



Low serum brain-derived neurotrophic factor is associated with suicidal ideation in major depressive disorder



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ARTICLE INFO

Keywords:
BDNF
Suicide
Depression

ABSTRACT

The “neurotrophic hypothesis of depression” posits that low levels of brain-derived neurotrophic factor (BDNF) are associated with Major Depressive Disorder (MDD). Low levels of BDNF have also been found in individuals with suicide attempts, in MDD or other disorders, suggesting that low BDNF may also be associated with suicidality. We assessed serum BDNF in 68 physically healthy and unmedicated (for at least 6 weeks) MDD subjects, who expressed no suicidal ideation (NSI; $N = 40$) or endorsed suicidal ideation (SI; $N = 28$), but were not actively suicidal, and in healthy controls (HC; $N = 76$). Serum BDNF levels were significantly lower in MDD with SI compared to NSI MDD but were not significantly correlated with total Hamilton Depression Rating Scale (HDRS-17) severity or severity on any HDRS subscale. Covarying for age, sex, body mass index, platelets, perceived stress, smoking and physical activity did not alter the significant association between BDNF and SI. SI status was not significantly different between HC and MDD. Our findings show an association between low serum BDNF and SI in individuals with less than severe and non-active suicidal intent, suggesting that the individual symptom of suicidality may extend the neurotrophic hypothesis of depression to include suicidal ideation within MDD.

1. Introduction

Major Depressive Disorder (MDD) affects 300 million people globally. It is a leading cause of disability, and is associated with increased risk of suicidal ideation (SI), suicide attempts and completed suicide (World Health Organization, 2017). An estimated 8.3% of the general population have suicidal thoughts in a given 12-month period (Crosby et al., 1999), and an estimated 50 percent of people who commit suicide also have MDD (Center for Disease Control and Prevention, 2015; Schimelpfening, 2017).

The “neurotrophic hypothesis of depression” seeks to understand depression through regulatory proteins such as brain-derived neurotrophic factor (BDNF) that promote neuroplasticity and adult neurogenesis (Duman and Monteggia, 2006). Generally, low levels are reported in blood in unmedicated individuals with MDD (Castrén and Kojima, 2017; Kishi et al., 2018; Lee and Kim, 2010; Molendijk et al., 2014), although there are some mixed results showing no significant

association between BDNF and MDD (Ihara et al., 2016), or even contradictory results, and the neurotrophic hypothesis may need to be reassessed to “provide a more valid account of the complex relationship between growth factors, mood disorders and their treatment” (Groves, 2007). It is uncertain whether low BDNF levels typify MDD in general or relate more specifically to certain symptoms. It is possible, although inadequately investigated, that low BDNF levels relate to suicidality rather than to MDD specifically (Ahrens and Linden, 1996; Lee and Kim, 2011). Previous postmortem studies found lower levels of BDNF in the prefrontal cortex and hippocampus of patients who committed suicide, regardless of psychiatric diagnosis (Dwivedi et al., 2003; Karege et al., 2005). Moreover, low levels of plasma BDNF have been reported in MDD subjects who attempted suicide when compared to non-suicidal MDD and healthy controls (Kim et al., 2007).

While these studies investigated actively suicidal MDD, the present study aims to assess the relationship between BDNF and mild-moderate SI in MDD. We quantified serum BDNF levels in MDD subjects with or

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<https://doi.org/10.1016/j.psychres.2019.01.013>

Received 23 October 2018; Received in revised form 2 January 2019; Accepted 3 January 2019

Available online 03 January 2019

0165-1781/ © 2019 Published by Elsevier B.V.

without SI to examine the relationship between low serum BDNF to SI vs general depressive symptomatology. We also sought to isolate BDNF's relationship with SI by also assessing its relationship with other aspects of depression, such as anxiety, overall severity of depression, appetite disturbance, physical activity, smoking and stress. While several studies have examined serum BDNF levels in actively suicidal patients with MDD or other psychiatric diagnosis, to our knowledge there are no studies that have examined serum BDNF levels in MDD patients with milder forms of suicidal ideation (i.e., non-lethal ideation in the absence of attempts or completed suicide). Investigation of the neurobiology of mild-to-moderate SI, not just active or completed suicides, is important in order to understand and identify an effective solution for suicide prevention. In this study, we sought to explore whether serum BDNF in MDD subjects with mild-to-moderate, sub-lethal suicidal ideation was lower than in MDD subjects with no suicidal ideation.

2. Methods

2.1. Subjects

The study was approved by the University of California, San Francisco (UCSF) Committee on Human Research and all subjects gave written informed consent to participate. Data are from the NIMH-funded "Cell Aging in Major Depression" study (R01MH083784). All subjects enrolled in this study through 12/24/2014, and who had BDNF data available, were included. We enrolled 68 unipolar MDD subjects who were all outpatients and were recruited by clinical referrals, newspaper advertisement, flyers, bulletin board notices, and Craigslist postings.

Healthy Controls (HC) were recruited by the same means and matched for age, gender, and ethnicity; 76 control subjects were enrolled. All psychiatric diagnoses, including MDD, were determined through Structural Clinical Interview for the DSM-IV (SCID-IV) (First et al., 1997) and were confirmed through an additional clinical interview with a board-certified psychiatrist. Control subjects had no history of any DSM-IV-TR axis disorder, which was also confirmed by SCID-IV interview and MDD subjects must have scored a minimum of 17 on the 17-item Hamilton Depression Rating Scale (HDRS-17; Hamilton, 1960). All subjects must have been free of any psychotropic medication for at least six weeks, with the exception of prn short-acting sedative hypnotics, which were allowed in the MDD group for treating insomnia, up to a maximum of three times per week, but none within one week prior to enrollment and venipuncture for BDNF. Subjects were also free from any steroid-containing contraceptives, exogenous steroids, hormone supplements or vitamin supplements above the United States Recommended Daily Allowances, and any other potentially confounding medications for six weeks prior to enrollment.

Table 1
Sample demographics and clinical characteristics.

	HC (N)	MDD with No Suicidal Ideation (N)	MDD with Suicidal Ideation (N)	MDD NSI vs. MDD SI p-value	Three Group Comparison p-value
Sex (% female)	61.84	60.00	57.14	0.817	0.910
BMI (kg/m ² ; M ± SD)	24.44 ± 4.58 (76)	26.21 ± 4.95 (40)	25.08 ± 3.80 (28)	0.290	0.140
Age (years; M ± SD)	37.16 ± 13.29 (76)	38.33 ± 14.75 (40)	40.04 ± 12.54(28)	0.619	0.625
Years of education (M ± SD)	16.74 ± 1.81 (76)	16.13 ± 2.21 (40)	16.25 ± 2.3 (28)	0.822	0.250
Smoking status (% smoking)	7 (9.2)	9 (22.5)	8 (27.6)	0.628	0.038*
Platelet count (M ± SD)	225.24 ± 46.93 (71)	215.79 ± 54.57 (39)	204.44 ± 60.75 (27)	0.431	0.200
PSS score (M ± SD)	8.88 ± 4.68 (76)	22.89 ± 6.98 (38)	26.60 ± 7.44 (25)	0.049*	<0.001*
HDRS-17 score (M ± SD)	–	19.13 ± 2.27 (40)	21.36 ± 3.99 (28)	0.005*	–
Lifetime Depression Chronicity (months; adjusted; M ± SD)	–	106.95 ± 102.94 (40)	140.13 ± 130.04 (27)	0.249	–
BDNF (z-scores)	–0.08 ± .97 (75)	.34 ± 1.07 (40)	–0.26 ± .82 (28)	.016	.029
YPAS (frequency x duration)	4.86 ± 3.14 (71)	3.21 ± 3.74 (38)	2.90 ± 3.23 (29)	0.719	0.008*

*Significant at the $p < 0.05$ level.

BMI: body mass index, PSS: perceived stress scale, HDRS-17: 17 item Hamilton Depressive Rating Scale, YPAS: Yale Physical Activities Scale.

Demographics including group size, age, sex, body mass index (BMI), tobacco consumption, and platelet count are presented in Table 1. Data relating serum BDNF levels to SSRI treatment response were previously reported in a subsample of the present sample (Wolkowitz et al., 2011).

Subjects were excluded if they were actively suicidal through clinician assessment and HDRS-17 ratings or had current psychosis or a history of bipolar disorder or psychotic symptoms that existed outside a major depressive episode. Subjects were also excluded if they had an eating disorder or post-traumatic stress disorder (PTSD) within one month of entering the study, or alcohol or substance dependence or abuse within six months of entering the study. Comorbid anxiety disorder diagnoses were allowed if the MDD diagnosis was judged to be primary.

Medical conditions were assessed with medical history, physical examination and routine blood screenings (chemistry panel, complete blood count, thyroid stimulating hormone, liver enzymes, cholesterol and lipids). Subjects were excluded if they had acute illnesses, infections, neurological disorders, chronic inflammatory disorders, or other major medical conditions that could potentially be confounding or if they had vaccinations within two months of the study.

2.2. Procedures

Subjects fasted since 22:00 h the night before, except water, and were admitted as outpatients to the UCSF Clinical and Translational Science Institute between 08:00 and 11:00 h. Once admitted, subjects had to first test negative on a urine toxicology screening and, if applicable, a urine pregnancy test. A blood draw was started after 25–45 min of relaxation. Blood for BDNF was collected into serum separator tubes (Vacutainer; BD, Franklin Lakes, NJ). After sitting at room temperature for one hour to allow clotting, blood was centrifuged at $2000 \times g$ for 20 min, serum was stored at -80°C until assay.

After the blood draw, depression symptoms (including SI) were rated using the HDRS-17. The presence and the extent of suicidality was assessed through clinical interview and response to HDRS-17 item #3. In the event that SI was endorsed, study staff and clinicians followed risk-assessment protocols to determine the extent to which subjects may be a risk to themselves. Individuals who were determined by a clinician as having current active suicidal intent were excluded from the present study, due to its outpatient nature. Because of this, no subjects had HDRS-17 ratings of "4" on item #3 (see below for definitions of severity scores on this item), as this would indicate that the subjects had attempted suicide in the past week or were of imminent danger to themselves.

2.3. Assay for BDNF

Serum for BDNF was assayed in three batches due to different recruitment dates; the batches did not significantly differ in the proportion of SI vs non-SI subjects. To account for possible batch effects, BDNF data within each batch were standardized to z-scores, which were then combined across the batches. Serum BDNF values, therefore, are expressed in z-scores.

Serum was assayed for BDNF in duplicate, using a commercial BDNF ELISA assay kit (R&D Systems, Minneapolis, MN, USA, catalog # DBD00). Sera were diluted 1:60 with diluent supplied by the kit manufacturer, to obtain BDNF concentrations within the linear range of the standard curve. To evaluate inter-assay variability, an internal control consisting of serum obtained from a single individual, frozen in multiple aliquots, was run on each plate processed. BDNF concentrations of this control sample were measured on several different days and multiple 96-well plates. The R&D Systems Human BDNF Quantikine ELISA Kit was found to have an acceptable 8–14% inter-assay variability of this control sample, when measured on each plate run with MDD samples. Intra-assay CV was <10%, or samples were re-assayed.

2.4. Measures

2.4.1. Depression, suicidal ideation and psychopathological dimensions

The total HDRS-17 score was used to measure overall depression severity during the past week. The suicide item #3 was used as the rating for suicidal ideation, which has been studied as a valid measure for suicidal ideation (Desseilles et al., 2012). Subjects' SI ratings ranged from 0 to 3, with scores of 3 indicating a higher degree of current suicidal plans or gestures (i.e., ideas or plans related to suicide, without current intent), scores of 2 representing a moderate degree of SI (i.e., wishes they were dead), scores of 1 representing a low degree of SI (i.e., feelings like life isn't worth living), and scores of 0 indicating the absence of any SI. Subjects with ratings of 0 were classified as MDD with NSI, while those with ratings of 1–3 were classified as MDD with SI. As mentioned above, subjects with scores of 4 (attempts at suicide) were not admitted to the study.

The HDRS-17 can be divided into four psychopathological dimensions or subscales: "Somatic Anxiety/Somatization," "Psychic Anxiety," "Pure Depressive," and "Anorexia" (Pancheri et al., 2002). Past research found that these four subscales are a reliable factor structure found in the HDRS and are prominent in depression (Konstantakopoulos et al., 2013).

2.4.2. Stress

Stress was measured using the Perceived Stress Scale (PSS) questionnaire, a widely used psychological instrument for measuring the perception of stress (Cohen et al., 1983). The questionnaire consists of 10-items and asks participants the level of stress they experienced in the past month. Each item was rated from 0 (never) to 4 (very often), with higher scores reflecting greater perceived stress.

2.4.3. Physical activity

Physical activity was measured using a modified Yale Physical Activity Survey (YPAS; Dipietro et al., 1993). Subjects self-reported frequency and duration of vigorous physical activity in the past month. This modified YPAS "vigorous activity" measure was calculated by multiplying the subject's frequency of vigorous exercise by the duration of activity.

2.5. Data analysis

Statistical analyses were performed with IBM SPSS Statistics, version 22. Between-group comparisons of demographic and clinical characteristics were performed using *t*-test and Chi-Square tests as appropriate. BDNF levels were standardized to account for inter-assay

batch variability and were shown to be normally distributed. Comparisons of BDNF between SI and NSI MDD subjects were conducted using independent sample *t*-test. Analysis of Covariance (ANCOVA) was used to additionally account for effects of potential confounds (age, sex, BMI, platelet count, and PSS) since these variables may be associated with BDNF (Duman and Monteggia, 2006; Lee et al., 2007). Differences in serum BDNF levels by suicidality status were assessed by between-group comparisons rather than my linear regression, due to the small number of subjects with the highest scores on the single HDRS suicidality item and due to the narrow range of values associated with a single item. These constraints did not apply to assessing the relationships between serum BDNF levels and total HDRS ratings and HDRS subscale ratings. Therefore, the latter were assessed by regression analysis, specifically, standard linear regressions were conducted to explore any associations between BDNF, depression severity and the four HDRS-17 subscales of depression identified by Pancheri et al. (2002). All tests were 2-tailed with an alpha = 0.05.

3. Results

3.1. Sample demographics

Subjects are grouped into Healthy Controls (HC), MDD with No Suicidal Ideation (MDD NSI) and MDD with Suicidal Ideation (MDD SI). Demographic and clinical characteristics of each group are included in Table 1. We found no significant between-group differences with regards to sex, ethnicity, BMI, age, years of education, or platelet count. PSS scores were significantly different between all three groups ($p < 0.001$), with the HC group scoring the lower than both MDD groups. PSS was significantly different between SI and NSI groups, ($p = 0.049$) with SI groups scoring higher, although this was not significantly related to BDNF levels ($p = 0.884$). YPAS scores were significantly different between all three groups ($p = 0.008$), but not significantly different between SI and NSI groups. Smoking status were also significantly differently between all three groups ($p = 0.038$), but also not significantly different between SI and NSI groups.

3.2. Comparisons with healthy controls

BDNF concentrations were not significantly different between healthy controls and all MDD subjects combined ($df = 141$, $p = 0.292$). When comparing MDD ($N = 68$) subjects to HC ($N = 76$) based on their SI status (NSI and SI) we found that there was a significant difference between HC, NSI and SI ($df = 2$, $F = 3.641$, $p = 0.029$). Post-hoc analysis revealed only significant differences between MDD with SI and MDD with NSI ($p = 0.038$), while the differences between HC and MDD SI ($p = 0.074$) and HC and MDD NSI ($p = 0.70$) were not significant.

3.3. BDNF and suicidal ideation

Serum BDNF levels were significantly lower in MDD with SI ($N = 28$) compared to MDD with NSI and the effect size of the two-group comparison was moderate ($N = 40$; $t = 2.468$, $p = 0.016$, $d = 0.622$) (Fig. 1). Further, this group difference remained significant when controlling for potential confounds (age, sex, BMI, platelet count and Perceived Stress Score, YPAS and smoking; $df = 1$, $F = 4.442$, $p < 0.05$). The following variables had no significant relationship with serum BDNF levels as follows: age ($df = 1$, $F = 2.666$, $p = 0.108$), sex ($df = 1$, $F = 1.039$, $p = 0.313$), BMI ($df = 1$, $F = 0.090$, $p = 0.765$), platelet count ($df = 1$, $F = 0.053$, $p = 0.818$), and PSS ($df = 1$, $F = 0.021$, $p = 0.884$).

3.4. BDNF and other depressive symptomatology

HRDS-17 total scores were significantly higher in the SI group compared to the NSI group ($p = 0.005$). However, when we excluded

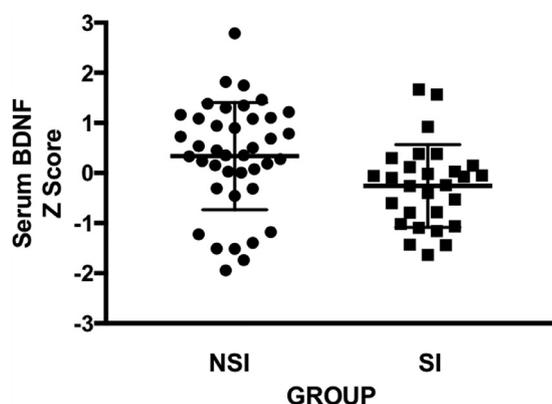


Fig. 1. Scatter plot of standardized serum BDNF concentrations for MDD with no suicidal ideation (MDD NSI $N = 40$) and MDD with suicidal ideation (MDD SI $N = 28$).

the HDRS-17 suicide item from the total score, the two groups' scores did not remain significantly different ($p = 0.465$). Serum BDNF levels were not significantly associated with overall depression severity (total HDRS-17 score; $df = 1$, $\beta = -0.098$, $p = 0.424$). Further, BDNF was not significantly associated with any HDRS-17 subscales that were assessed as exploratory independent variables (Pancheri et al., 2002). These results were as follows: somatic anxiety ($df = 1$, $\beta = 0.78$, $p = 0.525$), psychic anxiety ($df = 1$, $\beta = -0.160$, $p = 0.192$), pure depressive dimension ($df = 1$, $\beta = -0.077$, $p = 0.531$), anorexia ($df = 1$, $\beta = -0.083$, $p = 0.501$).

4. Discussion

We found that serum BDNF levels in unmedicated subjects with MDD were significantly lower in those who expressed mild to moderate SI than those with NSI. To the best of our knowledge, this is the first study to find significantly lower BDNF levels in unmedicated MDD subjects with SI (in the absence of active attempts or recent attempts) compared to MDD with NSI. Our results are consistent with previous studies linking lower BDNF with suicidal behavior (Sher, 2011), and extend these findings by including MDD subjects with only mild to moderate suicidal ideation.

A small number of previous studies examined peripheral BDNF levels in suicidal attempters in MDD subjects (Kim et al., 2007; Lee et al., 2007), and one study was found to examine only suicide risk (Dawood et al., 2007). Dawood et al. (2007) found that there is a significantly lower jugular venous/peripheral arterial BDNF plasma concentration gradient (nominally reflecting lower brain production of BDNF) in MDD with medium to high risk for suicide as compared to MDD with low risk for suicide, indicating that there is a negative correlation between suicide risk and veno-arterial BDNF plasma levels (Dawood et al., 2007). Kim et al. (2007) found that suicide attempters with MDD had significantly lower plasma BDNF levels than non-suicide attempters with MDD and healthy controls (Kim et al., 2007). Lee et al. (2007) also found that plasma BDNF was significantly lower in suicidal MDD with a suicide attempt when compared to non-suicidal MDD patients (Lee et al., 2007). Apart from MDD, lower serum BDNF has also been found in individuals that made suicide attempts and had clinical diagnosis of personality disorder and adjustment disorder compared to healthy controls (Grah et al., 2014). To our knowledge, no studies have compared BDNF levels in individuals with mild-to-moderate suicidal ideation, vs. those with active suicidality or suicide attempts; therefore, it is not known whether these exist on a continuum, with even lower levels in the actively suicidal individuals.

Fewer studies have examined BDNF levels in post-mortem brain samples from subjects who committed suicide (Castrén and Kojima, 2017). Pandey et al. (2008) found low BDNF levels and

tyrosine kinase B receptor signaling in brains of teenage suicide victims (Pandey et al., 2008). Dwivedi et al. (2003) found lower levels of BDNF in post-mortem brain samples in suicide completers compared to healthy controls (Dwivedi et al., 2003). Lower BDNF levels in brain tissue have also been found in subjects who completed suicide but were diagnosed with other psychiatric conditions other than MDD when compared with non-psychiatric healthy controls. These diagnosis include alcohol abuse, drug abuse, bipolar disorder schizoaffective disorder (Banerjee et al., 2013; Dwivedi et al., 2003; Karege et al., 2005).

Although a number of previous studies have reported an association between low BDNF and suicidality, there are some inconsistencies in the literature. In one study, no significant association was found between BDNF levels and attempted suicide in subjects who completed suicide across different psychiatric diagnoses including MDD, anxiety disorder, alcohol abuse, substance abuse, eating disorder, and more, when compared to non-suicidal psychiatric controls and healthy controls (Eisen et al., 2016). However, in this study 40% of the suicidal subjects and 32% of the psychiatric controls were using antidepressants including SSRIs. This is relevant since antidepressants have been found to increase BDNF levels (Castrén and Kojima, 2017; Sen et al., 2008; Wolkowitz et al., 2011), and could account for the non-significant relationship between groups. In another study, Huang and Lee (2006) found that there was no significant difference in BDNF levels between schizophrenia patients with a lifetime history of a suicide attempt and schizophrenia patients who had never attempted suicide (Huang and Lee, 2006). However, the amount of time between suicide attempt and blood collection is unknown and BDNF levels may vary over time as a response to external stimuli such as drinking, smoking, diet and endurance training (Eisen et al., 2015). Therefore, mixed results found in other studies may be a result of differences in study design, such as subjects' use of medication and blood collection times.

We further examined this relationship between BDNF and suicidality in MDD by accounting for possible confounds, some of which have been previously studied in relation to MDD and suicidality. None of the possible confounds (age, sex, BMI and platelet count), additional variables that can affect BDNF levels (physical activity and smoking), or alternative ways of assessing depressive symptoms: overall depression severity, perceived stress, and the four HDRS subscales were found to be significantly associated with BDNF levels. Previous studies have found that sex may play a role in BDNF mRNA expression levels in suicidal patients. Specifically, male suicide victims had lower levels of BDNF mRNA than females (Kozicz et al., 2008). However, we did not find that adjusting for sex altered the significant relationship between SI and BDNF. Severity of depression has been studied previously as a possible correlate of lower BDNF in MDD subjects, and studies have found no relation between depression severity and BDNF (Caldieraro et al., 2017; Wolkowitz et al., 2011). Additionally, in a study of active suicidal behavior, it was found that there were no significant correlations between plasma BDNF and depression severity scores in suicide attempters (Ambrus et al., 2016). Other studies have found that depression severity is negatively associated with serum BDNF (Varambally et al., 2013). While the overall results are mixed, our findings agree with the studies that found no relationship between BDNF and depression severity. Another variable that has been examined is the relationship between decreased BDNF levels and exposure to stress. Animal studies found that after exposure to acute and chronic stress, mice and rats had reduced levels of BDNF (Duman and Monteggia, 2006; Smith et al., 1995). We found that perceived stress was significantly different between the SI and NSI groups, however, the perceived stress levels were not significantly related to BDNF. Physical activity, particularly endurance exercise, has been found to facilitate the production of proteins that regulate BDNF expression (Phillips, 2017), however we found no significant difference between SI and NSI groups.

Finally, our study did not find a significant difference in serum BDNF levels in unmedicated subjects with MDD (whether with SI or

NSI) vs. healthy controls, although our power was limited to detect significant differences (we could only detect effect sizes of 0.47 or greater with 0.80 power, given our sample size). Previous studies examining the relationship between HC and MDD generally found relatively lower serum BDNF levels, without accounting for SI, in the MDD subjects compared to HC (Molendijk et al., 2014; Phillips, 2017). However, our study found results similar to Kim et al. (2007) who found that actively suicidal patients had the lowest levels of BDNF, and no significant difference between non-suicidal MDD and HC. While our subjects were not actively suicidal, the lowest levels of BDNF were found in those with SI, suggesting that suicidal ideation may be more specifically associated with lower levels of BDNF. While our overall between-group findings differ from the original neurotrophic hypothesis of depression, the generalizability of this hypothesis has been questioned, with suggestions that, “now is a critical time to reassess the original BDNF hypothesis of depression, and look towards the formation of new models that can provide a more valid account of the complex relationships between growth factors, mood disorders and their treatment” (Groves, 2007).

According to the neurotrophic hypothesis, the altered expression of BDNF as seen in MDD subjects can lead to increased neuronal atrophy or decreased neurogenesis in key limbic brain regions including the hippocampus and prefrontal cortex (Duman and Monteggia, 2006). This has been further extended by studies of actively suicidal MDD, which suggest that since BDNF plays a role in neuronal survival and function, the decreased BDNF expression in the hippocampus may play a role in generating a suicide risk. Although the mechanisms are unclear, one proposal is that this reduces neuronal plasticity, impairing an individual's ability to adapt to stressful or crisis situations (Dawood et al., 2007; Dwivedi, 2012; Lee and Kim, 2011). Related to this, corticosteroids may decrease BDNF levels (Issa et al., 2010; Schaaf et al., 2000), providing another mechanism by which stress may decrease BDNF levels, although cortisol levels are not routinely elevated in individuals with suicide attempt histories (O'Connor et al., 2016). Other studies of actively suicidal subjects imply that addressing low BDNF levels with antidepressant treatment and therapy could strengthen neural integrity and aid in the recovery from mental disorders and also prevent suicide attempts (Schmidt and Duman, 2010). Our study was limited to an examination of serum BDNF levels, which bear an uncertain relationship to brain or CSF levels of BDNF, although it has been found that blood and plasma BDNF reflect brain tissue BDNF levels across several animal species (Klein et al., 2011).

Strengths of our study include the study of well-phenotyped, medically healthy MDD and control subjects who were unmedicated for at least six weeks prior to enrollment. Subjects with co-morbid psychiatric or medical illnesses that could potentially interfere with blood biomarkers were excluded. Further, we adjusted for several variables thought to be important in determining serum BDNF levels, and we found that none of these altered our findings. In addition, we assessed a more isolated relationship between SI and BDNF by assessing BDNF relationships with global severity and with severity of specific depressive subscales. Finally, our study adds to the literature by demonstrating a relationship with even mild-to-moderate SI, whereas the majority of prior studies have looked at severe SI through suicide attempts and completions.

Our study has several limitations. We assessed serum BDNF, and peripheral BDNF has an uncertain relationship with brain levels of BDNF (Kim et al., 2007; Salas-Magaña et al., 2017). The origins of serum BDNF levels are still uncertain and it is suggested to be derived from platelet stores and vascular endothelial cells as well as from neurons and glial cells in the brain if it crosses the blood-brain barrier (Guo et al., 2008; Kim et al., 2007). In addition, BDNF levels in human serum are found to be higher than in human plasma and according to some studies the relationship between plasma BDNF and depression varies (Bocchio-Chiavetto et al., 2010; Karege et al., 2005). Also, our findings are based on a single time point of BDNF measures, and our

sample size was relatively small and therefore a replication of this study with a bigger cohort and more serum BDNF assessments would strengthen these findings. Further, since this was a cross-sectional study, we cannot assess whether BDNF associations with SI are “state” or “trait” markers in this population. Lastly, there are many other relevant factors that affect BDNF levels, and we did not assess other factors such as epigenetics or genetic polymorphisms.

5. Conclusion

Our finding presents a novel extension of the neurotrophic hypothesis of depression to include BDNF levels as a peripheral marker associated with mild to moderate SI within MDD. While some studies have examined BDNF levels in suicidal attempts and completion, our assessment of SI and its relationship to BDNF levels provides some insight into the neurobiology of depression and suicidality and should be further explored to understand the mechanisms by which SI develops, although our data do not specifically address causal relationships.

Funding

This study was funded by grants from the National Institute of Mental Health (NIMH; Grant number R01-MH083784), the O'Shaughnessy Foundation, the Tinberg family, and grants from the UCSF Academic Senate, the UCSF Research Evaluation and Allocation Committee (REAC). This project was also supported by National Institutes of Health/National Center for Research Resources (NIH/NCRR) and the National Center for Advancing Translational Sciences, National Institutes of Health, through UCSF-CTSI Grant Number UL1 RR024131. The contents of this publication are solely the responsibility of the authors and do not necessarily represent the official views of the NIH. Daniel Lindqvist was supported by the Swedish Research Council (registration number 2015-00387), Marie Skłodowska Curie Actions, Cofund (Project INCA 600398), the Swedish Society of Medicine, the Söderström-Königskas Foundation, the Sjöbring Foundation, OM Persson Foundation and the province of Scania (Sweden) state grants (ALF). Christina Hough is supported by the Graduate Division of the University of California, Los Angeles, and the National Science Foundation Graduate Research Fellowship Program (NSF Grant Number DGE-1650604). None of the granting or funding agencies had a role in the design and conduct of the study; collection, management, analysis and interpretation of the data; and preparation, review, or approval of the manuscript. The Co-Principal Investigators, Owen Wolkowitz, MD, and Synthia Mellon, PhD, had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Acknowledgements

The authors gratefully acknowledge the technical assistance of Phuong Hoang and the nursing and other staff of UCSF CTSI Clinical Research Center, and all past and present UCSF PNE Lab volunteer research assistants, as well as all of the participants in this research.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.psychres.2019.01.013](https://doi.org/10.1016/j.psychres.2019.01.013).

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