Published in final edited form as:
Biol Psychiatry. 2013 August 15; 74(4): 287–295. doi:10.1016/j.biopsych.2013.01.024.

PET quantification of serotonin transporter in suicide attempters with major depressive disorder

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Abstract

Background—Several lines of evidence implicate abnormal serotonergic function in suicidal behavior and completed suicide, including low serotonin transporter binding in postmortem studies of completed suicide. We have also reported low *in vivo* serotonin transporter binding in major depressive disorder (MDD) during a major depressive episode using positron emission tomography with [^{11}C]McN5652. We quantified regional brain serotonin transporter binding *in vivo* in depressed suicide attempters, depressed non-attempters, and healthy controls using positron emission tomography and a superior radiotracer, [^{11}C]DASB.

Methods—51 subjects with DSM-IV current MDD, 15 of whom were past suicide attempters, and 32 healthy controls underwent PET scanning with [^{11}C]DASB to quantify *in vivo* regional brain serotonin transporter binding. Metabolite-corrected arterial input functions and plasma free-fraction were acquired to improve quantification.

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Financial Disclosures:
Dr. Ogden and Ms. Hesselgrave report no biomedical financial interests or potential conflicts of interest. Dr. Miller has received financial compensation for psychiatric evaluations of subjects enrolled in medication studies sponsored by Pfizer and Orexigen Therapeutics, unrelated to the current manuscript. His family owns stock in Johnson & Johnson. Dr. Sullivan serves as a member of the Scientific Advisory Board of TONIX Pharmaceuticals, Inc. and has received compensation in the form of stock shares; he has served as a consultant for Ono Pharma USA, Inc.; and he has a US patent application for a use of tianeptine. None is related to the current manuscript. Dr. Mann received past unrelated grants from GSK and Novartis, and royalties for a rating scale, C-SSRS. Dr. Oquendo receives royalties for the use of the Columbia Suicide Severity Rating Scale and received financial compensation from Pfizer for the safety evaluation of a clinical facility, unrelated to the current manuscript. She was the recipient of a grant from Eli Lilly to support a year of the salary for the Lilly Suicide Scholar, Enrique Baca-Garcia, MD, PhD. She has received unrestricted educational grants and/or lecture fees from Astra-Zeneca, Bristol Myers Squibb, Eli Lilly, Janssen, Otsuko, Pfizer, Sanofi-Aventis, and Shire. Her family owns stock in Bristol Myers Squibb. Dr. Parsey was the recipient of grants from Pfizer, Lundbeck, Sepracor, Novartis, and General Electric, all unrelated to this manuscript. He has a US patent on voxel-based methods for assessing subjects using PET.

Results—Depressed suicide attempters had lower serotonin transporter binding in midbrain compared with depressed non-attempters (p=0.031) and controls (p=0.0093). There was no difference in serotonin transporter binding comparing all depressed subjects to healthy controls considering six *a priori* regions of interest simultaneously (p=0.41).

Conclusions—Low midbrain serotonin transporter binding appears to be related to the pathophysiology of suicidal behavior rather than of major depressive disorder. This is consistent with postmortem work showing low midbrain serotonin transporter binding capacity in depressed suicides, and may partially explain discrepant *in vivo* findings quantifying serotonin transporter in depression. Future studies should investigate midbrain serotonin transporter binding as a predictor of suicidal behavior in MDD, and determine the cause of low binding.

Keywords

serotonin transporter; depression; suicide; PET; midbrain; [11C]DASB; pathophysiology

Introduction

Abnormal serotonergic function has been associated with suicidal behavior and completed suicide. Possible explanations for this association include serotonergic effects on aggression and on decision-making (1, 2). Post-mortem studies quantifying serotonin transporter (5-HTT) protein in the brain of completed suicides have reported low B_{max} (number of 5-HTT binding sites *in vitro*) in regions including prefrontal cortex (PFC), anterior cingulate, hippocampus, putamen, and hypothalamus, although others have reported no group differences, and one reported higher 5-HTT in frontal cortex (3, 4). One study reported low 5-HTT binding capacity (a product of receptor binding x region volume that is more analogous to PET outcome measures) in the dorsal raphe nuclei in depressed suicides (DRN) (5). Assessing the relationship between 5-HTT binding *in vivo* and suicidal behavior may clarify the pathophysiology of suicidal behavior, and could potentially identify a biomarker for predicting suicide risk in patients.

The serotonin (5-HT) neurotransmitter system has also been implicated in the pathophysiology of major depressive disorder (MDD). Acute tryptophan depletion provokes depressive symptoms in remitted depressed subjects and their relatives compared to healthy controls (6). Acute serotonergic challenges reveal blunted neuroendocrine responses in acutely depressed and remitted depressed subjects (7). The antidepressant efficacy of serotonergic medications in MDD is consistent with a role of 5-HT in the pathophysiology of depression (8, 9).

Many studies have examined the role of the 5-HTT specifically in the pathophysiology of MDD (10). Several, but not all, postmortem studies have found lower 5-HTT B_{max} (binding density of 5-HTT *in vitro*) in prefrontal cortical (PFC) regions in MDD compared to controls (11). *In vivo* comparisons of 5-HTT binding between MDD and healthy control groups using PET and SPECT are inconsistent (10). We previously described lower 5-HTT binding in 25 antidepressant-free MDD subjects during a current major depressive episode (MDE) compared with 43 healthy controls across six regions of interest (ROIs) implicated in the pathophysiology of MDD using the radiotracer [^{11}C]McN5652 (12). Post-hoc testing showed lower binding in midbrain and amygdala. The [^{11}C]McN5652 radiotracer has known limitations, including poor specific-to-nonspecific binding ratio and poor quantification of cortical binding (13, 14).

[^{11}C]DASB is a radiotracer that provides superior 5-HTT quantification compared to [^{11}C]McN5652 (13). Other groups have used [^{11}C]DASB to examine 5-HTT in MDD, with divergent findings. Three reports from one research group with partially overlapping subject

samples found no differences in [^{11}C]DASB binding between MDD subjects and healthy controls (15–17). One study found higher [^{11}C]DASB binding in MDD subjects than healthy control subjects across a broad anatomic distribution (18), while two others reported lower [^{11}C]DASB binding, one in thalamus specifically (19) and another across a broad range of cortical and subcortical regions (20). These divergent findings may be partially explained by demographic and clinical differences in in study populations, including rates of suicidal behavior, and by different PET outcome measures employed.

In addition to examining effects of diagnosis on binding, we previously examined the effect of a functional promoter polymorphism in the *5-HTT* gene (SLC6A4, polymorphism: 5-HTTLPR) that regulates *in vitro* expression of 5-HTT (21, 22). A gene-environment interaction between the 5-HTTLPR polymorphism and the severity of stressful life events may predict the presence and severity of subsequent depression as well as the later occurrence of suicidal behavior (23–25). We found no effect of 5-HTTLPR on 5-HTT binding using [^{11}C]McN5652 (26). I*n vivo* findings from other studies are discordant (reviewed in (27)). We also reported an effect of early life stress on 5-HTT binding using [^{11}C]McN5652, with low 5-HTT binding in MDD subjects reporting childhood abuse (28), but the sample size was too small to examine gene-environment interactions.

In the current study, we used [^{11}C]DASB in the largest MDD cohort examined to date to examine the relationship between depression and suicide attempt history on SERT binding *in vivo*. Our primary hypotheses were that 1) MDD subjects with a history of prior suicide attempt would have low [^{11}C]DASB binding compared to controls and MDD non-attempters in the regions identified from post-mortem studies of suicide: ventral prefrontal cortex (vPFC), anterior cingulate (ACN), and midbrain (containing DRN, which cannot be reliably delineated on MRI) and that 2) [^{11}C]DASB binding would be low in unmedicated current MDD subjects as compared to healthy controls across the six brain regions identified in our study using [^{11}C]McN5652. We anticipated that 5-HTTLPR genotype would not be associated with [^{11}C]DASB binding. In exploratory analyses, we examined the effects of reported childhood abuse, and of a gene-environment interaction between 5-HTTLPR and reported childhood abuse, on [^{11}C]DASB binding.

Methods

Sample

Currently depressed participants (n=51) with MDD and healthy controls (n=32) were recruited prospectively through print and online advertisements. Eligibility was assessed by psychiatric and medical history, chart review, physical examination, routine blood tests, pregnancy test, and urine toxicology. Axis I diagnoses were based on the Structured Clinical Interview for DSM-IV (SCID) (29), conducted by doctoral- or masters'-level psychologists and reviewed in a consensus conference of research psychologists and psychiatrists. Inclusion criteria for MDD subjects included: 1) current MDE; 2) 17-item Hamilton Depression Rating Scale (HDRS) ≥16 at screening; 3) age 18–65; 4) off all psychotropic and other types of drugs likely to interact with 5-HTT for a minimum of 14 days (off antipsychotics for ≥3 weeks). While this was the minimum duration according to inclusion criteria, 11 MDD subjects were antidepressant-naïve, and among the 40 MDD subjects with prior psychotropic medication exposure, the mean duration off psychotropic medication at time of scan was 122 weeks (median = 11.5 weeks, range = 14 days to 35.9 years). Short-acting benzodiazepines were allowed for distressing anxiety or insomnia up to 72 hours prior to PET scanning, but were only used by six subjects. Exclusion criteria included 1) current or past psychotic illness or bipolar disorder; anorexia nervosa or bulimia nervosa in the past year; drug or alcohol abuse within the past two months or dependence within six months; 2) first-degree family history of schizophrenia in subjects <33 years old to exclude

individuals possibly presenting with the prodrome of schizophrenia (mean onset of schizophrenia = 21.4 in males and 26.8 in females (30)); 3) significant active physical illness; 4) lack of capacity to consent to study participation; 5) pregnancy or lactation among women; 6) previous head injury with loss of consciousness; 7) exposure to 3,4-methylenedioxymethamphetamine (MDMA) on more than two occasions.

For healthy controls, inclusion criteria included: 1) absence of current or past DSM-IV Axis I diagnosis, with the exception of specific phobia; 2) absence of cluster B personality diagnosis as assessed using the SCID-II (31); 3) age 18–65. Exclusion criteria included MDD exclusion criteria 3–7 above as well as: 1) past or present alcohol/substance abuse or dependence; 2) first-degree relative with history of major depression, schizophrenia, schizoaffective disorder, or suicide attempt; two or more first-degree relatives with a history of substance dependence.

The Beck Depression Inventory (32) and HDRS (33) were used to assess depression severity and functional impairment. Lifetime history of aggression was measured by the Brown Goodwin Aggression History Scale (34). The Columbia Suicide History Form was used to assess suicide attempt history (35), and the Beck Medical Lethality Scale was used to rate the degree of medical damage caused by their most lethal attempt (36). The scale scores medical damage from 0 (no injury) to 8 (fatal), with anchor points dependent on the method of attempt. In a semi-structured interview, participants were asked whether they experienced physical and/or sexual abuse over the course of their lifetime. If subjects endorsed a history of abuse, they were asked whether the abuse took place before age 15.

Genotyping

Genotyping of the triallelic 5-HTTLPR polymorphism (L_A, L_G, and S) was performed as previously described.(21) The triallelic genotypes were classified by their reported level of *in vitro* expression as follows: L_A was reclassified as higher expressing L′; L_G and S were classified as lower expressing S′.

Radiochemistry and input function measurement

Preparation of [^{11}C]DASB, measurement of arterial input function, metabolites, and plasma free fraction (f_P) were performed as previously described (37, 38). The chemical purity of [^{11}C]DASB was ≥95%. Injected mass, injected dose, and f_P did not differ between MDD and controls, or between MDD suicide attempters and non- attempters (Table 1).

PET Protocol

Details of the PET protocol are described elsewhere (38). Briefly, a venous catheter was used for radiotracer injection and an arterial catheter was used to obtain arterial samples for the input function. A polyurethane head holder system (Soule Medical, Tampa, FL, USA) was molded around the subject's head for immobilization purposes. PET imaging was performed with the ECAT HR+ (Siemens/CTI, Knoxville, TN, USA). A 10-minute transmission scan was obtained prior to radiotracer injection. At the end of the transmission scan, [^{11}C]DASB was administered intravenously as a bolus over 30 seconds (Table 1). Emission data were collected in 3D mode for 100 minutes with 19 frames of increasing duration (38).

Magnetic Resonance Imaging

Acquisition of T1-weighted MRI images for co-registration of PET images and identification of ROIs was performed as previously described using a 1.5 T Signa Advantage or a 3 T Signa HDx system (General Electric Medical Systems, Milwaukee, WI) (39).

Image Analysis

To correct for subject motion, PET frames were registered to the eighth frame using the FMRIB linear image registration tool (FLIRT), version 5.0 (FMRIB Image Analysis Group, Oxford, UK). An automated algorithm identified ROIs (midbrain, vPFC, putamen, amygdala, thalamus, hippocampus, and ACN) as well as cerebellar gray matter (CGM) on individuals' T1-weighted MRIs (40). Each subject's mean PET image was coregistered to their MRI using FLIRT, optimized as previously described (41). Time activity curves were generated by plotting measured activity within ROIs over the time course of the PET acquisition.

Outcome Measure Estimation

As we previously demonstrated that no brain region is devoid of specific binding with [^{11}C]DASB (42), we used an outcome measure that does not rely on a reference region: V_T/f_P (where V_T = volume of distribution in the region of interest). This outcome measure has been used in several studies by different groups in cases where a reference region is not available (43–47). [^{11}C]DASB regional V_T values were derived using likelihood estimation in the graphical approach (LEGA), which reduces the noise- dependent bias inherent in the graphical approach (48, 49). Brain activity was corrected for the contribution of plasma activity assuming a 5% blood volume in the regions of interest (50). For purposes of comparison to other [^{11}C]DASB studies using different outcome measures, the following outcome measures were also estimated: BP_F $((V_{T(ROI)} - V_{T(REF)})/f_P)$; BP_P $(V_{T(ROI)} - V_{T(REF)})$; and BP_{ND} $((V_{T(ROI)} - V_{T(REF)})/V_{T(REF)})$, using CGM as reference region. As there is approximately 30% specific/displaceable [^{11}C]DASB binding in the reference region (42), $V_{T(REF)}$ overestimates the distribution volume of the nondisplaceable compartment (V_{ND}) (51), leading to biases in estimates of these binding potential measures (52). Results with these alternate outcome measures are described concisely in results section and are presented in greater detail in supplement 1.

Statistics

To borrow strength across all ROIs and properly account for correlation among ROIs measured on the same subject, we fit linear mixed-effects models to the ROI-level V_T/f_P estimates with region and diagnostic group as fixed effects and subject as the random effect, and this approach was taken for all analyses involving more than one ROI. Other fixed effects considered in linear mixed-effects modeling include sex, age, antidepressant exposure, depression severity, and genetic and environmental factors. Data entered in linear mixed-effects models were first log transformed, to remedy slight skewness of V_T/f_P estimates (53–55), to stabilize the variance, and because our principal hypothesis of a difference between groups specifies that differences in each ROI are proportional to each ROI's binding level. Log transformation has been used in numerous PET studies by our group and others to address these issues (12, 26, 28, 55–67). As the natural log is a monotone transformation, demonstrating a difference in $\log(V_T/f_P)$ is equivalent to demonstrating a difference (in the same direction) in V_T/f_P. Estimated V_T/f_P values were weighted in the model according to standard errors computed using a bootstrap algorithm taking into account errors in metabolite, plasma, and brain data (68). Analyses on single regions were performed using linear models. T-tests were performed in SPSS Statistics 19 (http://www.spss.com/software/statistics/). All other analyses were performed in R 2.10.0 (http://cran.r-project.org).

Results

Demographics

Demographic and clinical variables are presented in Table 2. Among MDD participants, 36 (70.6%) had at least one comorbid axis I diagnosis, including 8 (15.7%) with remitted alcohol or substance use disorder; 32 (62.8%) with current or past anxiety disorder; four (7.8%) with lifetime dysthymia; three (5.9%) with current ADHD; and one (2%) with remitted bulimia. Rates of these comorbidities did not differ between MDD attempters and non-attempters (remitted alcohol or substance use disorder: Fisher's exact p = 0.41; comorbid anxiety: p = 0.13; Table 2). MDD attempters had an earlier age of onset than MDD non-attempters. While age differed between MDD subjects and controls, it did not differ between MDD attempters and MDD non-attempters (Table 2). 5-HTTLPR genotype did not differ between MDD subjects and controls, nor between MDD attempters and MDD non-attempters (Table 3).

Possible Covariates

Across the six ROIs, there was no effect of sex (F=1.55, DF=1,79, p=0.22) or prior antidepressant exposure (F=0.68, DF=1,79, p=0.41) on 5-HTT binding. Because the MDD and control groups differed in age, we explored the relationship between age and binding. There was no effect of age on binding in the combined sample (F=0.02, DF=1,79, p=0.89) and no interactions were detected between age and diagnosis (F=2.13, DF=1,78, p=0.15) or age and region (F=1.60, DF=5,400, p=0.16) on binding. Nonetheless, as some studies have previously described a regional age-related decline in 5-HTT binding (15, 19, 69–77), we included age and age-by-region interaction as covariates in statistical models.

Suicide Attempt History

5-HTT binding differed between controls, MDD attempters, and MDD non-attempters in midbrain (Figure 1, F=3.77, DF=2,78, p=0.027), with MDD attempters having lower midbrain binding than both MDD non-attempters (F=5.88, DF=1,78, p=0.031) and controls (F=7.12, DF=1,78, p=0.0093); midbrain binding did not differ significantly between MDD non-attempters and controls (F=0.40, DF=1,78, p=0.53). Low midbrain 5-HTT binding in MDD suicide attempters compared to MDD non-attempters was significant in all analyses with alternative PET outcome measures examined (table S1 in Supplement 1; BP_F: F=7.27, DF=1,78, p=0.0086; BP_P: F=6.15, DF=1,78, p=0.015; BP_{ND}: F=7.51, DF=1,78, p=0.0076). 5-HTT binding did not differ as a function of suicide attempt history in the two other regions examined, vPFC and ACN (vPFC: F=0.87, DF=1,78, p=0.35; ACN: F=0.13, DF=1,78, p=0.72).

Diagnosis Effect

Considering six *a priori* ROIs simultaneously (dorsal putamen, amygdala, thalamus, hippocampus, midbrain, and anterior cingulate), 5-HTT binding did not differ between MDD and controls (table S2 in Supplement 1; F=0.69, DF=1,79, p=0.41). This finding was consistent for all alternative outcome measures examined (BP_F: F=1.53, DF=1,79, p=0.22; BP_P: F=3.49, DF=1,79, p=0.066; BP_{ND}: F=1.79, DF=1,79, p=0.19; table S2 in Supplement 1). Within the MDD group, we did not observe a relationship between depression severity assessed by the HDRS and binding across the 6 ROIs (F=0.009, DF=1,48, p=0.93).

Genetic and Environmental Effects

Considering 5-HTTLPR, we did not observe a stepwise effect of the number of L′ alleles on 5-HTT binding across the six ROIs (F=0.04, DF=1,74, p=0.84). MDD subjects reporting childhood abuse had higher binding than non-abused MDD subjects across the 6 ROIs

(F=4.34, DF=1,48, p=0.043). There was no gene-environment interaction detected between number of 5-HTTLPR L_A alleles and childhood abuse status on binding in MDD (F=0.65, DF=1,47, p=0.42). Including childhood abuse as a covariate did not alter the significance of the contrast of midbrain 5-HTT binding between MDD suicide attempters and non-attempters (F=6.31, DF=1,78, p=0.014).

Comment

Primary findings and comparison to existing literature

This study examined the effects of prior suicide attempt and diagnosis in the largest cohort to date of MDD subjects undergoing 5-HTT quantification using PET or SPECT. We observed lower 5-HTT binding in MDD attempters compared with both MDD non-attempters and controls in midbrain, and no differences as a function of suicide attempt history in vPFC or ACN. In addition, we found no difference in 5-HTT binding between MDD and control groups in six *a priori* regions. Taken together, these findings suggest that regionally specific, lower 5-HTT binding in midbrain in MDD attempters may be related to the pathophysiology of suicidal behavior, rather than of MDD. The lack of a depression effect on 5-HTT binding is consistent with a series of previous [^{11}C]DASB studies using the outcome measure BP_{ND} (15–17), although others have reported lower (19, 20) and higher (18) [^{11}C]DASB binding in MDD using BP_P and BP_{ND}. It is notable that the current finding was replicated with all alternative PET outcome measures examined (BP_F, BP_P, and BP_{ND}).

Our data suggest that discrepant [^{11}C]DASB PET findings in MDD may be at least partly due to differences in the proportion of suicide attempters in previous samples. Four of six previous [^{11}C]DASB MDD studies did not report rates of suicide attempt history in their samples.(15–17, 19) Of the two [^{11}C]DASB studies reporting suicide attempt status, one found lower 5-HTT binding in anteroventral striatum in MDD attempters compared with MDD non-attempters, in the same direction as our finding (18). The other study had only two attempters out of 12 MDD subjects, which did not allow direct examination of an effect of suicide attempt status on binding (20).

There are some clinical and demographic differences between the MDD attempters and non-attempters in our sample: while depression severity did not differ between attempters and non-attempters, attempters had an earlier onset of major depressive illness, consistent with previous studies (78). This raises the possibility that low midbrain 5-HTT binding among attempters is driven by specific genetic loading associated with early-onset depression (79). Moreover, attempters had a trend toward greater depression chronicity as measured by number of prior major depressive episodes. While this may be a potential confound in the interpretation of our results, we did not find a relationship between age of onset of major depressive illness and midbrain 5-HTT V_T/f_P (r=0.03, p=0.84).

We found no effect of suicide attempt status in vPFC or ACN. The low signal-to-noise ratio in vPFC (binding is only 14% higher in vPFC than in cerebellar gray matter) may have limited our ability to detect group differences. We did not examine the relationship between regional 5-HTT binding and suicide attempt lethality or objective medical damage, given the limited range of lethality in the current sample.

Interpretation of Findings

Low regional 5-HTT binding among MDD attempters may be due to less gene expression. Consistent with our previous findings, 5-HTT binding was not associated with 5-HTTLPR genotype in this study, but other functional promoter *5-HTT* loci need to be examined. Additionally, epigenetic differences may drive differential 5-HTT binding: studies in nonhuman primates find that DNA methylation, but not *5-HTT* genotype, is significantly

associated with peripheral blood mononuclear cell 5-HTT mRNA expression (80). Discrepant findings reported regarding the potential association between 5-HTT binding and 5-HTTLPR genotype may also be due to biallelic vs. triallelic genotyping, different brain imaging outcome measures, as well as racial stratification differences in study populations.

An alternative explanation for low regional 5-HTT binding among suicide attempters is that it is a result of accelerated 5-HTT internalization in response to low 5-HT release. Evidence supporting a 5-HT deficiency related to suicidal behavior includes low CSF 5-HIAA associated with suicidal behavior and risk of suicide (81), postmortem studies reporting lower brainstem 5-HT or 5-HIAA in suicides (82), and lower CSF 5-HIAA in more lethal suicide attempters with MDD (83).

Serotonergic abnormalities may contribute to suicidal behavior through effects on aggressive traits, decision-making or problem solving. Measures of aggression have been correlated with several serotonergic measures, including low *in vivo* 5-HT_{1A} receptor binding (84), blunted prolactin responses to serotonergic challenge with fenfluramine (85, 86), and low CSF 5-HIAA (87). However, we do not find an effect of lifetime aggression assessed via the Brown Goodwin Lifetime History of Aggression scale on 5-HTT V_T/f_P in vPFC (F=0.084, DF=1,77, p=0.77).

Reported Childhood Abuse

In exploratory analyses, we did not replicate our previous finding of low 5-HTT in MDD with reported childhood abuse history compared to MDD without childhood abuse history (28). Given these discrepant findings, and the report of lower HTT binding in adult monkeys with a history of maternal deprivation (88), replication is required with a larger sample, using a validated measure of childhood abuse such as the Childhood Trauma Questionnaire (89). We did not observe a gene-environment interaction between reported childhood abuse and 5-HTTLPR genotype on 5-HTT binding within the MDD sample. A definitive examination of a gene-environment interaction affecting 5-HTT binding as a mediator of depression risk would necessitate a large sample stratified across a continuous range of depression severity.

Strengths And Limitations

Strengths of this imaging study include the large sample size, favorable properties of [^{11}C]DASB, quantitative estimation of V_T/f_P using a metabolite-corrected arterial input function, and careful diagnostic assessment. A limitation of this study is the lack of age matching between MDD subjects and controls. This is unlikely to have impacted the reported findings for the following reasons: 1) we did not observe an effect of age on 5-HTT binding in our sample; 2) we co-varied for age in all analyses; 3) age did not differ between MDD attempters and MDD non-attempters, who nonetheless differed in midbrain 5-HTT binding; and 4) if age-related decline in 5-HTT binding were present, it would bias our results toward *lower* binding in MDD subjects than controls, which we did not observe.

A longer minimum antidepressant-free interval than the two-week minimum used in the present study may be preferable, but ethical requirements prevent this approach. An alternative strategy would be to recruit drug naïve participants. Nonetheless, in this sample, the median antidepressant-free interval in those MDD subjects with prior antidepressant-exposure was 11.5 weeks. Moreover, we did not observe a difference in 5-HTT V_T/f_P as a function prior antidepressant exposure status, nor did mean antidepressant-free interval differ between MDD attempters and MDD non-attempters, which makes the minimum antidepressant-free interval employed in this study an unlikely explanation for reported findings.

Other clinical and demographic factors have previously been associated with 5-HTT binding, including cigarette smoking (90, 91) and anxiety (19). We did not include these as covariates in the current analysis given the large number of covariates examined, and as smoking history did not differ between groups and anxiety comorbidity did not differ between MDD attempters and non-attempters. It should be noted that while differences in midbrain V_T/f_P between MDD suicide attempters and non-attempters are statistically significant, there is overlap between groups in binding, and as such this measure cannot be used alone to differentiate these groups. Future studies with improved 5-HTT quantification and the combination of imaging and clinical measures may improve group differentiation.

A limitation common to most studies quantifying 5-HTT *in vivo* is the lack of a reference region in the brain that is devoid of 5-HTT. We chose one approach to address this issue, using the outcome measure V_T/f_P, thereby avoiding the error introduced when using other available outcome measures that subtract out, or subtract and then divide by, the volume of distribution measured in a reference region that actually contains specific binding. Use of V_T/f_P does not account for non-specific binding in the brain, and it is thus possible that low midbrain binding in MDD attempters is due to differences in non-specific binding. Other approaches to address this methodological challenge have been proposed (52). However, our results were similar when using all other outcome measures that do attempt to correct for non-specific binding in the brain using a reference region (BP_F, BP_P, and BP_{ND}), so this methodological issue is unlikely to be driving our reported findings.

Conclusions

5-HTT binding is low *in vivo* in the midbrain of depressed suicide attempters. This abnormality is consistent with postmortem findings in suicides and with a serotonergic deficit model of suicidal behavior. We are currently studying the prognostic significance of low 5-HTT binding as a predictor of7 repeated suicide attempt.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Research presented in this manuscript was supported by NIMH grants 5P50 MH62185 (Dr. Mann, principal investigator) and 2 R01 MH040695 (Dr. Mann, principal investigator).

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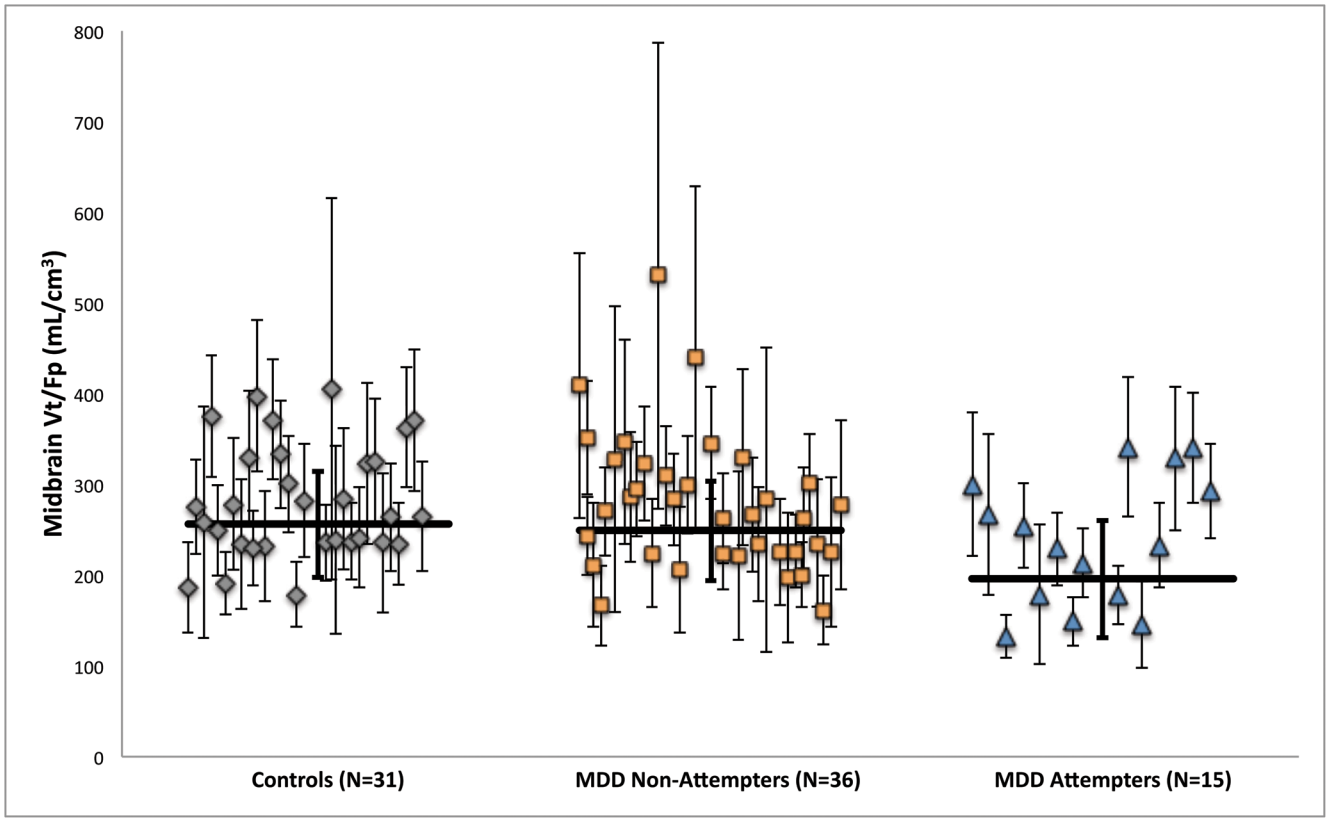

Figure 1.
Comparison of 5-HTT binding (raw VT/fP,) as a function of suicide attempt history in midbrain. Scatter plot displays each subject's midbrain VT/fP value with its associated standard error, computed using a bootstrap algorithm that takes into account errors in metabolite, plasma, and brain data. Horizontal lines indicate weighted means for each group; thick error bars indicate the corresponding equivalent of the standard deviation of the weighted means. Depressed suicide attempters have lower 5-HTT binding than depressed non-attempters (p=0.031) and than controls (p=0.0093).

Table 1

[^{11}C]DASB PET scan parameters of the sample.

	Controls (n=31)	MDD (n=51)	t, p-value	MDD Suicide Attempters (n=15)	MDD Non- Attempter (n=36)	t, p-value
Injected Dose (mCi)	16.14 ± 2.36	16.28 ± 2.14	−0.27, 0.79	16.34 ± 1.80	16.25 ± 2.29	0.13, 0.90
Injected Mass (micrograms)	4.36 ± 2.31	4.49 ± 2.18	−0.27, 0.91	5.07 ± 2.30	4.25 ± 2.11	1.24, 0.22
Free Fraction (fP)	0.12 ± 0.03	0.11 ± 0.02	1.59, 0.12	0.11 ± 0.03	0.11 ± 0.02	−0.13, 0.90

Table 2

Clinical and demographic characteristics of the sample.

	Controls N=31	***MDD N=51***	***Control v. MDD (χ^2, p-value)***	***MDD Suicide Attempters N=15***	***MDD Non-Attempters N=36***	***Attempter vs. Non-Attempter (χ^2, p-value)***
Females	16 (51.6%)	28 (54.9%)	0.08, p=0.77	8 (53.3%)	20 (55.6%)	0.021, 0.88
Inpatient	-	14 (27.5%)	-	6 (40.0%)	8 (22.2%)	2.13, 0.15
# with family history of MDD in 1st degree relatives	-	25 (49.0%)	-	5 (33.3%)	20 (55.6%)	2.09, 0.15
Current or Past Comorbid Anxiety Disorder	-	32	-	7 (46.7%)	25 (69.4%)	2.35, 0.13
Axis 2 Comorbidity	-	21 (37.2)	-	6 (40.0%)	13 (36.1%)	.069, .69
Race/Ethnicity			0.105*			0.09*
Asian	6 (19.4%)	3 (5.9%)		0 (0%)	3 (8.3%)	
African American	6 (19.4%)	5 (9.8%)		3 (20%)	2 (5.6%)	
Caucasian	15 (48.4%)	33 (64.7%)		8 (53.3)	26 (72%)	
Hispanic	2 (3.2%)	8 (15.7%)		2 (13.3%)	5 (13.9%)	
>1 Race	1 (3.2%)	2 (3.9%)		2 (13.3%)	0 (0%)	
Unknown	1 (3.2%)	0 (0%)		0 (0%)	0 (0%)	
Any Current Tobacco Use	2 (6.5%)	7 (13.7%)	0.47*	1 (6.7%)	6 (16.7%)	0.66*
			(t, p-value)			(t, p-value)
Age	32.6 ± 11.3	40.3 ± 10.7	−3.02, p=.004	38.5 ± 11.5	41.0 ± 10.5	−0.76, 0.45
Hamilton Depression Rating Scale (24 item)	1.7 ± 2.4	24.6 ± 6.4	−19.01, p<.001	26.5 ± 6.2	23.8 ± 6.4	1.40, 0.17
Beck Depression Inventory	1.3 ± 1.7	25.7 ± 8.8	−15.19, p<.001	27.5 ± 9.2	24.9 ± 8.7	0.94, 0.35
Median # of Depressive Episodes	-	4	-	5	2.5	−1.70, 0.088**
Median Length of Current Depressive Episode (weeks) ***	-		52	52	52	−1.15, 0.25**
Age at 1st Depressive Episode	-	19.3 ± 10.8	-	14.7 ± 5.8	21.2 ± 11.9	−2.03, 0.05
# of Suicide Attempters	-	15 (29.4%)	-	15 (100%)	-	-
Mean # of Attempts				2.1 ± 1.6	-	-
Maximum Lethality of Attempts****				2.3 ± 2.0	-	-
Lethality of Most Recent Attempt				1.5 ± 1.6	-	-

*Fisher's exact p-value as cells contain values too small to fulfill assumptions of χ^2 test

** Mann Whitney Test presented as (Z, p-value), as data are not normally distributed.

*** Best estimate from patient self report

**** From Columbia University Suicide History Form (details in methods)

Table 3

5-HTTLPR triallelic genotype distribution.

Goldman Functional Genotype	S′S′	L′S′	L′L′	Fisher's exact p- value	S′ allelic frequency	L′ allelic frequency	Chi^2 p- value
Controls (n=31)	11	13	3	0.32	35	19	0.21
MDD (n=51)	16	22	13		54	48	
MDD Attempters (n=15)	6	6	3	0.74	18	12	0.48
MDD Non- Attempters (n=36)	10	16	10		36	36	