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Neurocircuitry Of Suicidal Behavior In Adolescents And Young Adults With Bipolar And Major Depressive Disorder

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ABSTRACT

NEUROCIRCUITRY OF SUICIDAL BEHAVIOR IN ADOLESCENTS AND YOUNG ADULTS WITH BIPOLAR AND MAJOR DEPRESSIVE DISORDER

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Suicide is one of the leading causes of death in the adolescent and young adult population. Furthermore, it is estimated that for every completed suicide there are many more attempters. The majority of suicide attempters have a mood disorder and neuroimaging research on the neural circuitry of suicidal behavior has primarily focused on these individuals. However, few studies have been designed to compare suicidal behavior across diagnoses. We used diffusion tensor imaging (DTI) to investigate white matter (WM) integrity in Bipolar Disorder (BD) and Major Depressive Disorder (MDD) in adolescents and young adults with a history of suicide attempt. Participants included 21 BD attempters, 18 MDD attempters, 25 BD non-attempters, 17 MDD non-attempters and 43 healthy control (HC) subjects. Analyses were performed to identify similarities and differences in fractional anisotropy (FA) between attempters as compared to non-attempters and HCs. Correlations between FA values and several clinical variables were explored including childhood maltreatment, a risk factor for mood disorders and suicidal behavior. Across all attempters, there was decreased FA in WM in regions of the left and right dorsomedial prefrontal cortex (dmPFC), bilateral ventral anterior commissure/uncinate fasciculus (AC/UF), right anterior cingulate cortex (ACC), and a region within the right putamen. BD attempters showed distinct decreases in WM FA, compared to BD non-attempters, in bilateral uncinate fasciculus (UF), and the right orbitofrontal cortex (OFC). MDD attempters showed decreases in FA in WM within the

dorsolateral prefrontal cortex (dlPFC). Across all BD and MDD subjects, suicidal ideation was negatively correlated with FA values in the left dmPFC, right dmPFC bilateral AC/UF, and right ACC. In addition, across all attempters, physical abuse was positively correlated with values in the left dlPFC These results provide evidence for commonalites in suicide attempters across BD and MDD as well as differences within diagnoses. Commonalities within this age group may provide evidence for shared mechanisms of development of suicidal behavior. Further investigation of the differences may be useful for diagnosis-specific suicide prevention and treatment studies.

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INTRODUCTION

According to the World Health Organization, approximately 800,000 people die from suicide every year, making it the 15th cause of death worldwide.[1] For adolescents and young adults, suicide is the 3rd leading cause of death, taking the lives of more than 5000 adolescents and young adults in the U.S. each year.[2] For every suicide, there are likely to be more than 20 others who have made one or more suicide attempts.[1] According to the High School Youth Risk behavior survey, 12,000 high school students made suicide attempts in 2013.[3] In addition, a prior suicide attempt is the most important predictor of future death by suicide.[4]

Amongst those individuals who attempt suicide, 90% percent have at least one current Axis I major psychiatric disorder, most frequently an affective disorder (45-50%).[5] There is a 4-7% mortality rate due to suicide in individuals with a mood disorder and even greater, 8-15%, in those with a mood disorder who have been hospitalized.[6,7] While the majority of suicides in individuals with mood disorders occur while the individuals are experiencing a major depressive episode,[8] there is also evidence for a high prevalence of mixed (depression plus 3 or more co-occurring intradepressive hypomanic or manic symptoms), and agitated depression among suicide attempters[9] particularly amongst individuals with bipolar disorder (BD). While having a mood disorder is a major risk factor for suicide, the majority of individuals with a mood disorder do not attempt suicide and/or have suicidal behavior. Suicidal behavior often occurs in the setting of other psychosocial and demographic characteristics such as adverse childhood experiences and acute psychosocial stresses.[10] Gender is particularly important in regards to suicide attempts as women are more likely to make attempts and men more likely to complete them.[4,11] This is partially due to the fact that men engage in more lethal means of attempts.[12] In addition, prior to adolescence, the incidence of mood disorders between females and males is approximately the same, then around adolescence the risk of mood disorders, particularly Major Depressive Disorder (MDD), increases in women.[13] By adolescence, females are twice as likely to have considered, planned and attempted suicide as males.[14]

Despite our knowledge of risk factors for suicide, predicting and preventing suicides has been a difficult task. Theories of suicidal behavior have suggested that it is associated with 1) increased sensitivity to social disapproval, 2) reduced cognitive flexibility which includes difficulty believing that there are alternative options to suicide, 3) reduced ability to generate thoughts about positive future events leading to hopelessness, 4) tendency towards impulsive behavior and 5) the sense of insufficient capacity to solve problems.[15,16] These deficits in suicide attempters, have been found to be associated with impairments in the domains of attention[17], memory[18] and executive functioning[19] that are subserved by fronto-temporal circuitry.[16]

Neurobiological studies have offered some insight into the neural mechanisms that may contribute to these cognitive impairments. Early studies examining neurotransmitters in subjects with a history of suicide attempts primarily reported deficits in serotonin transmission.[20] Postmortem studies showed that suicide victims had decreased serotonin in brainstem tissue in comparison to control subjects[21] and serotonin receptor binding abnormalities in the ventral prefrontal cortex (vPFC).[22] In addition, cerebrospinal fluid (CSF) studies of suicide attempters showed lower CSF levels of 5-hydroxyindoleacetic acid compared to controls.[23] Peripheral measures of neurotransmitters do not provide information about the location of brain abnormalities and post-mortem studies are subject to alterations in neurotransmitter concentration that occur postmortem.[24] Neuroimaging techniques, such as functional magnetic resonance imaging (FMRI), positron emission tomography (PET), single photon emission tomography (SPECT) and diffusion tensor imaging (DTI), have also been employed and provide non-invasive or minimally invasive direct structural and functional measurements *in vivo* of the brain.

The following introduction will primarily focus on a comprehensive review of structural neuroimaging literature as it relates to suicidal behavior in adult subjects with a major affective disorder [BD or (MDD)] starting with an overview of the brain circuitry thought to be involved in suicidal behavior. A brief review of functional neuroimaging studies and their contribution to a model of suicidal behavior will also be discussed. As mentioned above, suicide is one of the leading causes of death in adolescents and young adults, it is also the time period when symptoms of many psychiatric disorders can begin to manifest.[25] Despite the importance of understanding suicidal behavior and the connection with mood disorders in this age group, to help identify risk profiles and develop early intervention strategies, few studies have focused on this developmental epoch. Most neuroimaging studies examining suicidal behavior have focused on adults and will therefore make up the majority of this introduction. Studies that have included children and adolescents will also be discussed. Finally, in investigating psychosocial stressors that may contribute to suicidal behavior in this age group, we focused on childhood maltreatment (CM), which can have lasting effects well into adulthood. Neuroimaging studies focusing on CM and how they may contribute to suicidal behavior will also be examined. The main body of the introduction is organized by imaging modality.

While there are many studies that examine structural abnormalities and suicidal behavior in subjects with affective disorders, few studies have been designed to compare structural abnormalities across disorders. After a review of the neuroimaging studies in adolescents, a rationale will be discussed for our current investigation of similarities and differences between WM integrity in adolescents and young adults with BD and MDD who have a history of at least one suicide attempt compared to non-attempter diagnostic controls using DTI.

Neural Circuitry of Suicidal Behavior

Though there are some variability in findings from neuroimaging studies, many of the brain areas reported to be associated with suicidal behavior are thought to be part of the emotion-regulating circuits. These circuits include the prefrontal cortex (PFC), the amygdala-hippocampus complex, the striatum and the extensive connections between these areas.[26] The PFC is responsible for a variety of executive functions and is often further subdivided in the literature into the orbitofrontal cortex (OFC), the ventromedial prefrontal cortex (vmPFC), the anterior cingulate cortex (ACC) and the dorsolateral prefrontal cortex (dlPFC). The OFC is involved in emotional and cognitive processes such as decision-making and the valuation of stimuli.[27] The vmPFC is thought to play a role in decision-making and the processing of fear and risk-taking.[28] Both the vmPFC and the OFC have reciprocal connections with the hypothalamus (central in functions such as sleep and appetite that are altered in mood disorders), ventral striatum (which signals rewards and motivational value) and the amygdala (which is involved in threat detection and fear conditioning and other emotional processes).[29] The ACC is separated into ventral and dorsal subdivisions. The ventral ACC is connected with limbic structures and participates in the regulation of emotional, autonomic and visceral responses.[30] The dorsal ACC is responsible for error monitoring and other complex functions, including processing of information with negative valence.[31,32] The dlPFC has primarily been associated with cognitive and executive functions such as the maintenance and manipulation of items in working memory, goal-directed action, abstract reasoning and attentional control.[33] The dlPFC receives input from sensory cortices and has dense interconnections with premotor areas, frontal eye fields and the lateral parietal cortex, it integrates this information and regulates the activity in other brain regions for adaptive responses.[34] In addition to being associated with suicidal behavior, abnormalities in these regions have been widely reported in subjects with MDD and BD.[35-37] The following sections will discuss studies that give evidence to support the involvement of these regions and others in suicidal behavior in subjects with mood disorders.

Structural Imaging Studies

CT

Structural brain imaging in psychiatric disorders has been used since the 1970's. An important study in 1976 by Johnstone et al. showed that increased ventricular size was related to cognitive impairment in schizophrenia.[38] After this study, neuroanatomical differences and their relationship to emotional or cognitive impairment in other mental disorders were explored. However it was not until 1989 that structural brain imaging was used to examine differences between suicidal and non-suicidal individuals. Schlegel et al. (1989) correlated ventricle-brain-ratio and several rating scales in 44 depressed subjects. In this study, an association between suicidal impulse and ventricular size was not detected.[39]

MRI

Further structural brain imaging has been carried out with MRI. It has provided evidence for both gray and white matter hyperintensities (WMH) and volume reductions in cortical and subcortical regions in adults with a history of at least one suicide attempt.

Gray and White Matter Hyperintensities

Gray and WMH appear as hyperintense signals on T-2 weighted sequences. They are often separated into deep white matter hyperintensities (DMWH) and periventricular hyperintensities (PVH). DMWH are thought to be vascular in etiology representing areas of ischemia.[40] PVH are thought to represent areas of increased water density due to ependymal loss or differing degrees of myelination.[41] Earlier studies of WMH showed associations with older age, hypertension, diabetes, and neurological diseases[42] but also found them to be more prevalent in subjects suffering from MDD[43] and BD[44,45]. The first study to investigate MRI hyperintensities in depressed subjects who had attempted suicide was by Ahearn et al. (2001), in which 20 MDD subjects with a history of suicide attempt and 20 subjects without a history of attempt were scanned. MDD subjects with attempts demonstrated significantly more subcortical gray matter hyperintensities (SCH) and a trend toward increased PVH, compared to subjects without an attempt history. While the authors did not give details as to the location of these hyperintensities, they hypothesize that individuals with MRI hyperintensities are at higher risk for mood disorders and suicide attempts because of disruption of critical neuroanatomical pathways.[46] A similar study was carried out by Ehrlich et al. (2005), comparing 62 psychiatric inpatients with MDD and a history of suicide attempt to 40 subjects with MDD but no attempt history. This study showed significantly increased PVH but not DWMH in the attempter group, as compared to the non-attempter group.[47] These findings were further supported by a study in 2008 by Pompili et al. that included 99 inpatients with a history of major affective disorder (BD type I or type II and MDD); 44% of the participants had made at least one previous suicide attempt. Again subjects with a history of suicide attempts were more likely to have PVH than those without, however there were no significant differences in DWMH. Also in this study, no differences were detected in WMH or PVH between diagnoses, although previous studies had shown a higher frequency of WMH in BD subjects as compared to MDD.[48,49] Taken together, these studies suggest that WMH may be a diagnostic feature of mood disorders, but PVH may be specifically related to suicide behavior. Further localization and understanding of the pathophysiology of these hyperintensities is necessary as they have the potential to serve as a marker of biological vulnerability to suicide.

Gray and White Matter Volume

Unlike the studies of WMH, studies of GM and WM volume have helped target the localization of structural abnormalities associated with suicidal behavior. Volume changes can be quantified by either voxel-based analysis or region-of-interest (ROI) methods. Whole-brain voxel-based analysis is used to investigate widespread or regional changes in GM or WM by spatially normalizing brain images across subjects, and performing statistical tests at each voxel.[50] In contrast, ROI methods, are used for testing anatomically specific hypotheses.[51] One study by Monkul et al. (2007) investigated GM volume in an adult female sample with depression using an ROI approach.[52] The study sample consisted of 7 MDD female subjects with an attempt history, 10 MDD non-attempter females and 17 HC females. Subjects with an attempt history had smaller left and right OFC GM volumes, as compared to HCs, and attempters had larger right amygdala volumes than non-attempters. Wagner et al. (2011) used VBM to study morphometric brain abnormalities in depressed subjects with high risk for suicide compared to those without. The study sample consisted of 15 individuals with MDD who had a high risk for suicidal behavior (personal history of suicide attempt and/or suicide or suicide attempt in first-degree relatives), 15 non-high risk MDD subjects and 30 matched HCs. Individuals with high risk for suicide showed significantly decreased GM density predominantly in ACC and subgenual cortex, caudate, and in contrast to the previous study by Monkul et al., decreased GM bilaterally in the amygdala-hippocampus complex as compared to HCs. Individuals with a high risk for suicidal behavior showed decreased GM in the caudate and rostral ACC, in comparison to low risk individuals.[53] Despite some variability in methods and subject populations, both of these studies provide evidence for disruptions in the fronto-limbic pathways in attempters compared to HCs that may confer vulnerability for suicide.

Gray matter and WM volume changes were investigated in a study of 70 late-onset (older than 50 years of age) depressed patients on a geriatric psychiatry ward with MDD and suicide attempt history. Late-onset depression is of particular interest for providing neuronanatomical insight into suicidal behavior as it has been thought to have a more “biological” etiology (ie.vascular pathology) manifested at the structural level.[54]

There were 27 MDD patients with a history of suicide attempt and 43 MDD without. Compared with their non-suicidal diagnostic controls, the suicidal group had decreased GM and WM volume in the frontal, parietal, insula and temporal cortices, lentiform nucleus, midbrain and cerebellum.[55] This study supports the findings in WMH of widespread cerebral volume reduction in discrete cortical and subcortical structures in suicide attempters.

While most studies of the relationship between suicide behaviors and GM and WM have focused on MDD, there have been a few studies to examine GM and WM in BD subjects. Matsuo et al. (2010) examined the relationship between impulsivity and corpus callosum (CC) area and suicidal behavior in adult females with BD.[56] Impulsivity was chosen because BD subjects with a history of suicide attempts often exhibit high impulsivity[57] and show higher trait impulsivity as compared to HCs.[58] The study included 10 BD female subjects with a history of suicide, 10 BD without and 27 HC females. While there was no significant difference among the three groups in regional CC areas, the BD suicidal subjects showed a significant inverse association between the anterior genu of the CC and total Barratt Impulsiveness scale (BIS) scores, and also in motor and non-planning impulsivity subscores on the BIS. In their previous study, the authors also found that smaller ACC volumes in BD subjects were also related to higher BIS scores.[59] The authors suggest that the anterior medial frontal region may be involved in the pathophysiology of impulsive suicidal behaviors in BD. Another study of BD subjects examined the relationship between lithium treatment and GM volume in depressed inpatients with BD. Fifty-seven individuals were studied in total including 19 with and 38 without a positive history of suicide attempts, 39 were unmedicated and 18 had ongoing lithium treatment. Suicide attempters showed reduced GM volumes in several brain areas including dlPFC, OFC, ACC, superior temporal cortex, parieto-occiptal cortex and basal ganglia. Long-term lithium treatment was associated with increased GM volumes in the same areas where suicide was associated with decreased GM.[60] This is a possible mechanism for the anti-suicide effects of lithium that have been documented in individuals with BD.[61] As seen in studies with MDD subjects, suicidal behavior in BD is also associated with reduced GM in frontal limbic networks.

Despite the heterogeneity of findings, these studies suggest a mechanism by which reduced WM and GM volume in the frontal lobe, striatum and limbic system may impair decision-making and mood regulation, predisposing individuals to attempt suicide.

DTI

Diffusion tensor imaging (DTI) measures diffusion characteristics of water molecules *in vivo* and can be used to identify the direction and integrity of fibers within WM.[62] DTI approaches have been used to map WM pathways in the human brain noninvasively and are now commonly used in clinical applications.[63] DTI data are acquired by measuring the apparent diffusivities in six or more non-collinear directions. The main reported DTI measure is FA, which reflects the directional coherence of water diffusion within WM tracts, their architecture or structural integrity. [64] Measures of diffusion anisotropy, like FA, are small in GM, reflecting nearly isotropic tensors and are much higher and heterogenous in WM.[65] FA in WM is modulated by a range of microstructural factors including myelination, axonal size and density, gliosis neoplasia, edema and inflammation.[51]

One of the first studies to use DTI to examine suicidal behavior included 52 subjects with MDD, 16 with suicide attempts and 36 without, and 52 HCs. A whole-brain voxel analysis was used to compare FA across the 3 groups and analyze the correlation with symptom severity. In addition, an ROI approach was applied to the bilateral hippocampus, thalamus and lentiform nucleus. FA was decreased in the left anterior limb of the internal capsule (ALIC) in suicide attempters, relative to both non-attempters and HC subjects, and in the right lentiform nucleus relative to non-attempters only. There was no significant correlation with symptom severity.[66] This same research group focused on the ALIC in another study where they used structural connectivity analysis and DTI-based determined tractography to characterize WM fiber projections passing through the ALIC and their potential alterations in MDD subjects with a history of suicidal behavior. The percentage of fibers projecting to ROIs was determined by calculating the percentage of fibers projecting to the ROI relative to the total number of fibers passing through the ALIC. The study included 63 individuals with MDD (23 attempters and 40 non-attempters). Both groups of depressed subjects had reduced fiber projections through the ALIC to the left medial frontal cortex (MFC), OFC and thalamus compared to HCs. Those with a history of suicide attempts had greater abnormalities than those without attempts in fibers to the left OFC and thalamus.[67] These two studies give useful insight into suicidal behavior of individuals with MDD. First, the authors identify the ALIC as an area of decreased FA in attempters compared to non-attempters and HCs. The ALIC is a WM tract located between the caudate nucleus medially and the lenticular nucleus laterally.[68] Furthermore the authors clarify the particular target fields of the ALIC to which projections are altered in attempters, these include projections to the left OFC and thalamus. This further supports the theory of frontal system deficits in suicidal behavior. The authors also discuss the role of these particular fiber projections as potential therapeutic targets.

Olvet et al. (2014) examined WM abnormalities with DTI using both an ROI and tract-based spatial statistics approach (TBSS). TBSS is a method designed to address registration issues associated with a whole brain voxel-based analyses by performing a non-linear registration to a WM skeleton that represents the center of the main fiber bundles.[69] DTI scans were acquired in 13 suicide attempters with MDD, 39 non-attempters with MDD and 46 HCs. Using the ROI approach, attempters had lower FA than non-attempters and HCs in the dorsomedial prefrontal cortex (dmPFC). Tract-based spatial statistical results supported significantly lower FA in a region in the right dmPFC in attempters, as compared to non-attempters.[64] Of note, the other ROIs in this study included the ACC and the medial OFC, but these regions were not significantly different between attempters and non-attempters. This is in contrast to previous studies discussed above that reported differences in these areas. These simultaneously distinct but heterogeneous findings may reflect differences in sample populations or represent clinical phenotypes of suicidal behavior that may be specific to certain deficits in particular regions of the brain. In addition, methodological differences may be of importance, TBSS studies for example only perform comparisons on a WM skeleton template that represents the center of the main fiber bundles. However these skeletons tend to be narrow, thus there may be less overlap of clusters within groups.

As most studies on suicide behavior tend to focus on subjects with MDD, there has only been one study that examined DTI and suicidal behavior in BD. In this study the investigators sought to study the relationship between suicidal behavior and impulsivity in BD I. Study subjects consisted of 14 BD attempters, 15 BD non-attempters and 15 HCs. BD subjects with a prior suicide attempt had lower FA within the left OFC region and higher overall impulsivity compared to subjects without a previous suicide attempt. Amongst the attempters, FA in the OFC WM regions was inversely correlated with motor impulsivity.[70] There has been more of a focus on correlating impulsivity and suicidal behavior in BD. This study suggested a relationship between the OFC and motor impulsivity in subjects with BD, with damage to the OFC potentially leading to disruptions in its connection with limbic structures such as the amygdala. As the OFC has also been identified as an area related to suicidal behavior in MDD subjects, impulsivity should also be explored within this group.

Overall, these DTI data extend GM and WM findings discussed above implicating corticostriatal-limbic systems (including WM connections within these systems) in suicide and further support the hypothesis that abnormal projections from frontal regions, particularly the OFC in both BD and MDD, may disrupt affective and cognitive functions to confer a heightened vulnerability for suicidal behavior.

Functional Studies

Functional neuroimaging studies serve as a complement to structural studies by providing insight into regional activity of the brain. Methods for functional imaging of the brain include fMRI, SPECT and PET. These are imaging techniques that are capable of providing measures of regional brain function by measuring estimates of regional brain blood flow or metabolism. SPECT and PET are also capable of quantifying receptor affinity using radioligand binding. Many of the early functional neuroimaging studies were designed to examine brain neurochemicals, primarily the serotonergic system, alterations in which have previously been linked to suicide behavior in both MDD and BD in studies of peripheral measures.[71,72]

PET and SPECT

The involvement of the serotonergic system in the pathophysiology of suicidal behavior has been investigated in PET and SPECT studies focusing on the 5-HT receptors. Studies have shown decreases in 5-HT2A binding potential in the PFC[73], associated with increased hopelessness and harm avoidance.[74] SPECT studies of the serotonin transporter (SERT) have shown no differences in regional levels of SERT binding potentials but have shown negative correlations between SERT binding and impulsivity.[75,76] More recent PET studies however have found decreased SERT binding in the midbrain, pons and putamen in suicide attempters.[77-79] A few studies have also examined dopamine transporter (DAT) in suicidal subjects but found no relationship to dopamine receptor binding potential and suicidal behavior.[75,76]

Other studies have used PET to examine differences in activity in specific regions of the brain that might be related to suicidal behavior. A study of high lethality versus low lethality attempters with MDD showed relative hypometabolism in high lethality attempters in the ventral, medial and lateral PFC. This difference was more pronounced after fenfluramine administration (fenfluramine increases the release of serotonin).[80] A more recent study by this research group examined MDD and BD attempters experiencing a major depressive episode. In comparison to non-attempters, relative hypometabolism was seen in the right dlPFC, which was increased after fenfluramine administration.[81] These studies again highlight the role of the PFC in suicidal behavior and support findings from previous studies implicating a role for 5-HT as a potential mediator of PFC activity in suicidal individuals. Based on their two studies, the authors suggest a model in which hypometabolism in the dlPFC and suicidal behavior increase on a continuum, with low lethality attempters showing greater hypometabolism than non-attempters and high lethality attempters showing greater hypometabolism than low-lethality attempters. No individual study has actually compared these three groups to test this hypothesis. In a retrospective comparative analysis of depressed psychiatric inpatients, suicide victims who had committed suicide 10 days to 3 years following a scan were compared to diagnostic controls who had also received a scan during their inpatient stay. There was lower regional cerebral blood flow in the suicide group, most significantly in the nucleus accumbens and extending into the vmPFC, and into the left and right putamen. While there was variability in the time from scan, this study highlights that deficits in these areas may predict risk for suicide attempts rather than be the result of the suicide attempt.[82]

FMRI Studies

A study examining response to emotional faces in men with MDD who attempted suicide showed greater activity in the right OFC as compared to non-attempters, in response to angry versus neutral faces.[83] Another study by this research group showed that male MDD suicide attempters had poorer performance on a gambling task and decreased activation in left lateral OFC and occipital cortex during risky relative to safe choices.[84] These studies support the role of the OFC in suicidal behavior as discussed in the structural studies above, particularly in its role in decision-making. The lateralization seen in these studies may be related to the nature of the task (face perception vs. numerical calculation). Increased activity in the right OFC in response to angry faces may be a result of the OFC's connection with the amygdala and as the authors hypothesize, may suggest increased sensitivity to other's disapproval, which could contribute to feelings of hopelessness and a higher propensity to act on negative emotions. In the gambling task, decreased left OFC activity represented an inability to assess risky choices, which could also be a marker of cognitive inflexibility, that in the context of depression could lead to someone choosing suicide over other "less risky" options for dealing with their depression.

Dombrovski et al. (2013) studied older adult attempters and reward learning using a reinforcement-learning model. Attempters showed decreases in vmPFC responses to unpredicted rewards, which were associated with impulsivity. [85] These participants tended to perseverate in their approach behavior even when it no longer paid off. Impulsive individuals may be ignoring key information in their environment and experiencing losses as a result. Negative emotions from these losses as well as their impulsivity may translate to suicidal behavior.

Studies in Children and Adolescents

Prevention of early-onset suicide attempt is identified as a mission of the U.S. National Institute of Mental Health. The identification of biomarkers of suicidal behavior in adolescents and young adults would not only help in the development of new methods for early detection, but may provide key inroads into the elucidation of the mechanisms that underlie the development of suicidal behavior in this age group, as well as their future risk in adulthood. Understanding these mechanisms, gives us the potential to target and reverse these pathogenic processes.

In order to understand suicidal behavior in children and adolescents, it is important to keep in mind the process of brain maturation in this age group. At birth, neurons express an excess of synapses, which allows for “plasticity” as the brain acquires new skills[86]. GM thickens throughout childhood as brain cells grow connections to other cells. A surge of connections occurs in early adolescence followed by a “pruning” of inefficient connections to achieve maximum efficiency. Part of this process also involves myelination of WM tracts, which also makes for more efficient connections.[87] In general this maturation process is thought to occur in a caudal to rostral manner, which means that the PFC, responsible for goal and priority setting, impulse control and decision-making, is one of the last regions to develop, with changes occurring into the mid 20’s.[88,89] It is therefore possible that vulnerability to suicidal behavior in adolescence reflects delayed or abnormal prefrontal cortical development, including the WM tracts that connect corticostriatal-limbic systems.

While 50% of lifetime cases of psychiatric disorders begin by age 14 years and 75% have begun by age 24 years,[25] there are substantially fewer neuroimaging studies of suicidal behavior in children and adolescents with mood disorders compared to adults. Similar to their study in adults, Ehrlich et al. (2004) investigated WMH of 153 child and adolescent psychiatry inpatients with varying diagnoses, 43 of who had made suicide attempts. Overall, WMH were not significantly associated with suicide attempts. However within the MDD subgroup, WMH were significantly associated with a higher prevalence of past suicide attempts.[90] A subanalysis of the location of these WMH was completed in a separate study in which DWMH and PVH's were examined in the same subjects. In contrast to studies in adults, DMWH's but not PVH were significantly associated with suicide attempt across all diagnostic groups. In addition DMWH's were only significantly associated with suicide attempts in the right posterior parietal lobe and not frontal lobe.[90,91] The posterior parietal lobe is considered to be critical for spatial cognition, attentional orienting, task switching, and consciousness.[92] It is possible that this area may be more relevant in childhood suicide attempt or alternatively as the frontal lobe is still developing in children and adolescents, it is possible that WMH may not have had time to develop in this region.

An fMRI study by Pan et al. (2011) of depressed adolescents with and without suicide attempts examined the neural circuitry supporting response inhibition in a go-no-go task. Contrary to their hypothesis, non-attempters but not attempters showed a different pattern of neural activity from HCs.[93] In another study by this group, fMRI was used to assess decision-making and learning-related neural activity during the Iowa Gambling Task (IGT). Again non-attempters, but not attempters were differentiated from HCs during the performance of the IGT, with non-attempters showing greater left hippocampal activation than HCs during low-risk decisions).[94] Attempters and HCs deactivated the left hippocampus during this task. Decreased hippocampal activation during low risk tasks may be a marker of improved task performance. Together, these two studies suggest that suicide behavior in adolescence may not be associated with abnormal activity in the neural circuitry underlying response inhibition and probabilistic learning. In their third study, this research group examined responses to emotional faces. They found that in response to angry faces, attempters showed greater activity than non-attempters in the ACC-dlPFC attentional control circuitry.[95] These findings are similar to those seen in the emotional processing study with adults described above[83] and suggest that adolescents attempters may also be sensitive to negative reactions from individuals in their environment. Given that these findings span both adolescence and older adulthood, this may suggest that hypersensitivity to negative reactions may be a mechanism contributing to the development of suicidal behavior that persist into adulthood. Early therapeutic interventions that target this increased sensitivity in adolescence may be helpful in preventing suicidal behavior later in life.

Childhood Maltreatment

Relationship to Suicide Risk

While there are various psychosocial factors that may contribute to suicidal behavior, CM is of particular interest. CM is a severe stressor that produces a cascade of physiological, hormonal, and neurochemical changes that can lead to enduring alterations in brain structure and function.[96,97] It is well-documented that early experiences of physical and sexual abuse are correlates of suicidal behavior in adolescents and adults.[98-100] As CM is also a risk factor for psychopathology[101,102], understanding the relationship between CM, psychiatric disorders and suicide behavior is important. Molnar et al. (2001) used data from the National Comorbidity Survey (n=5877, age range 15-54) to retrospectively examine the association between childhood sexual abuse and suicide attempts. Among those abused as children, odds of suicide attempts were 2-4 times higher in women and 4-11 times higher in men as compared with those who were not abused. These odd ratios were reduced, but were still significantly different, after controlling for psychiatric disorders. This suggests that there is a strong association between childhood sexual abuse and suicidal behavior that may be mediated by psychiatric comorbidity.[103] A prospective study using information from the Netherlands Mental Health Survey (n= 7076, age range 18-64 years) examined the association between childhood adversities and new onset of suicidal ideation over 3 years of longitudinal follow-up. Childhood neglect, psychological abuse and physical abuse were strongly associated with new onset suicidal ideation (odds ratio 2.8-4.6) and suicide attempts (3.6-5.4). The total number of adversities had a graded relationship to new attempts. In support of the findings from the National Comorbidity Survey, these associations remained significant after controlling for the effects of mental disorders.[99] These studies provide evidence for the role of CM as an independent risk factor for suicidal behavior.

Relationship to Brain Structure

As discussed above, adolescence is considered to be a critical neurodevelopmental period and childhood stress can affect maturational changes in both GM and WM organization.[104] Decreased hippocampal volumes have been observed in adolescents and adults reporting early life adversities.[105,106] The hippocampus plays an important role in learning and memory and decreased hippocampal volume has also been associated with MDD in many studies.[107,108] Opel et al. (2014) sought to investigate the disease-related or trait (risk-factor) function of hippocampal atrophy in MDD. Consistent with previous studies, MDD subjects showed reduced hippocampal volume compared to HCs, but hippocampal atrophy was associated with CM in both MDD and HCs.[105] The authors highlight CM as a potentially important confounder in structural studies involving MDD subjects and suggest that hippocampal volume loss may constitute a trait-like risk factor for developing depression later in life.

Studies have also focused on the PFC. Due to its prolonged development, the PFC is thought to be especially sensitive to effects from the environment during childhood and adolescence. One study of children who had been physically abused reported smaller right OFC volumes, compared to HCs. Greater academic difficulties and issues with the child-parent relationship were correlated with lower OFC volumes.[109,110] GM volume was decreased in the medial PFC, dlPFC, and the right ACC in young adults exposed to harsh corporal punishment.[111] While the majority of studies have focused on physical and sexual abuse, some studies have measured other forms of maltreatment including emotional abuse or neglect. Edmiston et al. (2011) found that adolescents with a history of emotional neglect had decreased GM volume in the dlPFC, OFC, striatum, amygdala, hippocampus and cerebellum.[112]

A few DTI studies have emerged examining CM and WM changes. One study by Choi et al. (2009) examined parental verbal abuse and WM tract integrity in young adults. FA was significantly decreased in the arcuate fasciculus in the left superior temporal gyrus, cingulum bundle by the tail of the left hippocampus and the left body of the fornix. FA in those areas was associated with parental verbal abuse scores and levels of maternal abuse.[113] In a recent study, Ugwu et al. (2014) investigated the effects of childhood adversity [defined by threshold cutoffs on the subscales of the Childhood trauma questionnaire (CTQ)] on WM diffusivity in tracts thought to be involved in emotional regulation in adults with MDD and HCs. Contrary to the previous study, in subjects with a history of childhood adversity, FA was greater in the rostral and dorsal cingulum in comparison to HCs. In the uncinate fasciculus (UF), and parahippocampal cingulum, FA was greater in the left hemisphere in the subjects with childhood adversity when compared with those without.[8] Depression did not significantly affect FA values.[8] It is unclear why decreased and increased FA values have been observed in these two studies in overlapping regions. The Ugwu study examined an older population (mean age = 40 years) and did not examine their results by CTQ subscale, therefore it is difficult to know what may be contributing to increased WM integrity.

In sum, the findings in these structural studies of CM converge on the same corticostriatal-limbic pathways that have previously been described in suicidal behavior. As CM has been suggested to be a potential confounder in structural abnormalities in individuals with psychiatric diagnoses, these findings also give evidence for CM as an important factor to be investigated in structural studies of suicidal behavior.

Summary of the Introduction

Suicide continues to be a major public health problem worldwide due to the difficulty in its prediction and prevention and has a particularly high prevalence in individuals with mood disorders. Structural and functional neuroimaging studies are promising tools for understanding the neurobiology of suicidal behavior. These studies have primarily converged on alterations in the PFC particularly in the areas of the OFC, dlPFC, and ACC, as well as the striatum and mesial temporal structures such as the amygdala and hippocampus. Abnormalities in these areas may contribute to dysfunction in emotional regulation and valuation of immediate vs. long-term rewards, which may contribute to impairments in decision-making and impulsivity; when combined with a depressive state, these impairments in decision-making and impulsivity paired with feelings of hopelessness and despair, could lead to suicidal behavior. Suicide is one of the leading causes of death in the adolescent and young adult populations and adolescence is considered to be a critical period in brain maturation. Studies of suicide attempts in children and adolescents, while limited, support findings found in adults. CM is associated with both suicide risk and psychiatric comorbidity, neuroimaging studies of CM show deficits in frontal and limbic regions suggesting a potential mechanism by which childhood maltreatment increases risk for suicidal behavior.

SPECIFIC AIMS

As reviewed above, there is a growing body of literature of structural and functional neuroimaging studies of suicidal behavior. One of the challenges in further elucidating the mechanisms of suicidal behavior is understanding the role of specific psychiatric disorders, particularly mood disorders, in suicide attempters. The majority of studies examining suicidal behavior in mood disorders have focused on MDD with fewer studies of subjects with BD. While there are a few studies that have examined suicidal behavior in subjects with different mood disorders, very few have examined the effects of diagnosis on their findings. Ehrlich et al.'s (2004) study of 153 child and adolescent psychiatry inpatients included subjects with various psychiatric diagnoses (22.9% BD, 31.4% MDD).[90] The authors did not find an association with WMH overall but when they examined the results by diagnosis, WMH were significantly associated with past suicide attempts in the MDD subgroup only. However, only 5% (2) of the BD subjects in the study had made an attempt as compared to 52% (25) of the MDD subjects, therefore the authors did not have the power to detect differences within the BD group. Sublette et al.'s (2013) PET study compared regional cerebral metabolic rates of glucose (rCMRglu) determined by ^{18}F-fluoro-2-deoxyglucose (FDG-PET) in suicide attempters and non-attempters meeting current criteria for major depressive episode in the context of MDD (N=23) or BD (N=6).[81] There was decreased rCMRglu in attempters in the right DLPFC, more pronounced after fenfluramine challenge and increased rCMRglu in vmPFC. Analyses were re-run without the BD subjects and showed the same pattern of low and high rCMRglu clusters observed in the combined sample, which survived to the same p value threshold for voxel intensity $p < .01$ but not voxel extent. The authors did not perform analyses for BD subjects alone because there were too few participants, which makes it unclear whether their results were purely driven by an MDD attempt phenotype or by features common to the two diagnoses. Pompili et al.'s (2008) study of WMH did have the power to detect differences between BD and MDD subjects. Overall, suicide attempters were more likely to have PVH but not DWMH than non-attempters. Comparing within diagnostic group, Pompili et al. observed both BD and MDD attempters were more likely to have PVH than non-attempters. This study did not discriminate by the location of DMWH, so there may be differences by diagnosis in location of DWMH. To our knowledge there has been no other structural imaging study reported that was designed with the intent of comparing suicidal behavior across BD and MDD suicide attempters. This information would be useful to help understand whether the pathogenesis underlying suicidal behavior has diagnosis-specific structural correlates and/or whether there are common areas of the brain that may be disrupted or dysregulated in attempters with mood disorders.

For the current study, we chose to use DTI as our imaging modality as it is a promising approach for investigating WM pathways in neuropsychiatry. While early studies focused on GM, recent converging evidence has increasingly implicated WM alterations in a number of psychiatric disorders.[114] Furthermore, as the majority of studies on suicidal behavior have suggested abnormalities in multiple regions, DTI has the advantage of being able to examine connections between these systems. Subjects were limited to adolescents and young adults (ages 14-25 years) because of the relative lack of studies focusing on suicidal behavior in this age group and because this developmental period has been linked to dynamic maturations in PFC, deficits in which have been linked to suicidal behavior as described above.[90,95] From a prevention standpoint, there is evidence that young suicide attempters have persistent negative health and social outcomes including substance dependence, additional suicide attempts, engagement in violent crimes, and unemployment.[115] Understanding and preventing early suicidal behavior may also help us to prevent these negative sequelae. To our knowledge, there have been no published DTI studies on suicide behavior or ideation in adolescents.

As reviewed above, it is well-documented that early experiences of physical and sexual abuse are correlates of suicidal behavior in adolescents and adults[99,100] and a history of CM may also constitute elevated risk for the development of mood disorders.[116] As adolescence is considered to be a critical neurodevelopmental period, childhood stress can affect maturational changes in PFC, that occur during adolescence, helping to regulate subcortical structures.[117] While there have been several studies examining the role of CM on WM integrity,[8,113,116] no study has examined the relationship between CM, suicidal behavior, psychiatric comorbidity and WM.

This objective of this study was to examine the differences in FA between adolescents/young adults with MDD and BD with and without a history of suicide attempt. As CM has previously been found to have an effect on structural abnormalities in mood disorders, the association of CM and FA in adolescents/young adults with suicide attempts was investigated. Based on the review of the above literature, it was hypothesized that MDD and BD suicide attempters would have decreased FA in the PFC, and in its connections to striatum and mesial temporal regions, compared to non-attempters. Similarities and differences in WM integrity associated with suicide attempts between BD and MDD were explored. We further hypothesized that the severity of CM would be negatively correlated with FA in the WM regions associated with suicide attempts. A whole brain voxel-based approach was used in order to detect group differences in regions that were not hypothesized a priori.

METHODS

Subjects

The sample in the study was comprised of 46 adolescents/young adults with BD, 35 with MDD and 43 HC adolescents/young adults. Our sample primarily consisted of female subjects due to a small number of male MDD attempters and our other groups were matched for gender accordingly. In this study, suicide attempts were specifically defined as a self-injurious act committed with at least some intent to die.[118] The attempt group included 21 participants with BD (BDatt) (mean age 20.3 ± 2.97, 86% female) and 18 participants with MDD (MDDatt) (mean age 18.7 ± 3.11, 83% female). The non-attempt group included 25 participants with BD (BDnatt) (mean age 20.2 ± 3.43, 84% female) and 17 participants with MDD (MDDnatt) (mean age 18.5 ± 2.29, 88% female) (Table 1). Participants were recruited from the medical centers of Yale School of Medicine and the surrounding communities. The subjects included in this study were scanned between December 2, 2009 and August 9, 2014. Diagnoses, the presence of rapid cycling (for BD participants) and mood states at scanning were determined by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID)[119] version 2.0 for participants ≥ 18 and The Schedule for Affective Disorders and Schizophrenia for School Aged Children- Present and Lifetime Version, (KSADS-PL)[120] for participants < 18 years of age. The HC group was compromised of 32 participants (mean age 20.3 ± 3.76, 84% female) without a personal history of a DSM-IV Axis I Disorder or a first-degree relative with a major mood, psychotic, anxiety or substance use disorder assessed by the Family History Screen for Epidemiologic Studies[121]. Additional exclusion criteria for all subjects included loss of consciousness for 5 or more minutes, history of neurological diseases, major medical disorders that could affect central nervous system functioning or contraindication to MR scanning.

While there is some evidence from functional neuroimaging studies of acute mood state related features,[122] less information is known about how acute mood state affects WM integrity.[123] For comparability between the two diagnoses, BD subjects with mania or hypomania at the time of scan were excluded from the study. BD participants with mixed mood states were included because of the depressive component of this state and evidence from the previous studies showing that mixed mood states are strongly correlated with suicidal behavior.[9] Among the BD subjects, 17%(8) were experiencing a mixed episode, 26%(12) a depressive episode and 57%(26) were euthymic. Among the MDD subjects, 23%(8) were experiencing a depressive episode and 77%(27) were euthymic. The majority (89%) of BD participants had Bipolar I disorder.

The participants also received comprehensive assessments, including the Beck Hopelessness Index (BHI), Brown Goodwin Aggression scale, Barratt Impulsiveness Scale (BIS), Childhood Trauma Questionnaire (CTQ), Hamilton Rating Scale for Depression (HAM-D) (participants ≥ 18) and Children's Depression Rating Scale (CDRS) (participants < 18). The Beck Scale for Suicidal Ideation[124] assessed degree of current and most severe suicide ideation. For attempters, lifetime history of suicide attempts was evaluated using the Columbia Suicide History Form[125] and medical lethality of the most severe and most recent attempt was measured by the Beck Medical Lethality Scale.[126]

Comorbidities

Substance use history was obtained from all subjects. Previous studies have shown that approximately 20-50% of individuals with mood disorders have comorbid substance abuse/dependence disorders.[127,128] Substance abuse and dependence have been shown in many studies to have an effect on the brain.[129,130] In order to balance the ability to generalize results of the study with minimizing confounds of current abuse or dependence, participants with substance abuse less than 6 months and substance dependence less than one year were excluded from the study, with the exception of nicotine dependence, which compared to other substance comorbidities in this population, has a particularly high prevalence (50-65%).[131,132] Those participants with a lifetime history of substance abuse or dependence included alcohol dependence [5%(1) BDatt, 6%(1) MDDatt], alcohol abuse [10%(2) BDatt, 12%(3) BDnatt, 6%(1) MDDnatt], cocaine dependence [8% BDnatt], cocaine abuse [5%(1) BDatt], cannabis dependence [10%(2) BDatt, 8%(2)BDnatt, 6%(1) MDDnatt] cannabis abuse [10%(2) BDatt, 4%(1) BDnatt], and polysubstance dependence [6%(1) MDDatt, 4%(1) BDnatt]. Table 1 provides further information including the mean duration of time since participants met criteria for abuse or dependence.

Current comorbid diagnoses included generalized anxiety disorder (GAD) [11% (2) MDDatt, 8%(2) MDDnatt, 6%(1) BDnatt], social phobia [5% (1) MDDatt, 6%(1) BDatt, 12%(3) MDDnatt], specific phobia [6%(1) MDDatt, 4%(1) BDnatt], agoraphobia [4%(1) BDnatt], post-traumatic stress disorder (PTSD) [5%(1) BDatt, 11%(2) MDDatt, 8%(2) BDnatt, 6%(1)MDDnatt], attention deficit hyperactivity disorder (ADHD) [14%(3) BDatt, 17%(3) MDDatt, 4%(1)BDnatt], oppositional defiant disorder [5%(1)

BDatt], impulse Disorder NOS [6%(1) MDDnatt], anorexia [6%(1) MDDatt, 6%(1)MDDnatt], binge eating disorder [6%(1) BDatt], and bulimia [4%(1) BDnatt].

Medication

Within the attempt group, 33% (13) were unmedicated at the time of scanning [38% (8) BD, 28% (5) MDD], and 52% (22) of non-attempters were unmedicated at the time of scanning [44% (11) BD, 65% (11) MDD]. Psychotropic medications prescribed to the other subjects included lithium carbonate [14% (3) BDatt, 12%(3) BDnatt], anticonvulsants [33% (7) BDatt, 17% (3) MDDatt, 24%(6) BDnatt], antipsychotics [29%(6) BDatt, 33%(6) MDDatt, 44%(11) BDnatt, 12%(2) MDDnatt], antidepressants [19%(4) BDatt, 67%(12) MDDatt, 16%(4) BDnatt, 24%(4) MDDnatt], stimulants [24%(5) BDatt, 17%(3) MDDatt, 16%(4)BDnatt , 6%(1) MDDnatt,], benzodiazepines [14%(3) BDatt, 6%(1) MDDatt, 12%(3)BDnatt], clonidine [11%(2) MDDatt, 8%(2) BDnatt] and naltrexone [5%(1) BDatt, 6%(1)MDDnatt].

Institutional Review

This research was approved by the Yale Human Investigation Committee (HIC), the Institutional Review Board of the Yale School of Medicine, and was performed in accordance with the Helsinki Declaration of 1975. Prior to participation, all subjects 18 years and older provided written informed consent. Participants under the age of 18 provided written assent and their parents/guardians provided written permission.

DTI Data Acquisition

DTI data acquisition was performed on a 3-Tesla Siemens Trio MR scanner (Siemens, Erlangen, Germany) with diffusion sensitizing gradients applied along 32 noncolinear directions with b-value=1000 sec/mm^2, together with an acquisition without diffusion weighting (b-value=0; TR=7400ms, TE=115 ms, matrix=128 x 128, FOV= 256 mm x 256 mm and 40 three-mm slices without gap).

DTI Data Processing

Diffusion-weighted data were first interpolated to 1.5-mm isotropic voxels and then denoised by a three-dimensional isotropic Gaussian kernel with Sigma 2 mm full-width-at-half-maximum (FWHM) Gaussian kernel. Diffusion eigenvectors, and corresponding eigenvalues (λ1, λ 2, λ 3) were acquired after diagonalization of the DTI data. FA was then calculated according to the methodology of Basser et al. (1996). Whole brain FA maps were normalized with Statistical Parametric Mapping 5 (SPM5) (http://www.fil.ion.ucl.ac.uk/spm) to the standard MNI space using a tissue probability map of WM as a template. The FA maps were resampled to 2 mm x 2 mm x 2 mm during the normalization. Furthermore, each FA map was spatially smoothed by a 10-mm FWHM. Brain regions were identified using the Atlas of Human Brain Connections.[133]

Statistics

Comparisons of demographic and clinical variables were evaluated using SPSS (SPSS Inc., Chicago, Illinois, USA, version 22) with independent t-tests for continuous variables and chi-square tests for categorical variables. Differences for all demographic and clinical scales except for the number of attempts and lethality were examined between attempters and non-attempters overall and between BD and MDD diagnostic groups overall. For variables related to attempts (number of attempts, highest and most recent lethality), comparisons were made between BD and MDD attempters. In examining both similarities and differences between attempters, the study was focused primarily on the hypothesized fronto-temporal regions. Areas outside of these regions were only examined if they survived an AlphaSim correction (cluster size 1387) for $p<.05$.

In order to assess similarities and differences between attempters and nonattempters with MDD or BD, a 2x2 factorial model was created within SPM8, with suicide behavior (att, natt) and diagnosis (MDD, BD) as factors. Images for the four groups (MDD att, BD att, MDD natt, BD natt) were entered into the second-level random-effects model. To assess similarities in attempters vs. non-attempters across diagnostic groups, we used the main effect of attempt from our 2x2 model in an analysis of variance (ANOVA) with age as a covariate. Results were considered significant at $p<0.05$ and 20 voxels. While this was not a very high threshold, this is the first work of its kind and can serve as a preliminary analysis for future studies. FA values were extracted from significant clusters showing a main effect of attempt status and examined in SPSS to determine directionality of change in the attempter group (using independent t-tests, considered significant at $p<0.05$). The values were additionally compared to those in the HCs in order to determine the direction from health and to assess for significant differences (with independent t-tests, considered significant at $p<0.05$).

To assess distinctions of attempt status between diagnostic groups, we looked at the suicide behavior x diagnosis interaction of our 2x2 model with age as a covariate. Results were considered significant at $p<0.05$ and 20 voxels. FA values were extracted from significant clusters in the interaction model of the ANOVA and comparisons between groups (MDatt, versus MDnatt, BDatt versus BDnatt, BDatt versus HC, and MDDatt versus HC) were examined using independent t-tests in SPSS. Exploratory analyses were also performed to assess the effect of demographic and clinical variables that were found to be significantly different between diagnoses or between attempters and non-attempters overall. This included mood state, history of psychosis, ADHD, lithium, anticonvulsant and antidepressant use. Independent t-tests between those with and those without the previous variables were examined at the significant clusters. Findings were considered significant at $p<0.05$.

Correlations between FA values and clinical, behavioral and risk variables (Brown Goodwin, BIS scales, CTQ scores) were examined with Pearson's correlations and Spearman's rho for non-normally distributed variables (HAM-D, CDRS, Suicidal Ideation) looking within all diagnostic subjects (attempters and non-attempters) and attempters alone. For variables describing attempts (number of attempts, lethality) Spearman's rho was used to assess relationship with FA values within all attempters. Correlations were considered significant at $p<0.05$.

Division of Labor

The medical student author of this study performed the literature review and wrote this paper. The subjects included in the study were recruited, interviewed, and scanned by other members of Dr. Blumberg's laboratory team. The medical student performed comprehensive reviews of all subject charts, determined the inclusion and exclusion criteria, and selected the subjects from the lab's database for inclusion in the study. The student also performed a comprehensive review of all clinical features of each subject and organized these into a database for analyses. The student inspected scan quality and organized the computer files containing the image data for the relevant subjects. Members of Dr. Blumberg's laboratory performed pre-processing of imaging data. The analyses of the results in this paper were performed independently by the student.

RESULTS

Demographic and Clinical measures

Demographic data are presented in Table 1. There were no significant differences in age or gender between attempters and non-attempters ($p > .05$). The overall BD group was significantly older than the MDD group ($p = .02$). There were no significant differences in mood state between attempters and non-attempters or between diagnoses with the exclusion of the mixed mood state, which was only found in BD participants. Only BD subjects had a history of psychosis, with no significant difference between BD attempters and BD non-attempters ($p > .05$). Of the comorbidities examined, ADHD was significantly more prevalent in attempters compared to non-attempters ($p < .05$). There were no significant differences in the percentage of subjects who were medicated between attempters and non-attempters or between diagnoses. There was a significant difference between BD and MDD subjects overall in lithium ($p < .001$), anticonvulsant ($p < .05$) and antidepressant use ($p < .05$). BD subjects had greater lithium and anticonvulsant use and MDD subjects had greater antidepressant use.

Clinical data are presented in Table 2. Among suicide attempters (BD vs. MDD), there was no significant difference in the number of attempts, lethality of the most recent attempt and highest lethality between diagnoses. Suicidal ideation for current and most severe ideation was greater in attempters than non-attempters, ($p < .001$) but did not differ between diagnostic groups. Attempters had more feelings of hopelessness than non-attempters, ($p = .03$) but there were no differences in hopelessness between diagnoses. Overall, compared to MDD subjects, BD subjects had significantly higher cognitive-attentional subscale and total impulsivity scores of the BIS scale, ($p = .02$ and $p = .03$)

respectively. For CTQ, attempters had higher total CTQ scores than non-attempters (p=.05) but there were no differences between diagnoses. There were no differences between attempters and non-attempters or between diagnoses on any of the CTQ subscales.

Table 1. Demographic Characteristics of Subjects by Attempt Status
Data are presented as percentages (# of subjects) unless otherwise stated

	Suicide Attempters			Non- Attempters		
	BD (N=21)	MDD (N = 18)	**BD+MDD (N=39)**	BD (N = 25)	MDD (N = 17)	**BD+MDD (N=42)**
Demographics						
Mean Age (STDev)[A]	20.3 (2.97)	18.7 (3.1)	**19.6 (3.1)**	20.2 (3.4)	18.5 (2.3)	**19.5 (3.1)**
Age range	14- 25	14-25	**14-25**	14 – 25	14 – 22	**14 – 25**
Female	86% (18)	83% (15)	**85% (33)**	84% (21)	88% (15)	**86% (36)**
Diagnosis						
BD1	86% (18)	N/A		92% (23)	N/A	
BD2	14% (3)	N/A		8% (2)	N/A	
Mood State at Scan						
Euthymic	43% (9)	72% (13)	**56% (22)**	68% (17)	82% (14)	**74% (31)**
Depressed	29% (6)	28% (5)	**28% (11)**	24% (6)	18% (3)	**21% (9)**
Mixed[B]	29% (6)	0% (0)	**15% (6)**	8% (2)	0% (0)	**5% (2)**
Substance Use Disorder History (includes mean years prior to scan since subjects met criteria)						
Alcohol Dependence	5% (1) 1.2yr	6% (1) 1.5yr	**5% (2) 1.4yr**	0% (0)	0% (0)	**0% (0)**
Alcohol Abuse	10% (2) 2yr	0% (0)	**5% (2) 2yr**	12% (3) 1.9yr	6% (1) 4yr	**8% (3)**
Cocaine Dependence	0% (0)	0% (0)	**0% (0)**	8% (2) 2.7yr	0% (0)	**5% (2)**
Cocaine Abuse	5% (1) 4yr	0% (0)	**3% (1) 4yr**	0% (0)	0% (0)	**0% (0)**
Cannabis Dependence	10% (2) 5yr	0% (0)	**5% (2) 5yr**	8% (2) 0.75yr	6% (1) 3yr	**6% (2)**
Cannabis Abuse	10% (2) 2.8yr	0% (0)	**5% (2) 2.8yr**	4% (1) 2yr	0% (0)	**0% (0)**
Heroin Dependence	0% (0)	0% (0)	**0% (0)**	4% (1) 1.5 yr	0% (0)	**3% (1)**
Polysubstance Dependence	0% (0)	6% (1) 1.5yr	**3% (1) 1.5yr**	4% (1) 4yr	0% (0)	**6% (2)**
Nicotine Use (Current)	67% (14)	33% (6)	**51% (20)**	40% (10)	12% (2)	**25% (9)**
Current Comorbidities						
ADHD[D]	14% (3)	17% (3)	**15% (6)**	4% (1)	0% (0)	**3% (1)**
Anorexia	0% (0)	6% (1)	**3% (1)**	0%(0)	6% (1)	**3% (1)**
Agoraphobia	0% (0)	0% (0)	**0% (0)**	4% (1)	0% (0)	**3% (1)**
Binge Eating Disorder	5% (1)	0% (0)	**3% (1)**	0% (0)	0% (0)	**0% (0)**
Bulimia	0% (0)	0% (0)	**0% (0)**	4% (1)	0% (0)	**3% (1)**
GAD	0% (0)	11% (2)	**5% (2)**	8% (2)	6% (1)	**8% (3)**
Impulse Disorder NOS	0% (0)	0% (0)	**0% (0)**	0% (0)	6% (1)	**3% (1)**
ODD	5% (1)	0% (0)	**3% (1)**	0% (0)	0% (0)	**0% (0)**
PTSD	5% (1)	11% (2)	**8% (3)**	8% (2)	6% (1)	**8% (3)**
Social Phobia	5% (1)	6% (1)	**5% (2)**	12% (3)	0% (0)	**8% (3)**
Specific Phobia	0% (0)	6% (1)	**3% (1)**	4% (1)	0% (0)	**3% (1)**
Hx of Psychosis[C]	43% (9)	0% (0)	**23% (9)**	32% (8)	0% (0)	**19% (8)**

Medications						
Unmedicated	38% (8)	28% (5)	**33% (13)**	44% (11)	65% (11)	**52% (22)**
Anticonvulsants[A]	33% (7)	17% (3)	**26% (10)**	24% (6)	0% (0)	**14% (5)**
Antipsychotics	29% (6)	33% (6)	**31% (12)**	44% (11)	12% (2)	**33% (12)**
Antidepressants[A]	19% (4)	67% (12)	**41% (16)**	16% (4)	24% (4)	**22% (8)**
Benzodiazepines	14% (3)	6% (1)	**10% (4)**	12% (3)	0% (0)	**6% (2)**
Clonidine	0% (0)	11% (2)	**5% (2)**	8% (2)	0% (0)	**6% (2)**
Lithium[C]	14% (3)	0% (0)	**8% (3)**	12% (3)	0% (0)	**8% (3)**
Naltrexone	5% (1)	0% (0)	**3% (1)**	0% (0)	6% (1)	**0% (0)**
Stimulants	24% (5)	17% (3)	**21% (8)**	16% (4)	6% (1)	**14% (5)**

A-Statistically significant between diagnoses, p< .05 B- Statistically significant between diagnoses p<.01, C--Statistically significant between diagnoses, p< .001 D- Statistically significant between attempters and non-attempters p<.05. ADHD- Attention Deficit Hyperactivity Disorder, GAD- Generalized Anxiety Disorder, ODD- Oppositional Defiant Disorder,

Table 2. Suicide Information and Clinical Variables by Attempt Status

Data are presented as means (standard deviation)

	Suicide Attempters			Non- Attempters		
Characteristic (scale range)	BD (N=21)	MDD (N = 18)	**BD+MDD (N=39)**	BD (N = 25)	MDD (N = 17)	**BD+MDD (N=42)**
Attempt Info						
# Of attempts	1.9 (1.3)	2.1 (1.6)	**2.0 (1.4)**	-	-	-
Highest Lethality (0-10)	2.4 (1.8)	2.5 (2.0)	**2.5 (1.9)**	-	-	-
Most Recent Attempt Lethality (0-10)	2.3 (1.7)	2.2 (2.0)	**2.3 (1.8)**	-	-	-
Depression Scale						
HAM-D Total (0-23)	8.7 (11.1)	6.6 (8.7)	**8.0 (10.2)**	6.4 (9.0)	4.0 (8.9)	**5.5 (8.9)**
CDRS (17-113)	25.0 (11.2)	31.4 (13.0)	**29.4 (12.5)**	32.2 (17.6)	20.6 (11.2)	**26.1 (15.4)**
Suicide Ideation-Most Recent[B] (0-38)	5.8 (9.3)	7.6 (9.6)	**6.6 (9.4)**	0.4 (1.8)	0.4 (1.6)	**0.4 (1.7)**
Suicide Ideation-Most Severe[B] (0-38)	17.3 (9.3)	18.8 (8.9)	**18.3 (9.0)**	5.8 (8.2)	2.9 (5.6)	**4.6 (7.3)**
BHI Total[A] (0-20)	7.2 (5.8)	8.5 (7.0)	**7.8 (6.3)**	5.6 (4.4)	3.9 (3.6)	**4.9 (4.1)**
Brown Goodwin (0-160)	17.2 (5.6)	16.4 (4.7)	**16.8 (5.1)**	15.7 (6.8)	14.1 (4.7)	**15.1 (6.0)**
BIS Non-Planning (11-55)	27.6 (5.5)	27.9 (4.4)	**27.7 (4.9)**	28.4 (5.7)	24.9 (5.5)	**27.0 (5.8)**
BIS Motor (11-55)	25.4 (5.3)	22.0 (3.7)	**23.6 (4.8)**	21.7 (3.9)	22.3 (5.2)	**21.9 (4.4)**
BIS Cognitive-Attentional[C] (8-40)	20.5 (4.5)	17.9 (3.5)	**19.2 (4.1)**	19.2 (4.4)	16.8 (4.3)	**18.2 (4.5)**
BIS Total[C] (30-150)	73.6 (13.8)	66.1 (8.4)	**69.7 (11.8)**	69.3 (10.6)	63.9 (12.3)	**67.1 (11.5)**
Childhood Trauma						
CTQ emotional abuse (5-25)	13.8 (6.3)	11.4 (3.4)	**12.6 (5.2)**	9.9 (4.5)	9.6 (4.6)	**9.7 (4.4)**
CTQ physical abuse (5-25)	8.3 (5.1)	6.1 (2.7)	**7.2 (4.2)**	6.8 (3.4)	6.0 (1.4)	**6.5 (2.7)**
CTQ sexual abuse (5-25)	9.5 (7.3)	9.3 (7.4)	**9.4 (7.2)**	7.6 (6.0)	5.5 (1.9)	**6.6 (4.7)**
CTQ emotional neglect (5-25)	13.6 (6.2)	11.2 (4.0)	**12.4 (5.3)**	11.1 (4.9)	10.0 (3.7)	**10.6 (4.4)**
CTQ physical neglect (5-25)	8.8 (5.3)	6.7 (2.2)	**7.7 (4.1)**	7.0 (2.9)	7.3 (2.5)	**7.1 (2.7)**
Total CTQ score[A] **(25-125)**	53.9 (28.1)	44.5 (13.0)	**49.2 (22.1)**	42.3 (17.5)	38.4 (8.4)	**40.5 (14.1)**

A-Statistically significant between att and natt group, *p*< .05, B- Statistically significant between att and natt group, *p*<.001, C- Statistically significant between diagnoses, *p*<.05

Regions of Common Decreases in Association with Suicide Attempts Across BD and MDD Groups

A significant main effect of attempt was observed in several fronto-temporal clusters (p<.05) (Fig.1), revealing significant decreases in FA in attempters compared to non-attempters. These clusters encompassed regions of left dmPFC, right dmPFC, bilateral regions that encompassed the anterior commissure (AC) and UF, as well as the right ACC and the putamen. None of the significant clusters outside of the hypothesized regions survived AlphaSim correction. Table 3 includes MNI coordinates, means and cluster sizes for significant clusters. Of these regions, the left AC/UF and the right ACC were also significantly decreased in attempters compared to HCs.

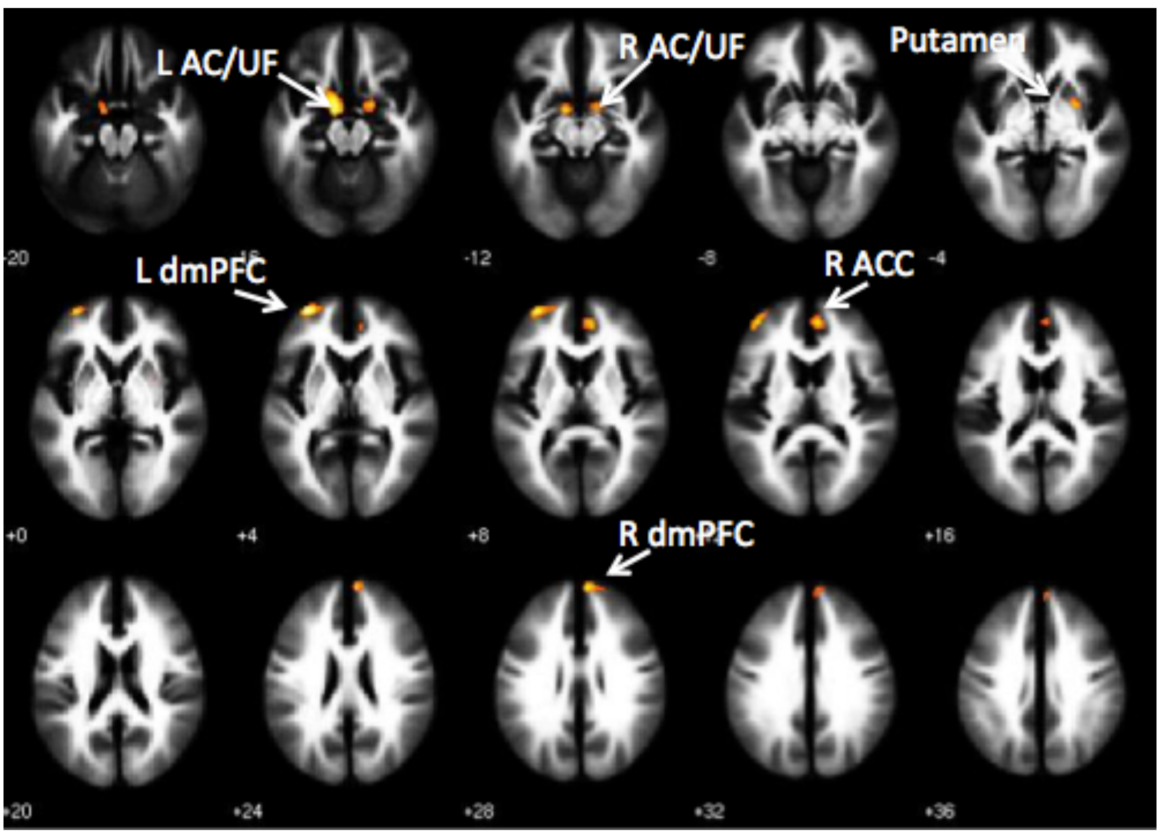

Fig. 1. The axial-oblique images display the hypothesized regions showing a main effect of attempt at a threshold of p<.05 and extent of 20 voxels. The numbers in the lower left

corner are the Montreal Neurological Institute Atlas Coordinates for the z plane in mm. The right side of the images show the right side of the brain.

Table 3. Coordinates, cluster size and FA (mean ± stdev) for significant clusters in the main effect of attempt model

	X	Y	Z	Size	Att (N= 39)	Natt (N= 42)	HC (N= 43)	Att vs. Natt *P**	Att vs. HC *P**
L dmPFC	-32	56	4	213	.069±.008	.076±.010	.074±.012	0.004	0.09
L AC/UF	-10	0	-16	184	.073±.013	.080±.010	.079±.012	0.01	0.03
R AC/UF	16	0	-14	102	.077±.013	.084±.011	.083±.015	0.02	0.09
R dmPFC	8	58	26	90	.060±.008	.064±.008	.064±.008	0.02	0.13
R ACC	8	48	10	54	.075±.009	.081±.013	.081±.009	0.02	0.02
R Putamen	28	4	-2	26	.174±.017	.164±.019	.172±.020	0.02	0.57

**P*-values calculated using independent t-tests in SPSS.

Regions of Decrease in Association with Suicide Attempts Specific to BD or MDD

The analysis revealed a significant interaction between attempt status and diagnostic group across several fronto-temporal regions including bilateral UF, right OFC, and dlPFC (Fig.2). None of the significant clusters outside of the hypothesized regions survived the AlphaSim correction. Post-hoc analyses described below examined which diagnosis these clusters corresponded to.

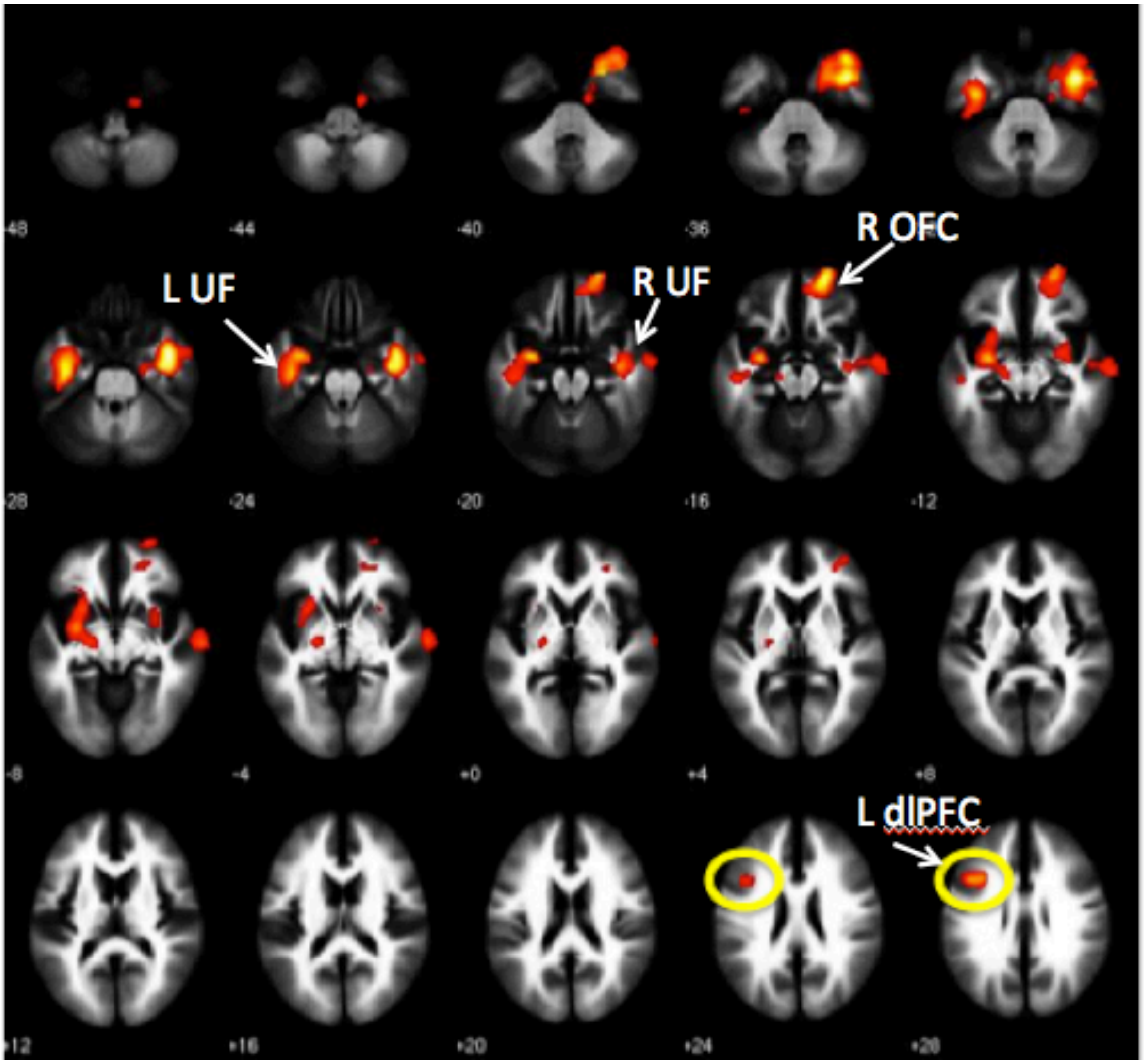

Fig. 2. The axial-oblique images display the significant clusters in hypothesized regions for the interaction model (attempt x diagnosis) at a threshold of p<.05 and extent of 20 voxels. Regions of significantly decreased FA in MDDatt group compared to the MDDnatt group are circled in yellow, all other regions had significantly decreased FA in the BDatt group compared to the BDnatt group. The numbers in the lower left corner are the Montreal Neurological Institute Atlas Coordinates for the z plane in mm. The right side of the images show the right side of the brain.

Regions of Decreased FA in Association with Suicide Attempts Specific to BD

The BDatt group had decreased FA compared to the BDnonatt group in the left and right UF, and right OFC (Fig.3). The right OFC was significantly different between attempters and HCs. Table 4 includes MNI coordinates, means and cluster sizes for the significant clusters.

Table 4. Coordinates, cluster size and FA (mean±stdev) for regions of significantly decreased FA in BD attempters compared to BD non-attempters in the interaction model

	X	Y	Z	Size	BDatt (N= 21)	BDNatt (N= 25)	HC (N= 43)	BDatt vs. BDnatt *P*	BDatt vs. HC *P*
L UF	-38	-12	-30	1910	.127±.015	.139±.015	.131±.022	0.01	0.47
R UF	40	2	-32	2739	.072±.007	.079±.007	.075±.014	0.002	0.41
R OFC	22	58	-16	724	.068±.011	.078±.012	.075±.013	0.006	0.04

**P*-values calculated using independent t-tests in SPSS.

Regions of Decreased FA in Association with Suicide Attempts Specific to MDD

The MDDatt group had decreased FA compared to the MDDnatt group in the left dlPFC (Fig.2). This region was also significantly decreased in MDD attempters as compared to HCs. Table 5 includes MNI coordinates, means and cluster sizes for the significant cluster.

Table 5. Coordinates, cluster size and FA (mean±stdev) for regions of significantly decreased FA in MDD attempters compared to MDD non-attempters in the interaction model

	X	Y	Z	Size	MDDAtt (N=18)	MDDNatt (N=17)	HC (N= 43)	MDDatt vs. MDDnatt *P**	MDDatt vs. HC *P**
L dlPFC	-36	14	30	358	.110±.013	.132±.025	.127±.017	0.004	<.001

**P*-values calculated using independent t-tests in SPSS.

Associations with Clinical Correlations

Exploratory analyses for potential effects of clinical factors did not reveal significant effects of a history of psychosis, mood state, ADHD comorbidity, lithium, anticonvulsant or antidepressant use in any of the significantly different clusters described above.

Across all BD and MDD subjects, FA values for the most severe suicidal ideation was negatively correlated with the left AC (r = -0.30, p =.008, n= 77), right AC (r = -0.23, p =.05, n= 77), right ACC (r = -0.272, p =.02, n= 77), and right dmPFC (r = -0.24, p =.04, n= 77).

CTQ scores

Across all BD and MDD subjects, total or subscale CTQ scores did not correlate significantly with any of the significant clusters. Across all attempters, physical abuse was positively correlated with FA values in the left dlPFC (r =.04, p= .03, n= 34).

DISCUSSION

This study is the first conducted to explicitly compare differences in WM integrity using DTI in suicide attempters versus non-attempters across BD and MDD diagnostic groups. The main findings from this study are that suicide attempters, across diagnoses, displayed decreased FA in comparison to non-attempters primarily in frontal-temporal regions, including the dmPFC, ACC, bilateral AC/UF as well as one region in the striatum. Differences in association with attempts were also found that were distinct to the disorders, particularly in their ventral relative to dorsal locations. Bipolar disorder attempters compared to BD non-attempters had decreases in WM integrity primarily in ventral regions including bilateral UF and OFC. MDD attempters had decreased FA in the dlPFC.

White Matter Differences Common to BD and MDD Attempters

Bipolar and MDD attempters demonstrated decreased FA as compared to non-attempters in fronto-temporal regions. The frontal regions included a portion of the left and right dmPFC and the right ACC. Of these three regions, only the right ACC was also decreased in attempters compared to HCs. Our findings are in line with several of the studies mentioned above that implicate dorsal prefrontal regions in suicidal behavior.[66] In particular, Olvet et al.'s (2014) DTI study also showed decreases in FA in the right dmPFC in an adult population of MDD attempters relative to non-attempters. Decreased activity in this area has also been reported in functional studies of adults in high lethality compared to low lethality attempters[80] and in attempters compared to non-attempters in response to angry faces.[83] This area may be relevant to suicidal behavior in adolescents and young adults as well.

The dmPFC is implicated in response inhibition,[134] memory and social cognitive functions and is an important part of the Default mode network (DMN).[135] The DMN is a network of brain regions that are most active when the brain is at rest. The DMN deactivates when the brain is directed towards a task or goal. The DMN consists of the medial PFC, anterior MFC, vmPFC, PCC, medial temporal and inferior parietal cortices and the temporo-parietal junction. While the function of the DMN is unclear, it is thought to be active when individuals are engaged in internally focused tasks including autobiographic memory retrieval, envisioning the future, self-referential processing and conceiving the perspectives of others.[136] The role of the dmPFC in the DMN is hypothesized to be related to its function in self-referential processing. The dmPFC is activated by many task situations that require participants to make self-referential judgments (ie. how likely they themselves would agree with opinion questions that focused on mental characteristics) [137] and engage in self-referential mental exploration such as envisioning oneself in the past or future.[138,139] The dmPFC has also been implicated in inferring the mental states of other people. Disruptions in connections between the dmPFC and other regions in this network could result in suicide attempters making negative judgments of themselves and inaccurately perceiving negative judgments by others, making them more prone to suicidal behaviors. Further investigation of the DMN as it relates to suicidal behavior is warranted.

As discussed above, the ACC has also been found to be associated with suicidal behavior. However, most structural studies in adults have focused on GM volume or cortical thickness in this area.[53,60,140] As the ACC serves as a bridge between limbic structures and the frontal lobe, abnormalities in this area may contribute to emotional dysregulation and vulnerability to suicidal behavior.

The ventral regions that were decreased across all attempters as compared to non-attempters included bilateral fronto-temporal regions that included portions of the AC and the UF. The AC is a WM tract that connects the temporal lobes and amygdala of both hemispheres. The size of the AC has been postulated to play a role in emotional intelligence and social sensitivity.[141] The AC has not previously been implicated in studies of suicidal behavior. However, one study by Saxena et al. (2012) reported decreased FA in the AC of youth (7-17) with BD and the AC was also negatively correlated with a lifetime history of aggression in these subjects.[142] As this was not a tract-based study, further work would need to be done to evaluate the potential role of the AC in suicidal behavior. A portion of the UF was also encompassed in this region, the significance of this tract will be discussed in the following section about distinct regions in BD attempters.

Finally, a small region within the striatum near the putamen was also decreased in attempters. The striatum is involved in cognition and reward studies and has been associated with decreased GM volume in suicide attempters.[55,85] The striatum connects with cortical and limbic regions via the basal ganglia-thalamocortical circuits. The circuit receives corticalstriate inputs that are processed in the thalamus and from there sent back to a single cortical area.[143] Projections from the amygdala modify serve to modify the transfer of information through this circuit. Abnormalities in this region may lead to short-sighted, immediate-reward decisions and promote impulsive suicidal acts in a depressive state.[144]

White Matter Differences Specific to BD Attempters

BD attempters demonstrated decreased FA compared to non-attempters primarily in ventral fronto-temporal regions including the bilateral UF and OFC. The UF is a WM tract that connects the OFC to the anterior temporal lobes through a direct, bidirectional pathway.[145] The UF is a tract with prolonged maturation and does not reach its developmental peak until the 3rd decade, which may make it more susceptible to insults related to psychiatric illness particularly in adolescents and young adults.[146,147] Functions of the UF are still being elucidated but traditionally it is considered a part of the limbic system. Recent hypotheses about the UF suggests that its function lies at the intersection of memory and social-emotional processes. It allows for temporal-lobe based mnemonic associations (e.g. the combination of a person's name, face, voice, and feelings about them) to modify behavior by interacting with systems in the lateral OFC, important for making associations between stimuli and rewards, and ultimately decision making. [145] While there have been no DTI findings reporting on the UF as it relates to suicidal behavior, there have been several studies looking at the UF in BD. Reduced FA has been found in the UF in adult BD subjects as compared to HCs in two studies,[148-150] although one study showed increased FA in adult subjects with BD[148]. This could suggest that altered WM integrity in UF might be a feature of the disorder. However in our study, we did not find any differences in FA between BD attempters and HCs suggesting that decreased FA in the UF may also distinguish attempters and non-attempters.

We also found decreases in FA in BD attempters within the right OFC, an area involved in emotional and cognitive processes, such as decision-making and valuation of actions and stimuli. As discussed previously, the OFC has been linked to suicidal behavior in both structural and functional neuroimaging studies.[15] The one DTI study to examine suicidal behavior in BD subjects found decreased FA in the left OFC in attempters as compared to non-attempters. This region also was also negatively correlated with impulsivity in attempters.[70] Impulsivity has been demonstrated to be a feature of bipolar phenomenology[57] However, in our study we did not see a correlation between the right OFC and impulsivity.

White Matter Findings Specific to MDD Attempters

MDD attempters demonstrated decreased FA compared to non-attempters and HCs in left dlPFC. As described in the introduction, the dlPFC has been implicated in suicidal behavior particularly in a fronto-cingulo-striatal network. Our findings support reports in the literature showing dlPFC deficits in suicidal behavior including decreased cortical thickness in MDD attempters compared non-attempters,[140] and decreased rCBF in attempters as compared to non-attempters.[80] This is also the first the study to report dlPFC deficits in adolescent and young adults with suicide attempts. This finding has potential clinical relevance, as the dlPFC has been a target of repetitive transcranial magnetic stimulation (rTMS). A study of 8 adolescents with treatment resistant MDD administered rTMS 5 days per week for 6-8 weeks in the left DLPFC and showed improvement in CDRS scores as well as suicidal ideation.[151] Thus the dlPFC may be a potential treatment target for individuals with MDD with a history of suicidal behavior or high risk for suicide.

Correlations with Clinical Variables

In this study across all BD and MDD subjects (attempters and non-attempters), suicidal ideation was negatively correlated with FA values in the left and right AC, right

ACC, and right dmPFC (regions that showed decreased FA in attempters compared to non-attempters). Suicidal ideation is important for understanding the development of risk for attempts. Of note, these findings were not seen when we examined correlations within attempters only, therefore it is possible that the correlation was driven by the non-attempter group. Currently there are no studies that have examined WM integrity in non-attempters with suicidal ideation and mood disorders. However there have been studies with epileptic[152] and traumatic brain injury[153] subjects that have showed alterations in WM in those with suicidal ideation as compared to those without. As prevention of suicide attempts is particularly important in this age group, structural markers that could help us predict which ideators will go on to actually complete attempts would be useful.

Childhood Maltreatment

Since CM has been shown to be a risk factor for both mood disorders and suicidal behavior, we investigated the role of childhood maltreatment, its relationship to WM changes and suicidal behavior in attempters. In our study, across all BD and MDD subjects, CTQ scores were not correlated with any of the significant clusters. However, across all attempters, physical abuse was positively correlated with FA values in the left dlPFC.

Contrary to our hypothesis, CM was associated with increased not decreased FA in the dlPFC in attempters. As this is the first study examining CM, WM integrity and suicidal behavior in MDD and BD, replication of these findings is necessary. Our findings of increased FA are supported by a recent DTI study of childhood adversity and WM integrity in adult MDD subjects which reported FA increases in the rostral cingulum, dorsal cingulum, left UF and left fronto-occipital cortex. Childhood adversity was defined using CTQ scores but results were not examined by type of childhood adversity.[8] It is possible that specific types of abuse may have differential impacts on WM integrity, some increasing or decreasing WM integrity. Differences in findings, and heterogeneity observed within this sample, could also be related to timing and duration of maltreatment, information that is not assessed by the CTQ but could be useful to examine in future studies.

Limitations

This study has several limitations. We had fewer MDD subjects than BD subjects and only 18 MDD suicide attempters as compared to 21 BD attempters. With a larger sample size, we may have had the power to detect other differences. In addition we had very few males in our groups due to the smaller number of male MDD attempters. It is possible that there are gender effects related to structural integrity and suicide attempt but we did not have the power to examine this association, which may impact the generalizability of these findings. The mean lethality scores of our attempters were in the lower range of the scale (mean = 2.5, scale range 0-10) with the highest lethality among attempters being 6. This may also be related to the fact that our attempters were predominantly female, it would be useful to examine whether these findings are also seen in high lethality attempters. While we tried to match BD and MDD diagnostic groups as closely as possible, we did include BD subjects with a mixed mood state even though this mood state is not represented in our MDD group, however in our analyses, we did not see an effect of mood state on our significant regions. A large proportion of our subjects were medicated at the time of scan, however we did not see any significant effects of medication status (medicated vs. unmedicated) on FA values or any effects by medication classes that were significantly different between groups. Of all the medications prescribed to the subjects, lithium is the one with one with the most evidence that it can be protective against suicide.[154] As only 6 (3 att, 3 natt) of our participants were taking lithium, we did not have the power to test whether there were any WM changes related to lithium use. In addition, we had varying time ranges from the most recent suicide attempt and the DTI scan. Ideally it would be optimal to acquire DTI scans in a time period as proximal to the event as possible to determine whether changes in WM integrity are predispositions to suicidal behavior or a result of the actual suicide attempt. In addition, we used a whole-brain approach to our study, and the identified WM tracts are approximations, a tract-based approach would help to confirm these findings. Finally our investigation of CM and its relationship to suicidal behavior was limited by the fact that many of our CTQ subscales had low scores. A study with a population chosen for history of CM may reveal more robust findings.

Conclusions and Future Directions

This is the first to study to examine structural integrity of WM tracts and their association with suicide attempts in adolescents/young adults with BD and MDD. Our results are in support of the adult literature showing decreased WM integrity in fronto-temporal circuitry, particularly the dmPFC across suicide attempters. Within diagnostic groups, we have evidence for decreased WM in ventral frontal regions for BD attempters, particularly within the bilateral UF and right OFC. As the UF connects the OFC with limbic structures in the temporal lobe, suicide behavior in adolescents/young adults with

BD may be related to dysfunction in this particular circuitry. In MDD attempters we also saw decreased WM integrity in the dlPFC. DlPFC deficits have been reported in studies of adults with suicidal behavior and depression. Decreases in depression severity have been seen when this area is targeted by rTMS in studies of children and adolescents. It will be important examine other imaging modalities such as functional connectivity to examine the connections between these areas and further characterize the similarities and differences associated with suicide behavior between diagnostic groups. Our study is also specific to adolescents and young adults, it would be useful to see if these differences persist into later adulthood as some of the changes we saw could be developmentally specific. We did find evidence for a relationship between physical abuse and the left UF in attempters. CM, especially as it relates to suicidal behavior in the adolescent/young adult age group, should continue to be a focus of studies, as growing evidence reveals it to be a potential mediator of the development of psychopathology and suicidal behavior. More robust findings may be revealed in other imaging modalities or in studies that specifically recruit participants with a history of CM.

Overall this study provides evidence for common and distinct areas of decreased WM integrity in adolescent/young adult MDD and BD suicide attempters. While some of these regions have previously been identified in the adult literature as being related to suicidal behavior, we also identified other regions including the UF and AC that had not been previously described. Future studies are needed to clarify these differences and identify potential clinical phenotypes, if they exist. Furthermore this study suggests that studies of suicidal behavior with subjects of varying diagnoses should control for diagnosis in their analyses, as combining subjects with different mood states could confound results. Finally, prevention and treatment studies in this age group can benefit from understanding both the commonalities and differences across diagnoses. As we begin to conceptualize MDD and BD on a spectrum of mood dysregulation, understanding commonalities in suicidal behavior may be particularly important for adolescent and young adults, where diagnoses may still be unclear. Understanding differences between diagnoses can also help us to make more targeted treatments.

REFERENCES

1. World Health Organization. Preventing suicide: A global imperative. 2014.
2. Web-based Injury and Statistics Query and Reporting System (WISQARS). 2011. (Accessed July 21st, 2014, at http://www.cdc.gov/injury/wisqars/leading_causes_death.html.)
3. Eaton DK, Kann L, Kinchen S, et al. Youth risk behavior surveillance-United States, 2011. Morbidity and mortality weekly report Surveillance summaries (Washington, DC: 2002) 2012;61:1-162.
4. Crosby A, Gfroerer J, Han B, Ortega L, Parks SE. Suicidal thoughts and behaviors among adults aged>_18 Years--United States, 2008-2009: US Department of Health and Human Services, Centers for Disease Control and Prevention; 2011.
5. Arsenault-Lapierre G, Kim C, Turecki G. Psychiatric diagnoses in 3275 suicides: a meta-analysis. BMC psychiatry 2004;4:37.
6. Bostwick JM, Pankratz VS. Affective disorders and suicide risk: a reexamination. American Journal of Psychiatry 2000;157:1925-32.
7. Nordentoft M, Mortensen PB, Pedersen CB. Absolute risk of suicide after first hospital contact in mental disorder. Archives of general psychiatry 2011;68:1058-64.
8. Ugwu ID, Amico F, Carballedo A, Fagan AJ, Frodl T. Childhood adversity, depression, age and gender effects on white matter microstructure: a DTI study. Brain Structure and Function 2014:1-13.
9. Balázs J, Benazzi F, Rihmer Z, Rihmer A, Akiskal KK, Akiskal HS. The close link between suicide attempts and mixed (bipolar) depression: implications for suicide prevention. Journal of affective disorders 2006;91:133-8.
10. Rihmer Z. Suicide risk in mood disorders. Current Opinion in Psychiatry 2007;20:17-22.
11. Mościcki EK. Gender differences in completed and attempted suicides. Annals of Epidemiology 1994;4:152-8.
12. Nock MK, Kessler RC. Prevalence of and risk factors for suicide attempts versus suicide gestures: analysis of the National Comorbidity Survey. Journal of abnormal psychology 2006;115:616.
13. Nolen-Hoeksema S, Girgus JS. The emergence of gender differences in depression during adolescence. Psychological bulletin 1994;115:424.
14. Center for Disease Control and Prevention. Percentage of U.S. High School Students Reporting Considering, Planning, or Attempting Suicide in the Past 12 Months, by Sex, United States, 2009. 2009.
15. Van Heeringen C, Bijttebier S, Godfrin K. Suicidal brains: a review of functional and structural brain studies in association with suicidal behaviour. Neuroscience & Biobehavioral Reviews 2011;35:688-98.
16. Desmyter S, Van Heeringen C, Audenaert K. Structural and functional neuroimaging studies of the suicidal brain. Progress in Neuro-Psychopharmacology and Biological Psychiatry 2011;35:796-808.
17. Keilp JG, Sackeim HA, Brodsky BS, Oquendo MA, Malone KM, Mann JJ. Neuropsychological Dysfunction in Depressed Suicide Attempters. American Journal of Psychiatry 2001;158:735-41.

18. Sidley GL, Whitaker K, Calam RM, Wells A. The relationship between problem-solving and autobiographical memory in parasuicide patients. Behavioural and Cognitive Psychotherapy 1997;25:195-202.
19. Williams J, Pollock L. Psychological aspects of the suicidal process. Understanding suicidal behaviour 2001:76-93.
20. Maris RW. Suicide. Lancet 2002;360:319-26.
21. Lloyd KG, Farley IJ, Deck J, Hornykiewicz O. Serotonin and 5-hydroxyindoleacetic acid in discrete areas of the brainstem of suicide victims and control patients. Advances in biochemical psychopharmacology 1973;11:387-97.
22. Arango V, Underwood MD, Mann JJ. Postmortem Findings in Suicide Victims. Implications for in Vivo Imaging Studiesa. Annals of the New York Academy of Sciences 1997;836:269-87.
23. Åsberg M, Träskman L. Studies of CSF 5-HIAA in depression and suicidal behaviour. Serotonin: Springer; 1981:739-52.
24. Palmer A, Lowe S, Francis P, Bowen D. Are post-mortem biochemical studies of human brain worthwhile? Biochemical Society transactions 1988;16:472-5.
25. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the national comorbidity survey replication. Archives of General Psychiatry 2005;62:593-602.
26. Soares JC, Mann JJ. The anatomy of mood disorders—review of structural neuroimaging studies. Biological psychiatry 1997;41:86-106.
27. Salzman CD, Fusi S. Emotion, Cognition, and Mental State Representation in Amygdala and Prefrontal Cortex. Annual Review of Neuroscience 2010;33:173-202.
28. Koenigs M, Grafman J. The functional neuroanatomy of depression: Distinct roles for ventromedial and dorsolateral prefrontal cortex. Behavioural Brain Research 2009;201:239-43.
29. Öngür D, Price JL. The Organization of Networks within the Orbital and Medial Prefrontal Cortex of Rats, Monkeys and Humans. Cerebral Cortex 2000;10:206-19.
30. Alexopoulos GS, Gunning-Dixon FM, Latoussakis V, Kanellopoulos D, Murphy CF. Anterior cingulate dysfunction in geriatric depression. International Journal of Geriatric Psychiatry 2008;23:347-55.
31. Kennerley SW, Walton ME, Behrens TEJ, Buckley MJ, Rushworth MFS. Optimal decision making and the anterior cingulate cortex. Nat Neurosci 2006;9:940-7.
32. Phan KL, Liberzon I, Welsh RC, Britton JC, Taylor SF. Habituation of rostral anterior cingulate cortex to repeated emotionally salient pictures. Neuropsychopharmacology 2003.
33. Miller EK, Cohen JD. An Integrative Theory of Prefrontal Cortex Function. Annual Review of Neuroscience 2001;24:167-202.
34. Barbas H. Connections underlying the synthesis of cognition, memory, and emotion in primate prefrontal cortices. Brain Research Bulletin 2000;52:319-30.
35. Arnone D, McIntosh AM, Ebmeier KP, Munafò MR, Anderson IM. Magnetic resonance imaging studies in unipolar depression: Systematic review and meta-regression analyses. European Neuropsychopharmacology 2012;22:1-16.
36. Groenewold NA, Opmeer EM, de Jonge P, Aleman A, Costafreda SG. Emotional valence modulates brain functional abnormalities in depression: Evidence from a meta-analysis of fMRI studies. Neuroscience & Biobehavioral Reviews 2013;37:152-63.

37. Blond BN, Fredericks CA, Blumberg HP. Functional neuroanatomy of bipolar disorder: structure, function, and connectivity in an amygdala–anterior paralimbic neural system. Bipolar disorders 2012;14:340-55.

38. Johnstone E, Frith C, Crow T, Husband J, Kreel L. Cerebral ventricular size and cognitive impairment in chronic schizophrenia. The Lancet 1976;308:924-6.

39. Schlegel S, Maier W, Philipp M, et al. Computed tomography in depression: Association between ventricular size and psychopathology. Psychiatry research 1989;29:221-30.

40. Thomas AJ, O'Brien JT, Davis S, et al. Ischemic basis for deep white matter hyperintensities in major depression: A neuropathological study. Archives of General Psychiatry 2002;59:785-92.

41. Thomas AJ, Perry R, Barber R, Kalaria RN, O'Brien JT. Pathologies and Pathological Mechanisms for White Matter Hyperintensities in Depression. Annals of the New York Academy of Sciences 2002;977:333-9.

42. Steffens DC, Krishnan K. Structural neuroimaging and mood disorders: recent findings, implications for classification, and future directions. Biological psychiatry 1998;43:705-12.

43. Coffey C, Wilkinson WE, Weiner RD, et al. Quantitative cerebral anatomy in depression: A controlled magnetic resonance imaging study. Archives of General Psychiatry 1993;50:7-16.

44. Ahearn EP, Steffens DC, Cassidy F, et al. Familial Leukoencephalopathy in Bipolar Disorder. American Journal of Psychiatry 1998;155:1605-7.

45. Swayze VW, Ii, Andreasen NC, Alliger RJ, Ehrhardt JC, Yuh WC. Structural brain abnormalities in bipolar affective disorder: Ventricular enlargement and focal signal hyperintensities. Archives of General Psychiatry 1990;47:1054-9.

46. Ahearn EP, Jamison KR, Steffens DC, et al. MRI correlates of suicide attempt history in unipolar depression. Biological psychiatry 2001;50:266-70.

47. Ehrlich S, Breeze JL, Hesdorffer DC, et al. White matter hyperintensities and their association with suicidality in depressed young adults. Journal of affective disorders 2005;86:281-7.

48. Videbech P. MRI findings in patients with affective disorder: a meta-analysis. Acta Psychiatrica Scandinavica 1997;96:157-68.

49. Dupont RM, Butters N, Schafer K, Wilson T, Hesselink J, Gillin JC. Diagnostic specificity of focal white matter abnormalities in bipolar and unipolar mood disorder. Biological Psychiatry 1995;38:482-6.

50. Bandettini PA. What's new in neuroimaging methods? Annals of the New York Academy of Sciences 2009;1156:260-93.

51. Lee JE, Chung MK, Lazar M, et al. A study of diffusion tensor imaging by tissue-specific, smoothing-compensated voxel-based analysis. Neuroimage 2009;44:870-83.

52. Monkul E, Hatch JP, Nicoletti MA, et al. Fronto-limbic brain structures in suicidal and non-suicidal female patients with major depressive disorder. Molecular psychiatry 2006;12:360-6.

53. Wagner G, Koch K, Schachtzabel C, Schultz CC, Sauer H, Schlösser RG. Structural brain alterations in patients with major depressive disorder and high risk for suicide: evidence for a distinct neurobiological entity? Neuroimage 2011;54:1607-14.

54. Van den Berg MD, Oldehinkel AJ, Bouhuys AL, Brilman EI, Beekman AT, Ormel J. Depression in later life: three etiologically different subgroups. Journal of Affective Disorders 2001;65:19-26.
55. Hwang J-P, Lee T-W, Tsai S-J, et al. Cortical and subcortical abnormalities in late-onset depression with history of suicide attempts investigated with MRI and voxel-based morphometry. Journal of geriatric psychiatry and neurology 2010.
56. Matsuo K, Nielsen N, Nicoletti MA, et al. Anterior genu corpus callosum and impulsivity in suicidal patients with bipolar disorder. Neuroscience letters 2010;469:75-80.
57. Swann AC, Dougherty DM, Pazzaglia PJ, Pham M, Steinberg JL, Moeller FG. Increased impulsivity associated with severity of suicide attempt history in patients with bipolar disorder. American Journal of Psychiatry 2005;162:1680-7.
58. Swann AC, Lijffijt M, Lane SD, Steinberg JL, Moeller FG. Increased trait ‐ like impulsivity and course of illness in bipolar disorder. Bipolar disorders 2009;11:280-8.
59. Matsuo K, Nicoletti M, Nemoto K, et al. A voxel-based morphometry study of frontal gray matter correlates of impulsivity. Human Brain Mapping 2009;30:1188-95.
60. Benedetti F, Radaelli D, Poletti S, et al. Opposite effects of suicidality and lithium on gray matter volumes in bipolar depression. Journal of affective disorders 2011;135:139-47.
61. Goodwin FK, Fireman B, Simon GE, Hunkeler EM, Lee J, Revicki D. Suicide risk in bipolar disorder during treatment with lithium and divalproex. Jama 2003;290:1467-73.
62. Taylor WD, Hsu E, Krishnan K, MacFall JR. Diffusion tensor imaging: background, potential, and utility in psychiatric research. Biological psychiatry 2004;55:201-7.
63. Yamada K, Sakai K, Akazawa K, Yuen S, Nishimura T. MR tractography: a review of its clinical applications. Magnetic Resonance in Medical Sciences 2009;8:165-74.
64. Olvet DM, Peruzzo D, Thapa-Chhetry B, et al. A diffusion tensor imaging study of suicide attempters. Journal of psychiatric research 2014;51:60-7.
65. Alexander AL, Lee JE, Lazar M, Field AS. Diffusion tensor imaging of the brain. Neurotherapeutics 2007;4:316-29.
66. Jia Z, Huang X, Wu Q, et al. High-field magnetic resonance imaging of suicidality in patients with major depressive disorder. American journal of psychiatry 2010;167:1381-90.
67. Jia Z, Wang Y, Huang X, et al. Impaired frontothalamic circuitry in suicidal patients with depression revealed by diffusion tensor imaging at 3.0 T. Journal of psychiatry & neuroscience: JPN 2014;39:170.
68. Chowdhury F, Haque M, Sarkar M, Ara S, Islam M. White fiber dissection of brain; the internal capsule: a cadaveric study. Turkish neurosurgery 2010;20:314-22.
69. Smith SM, Jenkinson M, Johansen-Berg H, et al. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. Neuroimage 2006;31:1487-505.
70. Mahon K, Burdick KE, Wu J, Ardekani BA, Szeszko PR. Relationship between suicidality and impulsivity in bipolar I disorder: a diffusion tensor imaging study. Bipolar disorders 2012;14:80-9.

71. Sun Y, Zhang L, Johnston NL, Torrey EF, Yolken RH. Serial analysis of gene expression in the frontal cortex of patients with bipolar disorder. The British Journal of Psychiatry 2001;178:s137-s41.
72. Heils A, Teufel A, Petri S, et al. Allelic variation of human serotonin transporter gene expression. Journal of neurochemistry 1996;66:2621-4.
73. Audenaert K, Van Laere K, Dumont F, et al. Decreased frontal serotonin 5-HT2A receptor binding index in deliberate self-harm patients. European journal of nuclear medicine 2001;28:175-82.
74. Van Heeringen C, Audenaert K, Van Laere K, et al. Prefrontal 5-HT2a subreceptor binding index, hopelessness and personality characteristics in attempted suicide. Journal of affective disorders 2003;74:149-58.
75. Lindström MB, Ryding E, Bosson P, Ahnlide J-A, Rosén I, Träskman-Bendz L. Impulsivity related to brain serotonin transporter binding capacity in suicide attempters. European Neuropsychopharmacology 2004;14:295-300.
76. Ryding E, Ahnlide J-A, Lindström M, Rosén I, Träskman-Bendz L. Regional brain serotonin and dopamine transporter binding capacity in suicide attempters relate to impulsiveness and mental energy. Psychiatry Research: Neuroimaging 2006;148:195-203.
77. Nye JA, Purselle D, Plisson C, et al. Decreased Brainstem and Putamen SERT Binding Potential in Depressed Suicide Attempters Using [11C] ‐ ZIENT PET Imaging. Depression and anxiety 2013;30:902-7.
78. Miller JM, Hesselgrave N, Ogden RT, et al. Positron emission tomography quantification of serotonin transporter in suicide attempters with major depressive disorder. Biological psychiatry 2013;74:287-95.
79. Cannon DM, Ichise M, Fromm SJ, et al. Serotonin Transporter Binding in Bipolar Disorder Assessed using [11C] DASB and Positron Emission Tomography. Biological psychiatry 2006;60:207-17.
80. Oquendo MA, Placidi GP, Malone KM, et al. Positron emission tomography of regional brain metabolic responses to a serotonergic challenge and lethality of suicide attempts in major depression. Archives of General Psychiatry 2003;60:14-22.
81. Sublette ME, Milak MS, Galfalvy HC, Oquendo MA, Malone KM, Mann JJ. Regional brain glucose uptake distinguishes suicide attempters from non-attempters in major depression. Archives of Suicide Research 2013;17:434-47.
82. Amen D, Prunella J, Fallon J, Amen B, Hanks C. A comparative analysis of completed suicide using high resolution brain SPECT imaging. The Journal of neuropsychiatry and clinical neurosciences 2009;21:430-9.
83. Jollant F, Lawrence N, Giampietro V, et al. Orbitofrontal cortex response to angry faces in men with histories of suicide attempts. American Journal of Psychiatry 2008;165:740-8.
84. Jollant F, Lawrence NS, Olie E, et al. Decreased activation of lateral orbitofrontal cortex during risky choices under uncertainty is associated with disadvantageous decision-making and suicidal behavior. Neuroimage 2010;51:1275-81.
85. Dombrovski AY, Szanto K, Clark L, Reynolds CF, Siegle GJ. Reward signals, attempted suicide, and impulsivity in late-life depression. JAMA psychiatry 2013;70:1020-30.

86. Rakic P, Bourgeois J-P, Eckenhoff MF, Zecevic N, Goldman-Rakic PS. Concurrent overproduction of synapses in diverse regions of the primate cerebral cortex. Science 1986;232:232-5.
87. Yakovlev PI, Lecours A-R. The myelogenetic cycles of regional maturation of the brain. Regional development of the brain in early life 1967:3-70.
88. Weinberger DR, Elvevag B, Giedd JN. The adolescent brain: a work in progress. 2005.
89. Sowell ER, Peterson BS, Thompson PM, Welcome SE, Henkenius AL, Toga AW. Mapping cortical change across the human life span. Nature neuroscience 2003;6:309-15.
90. Ehrlich S, Noam GG, Lyoo IK, Kwon BJ, Clark MA, Renshaw PF. White matter hyperintensities and their associations with suicidality in psychiatrically hospitalized children and adolescents. Journal of the American Academy of Child & Adolescent Psychiatry 2004;43:770-6.
91. Ehrlich S, Noam GG, Lyoo IK, Kwon BJ, Clark MA, Renshaw PF. Subanalysis of the location of white matter hyperintensities and their association with suicidality in children and youth. Annals of the New York Academy of Sciences 2003;1008:265-8.
92. Taylor JG. The central role of the parietal lobes in consciousness. Consciousness and cognition 2001;10:379-417.
93. Pan LA, Batezati-Alves SC, Almeida JR, et al. Dissociable patterns of neural activity during response inhibition in depressed adolescents with and without suicidal behavior. Journal of the American Academy of Child & Adolescent Psychiatry 2011;50:602-11. e3.
94. Pan L, Segreti A, Almeida J, et al. Preserved hippocampal function during learning in the context of risk in adolescent suicide attempt. Psychiatry Research: Neuroimaging 2013;211:112-8.
95. Pan L, Hassel S, Segreti A, Nau S, Brent D, Phillips M. Differential patterns of activity and functional connectivity in emotion processing neural circuitry to angry and happy faces in adolescents with and without suicide attempt. Psychological medicine 2013;43:2129-42.
96. Teicher MH, Tomoda A, Andersen SL. Neurobiological consequences of early stress and childhood maltreatment: are results from human and animal studies comparable? Annals of the New York Academy of Sciences 2006;1071:313-23.
97. Hart H, Rubia K. Neuroimaging of child abuse: a critical review. Frontiers in human neuroscience 2012;6.
98. Dube SR, Anda RF, Felitti VJ, Chapman DP, Williamson DF, Giles WH. Childhood abuse, household dysfunction, and the risk of attempted suicide throughout the life span: findings from the Adverse Childhood Experiences Study. Jama 2001;286:3089-96.
99. Enns MW, Cox BJ, Afifi TO, De Graaf R, ten Have M, Sareen J. Childhood adversities and risk for suicidal ideation and attempts: a longitudinal population-based study. Psychological medicine 2006;36:1769-78.
100. Brodsky BS, Stanley B. Adverse childhood experiences and suicidal behavior. Psychiatric Clinics of North America 2008;31:223-35.

101. Green JG, McLaughlin KA, Berglund PA, et al. Childhood adversities and adult psychiatric disorders in the national comorbidity survey replication I: associations with first onset of DSM-IV disorders. Archives of general psychiatry 2010;67:113-23.
102. Scott KM, Smith DR, Ellis PM. Prospectively ascertained child maltreatment and its association with DSM-IV mental disorders in young adults. Archives of general psychiatry 2010;67:712-9.
103. Molnar BE, Berkman L, Buka SL. Psychopathology, childhood sexual abuse and other childhood adversities: relative links to subsequent suicidal behaviour in the US. Psychological medicine 2001;31:965-77.
104. de Graaf-Peters VB, Hadders-Algra M. Ontogeny of the human central nervous system: what is happening when? Early human development 2006;82:257-66.
105. Opel N, Redlich R, Zwanzger P, et al. Hippocampal Atrophy in Major Depression: a Function of Childhood Maltreatment Rather than Diagnosis? Neuropsychopharmacology 2014;39:2723-31.
106. Rao U, Chen L-A, Bidesi AS, Shad MU, Thomas MA, Hammen CL. Hippocampal changes associated with early-life adversity and vulnerability to depression. Biological psychiatry 2010;67:357-64.
107. Cole J, Costafreda SG, McGuffin P, Fu CHY. Hippocampal atrophy in first episode depression: A meta-analysis of magnetic resonance imaging studies. Journal of Affective Disorders 2011;134:483-7.
108. MacQueen G, Frodl T. The hippocampus in major depression: evidence for the convergence of the bench and bedside in psychiatric research? Mol Psychiatry 2011;16:252-64.
109. Hanson JL, Chung MK, Avants BB, et al. Early stress is associated with alterations in the orbitofrontal cortex: a tensor-based morphometry investigation of brain structure and behavioral risk. The Journal of neuroscience 2010;30:7466-72.
110. Andersen S, Tomada A, Vincow E, Valente E, Polcari A, Teicher M. Preliminary evidence for sensitive periods in the effect of childhood sexual abuse on regional brain development. The Journal of neuropsychiatry and clinical neurosciences 2008;20:292-301.
111. Tomoda A, Suzuki H, Rabi K, Sheu Y-S, Polcari A, Teicher MH. Reduced prefrontal cortical gray matter volume in young adults exposed to harsh corporal punishment. Neuroimage 2009;47:T66-T71.
112. Edmiston EE, Wang F, Mazure CM, et al. COrticostriatal-limbic gray matter morphology in adolescents with self-reported exposure to childhood maltreatment. Archives of Pediatrics & Adolescent Medicine 2011;165:1069-77.
113. Choi J, Jeong B, Rohan ML, Polcari AM, Teicher MH. Preliminary evidence for white matter tract abnormalities in young adults exposed to parental verbal abuse. Biological psychiatry 2009;65:227-34.
114. Szeszko PR, Ardekani BA, Ashtari M, et al. White matter abnormalities in obsessive-compulsive disorder: a diffusion tensor imaging study. Archives of General Psychiatry 2005;62:782-90.
115. Goldman-Mellor SJ, Caspi A, Harrington H, et al. Suicide attempt in young people: A signal for long-term health care and social needs. JAMA Psychiatry 2014;71:119-27.

116. Huang H, Gundapuneedi T, Rao U. White matter disruptions in adolescents exposed to childhood maltreatment and vulnerability to psychopathology. Neuropsychopharmacology 2012;37:2693-701.
117. Liu J, Chaplin TM, Wang F, Sinha R, Mayes LC, Blumberg HP. Stress reactivity and corticolimbic response to emotional faces in adolescents. Journal of the American Academy of Child & Adolescent Psychiatry 2012;51:304-12.
118. Posner K, Oquendo M, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. American Journal of Psychiatry 2007;164:1035-43.
119. First MB, Spitzer RL, Gibbon M, Williams JB. SCID-I/P. 2007.
120. Kaufman J, Birmaher B, Brent D, et al. Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): initial reliability and validity data. Journal of the American Academy of Child & Adolescent Psychiatry 1997;36:980-8.
121. Andreasen NC, Endicott J, Spitzer RL, Winokur G. The family history method using diagnostic criteria: reliability and validity. Archives of General Psychiatry 1977;34:1229-35.
122. Liu J, Blond BN, van Dyck LI, Spencer L, Wang F, Blumberg HP. Trait and state corticostriatal dysfunction in bipolar disorder during emotional face processing. Bipolar disorders 2012;14:432-41.
123. Wang F, Kalmar JH, He Y, et al. Functional and structural connectivity between the perigenual anterior cingulate and amygdala in bipolar disorder. Biological psychiatry 2009;66:516-21.
124. Beck AT, Kovacs M, Weissman A. Assessment of suicidal intention: the Scale for Suicide Ideation. Journal of consulting and clinical psychology 1979;47:343.
125. Oquendo MA, Halberstam B, Mann JJ. Risk factors for suicidal behavior. Standardized evaluation in clinical practice 2003;22:103-29.
126. Beck AT, Kovacs M, Weissman A. Hopelessness and suicidal behavior: An overview. Jama 1975;234:1146-9.
127. Grant BF, Stinson FS, Dawson DA, et al. Prevalence and Co-occurrence of Substance Use Disorders and IndependentMood and Anxiety Disorders: Results From the National Epidemiologic Survey on Alcohol and RelatedConditions. Archives of general psychiatry 2004;61:807-16.
128. Quello SB, Brady KT, Sonne SC. Mood disorders and substance use disorder: a complex comorbidity. Science & Practice Perspectives 2005;3:13.
129. Goldstein RZ, Volkow ND. Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. Nature Reviews Neuroscience 2011;12:652-69.
130. Hester R, Garavan H. Executive dysfunction in cocaine addiction: evidence for discordant frontal, cingulate, and cerebellar activity. The journal of neuroscience 2004;24:11017-22.
131. de Leon J, Diaz FJ, Rogers T, Browne D, Dinsmore L. Initiation of daily smoking and nicotine dependence in schizophrenia and mood disorders. Schizophrenia Research 2002;56:47-54.

132. Kalman D, Morissette SB, George TP. Co - Morbidity of Smoking in Patients with Psychiatric and Substance Use Disorders. The American Journal on Addictions 2005;14:106-23.
133. Catani M, de Schotten MT. Atlas of human brain connections: Oxford University Press; 2012.
134. Floden D, Stuss DT. Inhibitory control is slowed in patients with right superior medial frontal damage. Journal of cognitive neuroscience 2006;18:1843-9.
135. Eickhoff SB, Laird AR, Fox PT, Bzdok D, Hensel L. Functional Segregation of the Human Dorsomedial Prefrontal Cortex. Cerebral Cortex 2014.
136. Buckner RL, Andrews-Hanna JR, Schacter DL. The Brain's Default Network. Annals of the New York Academy of Sciences 2008;1124:1-38.
137. Lombardo MV, Chakrabarti B, Bullmore ET, et al. Shared Neural Circuits for Mentalizing about the Self and Others. Journal of cognitive neuroscience 2009;22:1623-35.
138. Szpunar KK, Watson JM, McDermott KB. Neural substrates of envisioning the future. Proceedings of the National Academy of Sciences 2007;104:642-7.
139. Andrews-Hanna JR, Reidler JS, Sepulcre J, Poulin R, Buckner RL. Functional-Anatomic Fractionation of the Brain's Default Network. Neuron 2010;65:550-62.
140. Wagner G, Schultz CC, Koch K, Schachtzabel C, Sauer H, Schlösser RG. Prefrontal cortical thickness in depressed patients with high-risk for suicidal behavior. Journal of Psychiatric Research 2012;46:1449-55.
141. Clark DL, Boutros NN, Mendez MF. The brain and behavior: an introduction to behavioral neuroanatomy: Cambridge University Press; 2010.
142. Saxena K, Tamm L, Walley A, et al. A preliminary investigation of corpus callosum and anterior commissure aberrations in aggressive youth with bipolar disorders. Journal of child and adolescent psychopharmacology 2012;22:112-9.
143. Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annual review of neuroscience 1986;9:357-81.
144. Zhang H, Chen Z, Jia Z, Gong Q. Dysfunction of neural circuitry in depressive patients with suicidal behaviors: A review of structural and functional neuroimaging studies. Progress in Neuro-Psychopharmacology and Biological Psychiatry 2014;53:61-6.
145. Von Der Heide RJ, Skipper LM, Klobusicky E, Olson IR. Dissecting the uncinate fasciculus: disorders, controversies and a hypothesis. Brain 2013:awt094.
146. Lebel C, Gee M, Camicioli R, Wieler M, Martin W, Beaulieu C. Diffusion tensor imaging of white matter tract evolution over the lifespan. NeuroImage 2012;60:340-52.
147. Paus T, Keshavan M, Giedd JN. Why do many psychiatric disorders emerge during adolescence? Nat Rev Neurosci 2008;9:947-57.
148. Versace A, Almeida JC, Hassel S, et al. ELevated left and reduced right orbitomedial prefrontal fractional anisotropy in adults with bipolar disorder revealed by tract-based spatial statistics. Archives of General Psychiatry 2008;65:1041-52.
149. McIntosh AM, Maniega SM, Lymer GKS, et al. White Matter Tractography in Bipolar Disorder and Schizophrenia. Biological Psychiatry 2008;64:1088-92.
150. Sussmann JE, Lymer GKS, McKirdy J, et al. White matter abnormalities in bipolar disorder and schizophrenia detected using diffusion tensor magnetic resonance imaging. Bipolar Disorders 2009;11:11-8.

151. Wall CA, Croarkin PE, Sim LA, et al. Adjunctive use of repetitive transcranial magnetic stimulation in depressed adolescents: a prospective, open pilot study. The Journal of clinical psychiatry 2011;72:1263-9.
152. Caplan R, Siddarth P, Levitt J, Gurbani S, Shields WD, Sankar R. Suicidality and brain volumes in pediatric epilepsy. Epilepsy & Behavior 2010;18:286-90.
153. Yurgelun-Todd DA, Bueler CE, McGlade EC, Churchwell JC, Brenner LA, Lopez-Larson MP. Neuroimaging correlates of traumatic brain injury and suicidal behavior. The Journal of head trauma rehabilitation 2011;26:276-89.
154. Cipriani A, Hawton K, Stockton S, Geddes JR. Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis. BMJ: British Medical Journal 2013;346.