Reported childhood abuse is associated with low serotonin transporter binding *in vivo* in major depressive disorder

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Abstract

Background—Physical or psychological adversity in childhood is associated with a higher risk for depression in adulthood, and with persistent serotonergic abnormalities in humans and in animal models. We hypothesized that reported childhood abuse would be associated with lower brain serotonin transporter (5-HTT) binding potential (BP_P, proportional to the number of available transporters) in adults. We examined healthy volunteers and subjects with major depressive disorder, a sample enriched for childhood abuse.

Methods—Regional brain 5-HTT BP_P was measured using positron emission tomography with [^{11}C]McN 5652 and a metabolite corrected arterial input function in 43 healthy volunteers and 23 subjects in a major depressive episode, ten of whom reported a history of sexual and/or physical abuse before age 15, and 13 of whom did not. As only two healthy volunteers reported childhood abuse, primary analyses were restricted to the depressed sample, with healthy controls presented as comparators.

Results—Depressed subjects reporting childhood abuse had lower 5-HTT BP_P than non-abused depressed subjects across all brain regions examined (p=0.017). The groups did not differ in relevant demographic or clinical variables. Genotype frequencies of a functional polymorphism in the *5-HTT* gene promoter (5-HTTLPR) did not differ between the groups.

Conclusions—Reported childhood abuse is associated with lower 5-HTT BP_P in this sample of subjects with major depression, consistent with other reports that childhood adversity can lower serotonergic function permanently. Lower 5-HTT BP_P may represent a biological pathway

through which early life stress predisposes to the development of subsequent psychiatric illness, including major depressive disorder.

Keywords

serotonin transporter; abuse; positron emission tomography

Introduction

Adverse experiences early in life may alter brain function and increase the risk of developing subsequent psychiatric illness (Meaney, 2001; Nemeroff and Vale, 2005). In animal models and in humans, early stress or adversity appears to reduce brain 5-HT function. Deficiency in the serotonin (5-HT) system is associated with psychiatric conditions including major depressive disorder (MDD) (Mann and Arango, 1999), as well as suicidal and aggressive behaviors (Coccaro et al., 1997; Currier and Mann, 2008). Adult rhesus macaques that have previously experienced high rates of rejection from their mothers or repeated maternal separation (among females) have lower levels of the serotonin metabolite 5-HIAA in CSF (Higley et al., 1992; Maestripieri et al., 2006), and lower serotonin transporter (5-HTT) binding on PET scanning (Ichise et al., 2006). Such maternal separation in monkeys has been associated with subsequent depressive behaviors (Harlow and Suomi, 1974), as well as anxiety-like behavior, increased aggression, and increased alcohol consumption (Higley et al., 1991; Suomi et al., 1992).

Similarly, humans raised in low socioeconomic circumstances or who report high rates of neglect early in life exhibit impaired 5-HT function, including blunted prolactin response to fenfluramine challenge (Manuck et al., 2005), and lower cerebrospinal fluid (CSF) 5-hydroxyindoleacetic acid (5-HIAA) (Roy, 2002). Childhood abuse and neglect in humans have been associated with increased risk for MDD in adulthood (Widom et al., 2007), suggesting a consistent association between childhood adversity, abnormal serotonergic markers, and psychopathology in both humans and in animal models.

Alterations in markers of 5-HT signaling as a result of early-life stress may be attributable to changed receptor availability and/or function. The serotonin transporter (5-HTT) is responsible for 5-HT reuptake from the synaptic cleft, and availability of this protein is associated with neural 5-HT function and depression-related behavior (Ansorge et al., 2004; Fuller et al., 1991; Parsey et al., 2006b). 5-HTT availability is correlated with the density of serotonergic axons, suggesting that 5-HTT binding is reflective at least of axonal density, if not of serotonergic neuronal density (Soucy et al., 1994). Rats experiencing nutritional deprivation or repeated maternal separation as infants exhibit reduced neural 5-HTT protein in the raphe nucleus as adults (Jahng et al., 2007; Lee et al., 2007). This could be indicative of a reduction in serotonergic neuron density in the raphe nucleus. As all cortical and subcortical serotonergic fibers arise from the raphe, a reduction in serotonergic fibers from the raphe would likely be accompanied by reduced 5-HTT in these regions. Indeed, maternally-deprived rhesus macaques exhibit lower 5-HTT availability across a broad array of cortical and subcortical structures (Ichise et al., 2006), suggesting a generalized effect of childhood adversity on 5-HTT across the post-synaptic terminal field of serotonergic neurons. While there are clearly pleiotropic neurochemical and morphological effects of early life stress on brain development (see discussion as well as (De Bellis, 2005; Nemeroff, 2004; Teicher et al., 2003)), these data suggest one possible pathway of childhood adversity leading to impaired serotonergic neurotransmission, reflected in reduced 5-HTT, predisposing to the development of subsequent psychopathology including MDD.

To our knowledge, the impact of reported childhood adversity on adult brain 5-HTT binding in humans has never been assessed. Therefore, we set out to explore the relationship of reported childhood abuse on 5-HTT regional brain binding in adulthood. We have previously shown that 5-HTT BP_P is significantly lower in major depressive disorder (MDD) than among healthy controls using PET with the [^{11}C]McN 5652 radioligand (Parsey et al., 2006b). In the current study, we compared 5-HTT binding in the brain between subjects from that sample with and without a reported history of childhood abuse. While we intended to examine the effects of reported childhood abuse on 5-HTT among subjects with MDD as well as among healthy controls, only two of 43 healthy controls in that sample endorsed a history of childhood abuse. We therefore restricted our primary hypothesis and analysis to subjects with MDD, a sample with a higher prevalence of childhood abuse. We included healthy controls as an additional comparison group, but did not include them in statistical analyses to avoid confounding the effect of diagnosis with that of childhood abuse. We hypothesized that depressed subjects reporting childhood physical or sexual abuse would have lower 5-HTT binding in brain regions previously associated with serotonergic abnormalities in depression compared with depressed subjects denying childhood abuse. In an exploratory fashion in this small group, we acquired data regarding clinical course following naturalistic treatment for depression after PET scanning, to assess whether reported childhood abuse was associated with differential clinical outcomes, given previous reports of diminished response to the antidepressant nefazodone among subjects with a history of childhood trauma (Nemeroff et al., 2003). While the current study was not powered to assess gene-environment interactions on 5-HTT binding, we also characterized the genotype of a functional polymorphism in the *5-HTT* gene (5-HTTLPR) in this sample (Hu et al., 2005; Lesch et al., 1996), for which there is evidence of gene-environment interactions predisposing to the development of MDD (reviewed in (Caspi and Moffitt, 2006)).

Materials and Methods

Subjects

This is a further analysis of data from a previous study of 5-HTT binding in depression, which contains details regarding the clinical sample and imaging methods (Parsey et al., 2006b). All depressed subjects met the following inclusion criteria: (1) age 18 to 65 years; (2) DSM-IV criteria for a current major depressive episode (MDE); (3) ≥ two week medication-free period prior to PET scanning (four weeks for oral neuroleptics, six weeks for fluoxetine, and an exception of three days for short-acting benzodiazepines); (4) absence of current or lifetime history of alcohol or other drug abuse or dependence; (5) no lifetime exposure to 3,4-methylenedioxymethamphetamine (MDMA); (6) absence of significant current medical conditions; (7) absence of pregnancy; and (8) capacity to provide informed consent. In the previous study, we recruited 25 subjects currently in a major depressive episode. From that group, 23 subjects who supplied information regarding childhood history of abuse were included in the present study. Inclusion criteria for 43 healthy comparison subjects were similar; these subjects were required to have no psychiatric history and no history of a mood or psychotic disorder in their first-degree relatives. All subjects gave written informed consent for participation in this study. The study protocol was approved by the Institutional Review Board of the New York State Psychiatric Institute, and was carried out in accordance with the ethical guidelines enumerated in the Declaration of Helsinki.

Clinical Assessments

Diagnoses were determined using the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1995), conducted by experienced research masters and Ph.D. level psychologists. A team of experienced clinical research psychologists and psychiatrists

reviewed all diagnoses. As part of a semi-structured interview, participants were asked whether they had a history of physical and/or sexual abuse over the course of their lifetime. If subjects endorsed a history of abuse, they were asked whether this abuse took place before age 15. Subjects who endorsed a history of abuse before age 15 were compared to those who did not. The Beck Depression Inventory (BDI) (Beck et al., 1961), Hamilton Depression Rating Scale (HAMD) (Hamilton, 1960), and Global Assessment Scale (GAS) (Endicott et al., 1976) were administered to assess depression severity and functional impairment. Lifetime history of aggression was measured using the Brown Goodwin Aggression History Scale (Brown et al., 1979). 10 of the 23 depressed subjects (43.5%) had made at least one prior suicide attempt. 11 depressed subjects (47.8%) had current co-morbid Axis I disorders, all of which were anxiety disorders (Table I).

Following baseline assessment and PET scans, depressed patients received open, non-standardized antidepressant treatment. Remission, defined as ≥50% reduction of HAMD-24 score from baseline and final HAMD-24 score <10, was assessed among the 19 subjects who returned for clinical assessments one year following PET scanning to provide further clinical characterization of the sample; this clinical assessment was previously described in the absence of the characterization of abuse (Miller et al., 2008).

Genotyping

Genotyping of a functional polymorphism in the promoter region of the *5-HTT* gene (5-HTTLPR) was performed as previously described (Parsey et al., 2006a). Triallelic genotypes were reclassified by level of *in vitro* expression as follows: S'S' = ($L_GS=L_GL_G=SS$); L'S' = ($L_AS=L_ALG$); L'L' = $L_A L_A$ (Hu et al., 2005).

Radiochemistry

$[^{11}C](+)$-McN 5652, (+)-McN butyryl thioester tartrate, was produced as previously described (Frankle et al., 2004b). The injected dose of $[^{11}C]$McN5652 did not differ between abused (mean=13.8mCi, SD=5.0) and non-abused (14.6mCi, SD=3.0) groups (t=0.47, df=21, p=0.65). Similarly, the injected mass of $[^{11}C]$McN5652 did not differ between abused (mean=4.04μg, SD=1.53) and non-abused (mean=4.42μg, SD=1.07) groups (t=0.70, df=21, p=0.49).

Image Analysis and Modeling

PET and magnetic resonance imaging (MRI) data acquisition, analysis, and measurement of metabolite corrected arterial input functions were performed (for details, see (Parsey et al., 2006a; Parsey et al., 2006b; Parsey et al., 2000)). After a ten-minute transmission scan, $[^{11}C]$McN5652 was injected intravenously and emission data acquired for 130 minutes. Regions of interest (ROIs) were traced on T1-weighted MRIs obtained for each individual subject using brain atlases (Duvernoy, 1991; Talairach and Tournoux, 1988) and published reports (Kates et al., 1997; Killiany et al., 1997). Six ROIs previously associated with serotonergic abnormalities in depression were included in this study: the anterior cingulate, amygdala, putamen, hippocampus, midbrain, and thalamus (Parsey et al., 2006b). Derivation of $[^{11}C]$McN5652 regional distribution volumes (V_T) was performed using likelihood estimation in graphical analysis (LEGA) (Ogden, 2003; Ogden et al., 2002; Parsey et al., 2003). V_T is the sum of the specific (V_S) and non-displaceable (free plus nonspecific binding = V_{ND}) distribution volumes. Binding potential (BP_P) = $V_T - V_{ND} = f_pB_{avail}/K_D$ where f_p is the free fraction of radioligand in plasma, B_{avail} is the density of receptors available to bind radioligand *in vivo*, and K_D is the dissociation constant, equal to k_{off}/k_{on}. This terminology is consistent with a recent consensus statement on outcome measure nomenclature in PET studies (Innis et al., 2007). We utilized a 12.1 ± 1.5 mL sample of the cerebellar gray matter as a measure of V_{ND} (Parsey et al., 2006b).

Statistics

Considering six ROIs at once, data from the two groups (depressed subjects with and without a reported history of childhood abuse) were analyzed using linear mixed effects models with brain region and group as fixed effects and subject as the random effect. To stabilize the variance and ensure modeling assumptions were met, analysis was performed on the natural log of the data, after first adding a quantity (2) to all measures to ensure positivity. The log transform was necessary primarily because of the unequal standard deviations (SD) of measurements across regions with differing binding levels (each SD is roughly proportional to its corresponding mean binding level). We have taken this approach to allow for valid statistical analysis of ROI-based PET data in mixed effects models (Miller et al., 2008; Oquendo et al., 2007; Parsey et al., 2006a; Parsey et al., 2006b; Parsey et al., 2006c; Parsey et al., 2006d; Sullivan et al., 2005). Others have used related statistical approaches, including linearizing transformation (Rabiner et al., 2002) and non-parametric testing (Meltzer et al., 2004) to address this issue in analyzing PET data. As the natural log is a monotone transformation, showing a difference in $log(BP_P)$ is equivalent to showing a difference (in the same direction) in BP_P. Graphs of binding potential use actual (not log-transformed) BP_P values. Reported p-values correspond to two-sided tests. Linear mixed effects models of binding were performed in R 2.1.0 (http://cran.r-project.org). Student's t-tests were performed in Excel (Microsoft, 2003). Chi-square tests and Fisher's exact tests were performed in SPSS for Macintosh OS X Version 11 (SPSS, Chicago, IL) to examine clinical and demographic variables. Statistics are presented as (test statistic, degrees of freedom, p-value).

Results

Clinical Characteristics

Table I presents demographic, clinical, and genetic information regarding the depressed subjects with or without a reported history of childhood abuse as well as healthy comparison subjects, who are not sub-divided by abuse history given the small number of healthy subjects reporting childhood abuse. Abused and unabused depressed subjects were comparable in terms of age, level of education obtained, severity of current depression, number of prior major depressive episodes, and frequency of comorbid anxiety disorders including post-traumatic stress disorder. While depressed subjects with a reported history of childhood abuse had a lower rate of remission following one year of naturalistic treatment than those who did not report abuse (22.2% vs. 50%), this difference was not statistically significant in this small sample (Fisher's exact, p=0.35). Differences in sex ratio, history of prior suicide attempts, and length of current depressive episode were not statistically significant (Table I).

Serotonin Transporter Binding

5-HTT BP_P was significantly lower in depressed subjects with a reported history of childhood abuse compared with depressed subjects without a reported history of childhood abuse with all regions of interest included in the model (Figure 1; F=6.76, df=1,21, p=0.017). Post-hoc analyses confirmed that this difference was significant in all regions examined: anterior cingulate (Figure 2; F=7.14, df=1,21, P=0.014), amygdala (F=4.60, df=1,21, p=0.044), dorsal putamen (F=4.48, df=1,21, p=0.046), hippocampus (F=4.63, df=1,21, p=0.043), midbrain (F=5.27, df=1,21, p=0.032), and thalamus (F=4.95, df=1,21, p=0.037). We did not find evidence for a differential effect of reported childhood abuse across the 6 brain regions examined (region by group interaction: F=0.91, df=5,105, p=0.48). There was no difference between the two groups in non-specific binding as quantified by log cerebellar V_T (F=0.38, df=1,21, p=0.54).

Genotype

There was no difference in the distribution of 5-HTTLPR functional genotypes between the depressed groups with and without a reported history of childhood abuse (Table I; Fisher's exact, p=0.64).

Discussion

In this first pilot study, MDD subjects with a reported history of physical or sexual abuse before age 15 had lower 5-HTT BP_P than depressed subjects without such an abuse history in all brain regions examined: midbrain, putamen, amygdala, thalamus, hippocampus, and anterior cingulate. The association of childhood abuse and lower 5-HTT binding is consistent with our hypothesis, and with a previous report of lower 5-HTT binding in maternally-deprived macaques as assessed by PET (Ichise et al., 2006). Lower platelet 5-HTT availability has also been demonstrated in subjects with bulimia who reported early sexual abuse (Steiger et al., 2004). While there are many factors leading to differential regulation of 5-HTT in platelets and brain, the direction of this finding is consistent with the data presented here.

We interpret lower 5-HTT BP_P among subjects with a reported history of childhood abuse to reflect lower 5-HTT density. As BP_P is equal to the product of the receptor density, receptor affinity ($1/K_D$), and the free fraction of radioligand in plasma (f_P), it is possible that observed differences in BP_P reflect differences in $1/K_D$ or f_P. In a previous post-mortem study, however, lower 5-HTT binding among subjects with MDD was not associated with lower affinity (Perry et al., 1983). As f_p is not measurable for the [^{11}C]McN 5652 radioligand, we cannot exclude the possibility of differences in f_p between groups. The results reported here cannot be explained by differences in intrasynaptic 5-HT concentrations, as the [^{11}C]McN 5652 radioligand does not appear to be sensitive to endogenous neurotransmitter levels (Hummerich et al., 2006).

How early environment influences 5-HTT availability in adulthood is not known. Neuroanatomical, physiological or genomic alterations may contribute to low 5-HTT availability resulting from childhood abuse. The findings of lower CSF 5-HIAA in maternally-rejected or deprived monkeys (Higley et al., 1992; Maestripieri et al., 2006) suggest decreased serotonin release or neuron firing following these stressors. Lower 5-HTT BP_P observed among depressed subjects with a reported history of abuse may therefore reflect a compensatory response to lower intra-synaptic 5-HT. Alternatively, it may reflect a deficit of serotonergic neurons in the raphe nuclei, of projections from these neurons to their terminal field, or of 5-HTT in terminal projections. The involvement of both cortical and sub-cortical regions is consistent with a previous finding in rhesus macaques (Ichise et al., 2006). As 5-HTT has been highly correlated with serotonergic neuron density (Soucy et al., 1994) and early footshock stress has been associated with fewer 5-HT immunoreactive cells in the medial raphe nucleus in rats (Konno et al., 2007), the diffuse reduction in 5-HTT BP_P that we observed in abused subjects may reflect a reduction of serotonergic neurons in the raphe nuclei, which is not measurable non-invasively *in vivo*. While a *greater* number of serotonergic neurons in the dorsal raphe nucleus was previously reported among suicide victims compared to healthy controls assessed post-mortem (Underwood et al., 1999), that study did not examine the effects of childhood adversity, and focused on the phenomenon of suicide rather than the diagnosis of major depression. Methylation a CpG island downstream of the 5-HTT promoter region may be associated with less 5-HTT expression and onset of depression (Philibert et al., 2008), and could be a target for epigenetic effects of maternal deprivation or abuse. These effects could result in adult serotonin deficiencies associated with recurrent MDD in adulthood (Bhagwagar et al., 2002; Flory et al., 1998; Neumeister et al., 2004; Ruhe et al., 2007). Alternative possible mechanistic explanations for the observed

association between 5-HTT BP_P and reported abuse include reciprocal interactions between the serotonin system and the hypothalamic-pituitary-adrenal (HPA) axis (Tafet et al., 2001; Weidenfeld et al., 2002), which is dysregulated in individuals who experience childhood abuse (Nemeroff, 2004), or effects of brain-derived neurotrophic factor (BDNF) on serotonergic neuron differentiation and survival (Eaton and Whittemore, 1996; Mamounas et al., 2000; Mamounas et al., 1995), given a previous finding of decreased BDNF expression following acute stress (Smith et al., 1995).

If corroborated in subsequent prospective studies, this finding has potential clinical implications. Lower 5-HTT BP_P in subjects with a history of childhood abuse may predispose to the development of depression. Several brain imaging studies have reported lower 5-HTT among subjects with major depressive disorder (Lehto et al., 2006; Malison et al., 1998; Newberg et al., 2005; Parsey et al., 2006b), although other studies have not replicated this finding (Cannon et al., 2007; Herold et al., 2006; Ichimiya et al., 2002; Meyer et al., 2004). While differences in radioligands, outcome measures used, and clinical characteristics may explain some of these discrepancies, the current study suggests that differential rates of childhood abuse among these samples may also contribute to variation in findings. Further, lower 5-HTT availability resulting from childhood abuse may limit the effectiveness of antidepressant medications. We have recently found that non-remission from MDD is associated with lower 5-HTT levels, consistent with this hypothesis (Miller et al., 2008). While not statistically significant in this modest sample, the group reporting childhood abuse had lower absolute rates of remission after one year of naturalistic antidepressant treatment than the non-abused group. If this were confirmed in a larger sample, it would raise the possibility that childhood abuse contributes to treatment resistance in depression due to a lack of availability of 5-HTT for pharmacological manipulation, or through lower serotonin release that would lessen the impact of serotonin reuptake inhibition. Consistent with this idea, a randomized controlled trial of the serotonin reuptake inhibitor and serotonin 2A receptor antagonist nefazodone versus structured psychotherapy for chronic depression found that subjects with a history of childhood trauma had lower remission rates with nefazodone than with structured psychotherapy (Nemeroff et al., 2003).

This study has limitations. Our analysis of the effects of abuse on SERT binding was confined to subjects with MDD, as our available sample of 43 healthy controls included only two subjects who reported childhood abuse. Of note, mean 5-HTT BP_P among the two healthy volunteers reporting a history of childhood abuse was 16.4% lower across all regions compared with the 41 healthy volunteers denying childhood abuse, in the same direction as our finding among MDD subjects. This should be interpreted with caution given the very small sample size of abused controls. If childhood abuse is found to be associated with low 5-HTT among healthy controls in larger samples, this might suggest that low 5-HTT related to childhood adversity is not *sufficient* to produce a phenotype of adult depression, or that these healthy controls may be at higher risk for the development of subsequent psychiatric illness. Our sample was too small to evaluate gene-environment interactions with the 5-HTTLPR polymorphism. We and others have previously reported a lack of effect of 5-HTTLPR genotype on 5-HTT BP_P (Murthy et al., 2008; Oquendo et al., 2007; Parsey et al., 2006a), although some studies have found such an effect (Praschak-Rieder et al., 2007; Reimold et al., 2007). Larger future studies could examine whether the ability to detect an effect of 5-HTTLPR genotype on *in vivo* 5-HTT binding is contingent on considering interactions between genotype and early life stress. The [^{11}C]McN 5652 radioligand does not permit measurement of free-fraction in plasma (f_P), which is required to estimate the more robust binding measure BP_F ($=B_{avail}/K_D$); in addition, [^{11}C]McN 5652 has higher non-specific uptake than the radioligand [^{11}C]DASB, for which f_p is measurable (Frankle et al., 2004a). We did not examine the effects of physical or sexual abuse after age fifteen on 5-HTT BP_P. Among the group of thirteen depressed subjects without a history of

childhood abuse, only two endorsed a history of abuse from age fifteen or later, which limits any conclusions that could be drawn. Finally, childhood abuse history was assessed through the use of a semi-structured interview, and was not independently corroborated.

This study provides the first direct evidence of lower 5-HTT BP_P in adulthood associated with a reported history of childhood abuse. Future studies with larger sample sizes may assess whether there is a critical period for the effects of abuse. The experience of adversity in childhood, a period of great neuroplasticity (Black et al., 1998), may be more salient for 5-HTT regulation than abuse experienced in adulthood. Use of a more detailed measure of childhood abuse, such as the childhood trauma questionnaire (Bernstein and Fink, 1998), will facilitate such studies. Targeted recruitment of psychiatrically healthy adults with and without a history of childhood abuse for 5-HTT quantification will allow us to assess the generalizability of this finding, and may speak to the neurobiological underpinnings of resiliency.

Acknowledgments

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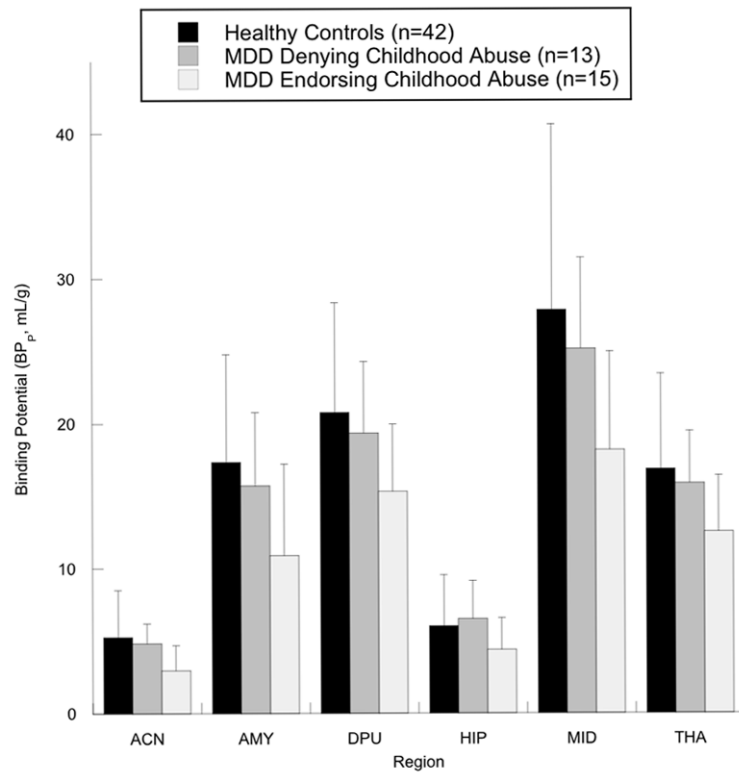
Figure 1.
Depressed subjects with a reported history of childhood abuse have lower serotonin transporter binding potential than those who do not report childhood abuse ($p < 0.05$ for all regions considered simultaneously in linear mixed effects model, and for each individual region considered separately). Healthy controls included as additional comparison group in figure. MDD = major depressive disorder, ACN = anterior cingulate, AMY = amygdala, DPU = dorsal putamen, HIP = hippocampus, MID = midbrain, THA = thalamus.

Table I

Clinical and Demographic Characteristics of the Sample

Variable	MDD Reporting Childhood Abuse (N=10)		MDD Reporting No Childhood Abuse (N=13)		Healthy Controls (N=43)		T-test (depressed abused vs. unabused)
Continuous Variables	**Mean**	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**	**p-value**
Age (yrs)	39.1	16.1	39.2	11.4	38.8	15.9	0.98
24-item Hamilton Depression Rating Scale	24.2	7.2	25.8	7.6	0.68	0.91	0.62
Beck Depression Index	21.4	11.5	25.4	10.4	1.7	2.4	0.39
Global Assessment Scale	48.2	12.4	51.0	12.9	89.8	4.5	0.60
# of prior major depressive episodes (MDEs)	4.5	3.4	4.2	2.9	0	0	0.79
Length of Current MDE (days)[1]	91.6	177.5	47.9	76.3	N/A	N/A	0.43
# of 1st degree relatives with Major Depression	1.0	1.2	1.0	1.0	0	0	1.00
Years of Education	14.8	1.8	15.0	3.6	16.4	2.9	0.79
Lifetime Aggression Score	16.7	4.9	15.3	3.6	14.1	3.9	0.48
Categorical Variables	**N**	**%**	**N**	**%**	**N**	**%**	**Fisher's Exact p-value (depressed abused vs. unabused)**
Gender							
Male	4	40.0	2	15.4	22	51	0.34
Female	6	60.0	11	84.6	21	49	
Prior Suicide Attempts:							
Yes	6	60.0	4	30.8	0	0	0.22
No	4	40.0	9	69.2	43	100	
Comorbid Anxiety Disorder							
Yes	4	40.0	7	53.9	0	0	0.68
No	6	60.0	6	46.2	43	100	
Comorbid Post-Traumatic Stress Disorder							
Yes	1	10.0	3	23.1	0	0	0.60
No	9	90.0	10	76.9	43	100	
Variable	**MDD Reporting Childhood Abuse (N=10)**		**MDD Reporting No Childhood Abuse (N=13)**		**Healthy Controls (N=43)**		**Fisher's Exact p-value (depressed abused vs. unabused)**

Variable	MDD Reporting Childhood Abuse (N=10)		MDD Reporting No Childhood Abuse (N=13)		Healthy Controls (N=43)		T-test (depressed abused vs. unabused)
Continuous Variables	Mean	S.D.	Mean	S.D.	Mean	S.D.	p-value
	N	%	N	%	N	%	
Remission Status at 1 year[2]							
Remitter	2	22.2	5	50.0	N/A	N/A	0.35
Non-Remitter	7	77.8	5	50.0	N/A	N/A	
5-HTTLPR Functional Genotype							
L'L'	3	30.0	2	15.4	10	23.8	0.64
L'S'	4	40.0	8	61.5	16	38.1	
S'S'	3	30.0	3	23.1	16	38.1	
Type of Reported Childhood Abuse							
Sexual	4	40.0	N/A		2	4.6	
Physical	3	30.0	N/A		0	0	
Both	3	30.0	N/A		0	0	

[1] one subject in the abused group is an outlier (584 days), accounting for observed non-statistically significant difference between groups.

[2] clinical follow-up was not available for four subjects.