ORIGINAL INVESTIGATION

Suicidal ideation modulates the reduction in serotonin transporter availability in male military conscripts with major depression: A 4-[\(^{18}\)F]-ADAM PET study

YI-WEI YEH\(^1,2\), PEI-SHEN HO\(^3\), CHUN-YEN CHEN\(^1,4\), SHIN-CHANG KUO\(^1,4\), CHIH-SUNG LIANG\(^3,4\), CHE-HUNG YEN\(^1,5\), CHANG-CHIH HUANG\(^1,6\), CHUNG-YANN SHHUE\(^7\), WEN-SHENG HUANG\(^7,8\), KUO-HSING MA\(^9\), RU-BAND LU\(^{10}\) & SAN-YUAN HUANG\(^{1,4*}\)

\(^1\)Department of Psychiatry, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, \(^2\)Department of Psychiatry, Penghu Branch, Tri-Service General Hospital, Penghu, Taiwan, \(^3\)Department of Psychiatry, Beitou Branch, Tri-Service General Hospital, Taipei, Taiwan, \(^4\)Graduate Institute of Medical Sciences, National Defense Medical Center, Taipei, Taiwan, \(^5\)Department of Neurology, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, \(^6\)Department of Psychiatry, Tzu Chi General Hospital, Taipei, Taiwan, \(^7\)Department of Nuclear Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, \(^8\)Department of Nuclear Medicine, Changhua Christian Hospital, Changhua, Taiwan, \(^9\)Department of Biology & Anatomy, National Defense Medical Center, Taipei, Taiwan, and \(^10\)Department of Psychiatry, National Cheng Kung University, Tainan, Taiwan

Abstract

Objectives. Suicide is an important issue in the military service, since it can influence military morale and create dangerous situations for other personnel. The serotonin transporter (SERT) has been suggested to be involved in the pathophysiology of depression and suicidal behaviours. The aims of this study were to examine whether the brain SERT availability differs between military conscripts with depression and control subjects, and whether suicidal ideation is correlated with SERT availability. Methods. We used N,N-dimethyl-2-(2-amino-4-[\(^{18}\)F]-fluorophenylthio)benzylamine (4-[\(^{18}\)F]-ADAM) as a radioligand for positron emission tomography (PET) imaging. All participants completed the Hamilton Depression Rating Scale and Beck Scale for Suicide Ideation (BSS) prior to PET imaging. Results. The effect of major depression and BSS scores had an interaction on SERT availability. After adjusting for the BSS score, subjects with depression had lower SERT availability than control subjects (F\(_{1,17} = 23.85, P < 0.001\)). A positive correlation between SERT availability and BSS scores was observed in the depression group (F\(_{1,8} = 30.67, P = 0.001\)). The status of depression and intensity of suicidal ideation exert opposite effects on SERT availability. Conclusions. The extent of suicidal ideation may moderate the reduction effect in SERT binding observed in major depression in male military conscripts.

Key words: suicide, depression, military conscript, serotonin transporter, 4-[\(^{18}\)F]-ADAM

Introduction

Suicide is among the top 20 leading causes of death among people of all ages worldwide; a million people commit suicide every year in the world (World-Health-Organization 2012). In Taiwan, suicide is a serious public health problem and was one of the 10 leading causes of death for all ages from 1997 to 2009 (http://www.mohw.gov.tw). From 1997 to 2013, suicide was the second or third cause of death in young adults (15–24, and 25–44 years old). In addition, suicide among military personnel is a critical issue since it can influence military morale and result in dangerous situations for other personnel. In Taiwan, the military has practiced conscription for more than 60 years, and most young men are compelled into the armed service by law. During
military service, approximately 3.67 per thousand of the personnel use psychiatric services, and approximately 7.1 per 100,000 commit suicide (Ministry of National Defense, ROC, 2012). Although the suicide rate in the military is lower than those in the general population (around 19.5 per 100,000 in males) (Fu et al. 2013), suicides are now the second major cause of mortality in the army in Taiwan and other countries (Desjieux et al. 2004; Hyman et al. 2012). Therefore, developing a means to precisely assess the risk of suicide in a military population is imperative.

Many studies have extensively investigated suicide-associated demographic factors. In one prospective follow-up study, suicide risk was found to be independently associated with males and psychiatric disorders, but not with military-specific variables (LeardMann et al. 2013). In a Taiwanese study, maladjustment to the military environment and previous suicide attempts were the most important predictive factors for suicide attempts (Wu et al. 2013). However, demographic data cannot be used to predict current suicide risk with sufficient accuracy, and to the best of our knowledge, no biomarkers for predicting suicide attempts were available at the time of the study.

The central serotonergic system has been suggested to play an important role in the pathogenesis of depressive disorders and suicidal behaviours (Mann 1999; Arango et al. 2002; Mann 2013). Serotonergic neurons are located in the dorsal raphe nuclei (DRN), and project their axons widely throughout the brain and secrete neurotransmitter serotonin (5-HT). The serotonin transporter (SERT), which is present in these neurons, can regulate 5-HT neurotransmission through 5-HT reuptake from the synapse into the presynaptic serotonergic cells and may be important in the pathophysiology of depression and suicide (Purselle and Nemeroff 2003). Certain antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), selectively affect SERT’s through inhibition of 5-HT reuptake, thus increasing synaptic levels of 5-HT (Mann 1999). A serotonin transporter gene polymorphism (5-HTTLPR) has been shown to be associated with depressive symptoms (Yu et al. 2002) and suicidal behaviours (Li and He 2007). Thus, measurement of SERT density in vivo may provide a potential biomarker for depression and suicidal behaviours (Owens and Nemeroff 1994; Purselle and Nemeroff 2003).

In a post mortem study using autoradiography with [1H]cyclohexazin, suicide victims with depression (including eight with MDD, one with schizoaffective disorder, and one with schizotypal personality disorder) showed decreased SERT binding in the DRN, fewer SERT-expressing neurons, and higher SERT mRNA (messenger RNA) expression per neuron compared to normal controls (Arango et al. 2001). In contrast, in two other post mortem studies, suicide victims who had major depression and controls did not significantly differ in SERT binding or SERT expression in the DRN (Bligh-Glover et al. 2000) and frontal cortex (Little et al. 1997). However, post mortem studies may not be truly representative of the in vivo condition. In the past 10 years, many in vivo studies have used radioligands to measure SERT density (Brust et al. 2006; Meyer 2007). To determine the brain uptake of a radioligand, the binding potential (BP) is defined as the ratio of $B_{\text{max}}$ (receptor density) to $K_D$ (ligand equilibrium dissociation constant) (Mintun et al. 1984). The affinity of ligand binding is the inverse of $K_D$, and the BP can be equal to the product of $B_{\text{max}}$ and the affinity. SERT availability is equivalent to the density of available receptors that can be occupied by radioligands (Innis et al. 2007). Among these in vivo imaging studies, many have compared subjects with MDD to healthy controls, such as SPECT studies using $[\text{123}^\text{I}]$-\text{\textbeta}-\text{CIT} (Lindstrom et al. 2004; Ryding et al. 2006) or $[\text{123}^\text{I}]$ADAM (Newberg et al. 2005; Ho et al. 2013), and PET studies using $[\text{11}^\text{C}]$-(+)-\text{McN}5652 (Ichimiy et al. 2002; Reivich et al. 2004; Parsey et al. 2006) or $[\text{11}^\text{C}]$-DASB (Meyer et al. 2004; Cannon et al. 2007; Reimold et al. 2008; Selvaraj et al. 2011; Miller et al. 2013). However, these studies have yield inconsistent results, may be due to the differences in the inclusion criteria, and the use of non-specific radioligands.

Therefore, we used a SERT-specific radioligand, $N,N$-dimethyl-2-(2-amino-4-$[^{18}\text{F}]$fluorophenylthio) benzylamine ($4-[^{18}\text{F}]$-ADAM), in the present study (Huang et al. 2013) in order to calculate in vivo SERT binding potential (BP) in the human brain. The goals of this study were to determine whether SERT binding differs between subjects with MDD and healthy controls in the military, and whether SERT availability differs between subjects with MDD who have and those who have not attempted suicide. An additional aim was to establish the correlation of SERT BP with the degree of depressive symptoms as well as the degree of suicidal ideation.

**Materials and methods**

**Recruitment of participants**

The experimental protocol was approved by the Institutional Review Board for the Protection of Human Subjects at the Tri-Serice General Hospital, National Defense Medical Center in Taipé, Taiwan.
All subjects gave written informed consent after the procedures of the study were fully explained to them. The patient group consisted of 10 drug-naive military conscripts with MDD recruited from the inpatient population of the Department of Psychiatry, Tri-Service General Hospital from 2009 to 2011. Four patients with MDD exhibited double depression (concurrency of MDD and dysthymic disorder). The age of the depressed subjects ranged from 20 to 25 years. Their psychiatric diagnosis was based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR). The exclusion criteria for depressed subjects was previous exposure of psychotropic medication, for example, antidepressants, mood stabilizers, or antipsychotics. The control group included 10 healthy volunteers recruited from the military, who had adapted to military life well for half a year. A Chinese version of the modified Schedule of Affective Disorder and Schizophrenia-Lifetime (SADS-L) (Endicott and Spitzer 1978) was used to screen psychiatric conditions in both patients and control subjects. Inter-rater reliability coefficients (κ values) for SADS-L ratings were good to excellent for major depression, bipolar disorder, anxiety disorder, schizophrenia, and substance abuse/dependence, and personality disorders (Huang et al. 2004). The control subjects were free of past or present major and minor mental illness, and their first-degree relatives had no family history of psychiatric disorders or substance abuse or dependence. The exclusion criteria for healthy controls was the score in Beck Scale for Suicide Ideation (BSS) (Beck et al. 1979) more than zero.

Psychological measures of depression and suicide ideation

The 21-item Hamilton Depression Rating Scale (HDRS) (Hamilton 1960) and the BSS (Beck et al. 1979) were used to assess the current severity of depression and intensity of suicide ideation. A higher score on the HDRS indicates an overall greater severity of depression. A higher score on the BSS indicates an overall greater severity of suicidal intent. All participants completed the HDRS and BSS assessment immediately prior to positron emission tomography (PET) imaging, to avoid time-interval effects.

PET procedure

4-[^18]F]-ADAM was synthesized in an automated synthesizer, as described previously (Peng et al. 2008). All 20 subjects underwent a low-dose CT scan (130 kVp, 50 mAs) and then a static imaging in three-dimensional mode at 120 min after an intravenous bolus injection of 8.43 ± 1.21 mCi of 4-[^18]F]-ADAM using with a BIOGRAPH PET/computed tomography (CT) scanner (Biograph Duo, Siemens, USA). This scanner had a transverse field-of-view (FOV) of 58.5 cm, an axial FOV of 15.5 cm, and a spatial resolution of 4.8 mm. Emission images were reconstructed in a 512 × 512 × 64 matrix with a pixel size of 0.519 × 0.519 × 2.4 mm using the ordered subset expectation maximization (OSEM) method (six iterations and 16 subsets) with a Gaussian filter of 3 mm full-width half maximum (FWHM). During PET imaging, all depressed participants were accompanied by their families and a medical doctor, to ensure their safety.

Image data acquisition

All reconstructed PET images were analysed using PMOD commercial software (version 3.0, PMOD Technologies, Zürich, Switzerland). Each subject’s PET image was automatically co-registered with the corresponding CT scan and was then finely adjusted manually by an experienced physician. The CT was loaded to provide an anatomical reference and regions-of-interest (ROIs) were defined on reconstructed and summatated PET images and drawn over the cerebellum, midbrain, striatum, thalamus, and prefrontal cortex (PFC) (Figure 1), as previously described (Yeh et al. 2015). We used the cerebellum as a background reference because it has a very low concentration of SERT compared to other brain regions. To reduce the specific binding of SERT in the cerebellum, only the posterior half of the cerebellar cortex was delineated, and a margin of several millimetres around the outer border was left to prevent spill-over from venous sinuses. The binding potential of 4-[^18]F]-ADAM was quantified using the ratio of specifically bound radioligand to that of nondisplaceable radioligand in brain tissue (BP\textsubscript{ND}) at equilibrium. Because an earlier study reported that the uptake of 4-[^18]F]-ADAM reached an equilibrium at about 120–140 min after injection of 4-[^18]F]-ADAM in human subjects, we applied the 120 min of the frames for the ratio method in our modelling.

The BP\textsubscript{ND} of 4-[^18]F]-ADAM in the target region was calculated by subtracting the tissue radioligand activity in the nondisplaceable region-cerebellum (C\textsubscript{CB}) from the tissue radioligand activity in the target region (C\textsubscript{ROI}), and then dividing the result by the tissue radioligand activity in the nondisplaceable region: BP\textsubscript{ND} = BP = (C\textsubscript{ROI} – C\textsubscript{CB})/C\textsubscript{CB} (Ichise et al. 2001; Innis et al. 2007). The operator of PMOD software was blinded to the participant’s information.
scores within the depressed group. The effect size $q$ in Spearman’s rank correlation between the two groups was calculated using G-power 3.1 software (Buchner et al. 1992). All data were analysed using SPSS software for Windows (version 17, SPSS, Chicago, IL, USA). A $P$ value $\leq 0.05$ was considered to be statistically significant (two-tailed).

Results

Demographic characteristics

The characteristics of all participants are summarized in Table I. All participants were young male conscripts from the Han Chinese population. The mean age of healthy controls (26.9 ± 3.1 years) was significantly higher than that of depressed subjects (22.9 ± 1.7 years) ($t = 3.56$, df = 18, $P = 0.002$). The BMI of healthy controls (24.3 ± 2.3 kg/m$^2$) was also significantly higher than that of depressed subjects (21.1 ± 2.7 kg/m$^2$) ($t = 2.87$, df = 18, $P = 0.01$). Depressed subjects had a significantly higher mean HDRS scores (29.1 ± 6.8) and mean BSS scores (22.7 ± 10.8) than healthy controls ($P < 0.001$). The incidence of smokers was 40% in depressed group and 20% in control groups ($P = 0.63$). There was no difference in the mean injection dose of 4-[$^{18}$F]-ADAM between the depressed (8.01 ± 0.84 mCi) and control subjects (8.70 ± 1.50 mCi) ($t = -1.27$, df = 14.18, $P = 0.22$). The mean

Figure 1. This demonstrates the delineation of the four ROIs. The red colour indicates the highest uptake and the blue colour indicates the lowest uptake of the 4-[$^{18}$F]-ADAM.
Table I. Demographic data for all participants in this study ($n = 20$).

| Age | Axis I diagnoses | Axis II diagnoses | Onset age | Duration of illness (y, year; m, month) | No. of MDE | Duration of current MDE (months) | Latency period between the previous attempts and PET scan (d, days) | HDRS$_{21}$ score | BSS score | Body mass index | Daily smoking amount (cigarettes/day) | No. of suicide attempts | Suicide method |
|-----|------------------|-------------------|-----------|----------------------------------------|------------|----------------------------------|---------------------------------------------------------------|----------------|-----------|----------------|--------------------------------------|----------------------|-----------------|
| 20  | Double depression | Borderline mental insufficiency | 15 | 5y | 3 | 3.0 | 31d | 31 | 36 | 19.15 | 0 | 3 | Drug overdosing x 2; Jumping from a height x 1 |
| 21  | Double depression | None | 16 | 5y | 1 | 1.5 | 12d | 36 | 32 | 19.38 | 20 | 2 | Drug overdosing x 1; Crashing the wall x 1 |
| 23  | Double depression | Cluster B PD | 21 | 2y | 1 | 4.5 | 15d | 28 | 27 | 25.35 | 20 | 4 | Cutting wrist x 4 |
| 25  | Double depression | None | 15 | 10y | 3 | 1.0 | NA | 31 | 17 | 25.25 | 0 | 0 | None |
| 23  | MDD | None | 23 | 1.5m | 2 | 1.5 | 21d | 27 | 34 | 18.94 | 10 | 1 | Cutting wrist x 1 |
| 24  | MDD | Cluster B PD | 24 | 0.5m | 1 | 0.5 | 11d | 32 | 30 | 19.72 | 0 | 3 | Cutting wrist x 3 |
| 22  | MDD | None | 22 | 2m | 1 | 2.0 | NA | 14 | 14 | 21.39 | 0 | 0 | None |
| 24  | MDD | None | 24 | 2m | 1 | 2.0 | NA | 31 | 3 | 23.66 | 0 | 0 | None |
| 25  | MDD | None | 25 | 1m | 1 | 1.0 | NA | 38 | 21 | 20.70 | 20 | 0 | None |
| 22  | MDD | Cluster B PD | 22 | 2m | 1 | 2.0 | NA | 23 | 13 | 17.86 | 0 | 0 | None |
| 21  | None | NA | NA | NA | NA | NA | NA | 0 | 0 | 23.50 | 10 | NA | NA |
| 23  | None | NA | NA | NA | NA | NA | NA | 0 | 0 | 24.49 | 0 | NA | NA |
| 31  | None | NA | NA | NA | NA | NA | NA | 0 | 0 | 23.66 | 0 | NA | NA |
| 30  | None | NA | NA | NA | NA | NA | NA | 0 | 0 | 24.09 | 0 | NA | NA |
| 30  | None | NA | NA | NA | NA | NA | NA | 0 | 0 | 24.99 | 0 | NA | NA |
| 28  | None | NA | NA | NA | NA | NA | NA | 0 | 0 | 27.13 | 0 | NA | NA |
| 27  | None | NA | NA | NA | NA | NA | NA | 0 | 0 | 27.47 | 20 | NA | NA |
| 26  | None | NA | NA | NA | NA | NA | NA | 0 | 0 | 23.31 | 0 | NA | NA |
| 26  | None | NA | NA | NA | NA | NA | NA | 0 | 0 | 21.97 | 0 | NA | NA |
| 27  | None | NA | NA | NA | NA | NA | NA | 0 | 0 | 21.91 | 0 | NA | NA |

HDRS$_{21}$, 21-item Hamilton Depression Rating Scale; BSS, Beck Scale for Suicide Ideation; MDD, Major depressive disorder; MDE, major depressive episode; PD, Personality disorder; NA, not applicable; Participants were all male Han Chinese and drug-naïve condition prior to PET scan.
duration of the current major depressive episode in the depressed subjects was 1.9 ± 1.1 months. Control subjects were all recruited from Army and depressed subjects were five from the Army, four from the Navy and one from the Air Force. Three of 10 depressed subjects had cluster B personality disorder, and one of 10 had borderline mental insufficiency. Within the depressed subjects, five subjects had at least one past suicide attempt, and the other five subjects had no prior suicide attempt.

The effects of diagnosis and past suicide history on SERT BP<sub>ND</sub>

The mean BP<sub>ND</sub> in drug-naïve depressed military conscripts and control subjects in the four ROIs are presented as a scatter plot and a box plot in Figure 2. The mean values of BP<sub>ND</sub> (mean ± standard deviation) in depressed subjects for the midbrain, thalamus, striatum, and PFC were 1.12 ± 0.38, 0.90 ± 0.29, 0.71 ± 0.20, and 0.31 ± 0.13, respectively. The values of BP<sub>ND</sub> in control subjects for the midbrain, thalamus, striatum, and PFC were 1.33 ± 0.16, 0.99 ± 0.20, 0.80 ± 0.17, and 0.28 ± 0.09, respectively. SERT BP<sub>ND</sub> across the four ROIs did not differ between the depressed and control groups (F = 1.22, df = 1.18, P = 0.28). The effect size Hedges’ g of mean difference in SERT binding between depressed and control groups were midbrain (0.69), thalamus (0.35), striatum (0.46), and PFC (0.26), respectively. Within the depressed group, the effect of past suicide attempts on SERT binding was significant (F = 11.22, df = 1.8, P = 0.010). Lower SERT binding was observed in MDD subjects without any suicide attempts than in MDD subjects with past suicide attempts. Neither dysthymic disorder nor Axis II diagnosis showed a significant effect on SERT binding (P > 0.05).

Effects of other potential factors on SERT BP<sub>ND</sub>

Because the depressed and control groups differed in age and BMI, we explored the relationship between age and BMI in association with SERT BP. Across the four ROIs, there was no effect of age (F = 0.72, df = 1.17, P = 0.41) and BMI (F = 0.26, df = 1.17, P = 0.61) on SERT binding. SERT BP<sub>ND</sub> differed between the four ROIs (F = 150.74, df = 3.57, P < 0.001). A post-hoc analysis showed that the amount of BP<sub>ND</sub> from greatest to least, was midbrain > thalamus > striatum > PFC. Smoking status did not show any effect on SERT BP (F = 3.58, df = 1.17, P = 0.08). There was no effect of onset age, number of major depressive episodes, duration of illness, and latency period between the previous attempts and PET scan on SERT binding (P > 0.05).

The correlation between SERT BP<sub>ND</sub> and the BSS scores, as well as HDRS scores

Within the depressed group, we observed a significant effect of BSS scores on SERT BP<sub>ND</sub> across the four ROIs (F = 18.21, df = 1.8, P = 0.003); however, we did not observe any effect of HDRS scores and SERT BP<sub>ND</sub> (F = 0.45, df = 1.8, P = 0.52). Using Spearman’s ρ (rho) correlation, SERT BP<sub>ND</sub> showed a positively correlation with BSS scores in all four ROIs (Figure 3). Within the control group, there was no correlation between SERT BP<sub>ND</sub> and the BSS scores, as well as HDRS scores. The effect size q in Spearman’s rank correlation between two groups were 1.02, 0.96, 1.56, and 1.23, in the midbrain, thalamus, striatum, and PFC, respectively. The power were 0.50, 0.43, 0.83, 0.63, in the midbrain, thalamus, striatum, and PFC, respectively.

Interaction between the BSS score and a diagnostic effect on SERT BP<sub>ND</sub>

We further examined the interaction between the BSS score and a diagnostic effect of MDD on SERT binding. We found a significant effect of BSS-by-diagnosis interaction (F = 17.24, df = 1.17, P < 0.001, Figure 4), with power 0.97. After controlling for BSS score, the diagnostic effect became more significant on SERT binding (F = 18.64, df = 1.17, P < 0.001), with power 0.98. A post-hoc analysis showed that the SERT BP in the midbrain, thalamus and striatum, and PFC were lower in depressed conscripts than in controls after covariating the BSS score. Because
smoking status may be a potential confounding factor, we performed stratified analysis on the smoker and non-smoker clusters individually (Supplementary Figure 1 available online at http://informahealthcare.com/doi/abs/10.3109/15622975.2015.1048722).

Discussion

**SERT binding in military subjects with MDD and different degree of suicide ideation**

Suicides are now the second major cause of mortality in the European, American, and Taiwanese armies (Desjeux et al. 2004; Hyman et al. 2012). Therefore, developing a means to more accurately assess the suicide risk in a military population is crucial. To the best of our knowledge, this is the first study to recruit military conscripts for comparison of SERT BP in the cortical (the PFC) and subcortical areas (the thalamus, striatum, and midbrain) between subjects with depression and healthy controls. We report initial evidence of an interaction between the major depression and suicidal ideation scores on SERT binding. Greater suicidal ideation, as measured by the BSS, was correlated with higher SERT BP in military subjects with depression. This may explain why subjects with MDD who had attempted suicides (mean BSS score = 31.8) had a significantly higher SERT BP than subjects with MDD who had never attempted suicide (mean BSS score = 13.6). In contrast, subjects with depression showed a lower SERT BP than control subjects in analysis controlling for BSS scores. This finding suggests that high suicidal ideation may obscure the MDD-related reduction in SERT binding. This may lead to contradictory results for SERT binding in patients with depression, as have been reported by previous studies (Ichimiya et al. 2002; Lindstrom et al. 2004; Meyer et al. 2004; Reivich et al. 2004; Newberg et al. 2005; Parsey et al. 2006; Ryding et al. 2006; Cannon et al. 2007; Reimold et al. 2008; Selvaraj et al. 2011; Ho et al. 2013; Miller et al. 2013).

Figure 3. Spearman’s rank correlation between the Beck Scale for Suicide Ideation (BSS) scores and serotonin transporter binding potential (SERT BP) in the four ROIs in military depressed subjects.

Figure 4. The possible model of major depression and suicidal ideation on SERT binding. Intensity of suicide ideation can be a moderator on reduction effect by major depression. The numbers indicate the estimate coefficient of major depression and BSS score on SERT availability in linear mixed-effect model.
Association between suicide ideation and SERT binding

To our knowledge, only a few studies have investigated the association between suicidal ideation and SERT binding. The BSS is a clinician-rated scale that uses a semi-structured interview to evaluate a patient's current suicide risk (Beck et al. 1979). This scale consists of three dimensions of suicidal ideation, including active suicidal desire, specific plans for suicide, and passive suicidal desire, which provide a comprehensive assessment for suicidal risk. However, impulsivity had been proposed to play an important role in the pathogenesis of suicidal behaviours (Roy and Linnoila 1988; Oquendo and Mann 2000). A previous imaging study used the Marke–Nyman Temperament (MNT) scale to evaluate impulsivity in patients with a history of suicide attempts (Lindstrom et al. 2004), and reported a significantly positive correlation between whole-brain SERT binding and MNT solidity (reflecting impulsivity). Suicidal ideation may be positively correlated with SERT binding through the impulsivity dimension. Moreover, Lindstrom and colleagues (2004) observed lower SERT binding in subjects who had attempted suicide and had depression than in those who did not have depression, indicating that depression diagnosis has a negative impact on the amount of SERT. Therefore, suicidal ideation as well as impulsivity may counteract the depression-related reduction in SERT availability, resulting in no difference in SERT binding between the depression versus control groups. In another SERT imaging study, Meyer and colleagues (2004) used the Dysfunctional Attitudes Scale (DAS) to evaluate negative cognition in patients with MDD, and they observed a positive correlation between DAS scores and SERT BP in some brain regions. The DAS was originally designed as a measure of general cognitive vulnerability factor to depression, including negatively biased assumptions and beliefs regarding oneself, the world, and the future. Although scores on DAS subscales and total scores have been found to be unrelated to BSS scores, higher scores on DAS subscales (Vulnerability and Perfectionism) were present in those with suicidal ideation versus those who did not have suicidal ideation (Beck et al. 1993). This also supported our finding in that suicidal ideation had a positive correlation on SERT binding.

Possible reasons of contradictory results

Our result is concordant with previous imaging studies, in that a reduction in SERT binding in the midbrain (Newberg et al. 2005; Parsey et al. 2006; Selvaraj et al. 2011; Miller et al. 2013; Nye et al. 2013), thalamus (Selvaraj et al. 2011; Ho et al. 2013), and striatum (Selvaraj et al. 2011; Nye et al. 2013) has been observed in subjects with depression. However, our results differ from those of other studies that have reported no difference (Lindstrom et al. 2004; Meyer et al. 2004; Ryding et al. 2006) or elevated SERT binding (Ichimiya et al. 2002; Reivich et al. 2004; Cannon et al. 2006, 2007). Several factors may help to explain these divergent results. First, the primary aim of the previous studies was to investigate current depression, with or without past suicide attempts, not to assess current suicidal ideation or intent. Our present study focused on rating current suicidal ideation immediately prior to PET imaging; therefore, it may more precisely evaluate the real-time suicide intent and better examine the association between SERT binding and suicide ideation. Second, in animal studies antidepressants have been shown to either downregulate (Benmansour et al. 2002; Baudry et al. 2010) or upregulate SERT expression (Qiu et al. 2013; Shrestha et al. 2014). Therefore, brain SERT expression may be altered in subjects with depression who have received antidepressant treatment, which may influence the results of SERT imaging. However, because all of our participants were antidepressant-naive MDD subjects, our data may more accurately reflect SERT binding than data from antidepressant users. Third, in our study, all subjects with depression were young soldiers with unipolar depression. A bipolar depression may have existed in these early-onset depression, even though they only displayed unipolar depressive episodes and denied prior hypomania or mania during a semi-structured interview. Use of a mixed sample of subjects with unipolar (Ichimiya et al. 2002; Cannon et al. 2007; Selvaraj et al. 2011; Ho et al. 2013; Miller et al. 2013; Nye et al. 2013), and bipolar depression (Cannon et al. 2006; Oquendo et al. 2007; Chou et al. 2010) may have confounded our results. Finally, although SERT BP decreased in the MDD group, it was not correlated with the severity of depression, which was measured by HDRS. Two reasons may explain this: (1) the HDRS (Hamilton 1960), which was used to measure the severity of depression, focused more on mood symptoms rather than neuro-vegetative symptoms, and may have missed certain dimensions of depression assessment; (2) the SERT BP may merely be associated with depression status and not the severity of depression.

Biological evidence and implication based on our finding

In the current study, the relatively lower SERT BP in subjects with depression than in controls indicated reduced SERT density in these ROIs. This may due to fewer serotonergic neurons and/or axons fibers projecting to these target regions (the thalamus, striatum, and PFC). Down-regulation of SERTs could com-
pensate for the 5-HT deficiency by decreasing 5-HT reuptake from synapse in order to maintain 5-HT concentration in the remaining serotonergic neurons and fibres. In addition, a positive correlation between suicidal ideation scores and SERT density in the striatum and prefrontal cortex of subjects with depression, may lead to lower 5-HT neurotransmission in these brain regions thus enhancing suicidal ideation. Increased SERT binding in depression may contribute to suicidal ideation, or conversely, suicidal ideation may moderate the reduction in SERT binding in major depression, as shown in Figure 4.

Limitation

The present study has some limitations. First, the sample size was small (n = 20) and may limit generalization of our findings. Only young male military subjects were recruited because only young men are compelled into the armed service by law in Taiwan. Therefore, the current findings may only be extrapolated to young males, but not to females or older individuals (Staley et al. 2006). Second, the mean age for the control group was greater than that for the depression group. However, age did not have a significant influence on SERT BP, as shown by the regression model. Third, we did not investigate the genetic effects on SERT availability because of our previous negative finding for a correlation between SLC6A4 gene polymorphisms and SERT availability using [123]IADAM SPECT (Ho et al. 2013). Fourth, we did not collect any data on childhood experiences to evaluate gene × environment interactions on SERT availability.

In conclusion, our study indicated that suicidal ideation scores were positively correlated with SERT binding in subjects with depression, but not in control subjects. This study also showed that a diagnosis of depression was correlated with a reduction in SERT binding. Interestingly, current depressive status and suicidal ideation exert the opposite effects on SERT availability. Our results may provide an alternate perspective for exploration of SERT binding in association with the interaction between suicide and depression in the military service, in terms of both assessment and treatment. The extent of suicidal ideation may modulate the reduction in SERT binding observed in major depression in male military conscripts.

Acknowledgments

This study was supported by grants from National Science Council, Taiwan NSC97-2314-B-016-001-MY2, NSC99-2314-B-016-019-MY3 (SYH) NSC100-2314-B-016-036-MY3 (WSH); and by grants from Medical Affairs Bureau, Ministry of National Defense, Taiwan, DOD99-C04-04, DOD100-C09-03 (YWW, CYC), parts of DOD100-C09-01 and MAB102-68 (SYH); and by grants from Tri-Service General Hospital TSGH-C08-09-S02, TSGH-C09-008-9-S02, TSGH-C100-009-008-9-S02 (YWW, CYC), parts of TSGH-C101-122, TSGH-C102-123 and TSGH-C103-133 (SYH). We would like to thank Miss Mei-Chen Shih and Yun-Hsin Lin for their assistance in the preparing this manuscript.

Statement of Interest

None to declare.

References

Arango V, Underwood MD, Boldrini M, Tamir H, Kassir SA, Hsiung S, et al. 2001. Serotonin 1A receptors, serotonin transporter binding and serotonin transporter mRNA expression in the brainstem of depressed suicide victims. Neuropsychopharmacology 25:892–903.

Arango V, Underwood MD, Mann JJ. 2002. Serotonin brain circuits involved in major depression and suicide. Prog Brain Res 136:443–453.

Baudry A, Mouillet-Richard S, Schneider B, Launay JM, Kellermann O. 2010. mR-16 targets the serotonin transporter: a new facet for adaptive responses to antidepressants. Science 329:1537–1541.

Beck AT, Kovacs M, Weissman A. 1979. Assessment of suicidal intention: the Scale for Suicide Ideation. J Consult Clin Psychol 47:343–352.

Beck AT, Steer RA, Brown G. 1993. Dysfunctional attitudes and suicidal ideation in psychiatric outpatients. Suicide Life Threat Behav 23:11–20.

Benmansour S, Owens WA, Cecchi M, Morilak DA, Frazer A. 2002. Serotonin clearance in vivo is altered to a greater extent by antidepressant-induced downregulation of the serotonin transporter than by acute blockade of this transporter. J Neurosci 22:6766–6772.

Bligh-Glover W, Kolli TN, Shapiro-Kulnane L, Dilley GE, Friedman L, Balraj E, et al. 2000. The serotonin transporter in the midbrain of suicide victims with major depression. Biol Psychiatry 47:1015–1024.

Brust P, Hesse S, Muller U, Szabo Z. 2006. Neuroimaging of the serotonin transporter – possibilities and pitfalls. Curr Psychiatry Rev 2:111–149.

Buchner A, Faul F, Erdfelder E. 1992. G*Power: A priori-, post hoc-, and compromise power analyses for the Macintosh. Bonn University: Bonn.

Cannon DM, Ichise M, Fromm SJ, Nugent AC, Rollis D, Gandhi SK, et al. 2006. Serotonin transporter binding in bipolar disorder assessed using [11C]DASB and positron emission tomography. Biol Psychiatry 60:207–217.

Cannon DM, Ichise M, Rollis D, Klaver JM, Gandhi SK, Charney DS, et al. 2007. Elevated serotonin transporter binding in major depressive disorder assessed using positron emission tomography and [11C]DASB; comparison with bipolar disorder. Biol Psychiatry 62:870–877.

Chou YH, Wang SJ, Lin CL, Mao WC, Lee SM, Liao MH. 2010. Decreased brain serotonin transporter binding in the euthymic state of bipolar I but not bipolar II disorder: a SPECT study. Bipolar Disord 12:312–318.

Djeuje G, Labarere J, Galosy-Guibal L, Ecochard R. 2004. Suicide in the French armed forces. Eur J Epidemiol 19:823–829.

Endicott J, Spitzer RL. 1978. A diagnostic interview: the schedule for affective disorders and schizophrenia. Arch Gen Psychiatry 35:837–844.

Y.-W. Yeh et al.
Fu TS, Lee CS, Gunnell D, Lee WC, Cheng AT. 2013. Changing trends in the prevalence of common mental disorders in Taiwan: a 20-year repeated cross-sectional survey. Lancet 381:235–241.

Hamilton M. 1960. A rating scale for depression. J Neurol Neurosurg Psychiatry 23:56–62.

Ho PS, Ho KK, Huang WS, Yen CH, Shih MC, Shen LH, et al. 2013. Association study of serotonin transporter availability and SLC6A4 gene polymorphisms in patients with major depression. Psychiatry Res 212:216–222.

Huang SY, Lin WW, Ko HC, Lee JF, Wang TJ, Chou VH, et al. 2004. Possible interaction of alcohol dehydrogenase and aldehyde dehydrogenase genes with the dopamine D2 receptor gene in anxiety-depressive alcohol dependence. Alcohol Clin Exp Res 28:374–384.

Huang WS, Huang SY, Ho PS, Ma KH, Huang YY, Yeh CB, et al. 2013. PET imaging of the brain serotonin transporters (SERT) with N,N-dimethyl-2-(2-amino-4-[18F]fluorophenylthio)benzylamine (4-[18F]-ADAM) in humans: a preliminary study. Eur J Nucl Med Mol Imaging 40:115–124.

Hyman J, Ireland R, Frost L, Cottrell L. 2012. Suicide incidence and risk factors in an active duty US military population. Am J Public Health 102(Suppl 1):S138–146.

Ichimiy T, Suhara T, Sudo Y, Okubo Y, Nakayama K, Nankai M, et al. 2002. Serotonin transporter binding in patients with mood disorders: a PET study with [11C](+)McN5652. Biol Psychiatry 51:715–722.

Ichise M, Meyer JH, Yonekura Y. 2001. An introduction to PET and SPECT neurotransmitter quantification models. J Nucl Med 42:755–763.

Innis RB, Cunningham VJ, Delforge J, Fujita M, Chrise M, Meyer J, et al. 2013. Decreased brainstem and putamen SERT binding potential in depressed suicide attempters using [11 C]-ZIEN T PET imaging. Depress Anxiety 30:902–907.

Jennings MA, Mann JJ. 2000. The biology of impulsivity and suicidality. Psychiatr Clin North Am 23:11–25.

Kilbourn MR, Wooten GS, Swanson RL, Shulfs J, et al. 2005. 123I-ADAM binding to serotonin transporters in patients with major depression and healthy controls: a preliminary study. J Nucl Med 46:973–977.

Kuo MC, Peng CJ, Linnoila M. 1988. Suicidal behavior, impulsiveness and risk factors in the biology of suicide. Neuropsychopharmacology 28:613–619.

Li D, He L. 2007. Meta-analysis supports association between serotonin transporter (5-HTT) and suicidal behavior. Mol Psychiatry 12:47–54.

Lindstrom MB, Ryding E, Bosson P, Ahnildie JA, Rosen I, Traskman-Bendz L. 2004. Impulsivity related to brain serotonin transporter binding capacity in suicide attempters. Eur Neuropsychopharmacol 14:295–300.

Little KY, McLaughlin DP, Ranc J, Gilmore J, Lopez JF, Watson S, et al. 1997. Serotonin transporter binding sites and mRNA levels in depressed persons committing suicide. Biol Psychiatry 41:1156–1164.

Mann JJ. 1999. Role of the serotonergic system in the pathogenesis of major depression and suicidal behavior. Neuropsychopharmacology 21:99–105S.

Mann JJ. 2013. The serotonergic system in mood disorders and suicidal behaviour. Phil Trans R Soc London B Biol Sci 368:20120537.

Meyer JH. 2007. Imaging the serotonin transporter during major depressive disorder and antidepressant treatment. J Psychiatry Neurosci 32:86–102.

Meyer JH, Houle S, Sagrat S, Carella A, Hussey DF, Ginovart N, et al. 2004. Brain serotonin transporter binding potential measured with carbon 11-labeled DASB positron emission tomography: effects of major depressive episodes and severity of dysfunctional attitudes. Arch Gen Psychiatry 61:1271–1279.

Miller JM, Hesselgrave N, Ogden RT, Sullivan GM, Quendo MA, Mann JJ, et al. 2013. Positron emission tomography quantification of serotonin transporter in suicide attempters with major depressive disorder. Biol Psychiatry 74:287–295.
World Health Organization. 2012. Public health action for the prevention of suicide. Geneva: WHO.
Wu YF, Chang KJ, Chang YC. 2013. An investigation of factors associated with suicidal attempts among male military personnel. Taiwanese J Psychiatry 27:41–51.
Yeh YW, Ho PS, Chen CY, Kuo SC, Liang CS, Ma KH, et al. 2015. Incongruent reduction of serotonin transporter associated with suicide attempts in patients with major depressive disorder: a positron emission tomography study with 4-[18F]-ADAM. Int J Neuropsychopharmacol 18. doi: 10.1093/ijnp/pyu065.
Yu YW, Tsai SJ, Lin CH, Hong CJ. 2002. Association study of the serotonin transporter promoter polymorphism and symptomatology and antidepressant response in major depressive disorders. Mol Psychiatry 7:1115–1119.

Supplementary material available online

Supplemental Figure 1 available online at http://informahealthcare.com/doi/abs/10.3109/15622975.2015.1048722).