the default mode, and the visual networks. They also found that size of regions in each network was behaviorally relevant as well as predictive of symptom scores on the MID. Specifically, there was a negative correlation between MID score and size of the ventral attention network, and a positive correlation between MID score and the size of the sensorimotor network (Lebois et al., 2021). Additionally, the Lebois et al., 2021 study found that severe dissociative symptoms were best predicted by a combination of region size and network connectivity rather than either region size or network connectivity on their own. This made it particularly relevant to our study investigating DID and suicidality given the use of MID score and the past research finding that increased dissociative symptoms are indicative of higher suicidality. The Lebois et al., 2021 findings that size of the network predicts dissociative symptoms and our study's findings that cortical thickness and subcortical volume (aspects of size) can predict past suicide attempt

implies that the combination of functional networks with our study's neuroanatomical findings can provide more understanding of those with suicidality in DID. The next paragraphs discuss the associations between our seven region's sizes, cortical thicknesses, subcortical volumes, and functionalities and what roles they play in suicidality in DID.

Left Isthmus Cingulate. Beginning with the Isthmus cingulate (ICC); which is mainly known to be associated with emotion regulation, sensing, and acting or reacting in response to emotional stimuli (Luu et al., 2003). Stressful and traumatic life events are associated with reduced ICC volume (Calati et al., 2018), which is supported by the development of DID being highly correlated with severe childhood trauma (Ellason et al., 1996). This could also support our finding of abnormal cortical thickness in the ICC given increased stress and overall, less life security in those with DID due to the nature of having several personality or identity states and lapses in memory. Prior research also found that higher scores on a depressive mood sub scale is also associated with decreased ICC (McLaren et al., 2016), which could imply that the variability we discovered in ICC cortical thickness could be related to the increased depressive mood of those with DID. Overall, these functions correlate with the limbic and default mode networks (Doyen et al., 2022). Since dissociation severity scores and symptom estimation have been found to correlate with the default mode network (Lebois et al., 2021), and is strengthened by region size, our finding of reduced cortical thickness in the left ICC could be relating the default mode network to the trauma and the ICC to the onset of dissociative disorders and symptoms. Past research also has shown an association between perceived limited emotional regulation strategies and suicidal thoughts (Hatkevich et al., 2019). More specifically those with an increased risk of suicide showed trouble in the downregulation of negative emotional experiences and the upregulation of positive emotional experiences (Ward-Ciesielski et al., 2018). This relates with

those with DID and those with high risk of suicide in terms of the failure to downregulate the negative emotions brought up by memories of past trauma and how those memories lead to often comorbid PTSD or worsened suicidality. Those with high risk of suicide display low self-esteem and low self-worth as well as tend to hyper-fixate on themselves and their perceived negative qualities (Pyszczynski & Greenberg, 1987). Past research shows that those with major depressive disorder (and thus may be at risk for suicide), showed abnormal self-referential processing; including abnormal processes and/or representations involved in the knowledge, awareness, and judgements of the self (Lou et al., 2019).

Left Pars Orbitalis. Abnormal cortical thickness of this region is associated with clinical psychotic symptoms and major depressive disorder (Van Lutterveld et al., 2014; Colloby et al., 2011). This could potentially suggest why we may find a similar variance in cortical thickness in those with psychotic symptoms as those with DID. Along with this, the comorbidity of major depressive disorder and DID could begin to suggest a relationship between the abnormal cortical thickness of the left pars orbitalis in our DID patients, but there is little previous research.

The pars orbitalis is known for its role in language processing, with the left hemisphere of this region being commonly referred to as Broca's area (Guenther, Tourville, and Bohland, 2015). Broca's area is responsible for the language processing of the production and comprehension of language (Novick, Trueswell, and Thompson-Schill, 2010) and that left hemisphere dysfunction is associated with apraxia of speech, or the inability to form the motor programs to form syllables (Guenther, Tourville, and Bohland, 2015). Since this region combines the motor functions of language as well as the processing of words themselves, this region would be involved in both the default mode and sensorimotor networks. Specifically, the size of the regions involved in the sensorimotor network have a positive correlation with MID score,

measuring dissociative symptoms and symptom severity (Lebois et al., 2021). This could indicate that dissociative symptoms are associated with dysfunctions in several types of motor function, like language, which could be related to the “out of body” experience patients often describe.

Left Temporal Pole. Decreased cortical thickness in this region has many implications in research that could relate to DID and its symptomology. For example, the memory loss at identity switch would mean that the individual may not recall any meaning they have associated with stimuli, that the new identity would apply a different associated meanings due to their experience, as well as they may not recall environments and locations they have been to before. The left temporal pole (Brodmann’s area) is known for its role in language and visuospatial and audio-spatial functions (Ardilla et al., 2014). More specifically, the left temporal pole has a role in semantic processing, speech comprehension, and naming as well as assigning meaning to auditory cues (Ardilla et al., 2014; Tsapkini et al., 2011). This region has an important role in many different function regions, including visual, salience, dorsal attention, and sensorimotor networks. This is because the process of visuospatial and audiospatial functions involve not only attention, but the cohesion of senses such as sight and hearing, memory of places been before, and the complex thought involved in applying meaning to stimuli. These regions and functional networks, in theory, would be heavily altered in those with DID because of the nature of having multiple identities. As mentioned prior, the sensorimotor network specifically is positively correlated with region size and MID score, but additionally, it introduces the ventral attention network. This network is negatively correlated with network size and MID score (Lebois et al., 2021). Given our study found decreased cortical thickness and subcortical thickness, this would complement the reduced size of the ventral attention network

found in the Lebois et al., 2021 study with increased MID scores (ie., higher severity and more present dissociative symptoms leads to reduced size of the ventral attention network). Along with this, reduced cortical thickness of this region has been negatively correlated with the Beck Depression Inventory scores of those with Panic Disorder (PD) (Kang et al., 2017). This suggests that reduced cortical thickness of the left temporal pole could be associated with depressive symptomology in PD and could also be the case in other disorders with depressive symptomology such as DID and PTSD. The area is specifically known for the retrieval of proper names for both unique and well-known entities (Waldron et al., 2014). Those with DID are associated with memory loss, especially after identity switch, which could also affect their abilities to retrieve proper names and be able to assign meaning to auditory stimuli – as some identities may not have encountered that stimuli and may have no memory/association of them.

Left Thalamus Proper. Substantial subcortical volume reduction in the left thalamus, as found in the present study, is associated in patients with schizophrenia and bipolar disorder type 1 (Rimol et al., 2010) along with those with DID. This is mainly due to overlapping symptomology including hallucinations, delusions, cognitive deficits, and mood symptoms (Yamada et al., 2020). Schizophrenia and DID have high levels of co-occurrence, with past research suggesting they co-occurred in 74.3% of their sample, which was surprisingly high given neither of the two diagnoses occur frequently on their own (Renard et al., 2017). Schizophrenia and DID have, especially in the first two editions of the DSM, additionally linked schizophrenia with dissociation and had nearly identical descriptions, with an early description of schizophrenia being a disorder where, “emotionally charged ideas or drives attain a certain degree of autonomy so that the personality falls into pieces. These fragments can then exist side by side and alternately dominate the main part of the personality, the conscious part of the

patient.” (Renard et al., 2017). This description and the overlapping symptomology of delusions, cognitive deficits, and various mood symptoms could be related to similar abnormal subcortical volume in this region for those with DID. Although there is a lack of research on the left thalamus proper in specific, the thalamus itself plays roles in several different functions. Those include arousal and pain regulation, regulation of sensory domains (except smell/olfaction), motor language function, cognitive functions, and mood and motivation (Torrice, 2019). Again, this region could be a major part of the sensorimotor network due to the similarities in overall function, as well as introducing the central executive and limbic networks due to the involvement in motivation and arousal. This could indicate that the left thalamus proper is involved with the sensorimotor network in addition to being involved with suicidality in DID.

Left Accumbens Area. Our study found reduced subcortical volume in the left nucleus accumbens area. This is unsurprising given that the nucleus accumbens area plays a role in mediating motivational and emotional processes (preference, learning, avoidance, impulsivity, risk-taking, feeding, sexual motivation, unpredictable reward), as well as has been connected to many different disorders, including depression and drug abuse and addiction, anxiety disorder, etc. (Salgado & Kaplitt, 2015). Based on function of this region, it could play a role in the frontoparietal, limbic, and central executive networks. In terms of DID, the frontoparietal network has been found to have connections with dissociation severity and symptom estimation scores on the MID (Lebois et al., 2021). The nucleus accumbens has also been associated with reduced subcortical volume in those with schizophrenia (van Erp et al., 2016), as well as reduced subcortical volume specifically in the left nucleus accumbens areas in heroin-dependent patients (Seifert et al., 2015). The reduced left nucleus accumbens area volume was negatively correlated with depression in the heroin-dependent patients (Seifert et al., 2015). There is a known

comorbidity of depression and DID (Bob et al., 2013; Goerlich, 2018), as well as anxiety known to be related to substance abuse (DuPont, 1995). This could be indicative that the decreased subcortical volume of the nucleus accumbens is more dependent on the consequences of drug use, being psychological distress, rather than the drug use itself. This can make it directly relatable to those with DID, given they share a similar psychological distress that is found in those with substance use disorder.

Right Hippocampus. The memory loss (including spatial memory) between identity shift in DID can be indicative of why this feature is significant to our predictive model's ability to assess past suicide attempt. The right hippocampus plays a role in spatial memory (Ezzati et al., 2016), which is what enables an individual to recall locations and spatial relations between objects (i.e., navigating through a familiar city) (Mobley, 2019). The region's focus on memory means it most likely plays a role in the limbic and central executive networks, however, there is little research about these network's role in those with DID. Studies have also found that either reduced or increased hippocampal volume is associated with several psychological disorders including PTSD, depression/Major Depressive Disorder, chronic stress, and bipolar disorder (Fink, 2016). These psychological disorders are often comorbid with DID, with our study's sample all having both DID and PTSD. The similarity in symptomology as well as the known symptom of memory loss (including spatial memory) between identity shift in DID can be indicative of why this feature is significant to our predictive model's ability to assess past suicide attempt.

Surface Holes. There is a severe lack of research discussing the implication of abnormal surface hole thickness, and even less research about the role of surface holes in functional connectivity – especially those in DID. Mostly research focuses on the overall

function of the cortex rather than the potential implications of abnormal physiologies of cortex features. Additionally, much of the research involving surface holes of the cortex are focused on various methods of surface mapping (Yotter et al., 2011; Pelizzari et al., 1989).

In summary, our provided regions can now act as a foundation for suicidality in those with DID for future research to build upon and investigate further. Along with this, this research can provide a potential connection to functional networks to better understand the functional connectome involved in those with DID. These regions could help inform treatment in the form of medications, as well as diagnostic treatments, and can begin to help improve the rate of suicide in those with DID by providing health care professionals with unique ways to infer suicidality based on structural data, and not depend on patient self-report.

Limitations and Future Research

There were some limitations to this study that could be corrected in future research. The most prominent limitation that researchers need to be aware of is the aversion to diagnosing patients as having DID, usually instead favoring PTSD, schizophrenia, bipolar disorder, etc., as mentioned earlier (Ashraf et al., 2016). However, since this research focused on suicidality in those with DID in the United States, the difference in perception and diagnosis does not affect the results of this study or remove the importance of continuing future research. This aversion and cultural disconnect could have limited our study by making the prevalence rate of DID lower than the actual rate. In theory, this would affect the suicide attempt rate in our study as well as global prevalence of the disease, making it appear as though only 1 to 1.5% of the population have DID when it could be more. Along with this, it could affect potential future research by restricting access to those who may have DID because they're being misdiagnosed with a different disorder.

Another potential limitation is that our sample involved only women, although this could be argued to be appropriate due to the 9 to 1 ratio of women to men being diagnosed with DID (Spitzer et al., 2003). However, men tend to have a higher suicide rate and a higher rate of suicide completion (O'Rourke et al., 2021). This could imply that men with DID could be more at risk for completing their suicides at a higher rate than women with DID, partially due to their preference for more lethal methods (Tsirigotis et al., 2011). Thus, it is essential to have future research include both men and women. Incorporating more males in the study sample may be difficult, given that men are more likely to complete their suicides (Joiner et al., 2002), so being able to find men with DID who have survived their first attempt may be difficult. To combat this, I suggest increasing community communication to various other locations that have ample DID samples – more specifically countries that have a less pronounced aversion to the DID diagnosis such as Canada, the United Kingdom, the Netherlands, New Zealand, etc., (Dissociative Identity Disorder Research, 2016). These places not only may have men with DID, but also men who have survived their first attempt. Finding a 77% past suicide attempt rate in our sample of just women may suggest that in a sample including men with DID, the suicide attempt rate would be higher, and more than enough to cause alarm and need attention. However, this suicide attempt rate is currently based on self-report from the patients themselves. As previously mentioned, those with DID have memory loss associated with an identity switch. This switch can cause their suicide attempts to be forgotten after a switch. Because of this, we expect the reported suicide attempt rate in this sample is lower than the actual rate amongst those with DID. As the next steps forward, researchers should attempt to collect a more accurate suicide attempt rate in this population by potentially incorporating an outside party verification of the attempt. This could be in the form of provider medical history, a family member, a 911 call, a hospital visit, etc.

The next limitation is based on a lack of past research. The brain regions we found with abnormal cortical thickness and subcortical volume are not well-researched in general or in association with DID and suicidality. There is some past research that specifies different functions per separate region and separate hemisphere, meaning a region will have different functions depending on whether it lies on the right or left side of the brain. Future research is needed to increase understanding of the functional differences of brain regions in the left or right hemisphere to fully comprehend the implications of decreased cortical thickness and subcortical volume in our found regions. Most specifically, we need research on why we are seeing these decreases only in the right hippocampus and not the left – what could this mean? Why is this important to those with DID? Additionally, what is the importance of the decreased volume of the brain's surface holes? Why is this found all over the cortex in those with DID? Is that related to suicidality in DID or in those with DID specifically? What even is the relevance of surface hole volume to our functionality? To answer some of these questions, researchers could incorporate surface holes into both neuroanatomical and functional research, as well as introduce neuroanatomical suicidality research in those without DID to begin making comparisons about potential hemisphere differences. For example, to see if right versus left hippocampus is significant only in DID suicidality and not in suicidality in general. Future research should investigate surface hole volume as a metric for early life trauma to see if there are similar effects in those with just PTSD or those who suffered from early childhood trauma, similar to the reduced corpus callosum volume found in those with childhood trauma (Saar-Ashkenazy et al., 2014).

Neuroscience research needs to integrate more multi-modal imaging data. Typically, much of the research in the neuroscience field that uses imaging data only presents one type of

data and it can limit the potential of the field. Along with this, future research may want to incorporate functional magnetic resonance imaging (fMRI) to see how the brain activity of those with DID (blood-oxygen-level-dependent (BOLD) signal). This is based on past research where researchers used a machine learning pipeline and introduced death and life related concepts (“death”, “cruelty”, “carefree”, “praise”, etc.) to predict those who struggle with suicidal ideation at a 91% accuracy rate (Just et al., 2017). It would be interesting for future research to perform a longitudinal study (with the hopes that overtime, the identity that suffers from suicidality will be present during a scan) with those with DID and recreate this same study to see if they achieve the same high predictive results. Our study alone will not be affected by this since we are predicting past suicide attempts, rather than current suicidal ideation, but it introduces an interesting future direction.

Additionally, because our model focused on predicting past suicide attempt, it brings up limitations in terms of the directionality of the neuroanatomical changes we found. Specifically, are the decreases in cortical thickness and subcortical volume from the first attempt itself, or are they caused by all aspects of suicidality including plans of suicide and ideation. To investigate this, I suggest researchers investigate a sample that includes those with DID that may only be considering suicide or suffering from other aspects of suicidality excluding the first attempt itself. If the same decreased cortical thickness and subcortical volume is found in those with DID that are suffering from suicide ideation or planning without being at risk to attempt suicide, we may be able to infer that these neuroanatomical changes are not just found in those who have already attempted suicide.

Along with this, there are different brain effects found that are dependent on the method of the suicide attempt (i.e., hanging, pills overdose, CO2 inhalation, etc.). For example, hanging,

which can cause more damage to the brain based on lack of oxygen availability to the brain and body tissues known as hypoxia (Jawaid et al., 2017). These damages usually are combined with ischemia (lack of blood to the brain or tissue), leading to brain necrosis or permanent death of brain tissue (Kaloeris et al., 2016; Woo, 2010; Miyamoto & Auer, 2000). To investigate this, researchers could incorporate those with DID who have not yet attempted suicide and see if the same decreases are found, as well as incorporate questions of what method was used to attempt using the second party verification method mentioned earlier (i.e., hospital visit, family member, 911 call).

There have been the beginnings of novel research involving measuring brain activity during an identity switch. Though complicated, this research could not only provide us with a new understanding of the DID brain but give us insights on why we are seeing decreases in cortical thickness and subcortical volume in these specific regions. Most importantly, this research could provide a stronger argument to why DID is a valid diagnosis that is separate from similar disorders such as PTSD. The main issue with these types of questions, such as investigating the brain activity at identity switch, is the ethics of the overall method itself. Those with DID often switch identities to protect themselves from trauma or reminders of traumatic events. This would mean, to investigate brain activity during a switch, researchers would need to remind patients of a traumatic event. Not only is this dangerous and distressing for the patient themselves, but it raises an important question: does informed consent cover every personality/identity state? Because of the memory loss at an identity switch, a patient who had consented to the study should no longer be considered to have consented after they switch identities. In this case, the memory loss alone could leave them vulnerable and unaware of their involvement in the study. To counter this, clinicians and researchers should treat those with DID

as the vulnerable population they are. The solution could be using several informed consents that should occur not only at the introduction of different identities, but by the provider and/or caretaker of the patient themselves. Since they are not able to advocate for every identity they may have, they may need a provider or caretaker to be aware of the study and provide the consent in addition to obtaining the consent of each identity state to avoid further confusion and distress of the patient themselves.

Overall, our research provided novel findings as well as important suggestions for future directions despite having limitations. More specifically, we provided seven specific regions with decreased cortical thickness and subcortical volume. Our regions fill a gap in research and provide key regions to guide and add to the understanding of suicidality in those with DID, but the work is not done. As those with DID are a group that show a high need for interventions for their high suicide attempt rate (that may be higher upon further analysis), future researchers will need these regions to help guide their research towards the goal of targeting treatments to these regions, and help address the many complications and limitations unique to working with those with DID (diagnostic aversion, cannot rely on self-report, directionality questions, etc). Our model predicted individuals with past suicide attempt based on the seven selected regions with decreased cortical thickness and subcortical volume and the combined knowledge from past research that those with DID are likely to attempt multiple times. However, moving forward, research should focus on whether our regions are caused by first attempt, survivor effects, or method of first attempt, or if we see the same decreased cortical thickness and subcortical volume in those who have yet to attempt. Along with this, having a sample that includes both men and women is essential given men with DID may be even more at risk for completing their suicide attempts. The biomarkers found in our study will provide a great foundation to be built

upon by future researchers, to help address a group in need and the unique complications found while working with them.

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Appendix A

Patient versus. Control			
Cortical Thickness			
Data type	<i>Original</i>	<i>Age Corrected</i>	<i>Scaled</i>
Features used	Left caudal anterior cingulate Left isthmus cingulate Left pars orbitalis Left perical carine Left precuneus Right lateral orbitofrontal Right perical carine Right posterior cingulate Right mean thickness	Left caudal anterior cingulate Left isthmus cingulate Left precentral gyrus Left precuneus Left rostral middle frontal gyrus Right banks of the superior temporal sulcus Right fusiform Right inferior temporal Right lateral orbitofrontal Right middle temporal Right posterior cingulate	Left caudal anterior cingulate Left isthmus cingulate Left precentral gyrus Left precuneus Right inferior temporal Right lateral orbitofrontal Right posterior cingulate
Subcortical Volume			
Data type	<i>Original</i>	<i>Age Corrected</i>	<i>Scaled</i>
Features used	Posterior corpus callosum Mask volume	Left palladium Left ventral DC Left vessel Right hippocampus Right choroid plexus Posterior corpus callosum Mid-anterior corpus callosum Cerebral white matter Mask volume to eTIV	4 th ventricle Left ventral DC Left vessel Right thalamus proper Right caudate Right hippocampus Right ventral DC Right choroid plexus Posterior corpus callosum Mid-anterior corpus callosum Mask volume to eTIV
Both			
Data type	<i>Scaled</i>		
Features used	Left caudal anterior cingulate Left isthmus cingulate Left precuneus Right inferior temporal Right middle temporal Right posterior cingulate Left hippocampus Left vessel Right hippocampus Right ventral DC Posterior corpus callosum		
	Mask volume to eTIV		
DID + DDNOS versus. PTSD + PTSDDS			
Cortical Thickness			
Data type	<i>Original</i>	<i>Age Corrected</i>	<i>Scaled</i>

Features used	Left cuneus Left entorhinal Left inferior temporal Left supramarginal Right caudal anterior cingulate Right inferior temporal Right medial orbitofrontal Right superior parietal	Left entorhinal <i>Left middle temporal</i> Right caudal anterior cingulate Right precentral Right superior parietal	Left entorhinal Left inferior temporal <i>Left middle temporal</i> Right caudal anterior cingulate Right precentral Right superior parietal
Subcortical Volume			
Data type	<i>Original</i>	<i>Age Corrected</i>	<i>Scaled</i>
Features used	Left lateral ventricle Left cerebellum white matter CSF Right choroid plexus Anterior corpus callosum	Left choroid plexus Left cortex volume	CSF Left choroid plexus Right choroid plexus Left cortex volume Cortex volume
Both			
Data type	<i>Scaled</i>		
Features used	Left entorhinal Right precentral gyrus Right superior parietal CSF Left choroid plexus Right lateral ventricle Right choroid plexus Anterior corpus callosum Left cortex volume Supratentorial volume BrainSeg volume to eTIV		
Suicide versus. Non-suicide			
Cortical Thickness			
Data type	<i>Original</i>	<i>Age Corrected</i>	<i>Scaled</i>
Features used	Left cuneus Left isthmus cingulate Left pars orbitalis Left frontal pole Left temporal pole	Left cuneus Left isthmus cingulate Left paracentral gyrus Left pars orbitalis Left temporal pole Right caudal middle frontal	Left isthmus cingulate Left postcentral
Subcortical Volume			
Data type	<i>Original</i>	<i>Age Corrected</i>	<i>Scaled</i>
Features used	Left cerebellum white matter Right hippocampus	Left cerebellum white matter Left thalamus proper Left caudate Left accumbens area Right hippocampus White matter hypointensities Mid-anterior corpus callosum Left surface holes	Left cerebellum white matter Left thalamus proper Left caudate Left accumbens area Right hippocampus
Both			

Data type	<i>Scaled</i>
Features used	Left isthmus cingulate Left pars orbitalis Left temporal pole Left thalamus proper Left accumbens area Right hippocampus Surface holes
