Positron Emission Tomography Quantification of Serotonin$_{1A}$ Receptor Binding in Suicide Attempters With Major Depressive Disorder

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Abstract

IMPORTANCE—Serotonergic system dysfunction has been associated with increased lethal suicide attempts and suicide. Dysfunction includes higher binding of serotonin$_{1A}$ autoreceptor in the brainstem raphe of individuals who die by suicide.

OBJECTIVES—To determine the relationships between brain serotonin$_{1A}$ binding and suicidal behavior in vivo in major depressive disorder (MDD) using positron emission tomography and the serotonin$_{1A}$ antagonist radiotracer carbon C 11 [^{11}C]–labeled WAY-100635.

DESIGN, SETTING, AND PARTICIPANTS—Cross-sectional positron emission tomography study at an academic medical center from 1999 through 2009. We compared serotonin$_{1A}$ binding between individuals with MDD who did not attempt suicide (nonattempters) (n = 62) and those who attempted suicide (attempters) (n = 29). We subdivided the attempters into those with lower (n = 16) and higher (n = 13) levels of lethality.

MAIN OUTCOMES AND MEASURES—The binding potential (BP$_F$) of [^{11}C]WAY-100635 (calculated as the number of receptors available divided by affinity) in the prefrontal cortex (PFC) and brainstem, estimated by kinetic modeling with an arterial input function; the severity of suicidal behaviors, including lethality and intent of suicide attempts; and suicidal ideation.

RESULTS—Using a linear mixed-effects model, we found no difference between attempters and nonattempters with MDD in serotonin$_{1A}$ BP$_F$ in the PFC regions ($F_{1,88}$ = 0.03; P = .87) or in the raphe nuclei ($F_{1,88}$ = 0.29; P = .59). Raphe nuclei serotonin$_{1A}$ BP$_F$ was 45.1% greater in higher-lethality attempters compared with lower-lethality attempters ($F_{1,25}$ = 7.33; P = .01), whereas no difference was observed in the PFC regions ($F_{1,25}$ = 0.12; P = .73). Serotonin$_{1A}$ BP$_F$ in the raphe nuclei of suicide attempters was positively correlated with the lethality rating ($F_{1,25}$ = 10.56; P = .003) and the subjective lethal intent factor ($F_{1,25}$ = 10.63; P = .003; R^2 = 0.32) based on the most recent suicide attempt. Suicide ideation in participants with MDD was positively correlated with serotonin$_{1A}$ BP$_F$ in the PFC regions ($F_{1,88}$ = 5.19; P = .03) and in the raphe nuclei ($F_{1,87}$ = 7.38; P = .008; R^2 = 0.12).

CONCLUSIONS AND RELEVANCE—Higher brainstem raphe serotonin$_{1A}$ BP$_F$ observed in higher-lethality suicide attempters with MDD is in agreement with findings in suicide studies and also with the finding of low cerebrospinal fluid levels of 5-hydroxyindoleacetic acid in higher-lethality suicide attempters. Higher brainstem raphe serotonin$_{1A}$ BP$_F$ would be consistent with lower levels of serotonin neuron firing and release and supports a model of impaired serotonin signaling in suicide and higher-lethality suicidal behavior. Severity of suicidal ideation in MDD is related to brainstem and prefrontal serotonin$_{1A}$ BP$_F$, suggesting a role for both regions in suicidal ideation. Lower levels of serotonin release at key brain projection sites, such as the prefrontal regions, may favor more severe suicidal ideation and higher-lethality suicide attempts.

Suicide claimed the lives of more than 38 000 individuals in the United States in 2010.[1] Although the majority of suicides occur in the setting of a current psychiatric disorder, most commonly major depressive disorder (MDD),[2] most individuals with MDD never attempt suicide. Of those who do, fewer make higher-lethality attempts, confounding efforts to detect and mitigate suicide risk. Thus, an urgent need exists for in vivo biomarkers of suicide risk to assist clinical identification and management of such high-risk patients.

Biological studies of suicidal behaviors occurring within major depressive episodes repeatedly have identified evidence of central serotonin system hypofunction. Low cerebrospinal fluid (CSF) levels of 5-hydroxyindoleacetic acid (5-HIAA), serotonin's primary metabolite within the central nervous system, have been associated with prior suicide attempts, particularly violent and/or highly lethal attempts, and the prospective risk for suicide.[2–10] Serotonin release in response to the serotonergic agent fenfluramine hydrochloride also appears to be impaired in individuals with higher-lethality suicide attempts (attempters), as indicated by a blunted prolactin response.[11] In higher-lethality

suicide attempters, the suicidal intent is greater and the CSF levels of 5-HIAA are lower; a lifetime history of more severe aggression is also correlated with lower CSF levels of 5-HIAA.[12–14] However, CSF measures and neuroendocrine challenge studies do not provide information about the anatomical location of brain abnormalities within the serotonergic system or offer an explanation of the mechanism responsible for lower-level functioning of the serotonin system.

Uptake of fludeoxyglucose F 18 (FDG) in positron emission tomography (PET) is lower in the ventral, medial, and lateral prefrontal cortex (PFC) in higher-lethality suicide attempters who are depressed compared with lower-lethality attempters who are depressed; these differences become more pronounced on challenge with fenfluramine and are related to higher levels of suicidal intent and lower levels of impulsiveness.[9] Suicidal intent is also related to lower uptake of carbon C 11 [^{11}C]–labeled methyltryptophan in the ventromedial PFC,[15] whereas aggression is related to lower ventromedial FDG uptake in the PFC[16,17] and lower serotonin transporter binding in the anterior cingulate.[18] These findings provide some possible regional specificity to serotonergic abnormalities related to suicidality.

Postmortem studies of individuals who die by suicide (completers) find differences in serotonergic system markers in the brainstem and PFC regions. Findings include higher binding of serotonin$_{1A}$ autoreceptor in the dorsal raphe nucleus in suicides,[19] particularly in the rostral dorsal raphe nucleus,[20] and higher levels of serotonin$_{1A}$ autoreceptor binding in the ventrolateral PFC,[21,22] although not all studies find the PFC difference.[23]

Cerebrospinal fluid 5-HIAA and PET FDG uptake studies in higher-lethality suicide attempters and serotonin$_{1A}$ binding in suicide completers post mortem suggest a common biological substrate between suicide and higher-lethality nonfatal suicide attempts in MDD. In contrast, serotonergic function in lower-lethality suicide attempters appears more similar to that of individuals who do not attempt suicide (hereinafter referred to as nonattempters). Therefore, we assessed the relationship between serotonin$_{1A}$ binding in vivo and a history of suicide attempts in a large cohort with current MDD using PET imaging and the serotonin$_{1A}$ antagonist radiotracer [^{11}C]WAY-100635. We hypothesized that we would find higher levels of binding in the PFC and midbrain raphe nuclei in higher-lethality suicide attempters with MDD compared with lower-lethality attempters with MDD. We also explored correlations between serotonin$_{1A}$ autoreceptor binding and the severity of suicidal ideation and depression psychopathology.

Methods

Participants

The institutional review board of the New York State Psychiatric Institute approved the protocol. All participants provided written informed consent for study procedures.

We included 91 individuals who met *DSM-IV* criteria for a current major depressive episode and a diagnosis of MDD in this secondary analysis of data from a sample largely overlapping but expanded from previous reports.[24–26] This sample included 29 suicide attempters (consisting of 16 lower-lethality and 13 higher-lethality suicide attempters

defined by a median split based on the lethality rating of the most recent suicide attempt). Inclusion criteria were assessed through psychiatric interview, medical record review, the Structured Clinical Interview for *DSM-IV*, Patient Edition,[27] physician-obtained medical history, review of systems, results of a physical examination, and results of laboratory tests. These tests included a complete blood cell count, chemistry panel, thyroid function tests, urinalysis, and urine screening for drugs; female participants also underwent pregnancy testing. The diagnosis of MDD based on the Structured Clinical Interview for *DSM-IV* was conducted by experienced research masters- and doctoral-level psychologists. A team of experienced clinical research psychologists and psychiatrists (G.M.S., M.A.O., and A.B.) reviewed all diagnoses. The scores for the MDD diagnosis were greater than 0.85. The Beck Depression Inventory,[28] Hamilton Depression Rating Scale (the 17-item scale for screening and the 24-item scale for severity correlations with binding),[29] and Global Assessment Scale[30] assessed subjective and objective depression severity and functional impairment, respectively. Diagnoses of Axis II personality disorder were determined using the Structured Clinical Interview for *DSM-IV* Axis II Personality Disorders.[31] The behavioral data reported on suicide attempts refer to the most recent attempt for participants reporting more than 1 attempt. All suicide attempt data were gathered using the Columbia Suicide History Form,[32] which uses clinical probes and anchor points to identify suicide attempts chronologically that meet the Columbia Classification Algorithm of Suicide Assessment criteria[33] and documents the method and medical damage of each suicide attempt. The Medical Lethality Scale[34] scores medical damage caused by a suicide attempt on a scale ranging from 0 (no injury) to 8 (fatal), with anchor points dependent on the method of the attempt. The assessment also incorporates the Beck Scale for Suicide Ideation[35] for all participants and the Beck Suicide Intent Scale[34] for attempters. Ratings of suicidal intent components were based on a 2-factor solution resulting from a prior analysis of the Beck Suicide Intent Scale.[36] Factor 1, termed *lethal intent*, is the sum of items pertaining to subjective intent. Factor 2, termed *planning*, is the sum of the items pertaining to the objective degree of planning for the attempt. Lifetime history of aggression was measured by the Brown-Goodwin Lifetime History of Aggression Scale.[37]

Inclusion criteria for all participants consisted of age 18 to 65 years, *DSM-IV* criteria for a current major depressive episode and MDD, a 17-item Hamilton Depression Rating Scale[29] score greater than 16, and the capacity to provide informed consent. Exclusion criteria were a history of alcohol or substance abuse or dependence not in remission for at least the preceding 6 months; lifetime exposure to 3,4-methylenedioxymethamphetamine more than 2 times; significant unstable medical conditions; pregnancy; and a diagnosis of psychosis, bipolar disorder, or schizophrenia. All participants were free of psychotropic medications for at least 2 weeks (6 weeks for fluoxetine hydrochloride and 4 weeks for neuroleptics) with the exception of short-acting benzodiazepines, which could be used as needed up to 72 hours before PET scanning for treatment of anxiety or insomnia. Results of the urine toxicology screen were negative for all participants enrolled.

Sixteen of the 91 participants met criteria for past alcohol or substance abuse or dependence (with remission for >6 months before the PET studies). Six participants had past cannabis abuse; 1, past cannabis dependence; 3, past cocaine abuse; 1, past stimulant abuse; 1, past

stimulant dependence; 8, past alcohol abuse; 3, past alcohol dependence; and 2, past hallucinogen abuse. None had a history of crack cocaine use disorder.

In this sample, the time from the most recent suicide attempt to PET imaging ranged from 9 days to 36.8 years. The mode was 1008 days, and the mean (SD) interval was 6.8 (9.5) years.

History of Medication Use

A previous study[26] has shown that antidepressant-naive individuals with current MDD have higher [^{11}C]WAY-100635 binding potential (BP$_F$) values in the brain, indicating higher serotonin$_{1A}$ binding compared with healthy volunteers. In a comprehensive replication of this effect of MDD on serotonin$_{1A}$ binding,[25] patients with MDD were categorized as not recently receiving medication (NRM) and recently receiving medication (RM), with NRM defined as no history of antidepressant exposure within the 4 years before the study. The NRM group included patients with MDD and no lifetime antidepressant exposure and patients with MDD who were not treated with antidepressants for at least the previous 4 years because those 2 groups did not differ in their composite binding data.

We used this classification in the present analyses, which include a larger sample of NRM (n = 49) and RM (n = 42) participants with MDD than in the previous studies.[25,26] Those participants who could not recall the name or dose of a medication or the duration of therapy and for whom records of medication history were otherwise unavailable were classified as *indeterminate* (n = 13) and were not included. Because lower levels of binding were observed in the RM group,[25] this potential medication effect was controlled for in all analyses.

The sample of NRM participants with MDD in the present study has 19 additional participants added to the previously described sample of 30 participants concerning the effect of MDD on serotonin$_{1A}$ binding.[25] Sixty-three additional participants with MDD were added to the 28 participants with MDD in the previous report of an effect of MDD on serotonin$_{1A}$ binding.[26]

Radiochemistry and Input Function Measurement

Preparation of [^{11}C]WAY-100635 and measurement of the arterial input function, metabolites, and plasma-free fraction (*f*$_P$) have been described previously.[38,39] Radioligand metabolite data were collected during the first 60 minutes; we were unable to quantify metabolites beyond this time point.

Image Acquisition and Analysis

The PET imaging was performed on a commercially available scanner (ECAT EXACT HR +; Siemens/CTI). Emission data were collected for 110 minutes as 20 successive frames of increasing duration. Image analysis was performed using graphics software (MATLAB 2006b; MathWorks) with extensions to the Functional Magnetic Resonance Imaging of the Brain's Linear Image Registration Tool (FLIRT), version 5.2[40]; the Brain Extraction Tool, version 1.2[41]; Statistical Parametric Mapping normalization[42]; and segmentation routines.[43]

To correct for participant motion during the PET scan, denoising filter techniques were applied to all PET images starting at frame 5. All frames were aligned using rigid-body FLIRT to frame 8. A mean of motion-corrected frames 8 through 18 was registered to the magnetic resonance image (MRI) using FLIRT. Acquisition of the T1-weighted MRI for coregistration of PET images and identification of regions of interest (ROIs) was performed as previously described using a 1.5-T (Signa Advantage; General Electric) or a 3-T (Signa HDx; General Electric) system.[39] The ROIs were hand drawn on the MRI by experienced technicians trained to reliably approximate these regions using brain atlases[44,45] and published reports[46,47] and who were blinded to the clinical data. The ROIs included the dorsolateral, medial, and ventral PFC and the anterior cingulate cortex. A fixed-volume elliptical ROI ($2 cm^3$) was placed on the raphe nuclei in the dorsal midbrain on a mean PET image, as previously described.[26] A cylindrical ROI was drawn in the cerebellar white matter (CWM), which served as the reference region.[38] The ROI contours were processed using the segmented MRI to confine analyses in cortical regions to gray matter voxels.

Derivation of Regional Outcome Measures

The outcome measure of choice in PET neuroreceptor studies is the total number of receptors available (B_{avail}) in vivo to bind the radioligand divided by the receptor ligand affinity (K_D). However, without multiple injections and occupancy of the receptors, current technology permits only measurement of $BP_F = B_{avail}/K_D$. Fortunately, no evidence exists for alterations in serotonin$_{1A}$ K_D in depression.[21] Regional distribution volumes (V) of [^{11}C]WAY-100635 are derived from kinetic analysis using the arterial input function and a 2-tissue compartment model.[39] The distribution volumes of the nondisplaceable (V_{ND}) and specific (V_S) compartments were defined.[48] The total regional equilibrium distribution volume (V_T) was equal to the sum of V_{ND} and V_S. Time activity curves were fit with a 2-tissue compartment model, with the K_1:K_2 ratio fixed to that of the CWM (the reference region with virtually no serotonin$_{1A}$). For the CWM, a1-tissue compartment model was used.[38] We calculated the BP_F as $(V_{T(ROI)} - V_{T(CWM)})/f_P$. The contribution of plasma total activity to the regional activity was calculated assuming a 5% blood volume in the ROI and subtracted from the regional activity before statistical analyses. Kinetic parameters were derived by nonlinear regression using software programmed in MATLAB. The BP_F measures maximum specific binding divided by K_D and involves the fewest assumptions about tracer delivery, clearance, and protein binding. Although some uncertainty remained in measuring f_P, we expected that the extent of the participant-to-participant variability in f_P relative to the noise in measuring it justifies adjusting for it on the participant level. Partial volume effects should be comparable for higher- and lower-lethality suicide attempters. To some degree, the effect of f_P and any other index on measurement error is mitigated by the weightings that we used.

Statistical Analysis

To borrow strength across ROIs and to account for correlation among ROIs properly in the same participant, we fit linear mixed-effects models to the ROI-level BP_F estimates, with region and group as fixed effects and participant as the random effect, providing a powerful test of our primary hypothesis without the need to correct for multiple comparisons. To stabilize variance across regions, adjust for slight skewness in distribution of binding

measures, and allow a proportional change in binding across regions, we fit the model to log-transformed binding potentials. Log transformation has been used in multiple previous PET studies[25,26,49–56] to address these issues. Other groups have used related statistical approaches, including linearizing transformation[57] and nonparametric testing,[58] to address these issues in analyzing PET data. Demonstrating a difference in log (BP_F) is equivalent to demonstrating a difference in the same direction of raw BP_F because the natural log is a monotone transformation. We computed estimated SEs using a bootstrap algorithm that takes into account errors in metabolite, plasma, and brain data,[59] with observations weighted accordingly. Analyses controlled for recent (within 15-1460 days of PET) history of antidepressant use (RM vs NRM) and sex.[25,60] Models were fit using the nlme package in the R software environment (http://www.r-project.org). Additional statistical analyses, including the *t* test, χ^2 test, and Fisher exact test, were performed using commercially available software (SPSS Statistics, version 20.0 [IBM Corp, 2011] or R software). All tests were 2 tailed.

Results

Serotonin$_{1A}$ BP$_F$ in Nonattempters Compared With Attempters

Clinical and demographic characteristics of the nonattempters and attempters with MDD are summarized in Table 1. The nonattempters were older than the attempters by a mean of about 6 years. Attempters had higher levels of suicidal ideation in the 2 weeks before PET, lower Global Assessment Scale scores, and greater hopelessness and were younger at the onset of MDD. Otherwise, the nonattempter and attempter groups were comparable on educational level, clinician- and self-rated depression severity, lifetime aggression, and the Reasons for Living Scale score. We found no group differences in radioligand administration parameters, that is, specific activity or injected dose of [^{11}C]WAY-100635, or in the injected mass of WAY-100635. In addition, we found no group differences in the radiotracer-free fraction (f_P) in plasma or in the V_T of the reference region ($V_{T(CWM)}$). Age was not related to serotonin$_{1A}$ BP$_F$ in the raphe nuclei ($P = .93$) or the PFC ($P = .62$). The age at onset of MDD was not related to serotonin$_{1A}$ BP$_F$ in the raphe nuclei ($P = .54$) or the PFC ($P = .20$). No differences were found in brainstem raphe serotonin$_{1A}$ BP$_F$ in relation to lifetime history of suicide attempts (ie, attempters vs nonattempters with MDD) ($F_{1,88} = 0.29$; $P = .59$) or in the PFC BP$_F$ ($F_{1,88} = 0.03$; $P = .87$) between these 2 groups.

Serotonin$_{1A}$ BP$_F$ in Lower- vs Higher-Lethality Attempters

Clinical and demographic characteristics of the lower- and higher-lethality attempters with MDD are summarized in Table 2. In addition to a higher mean lethality score of the most recent suicide attempt, the higher-lethality group also had greater suicidal intent. Otherwise, both attempter subgroups were comparable on demographic and clinical variables and the radiotracer administration parameters f_P and $V_{T(CWM)}$.

The higher-lethality attempters with MDD had higher serotonin$_{1A}$ BP$_F$ in the raphe nuclei compared with the lower-lethality attempters with MDD ($F_{1,25} = 7.33$; $P = .01$). Binding of the serotonin$_{1A}$ autoreceptor was 45.1% higher in the higher-lethality attempters. In all attempters with MDD, the lethality rating and serotonin$_{1A}$ BP$_F$ binding in the raphe nuclei

were positively correlated ($F_{1,25} = 10.56$; $P = .003$; $R^2 = 0.32$) (Figure 1). In contrast in the PFC, serotonin$_{1A}$ BP$_F$ did not differ between the higher- and lower-lethality attempter groups (X vs X; $F_{1,25} = 0.12$; $P = .73$). We found no relationship between lethality and the PFC serotonin$_{1A}$ BP$_F$ ($F_{1,25} = 1.70$; $P = .20$). No effects of sex ($F_{1,25} = 0.04$; $P = .85$) or prior anti-depressant status ($F_{1,25} = 1.04$; $P = .32$) on raphe nuclei binding were observed.

When the presence of a cluster B personality disorder diagnosis was considered as a predictor in the model, the effect of lethality on the raphe nuclei serotonin$_{1A}$ BP$_F$ remained significant ($F_{1,24} = 7.84$; $P = .01$), and no effect of cluster B personality disorder diagnosis on binding was found ($F_{1,24} = 0.01$; $P = .93$). The degree of intent to attempt suicide or the degree of planning correlates with the lethality of the attempt (29 participants; $R^2 = 0.617$; $P < .001$). This finding may reflect the lower lethality observed in more impulsive, less planned attempts. Similarly, considering lifetime aggression severity as measured by the Brown-Goodwin Lifetime History of Aggression Scale as a predictor in the model, the effect of lethality remained significant ($F_{1,24} = 7.29$; $P = .01$), and no effect of aggression history was observed ($F_{1,24} = 0.08$; $P = .78$).

Serotonin$_{1A}$ BP$_F$ and Suicide Intent Rating in Attempters

Total Beck Suicide Intent Scale score and the raphe nuclei serotonin$_{1A}$ BP$_F$ were positively correlated ($F_{1,25} = 7.89$; $P < .01$), which post hoc analyses showed was accounted for by factor 1 (subjective lethal intent) ($F_{1,25} = 10.63$; $P = .003$; $R^2 = 0.32$) (Figure 2) and not factor 2 (objective planning) ($F_{1,25} = 2.05$; $P = .16$). No relationship was found between the PFC region serotonin$_{1A}$ BP$_F$ and the Beck Suicide Intent Scale score ($F_{1,25} = 0.09$; $P = .76$) or with either factor score.

Relationships Among Serotonin$_{1A}$ BP$_F$, Suicide Ideation, and Depression Severity

In the entire MDD group, the Beck Scale for Suicide Ideation score was positively correlated with serotonin$_{1A}$ BP$_F$ in PFC regions ($F_{1,88} = 5.19$; $P = .03$), with a significant effect of prior antidepressant status ($F_{1,88} = 7.28$; $P < .01$). The Beck Scale for Suicide Ideation score was also related to serotonin$_{1A}$ BP$_F$ in the raphe nuclei ($F_{1,87} = 7.38$; $P = .008$; $R^2 = 0.12$) (Figure 3), but raphe nuclei binding was not significantly related to prior anti-depressant status ($F_{1,87} = 3.86$; $P = .053$). Depression severity, as rated on the 24-item version of the Hamilton Depression Rating Scale,[29] was not related to raphe nuclei ($F_{1,87} = 1.65$; $P = .20$) or to PFC ($F_{1,88} = 0.18$; $P = .67$) binding.

Discussion

Consistent with postmortem studies showing higher dorsal raphe nuclei serotonin$_{1A}$ binding in individuals who die by committing suicide[19,20] and with our hypothesis, we found that higher-lethality suicide attempters with MDD have higher raphe nuclei serotonin$_{1A}$ BP$_F$ compared with lower-lethality attempters with MDD. In contrast, serotonin$_{1A}$ BP$_F$ did not differ when all attempters with MDD were compared with all nonattempters with MDD. Within both suicide attempter groups with MDD (higher and lower lethality), lethality of the most recent suicide attempt was positively correlated with raphe nuclei binding; the Beck Suicide Intent Scale score[34–36] was also positively correlated with binding. The degree of

suicide intent correlated moderately with the lethality of suicide attempts, as has been reported.[34,35] Thus, higher serotonin$_{1A}$ binding in vivo in higher-lethality attempters and in postmortem examination of individuals who complete suicide may represent a common biological marker of risk for higher lethality and intent or more serious suicidal behavior. Such a biological commonality between suicide and more lethal suicide attempts is also apparent in the demographic similarities (more men and older individuals) and in the clinical picture of more depression and less impulsiveness. Less lethal suicide attempts are more characteristic of women and younger individuals and are more impulsive.

Somatodendritic serotonin$_{1A}$ autoreceptors in the raphe nuclei inhibit raphe serotonergic neuron firing and thus the frequency of serotonin release from terminals.[61,62] Therefore, higher raphe nuclei serotonin$_{1A}$ binding in higher-lethality attempters with MDD may indicate less neuronal firing and less serotonin release at terminal projection regions in the forebrain,[63,64] favoring higher-lethality suicide attempts. We also find greater suicide intent correlated with higher raphe nuclei serotonin$_{1A}$ binding, and suicide intent correlates with more lethal suicidal behavior.[65–67] This observation is also consistent with prior work in young suicide attempters[15] showing that less [^{11}C]methyltryptophan uptake in the medial ventral PFC correlates with greater suicide intent. Higher raphe nuclei serotonin$_{1A}$ autoreceptor binding in higher-lethality attempters would be expected to be associated with less serotonin neuron firing at PFC terminals, which in turn may result in less tryptophan uptake for production of serotonin at these PFC terminals.

Our finding of higher serotonin$_{1A}$ binding in higher-lethality suicide attempters with MDD is consistent with low CSF 5-HIAA levels in higher-lethality attempters with MDD and future suicide completers with MDD and is consistent with a blunted prolactin response to a fenfluramine-stimulated serotonergic challenge in higher-lethality suicide attempters.[11,68] These results further indicate that higher raphe nuclei serotonin$_{1A}$ binding may be a marker of more serious suicidal behavior in those at risk for suicide attempts.

Serotonin$_{1A}$ binding is 17% to 30% higher in PFC regions post mortem in individuals who complete suicide compared with those with nonsuicide deaths assayed using the serotonin$_{1A}$ agonist 8-OH-DPAT. Agonists bind to the subset of receptors in the agonist high-affinity state.[69] The antagonist radiotracer [^{11}C]WAY-100635 binds to agonist high- and low-affinity states of serotonin$_{1A}$. Nonhuman primate PET imaging comparing a serotonin$_{1A}$ agonist tracer and [^{11}C]WAY-100635 indicates that only about half of the total binding of [^{11}C]WAY-100635 in the PFC regions is attributable to high–agonist affinity receptors.[70] In serotonin$_{1A}$ BP$_F$ in the raphe nuclei, we detected more than 45.1% higher binding in higher-lethality attempters, a difference that is comparable to that reported in individuals who complete suicide. Our median split for dividing attempters into higher- and lower-lethality groups was a score between 1 and 2, whereas prior CSF studies had a cut point between 2 and 3.[7,11] We had fewer higher-lethality attempters in our study, which limited our power to detect binding differences associated with greater lethality.

Among all 91 participants with MDD, suicidal ideation in the 2 weeks before PET imaging was positively correlated, albeit weakly ($R^2 = 0.12$), with serotonin$_{1A}$ BP$_F$ in the raphe nuclei and PFC regions. This finding suggests a more general role for serotonin$_{1A}$ signaling

in determining suicidal ideation severity, and severity of suicidal ideation can predict risk for future suicide.[71]

Cluster B personality disorders are typically associated with more impulsive behaviors.[72] The lower-lethality attempter group had about 3 times the rate of cluster B personality disorders (46.2%) compared with the higher-lethality attempter group (16.7%). This difference suggests that the higher raphe nuclei serotonin$_{1A}$ binding in higher-lethality attempters represents a biomarker for suicide attempts that are associated with more intent and with less impulsive traits or fewer personality disorders. Consistent with this model, we find better planned, less impulsive suicide attempts are more lethal. Objective and subjective depression severity and hopelessness were comparable between the higher- and lower-lethality attempter groups, and, as previously reported, serotonin$_{1A}$ binding was not related to depression severity.[25,26]

In terms of the causes of higher serotonin$_{1A}$ binding that we observed in higher-lethality attempters with MDD, there are a few possibilities. The first is the C($-$1019)G genetic variant in the promoter of the serotonin$_{1A}$ gene (HTR1A [HGNC 5286]), where the G allele is associated with greater expression in the brainstem serotonin neurons,[73] and higher raphe nuclei autoreceptor binding is seen on PET imaging.[26] Second, animal studies of developmental adversity report that maternal deprivation in rodent models can upregulate binding in some brain regions, such as the hippocampus, although not the raphe nuclei autoreceptors.[74] In the non-human primate, peer rearing is associated with in vivo serotonin$_{1A}$ binding differences by PET that are sex dependent.[75] We did not detect an effect on binding of reported childhood (younger than 15 years) adversity. In fact, we found no effect of abuse at any age. Considering abuse in our model did not alter the significance of the lethality effect on binding. Therefore, we found no evidence that adversity explained the higher raphe nuclei binding or that it contributed to the effect of lethality.

Diminished serotonin activity could be caused by other factors, such as lower tryptophan hydroxylase 2 activity or expression. However, postmortem studies in depressed individuals who complete suicide have found *greater* tryptophan hydroxylase 2 expression and more serotonin neurons within raphe nuclei[76–78]; therefore, other mechanisms, such as serotonin$_{1A}$ autoreceptor overexpression, must be responsible for the hyposerotonergic state we observed in our sample of higher-lethality attempters.

This study has some limitations. Although this study has, to our knowledge, the largest sample size for a published PET study of this receptor, the numbers in the MDD attempter subgroups were too small to determine whether higher binding was associated with the G allele or reported childhood adversity. We detected lower serotonin$_{1A}$ binding in participants reporting use of antidepressants within 4 years of PET scanning, in agreement with a previous report.[25] All analyses therefore controlled for this factor. Recruiting a sample of antidepressant-naive participants is challenging logistically and is not representative of most clinical populations. The mean age of the attempters with MDD was about 6 years younger than that of the nonattempters with MDD, but previous studies have not identified an effect of age on the binding of [^{11}C]WAY100635 in the age range of this study.[25,61]

Conclusions

Other serotonin system findings on brain scanning include low brainstem serotonin transporter binding in attempters with MDD compared with nonattempters with MDD and healthy volunteers,[79] low serotonin-related lower FDG uptake in the PFC in higher-lethality attempters with MDD,[9] and lower [^{11}C]methyltryptophan uptake in ventromedial PFC in higher-intent suicide attempters.[15] Taken together with our findings of higher raphe nuclei serotonin$_{1A}$ binding in higher-lethality suicide attempters, these studies indicate key pathologic differences in serotonin system functioning in suicide attempters and particularly those at risk for more lethal and serious forms of suicidal behaviors.

Acknowledgments

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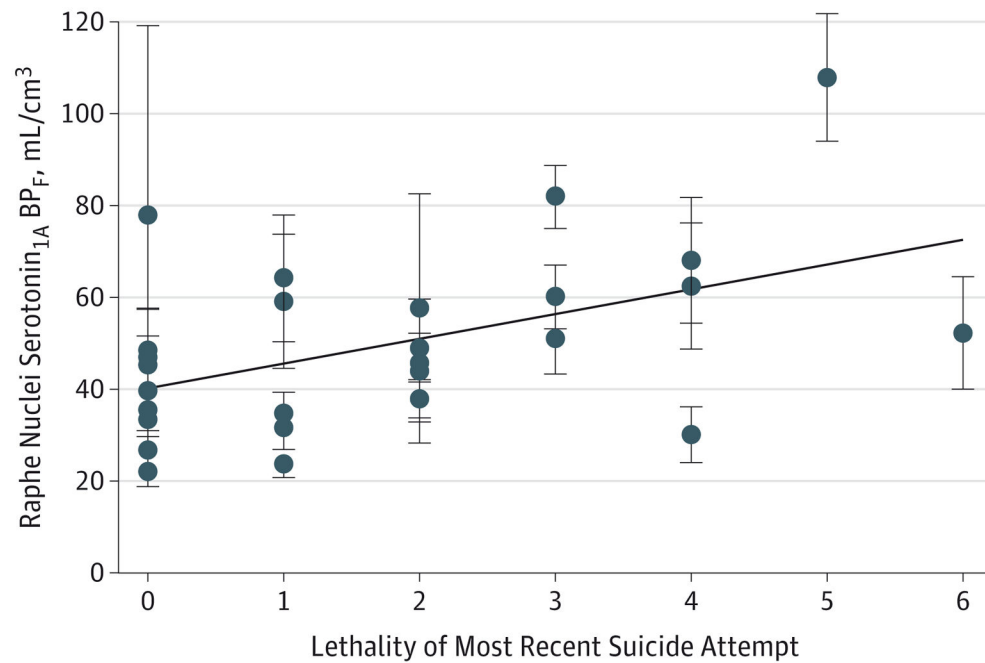
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Raphe Nuclei Serotonin$_{1A}$ BP$_F$, mL/cm^3
120
100
80
60
40
20
0
0
1
2
3
4
5
6
Lethality of Most Recent Suicide Attempt

Figure 1. Bivariate Plot of the Relationship Between Raphe Nuclei Serotonin$_{1A}$ Binding Potential (BP$_F$) and Lethality Rating of the Most Recent Suicide Attempt

Participants include the 29 suicide attempters with major depressive disorder (MDD). Error bars depict associated SE; diagonal line, the fitted curve; and slope, the correlation. Lethality of the attempt was measured using the Beck Medical Lethality Scale (scores range from 0 to 6, and the scale scores to 8, which designates a fatal attempt) ($F_{1,25} = 10.56$; $P = .003$; $R^2 = 0.32$). Displayed serotonin$_{1A}$ BP$_F$ estimates have been adjusted for sex and prior antidepressant use derived from the specific linear mixed-effects model examining the relationship of raphe nuclei serotonin$_{1A}$ BP$_F$ with lethality for all suicide attempters with MDD. For display purposes, 1 lower-lethality attempter with a very high serotonin$_{1A}$ BP$_F$ and SE is not included in this plot but was included in all the statistical analyses.
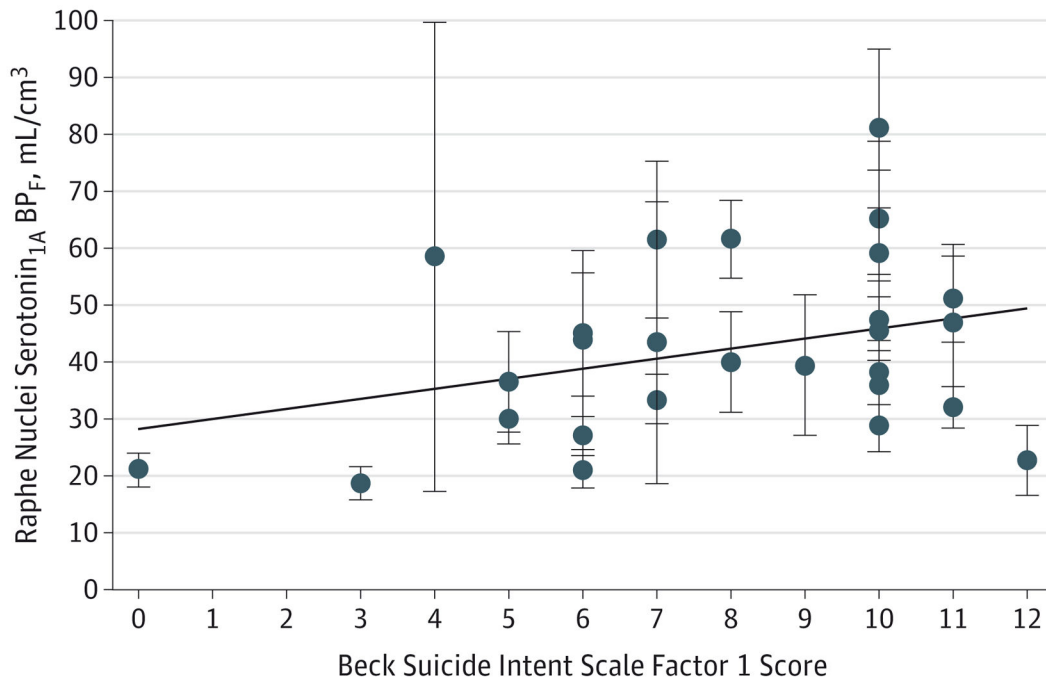
Figure 2. Bivariate Plot of the Relationship Between Raphe Nuclei Serotonin$_{1A}$ Binding Potential (BP$_F$) and the Beck Suicide Intent Scale Factor 1 Score in Suicide Attempters

Participants include the 29 suicide attempters with major depressive disorder (MDD). Error bars depict associated SE; diagonal line, best fit; and slope, correlation. Factor 1 indicates lethal intent (scores range from 0 to 12) ($F_{1,25} = 10.63$; $P = .003$; $R^2 = 0.32$). Displayed serotonin$_{1A}$ BP$_F$ estimates have been adjusted for sex and prior antidepressant medication status derived from the specific linear mixed-effects model examining the relationship of raphe nuclei serotonin$_{1A}$ BP$_F$ with the factor 1 score in all suicide attempters with MDD. For display purposes, 1 lower-lethality attempter with a very high serotonin$_{1A}$ BP$_F$ and SE is not included in this plot but was included in all the statistical analyses.
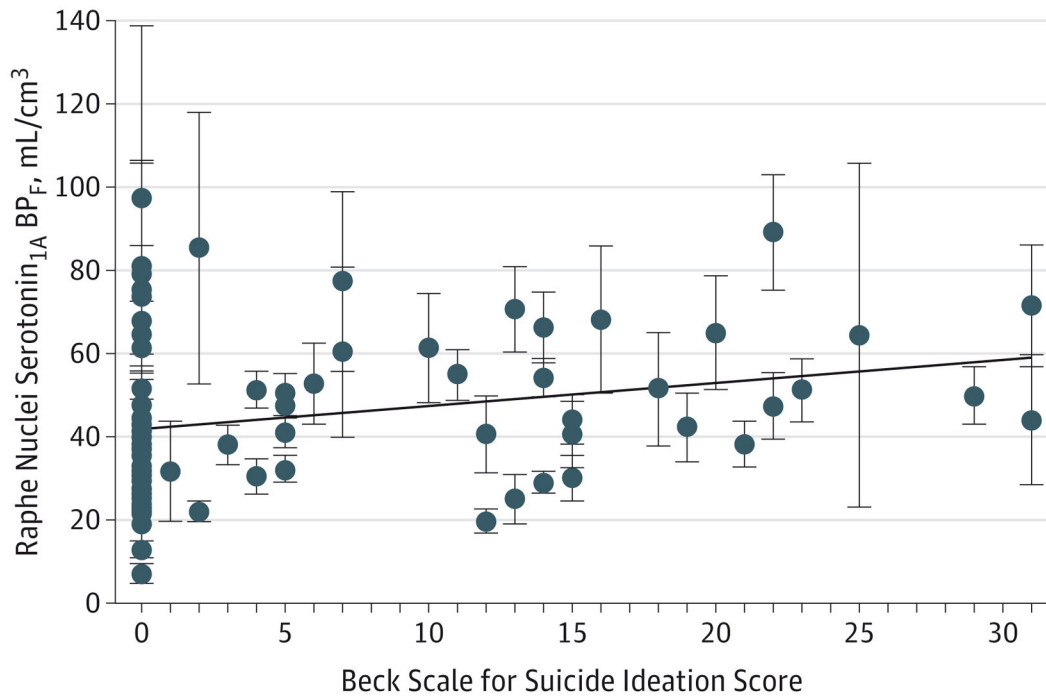
Figure 3. Bivariate Plot of the Relationship Between Raphe Nuclei Serotonin$_{1A}$ Binding Potential (BP$_F$) and the Beck Scale for Suicide Ideation Score in All Participants

Participants include the 91 patients with major depressive disorder (MDD). Error bars depict associated SE; diagonal line, best fit; and slope, correlation. Suicidal ideation scores in the 2 weeks before positron emission tomography range from 0 to 30 ($F_{1,87} = 7.38$; $P = .008$; $R^2 = 0.12$). Displayed serotonin$_{1A}$ BP$_F$ estimates have been adjusted for sex and prior antidepressant use derived from the specific linear mixed-effects model examining the relationship of raphe nuclei serotonin$_{1A}$ BP$_F$ with the Beck Scale for Suicide Ideation score in all participants with MDD. For display purposes, 1 lower-lethality attempter with a very high serotonin$_{1A}$ BP$_F$ and SE is not included in this plot but was included in all the statistical analyses.

Table 1

Demographic and Clinical Characteristics of the Attempter and Nonattempter MDD Groups[a]

Characteristic	Study Group		Group Comparison	
	Suicide Nonattempters (n = 62)	Suicide Attempters (n = 29)	Test Statistic	P Value
Age, y	40.4 (12.4)	34.6 (12.3)	$t_{89} = 2.11$	.04
Educational level, y	14.9 (3.2)	14.1 (4.3)	$t_{89} = 1.03$	.31
HDRS-24 score	25.7 (6.7)	27.6 (6.1)	$t_{89} = -1.29$	.20
Beck Depression Inventory score	26.8 (9.6)	30.7 (10.4)	$t_{87} = -1.73$	.09
Beck SSI score	3.4 (5.5)	9.7 (11.6)	$t_{89} = -3.52$	.001
Beck Suicide Intent Scale score	NA	14.4 (5.0)		
Lethality of attempt score	NA	1.6 (1.7)		
Lifetime aggression score[b]	18.2 (4.9)	19.2 (5.1)	$t_{75} = -0.83$	.41
Global Assessment Scale score	54.0 (10.6)	48.0 (10.9)	$t_{89} = 2.52$	.01
Reasons for Living Scale score	2.2 (2.4)	1.6 (1.9)	$t_{89} = 1.03$	.30
Beck Hopelessness Scale score	9.9 (6.7)	13.3 (5.3)	$t_{89} = -2.39$	.02
Age at onset of MDE, y	23.5 (12.1)	17.9 (10.3)	$t_{89} = 2.17$	.03
Female sex, %	64.5	65.5	$\chi_1^2 = 0.009$	.93
Cluster B personality disorder, %	12.2	32.0	Fisher exact test	.06
Lifetime history of abuse, %	56.7	60.7	$\chi_1^2 = 0.128$	.72
History of abuse before 15 years of age, %	45.0	46.4	$\chi_1^2 = 0.016$	.90
SSI score >0 at baseline, %[c]	37.1	48.3	$\chi_1^2 = 1.023$	.31
Specific activity, mCi/nmol	3.85 (1.80)	3.55 (1.85)	$t_{89} = 0.72$	.47
Injected dose, mCi/kg	0.09 (0.05)	0.10 (0.04)	$t_{89} = -0.96$	.34
Injected mass, mg/kg	0.02 (0.01)	0.03 (0.02)	$t_{89} = -1.69$	.09
f_P, %	6.44 (2.26)	6.21 (2.13)	$t_{89} = 0.45$	.65
$V_{T(CWM)}$, mL/cm^3	0.29 (0.09)	0.27 (0.10)	$t_{89} = 0.89$	.38

Abbreviations: fP, plasma-free fraction; HDRS-24, 24-item version of Hamilton Depression Rating Scale; MDD, major depressive disorder; MDE, major depressive episode; NA, not applicable; SSI, Scale for Suicide Ideation; $V_{T(CWM)}$, volume of distribution in cerebellar white matter.

SI conversion factor: To convert millicuries to millibecquerels, multiply by 3.7×10^{10}.

[a]Unless otherwise indicated, data are expressed as mean (SD).

[b]Determined using the Brown-Goodwin Lifetime History of Aggression Scale for 51 nonattempters and 26 attempters.

[c]Indicates some ideation is present at entry into the study.

Table 2

Demographic and Clinical Characteristics of the Higher- and Lower-Lethality Attempter Subgroups With MDD[a]

Characteristic	Study Subgroup		Group Comparison	
	Lower-Lethality Attempters (n = 16)	Higher-Lethality Attempters (n = 13)	Test Statistic	P Value
Age, y	30.8 (13.0)	39.2 (9.9)	$t_{27} = -1.92$	.07
Educational level, y	13.0 (5.4)	15.4 (1.8)	$t_{27} = -1.53$	.14
HDRS-24 score	27.1 (6.2)	28.2 (6.1)	$t_{27} = -0.48$	.64
Beck Depression Inventory score	28.8 (10.5)	32.9 (12.3)	$t_{27} = -1.03$	.31
Beck SSI score	6.4 (10.5)	13.7 (12.1)	$t_{27} = -1.73$	.09
Beck Suicide Intent Scale score	12.1 (5.1)	17.2 (3.2)	$t_{27} = -3.12$	.004
Lethality of attempt score	0.3 (0.5)	3.2 (1.3)	$t_{14.644} = -7.68$	<.001
Lifetime aggression score[b]	20.1 (5.0)	18.3 (5.4)	$t_{27} = 0.87$	.39
Global Assessment Scale score	49.4 (10.8)	46.2 (11.1)	$t_{27} = 0.77$	.45
Reasons for Living Scale score	2.1 (2.2)	1.1 (1.4)	$t_{27} = 1.40$	.17
Beck Hopelessness Scale score	13.6 (4.5)	13.0 (6.5)	$t_{27} = 0.28$	.78
Age at onset of MDE, y	17.9 (12.2)	17.9 (7.9)	$t_{27} = 0.01$	.99
Female sex, %	62.5	69.2	Fisher exact test	>.99
Cluster B personality disorder, %	46.2	16.7	Fisher exact test	.20
Lifetime history of abuse, %	80.0	38.5	$\chi_1^2 = 5.04$	.03
History of abuse before 15 years of age, %	60.0	30.8	$\chi_1^2 = 2.39$	.12
SSI score >0 at baseline, %[c]	37.5	61.5	$\chi_1^2 = 1.66$	.20
Specific activity, mCi/nmol	3.48 (1.56)	3.65 (2.21)	$t_{27} = -0.25$	.80
Injected dose, mCi/kg	0.10 (0.04)	0.10 (0.05)	$t_{27} = -0.13$	.90
Injected mass, mg/kg	0.02 (0.01)	0.03 (0.03)	$t_{27} = -0.57$	.57
f_P, %	6.36 (2.62)	6.03 (1.39)	$t_{27} = 0.42$	.68
$V_{T(CWM)}$, mL/cm^3	0.27 (0.10)	0.28 (0.12)	$t_{27} = -0.32$	.75

Abbreviations: See Table 1.

SI conversion factor: To convert millicuries to millibecquerels, multiply by 3.7×10^{10}.

[a]Unless otherwise indicated, data are expressed as mean (SD).

[b]Determined using the Brown-Goodwin Lifetime History of Aggression Scale for 13 higher- and 13 lower-lethality attempters.

[c]Indicates some ideation is present at entry into the study.