Published in final edited form as:

Biol Psychiatry. 2009 January 15; 65(2): 175–180. doi:10.1016/j.biopsych.2008.08.034.

PET imaging of the serotonin transporter and 5HT1A receptor in alcohol dependence

Diana Martinez, M.D.¹, Mark Slifstein, Ph.D.¹, Roberto Gil, M.D.¹, Dah-Ren Hwang, Ph.D.^{1,2}, Yiyun Huang, Ph.D.^{1,2}, Audrey Perez, R.N.¹, W. Gordon Frankle, M.D.¹, Marc Laruelle, M.D.^{1,2}, John Krystal, M.D.³, and Anissa Abi-Dargham, M.D.^{1,2}

¹ Department of Psychiatry, Columbia University College of Physicians and Surgeons, New York, NY 10032

² Department of Radiology, Columbia University College of Physicians and Surgeons, New York, NY 10032

³ Yale University, New Haven, CT, 06510

Abstract

Background—Rodent models as well as studies in humans have suggested alterations in serotonin (5HT) innervation and transmission in early onset genetically determined or type II alcoholism. This study examines two indices of serotonergic transmission, 5HT transporter levels and 5-HT_{1A} availability, in vivo, in type II alcoholism. This is the first report of combined tracers for pre and post-synaptic serotonergic transmission in the same alcoholic subjects and the first study of 5HT_{1A} receptors in alcoholism.

Method—Fourteen alcohol dependent subjects were scanned (11 with both tracers, 1 with [¹¹C] DASB only and two with [¹¹C]WAY100635 only). Twelve healthy controls (HC) subjects were scanned with [¹¹C]DASB and another 13 were scanned with [¹¹C]WAY100635. Binding Potential (BP_p, mL/cm³) and the specific to nonspecific partition coefficient (BP_{ND}, unitless) were derived for both tracers using 2 tissue compartment model and compared to HC across different brain regions. Relationships to severity of alcoholism were assessed.

Results—No significant differences were observed in regional BP_p or BP_{ND} between patients and controls in any of the regions examined. No significant relationships were observed between regional 5HT transporter availability, 5-HT_{1A} availability, and disease severity with the exception of a significant negative correlation between SERT and years of dependence in amygdala and insula.

Correspondence: Dr. Diana Martinez, New York State Psychiatric Institute, 1051 Riverside Drive, Box #31, New York, NY 10032, Telephone: (212) 543-6628, Fax: (212) 568-6171, email: dm437@columbia.edu.

Financial Disclosures: Dr. Krystal reports the following: Consulting: AstraZeneca Pharmaceuticals, LP, Cypress Bioscience, Inc., HoustonPharma, Schering-Plough Research Institute, Shire Pharmaceuticals, and Pfizer Pharmaceuticals; Advisory Boards: Bristol-Myers Squibb, Eli Lilly and Co., Forest Laboratories, GlaxoSmithKline, Lohocla Research Corporation, Merz Pharmaceuticals, Takeda Industries, and Transcept Pharmaceuticals, Inc.; Exercisable Warrant Options: Tetragenex Pharmaceuticals Inc.; Research Support: Janssen Research Foundation (through the VA); Pending Patents: glutamatergic agents for psychiatric disorders (depression, OCD), antidepressant effects of oral ketamine, and oral ketamine for depression. Dr. Abi-Dargham reports the following: Consulting: Otsuka American Pharmaceuticals, Eli Lilly, Sanofi-Aventis, Intra-cellular Therapies; Advisory Boards: Otsuka American Pharmaceuticals; Speakers Bureau: Bristol-Meyers Squibb, Otsuka American Pharmaceuticals; Research Support: Bristol-Meyers Squibb, GlaxoSmithKline. Dr. Slifstein reports the following: Consulting: GlaxoSmithKline and Amgen Inc. Dr. Huang reports the following: Research Support: Pfizer, Inc., Eli Lilly and Co., GlaxoSmithKline. Dr. Frankle reports the following: Consulting: Sepracor, Inc., Transcept Pharmaceuticals (formerly Transoral), Eli Lilly, Inc.; Speaking Fees: Bristol-Meyers Squibb, Inc.; Research Support: GlaxoSmithKline, Inc., Sepracor, Inc. Dr. Hwang is now a full time employee of Amgen, Inc. Dr. Laruelle is now a full time employee of GlaxoSmithKline. The other authors report no biomedical financial interests or potential conflicts of interest.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conclusion—This study did not find alterations in measures of 5-HT_{1A} or 5HT transporter levels in patients with type II alcoholism.

Keywords

Serotonin transporter; Serotonin 1A receptor; PET; Alcohol Dependence; human subjects

Introduction

Previous studies in rodents selectively bred for alcohol preference have shown deficits in serotonin (5-HT) transmission, including low brain 5-HT content, a decrease in 5-HT cells and fibers, and a compensatory upregulation of 5-HT_{1A} receptors (1,2). Since these deficits are thought to represent a risk for developing abnormal drinking behavior, alterations in serotonin transmission are thought to be more relevant to alcoholism type II, the early onset form of the disease (3–5). Consistent with this hypothesis, studies in humans have shown low CSF 5-HIAA, predominantly in type II alcoholics (6,7), and reduced 5-HT transporters (SERT) in the hippocampus in postmortem tissue (8).

More recently, brain imaging studies have been used to investigate serotonin innervation in alcohol dependent subjects, but have yielded conflicting findings. Using [¹²³I]β-CIT to label the SERT in the midbrain, Heinz et al. (9) found decreases in the serotonin transporter in male alcoholics. [¹¹C]McN 5652 was the first selective PET radiotracer developed to image the SERT (10,11), and Szabo et al (12) reported a decrease in SERT specific binding in the midbrain of alcoholics using this radiotracer. However, a subsequent study with the newer PET radiotracer [¹¹C]DASB did not find differences in binding between alcoholics and healthy controls (13).

The radiotracer [¹¹C]WAY 100635 has been shown to reliably measure serotonin 1A (5-HT_{1A}) receptors in the human brain and has been used in several clinical investigations (14). In alcohol preferring rodents, 5-HT_{1A} receptors are increased in brain regions receiving serotonin innervation (2,15) and reduced in the raphe nuclei, where they function as autoreceptors, consistent with a reduction in serotonin innervation (although see (16)).

Here, we measure with PET the distribution of the SERT using [¹¹C]DASB and the 5-HT_{1A} receptors with [¹¹C]WAY-100635 in patients with type II alcoholism (17) and matched controls. Based on previous studies, we tested the hypothesis that alcoholism is associated with a decrease in SERT and 5-HT_{1A} receptor density in the raphe nuclei, which are present on the serotonin cell body. While in the projection fields, especially in the limbic regions, we tested the hypothesis that alcoholism would be associated with decreases in SERT and a compensatory upregulation in 5-HT_{1A} postsynaptic receptors.

Methods

Human Subjects

The study was approved by the Institutional Review Boards of the New York State Psychiatric Institute and the VA Connecticut Healthcare System. All subjects provided informed consent. Inclusion criteria for the alcohol dependent subjects (ALD) were: 1) age 25–45; 2) DSM-IV criteria for alcohol dependence (prior to the age of 25) and no other current Axis I disorders; 3) no past or current abuse/dependence on other drugs except for nicotine; 4) past, but not current, marijuana use was allowed 5) medically healthy. Healthy controls subjects had no DSM-IV Axis I disorders.

The time-line follow-back interview (18) was used to estimate daily drinking over the 30 days prior to study entry and severity of alcoholism was assessed with the Alcohol Dependence Scale (ADS) (19). All PET scans were performed at the Columbia University Medical Center. Of the 14 ALD subjects, 10 were admitted to the New York State Psychiatric Institute (NYSPI) and 4 were admitted to the VA Connecticut Healthcare System. Those admitted to NYSPI underwent detoxification with chlordiazepoxide over the first 3–5 days of admission, and the PET scans were obtained 14 days following detoxification. Additional clinical information is available in the supplementary material.

Eleven of the alcohol dependent subjects were scanned with both radiotracers [^{11}C]DASB and [^{11}C]WAY100635. One additional ALD subject was scanned with [^{11}C]DASB only and another two ALD subjects were scanned with only [^{11}C]WAY100635. For each radiotracer, a separate group of HC subjects was studied.

PET scan acquisition

The PET scans were acquired and analyzed as described in the supplementary material. Regions of interest (ROIs) were drawn on each subjects' MRI as previously described (20, 21). The ROIs for each radiotracer are listed in the supplementary material and in tables 3 and 4.

Due to the lack of identifiable boundaries for the raphe nuclei, a standard rectangular region (3350 mm^3) was placed on each individual's MRI, as described previously (20) (also see supplementary material). Since most previous publications have reported on the midbrain for [^{11}C]DASB, rather than the raphe alone, a post-hoc analysis of this region was done for [^{11}C]DASB. The cerebellum was used as the reference region for both radiotracers.

PET outcome measures

Serotonin transporter and 5HT1a receptor availability were calculated using two outcome measures: [^{11}C]DASB and [^{11}C]WAY 100635 binding potential (BP_p , mL/g) and the specific to nonspecific partition coefficient (BP_ND , unitless) (22,23). The definitions of BP_p and BP_ND are provided in the supplementary material.

Statistical Analysis

Group demographic and PET scan parameters comparisons were performed with unpaired t tests. Differences in BP_p and BP_ND between the ALD and HC were analyzed with a repeated measures mixed model in the SPSS software environment (SPSS, Chicago, IL), with the region of interest as the repeated measure and diagnostic group as the co-factor. The Greenhouse-Geisser (GG) correction for non-sphericity was utilized when indicated (if the data did not conform to the covariance assumptions of the model).

In the alcohol dependent group, relationships between the PET scan outcome measures BP_ND , BP_p and the clinical measures of alcohol dependence were analyzed with the Pearson product moment correlation coefficient. The clinical measures included the alcohol dependence scale, years of alcohol abuse (corrected for age), and average daily alcohol consumption (standard drinks/day for 30 days prior to admission). For both radiotracers, BP_ND and BP_p in the raphe nuclei, anterior cingulate, and medial temporal structures (amygdala, hippocampus, parahippocampus, and entorhinal cortex) were chosen for this analysis. A two tailed probability value of $p < 0.05$ was chosen as significance level.

Results

Group comparison

The demographics for each group are shown in table 1. In the [^{11}C]DASB study, ALD subjects consumed 16 ± 8 standard drinks per day and had been drinking for 21 ± 9 years. In the [^{11}C]WAY100635 study, the ALD subjects consumed 15 ± 8 standard drinks/day and had been drinking for 21 ± 9 years. The average Alcohol Dependence Scale (ADS) score was 21.0 ± 8.2 for the [^{11}C]DASB study and 20.9 ± 8.3 for the [^{11}C]WAY100635 study. A score of 14–21 indicates an intermediate level of alcohol dependence, whereas a score of 22–30 indicates a substantial level of dependence (19).

PET scans

Table 1 shows the scan parameters for both radiotracers for each group. No significant differences were seen in the size of the ROIs between the alcohol dependent subjects and healthy controls (Main effect of diagnosis, $p = 0.44$, diagnosis by region interaction, $p = 0.645$ GG corrected).

The outcome measures for the [^{11}C]DASB study are shown in figure 1 (BP_p) and table 3 (BP_{ND}). No significant group differences were seen in any region for either BP_p or BP_{ND} (BP_p : main effect of group, $p = 0.36$, group by region interaction, $p = 0.20$ GG corrected, BP_{ND} : main effect of group, $p = 0.79$, group by region interaction 0.36 GG corrected). The post-hoc analysis of the midbrain showed no significant difference between the two groups (control subjects 2.1 ± 0.7 ; alcohol dependent subjects 1.9 ± 0.8 , $p = 0.6$). These results are similar to those of the DRN region (2.0 for HC and 1.8 for ALD, $p = 0.3$). No significant differences were seen for [^{11}C]WAY 100635 (BP_p : main effect of group, $p = 0.22$, group by region interaction, $p = 0.36$ GG corrected, BP_{ND} : main effect of group, $p = 0.69$, group by region interaction, $p = 0.30$ GG corrected), as shown in figure 2 and table 4. No group differences were seen for either radiotracer when the female subjects or non-smokers were removed from the analysis. No significant correlation was seen between SERT and 5-HT $_{1A}$ binding (both BP_{ND} and BP_p) in the eleven ALD subjects who were scanned with both radiotracers.

Correlations with clinical data

A negative correlation was seen between years of abuse and BP_{ND} for [^{11}C]DASB in the amygdala ($r = 0.75$, $p = 0.009$, corrected for age) and the insula ($r = 0.65$, $p = 0.009$, corrected for age). A post-hoc analysis using [^{11}C]DASB BP_p for these two regions showed similar results (amygdala $r = 0.67$, $p = 0.05$; insula $r = .69$, $p = 0.09$, both analyses corrected for age). No significant correlation was seen for the other regions.

A trend was observed in the correlation between the subjects' scores on the alcohol dependence scale and BP_{ND} for [^{11}C]DASB in the hippocampus and parahippocampus, after excluding a subject who scored very high on the ADS and also had a high value for BP_{ND} ($p > 0.07$). Prior to excluding this subject, a positive correlation was seen ($r = 0.48$, $p = 0.01$ hippocampus; $r = 0.56$, $p = 0.007$ parahippocampus). No significant correlation was seen between [^{11}C]DASB BP_{ND} for these regions and the standard drinks/day prior to admission.

No significant correlation was seen between [^{11}C]WAY 100635 binding or ROI size and ADS score, years of abuse, or standard drinks/day prior to admission.

Discussion

Previous studies in alcohol-preferring rodents have demonstrated a deficit in serotonin (5-HT) transmission, shown by low brain 5-HT content, a decrease in 5-HT cells and fibers, and a compensatory upregulation of 5-HT_{1A} receptors (1,2). Microdialysis studies of ethanol-naïve alcohol preferring and non-preferring rodents have shown either higher levels of serotonin in the preferring rodent or no difference between the two groups (24–26). However, ethanol pretreatment has been shown to result in decreased basal extracellular 5-HT levels in alcohol preferring rodents (24). Previous post-mortem studies in alcohol dependent subjects have shown a significant decrease in the SERT in multiple brain areas including the hippocampus, anterior cingulate, dorsal striatum, amygdala, and hypothalamus (8,27–30). Based on these findings, our hypothesis was that alcohol dependence would be associated with a decrease in serotonin transmission, which would be reflected as a decrease in SERT and 5-HT_{1A} receptor binding in the midbrain combined with a decrease in SERT and compensatory upregulation of the 5-HT_{1A} receptor in the projection fields. However, we did not find any specific alterations in 5-HT_{1A} receptor or SERT binding in alcohol dependent subjects compared to matched controls.

Our study does not replicate previous studies from two groups but agrees with a third group with respect to SERT binding. Using SPECT and [¹²³I]β-CIT, Heinz et al (9,31) reported a 30% reduction of SERT binding in the midbrain in male, but not female, alcohol dependent participants. In a subsequent study, this group reported a decrease in midbrain SERT only in alcoholics who were homozygous for the long allele of the promoter of the SERT gene compared to healthy controls with the same genotype (32).

Since these studies were conducted with the SPECT radiotracer [123I]βCIT measurement of the SERT was limited to the midbrain. Another group, using PET and the radiotracer [¹¹C]McN5652, reported a significant decrease in the distribution volume of [¹¹C]McN5652 in the midbrain, cortical brain regions, and reference region (cerebellum) in alcohol dependence (12). However, only the midbrain was significantly reduced when the authors reported on the specific binding of [¹¹C]McN5652. More recently, a third group (13) used [¹¹C]DASB, a radiotracer for SERT imaging with an improved signal to noise ratio (33), in a study of alcohol dependence and reported no difference in any brain region, including the midbrain.

Thus, two groups have reported a decrease in midbrain SERT in alcoholism while this study and that of Brown et al (13) did not. The reason behind this discrepancy is not clear, but may relate to differences in stage of withdrawal, data analysis, specifically of the midbrain regions, or patient heterogeneity. Duration of abstinence was somewhat varied between the studies (2 weeks in this study and the study of Brown et al, 3 to 5 weeks in the studies of Heinz et al, and 2 to 27 years in the study of Szabo et al). However, it should be noted that the two negative studies had the same duration of abstinence, whereas there was more variability in the studies showing decreased SERT binding. Thus, for the time of abstinence to explain this discrepancy, it would be necessary to hypothesize that the SERT is normalized early in abstinence, then decreases at 3 weeks of abstinence and remains decreased for years.

Due to a lack of clear borders for defining the raphe nuclei, it is possible that differences in methods of analysis of the midbrain region may explain the different findings. However, this study examined two methods of defining the raphe, and neither resulted in a difference between the two groups. Heterogeneity of the disease may play a role. Heinz et al showed an effect of genotype and depressive symptomatology may be an important factor (9,31). However, it should be noted that the study of Szabo et al did not include depressed alcohol dependent subjects (12). In addition, Brown et al. investigated the correlation between alcoholism, aggression, and SERT binding and found no effect. Gender is not likely to explain this

discrepancy. Heinz et al showed an effect in males only, and a re-analysis of this data without the 2 females did not change our outcome. A limitation of this study is that genotyping was not performed. A recent PET study reported that [^{11}C]DASB BP in the midbrain was significantly increased in the midbrain of subjects homozygous for the long allele of the serotonin transporter (34), although another study did not see a difference in the midbrain (35). The study above of Heinz et al reported that SERT binding was reduced only in alcohol dependent subjects who were carriers of the long allele (32), so that this factor could have affected our results. Finally, differences between tracers resulting from differences in the levels of endogenous transmitter between groups are possible, since both negative studies used the same radiotracer. Studies in the same cohorts with both tracers can inform us whether the discrepancies are related to illness heterogeneity or tracer's properties.

We observed a correlation between indices of severity of disease and levels of binding of the SERT in some brain regions that were a priori hypothesized to show alterations of radiotracer binding. These correlations were of small magnitude in general but reached statistical significance on occasion. The meaning of these correlations, in the absence of overall alterations of receptors, is unclear and they should be taken with caution.

Lastly, an important point is that this study used an indirect estimate of intrasynaptic serotonin, by measuring SERT and the 5-HT_{1A} receptor binding. In theory, low intrasynaptic serotonin should result in upregulation of the 5-HT_{1A} receptor, and low SERT binding should reflect a decrease in serotonergic fibers, as has been shown in animal studies (1,2). Ideally, one would measure intrasynaptic serotonin using PET imaging in conjunction with a pharmacologic probe that alters serotonin transmission. However, to date it has not been feasible to measure intrasynaptic serotonin directly using PET, although attempts to do this have been made (36, 37). Thus, the discrepancy in the studies reported above may simply result from the limitations associated with such indirect measures of serotonin transmission.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The authors would like to thank Mabel Torres, Erica Scher, Ingrid Gelbard-Stokes, Elizabeth Hackett, Hemant Belani, and Kris Wolff for excellent technical assistance. This study was supported by the Public Health Service, NIAAA IP50 AA-12870-01 and NIDA K23 DA00483.

References

1. Zhou FC, et al. Serotonergic neurons in the alcohol preferring rats. *Alcohol* 1994;11(5):397–403. [PubMed: 7818798]
2. Wong DT, et al. Higher density of serotonin-1A receptors in the hippocampus and cerebral cortex of alcohol-preferring P rats. *Life Sci* 1990;46(3):231–5. [PubMed: 2137548]
3. Buydens-Branchey L, et al. Age of alcoholism onset. II. Relationship to susceptibility to serotonin precursor availability. *Arch Gen Psychiatry* 1989;46(3):231–6. [PubMed: 2919952]
4. von Knorring AL, et al. Platelet MAO activity as a biological marker in subgroups of alcoholism. *Acta Psychiatr Scand* 1985;72(1):51–8. [PubMed: 4036659]
5. Limson R, et al. Personality and cerebrospinal fluid monoamine metabolites in alcoholics and controls. *Arch Gen Psychiatry* 1991;48(5):437–41. [PubMed: 1708656]
6. Virkkunen M, Linnoila M. Brain serotonin, type II alcoholism and impulsive violence. *Journal of Studies on Alcohol Supplement* 1993;11:163–9. [PubMed: 8410958]
7. Fils-Aime ML, et al. Early-onset alcoholics have lower cerebrospinal fluid 5-hydroxyindoleacetic acid levels than late-onset alcoholics. *Arch Gen Psychiatry* 1996;53(3):211–6. [PubMed: 8611057]

8. Chen HT, et al. 3H-paroxetine binding in brains of alcoholics. *Psychiatry Res* 1991;38(3):293–9. [PubMed: 1836640]
9. Heinz A, et al. Reduced central serotonin transporters in alcoholism. *Am J Psychiatry* 1998;155(11):1544–9. [PubMed: 9812115]
10. Suehiro M, et al. A PET radiotracer for studying serotonin uptake sites: carbon-11-McN-5652Z. *J Nucl Med* 1993;34(1):120–127. [PubMed: 8418252]
11. Szabo Z, et al. Positron emission tomography imaging of serotonin transporters in the human brain using [11C](+)McN5652. *Synapse* 1995;20(1):37–43. [PubMed: 7624828]
12. Szabo Z, et al. Positron emission tomography imaging of the serotonin transporter in subjects with a history of alcoholism. *Biol Psychiatry* 2004;55(7):766–71. [PubMed: 15039007]
13. Brown AK, et al. PET [11C]DASB imaging of serotonin transporters in patients with alcoholism. *Alcohol Clin Exp Res* 2007;31(1):28–32. [PubMed: 17207098]
14. Parsey RV, et al. Validation and reproducibility of measurement of 5-HT1A receptor parameters with [carbonyl-11C]WAY-100635 in humans: comparison of arterial and reference tissue input functions. *J Cereb Blood Flow Metab* 2000;20(7):1111–33. [PubMed: 10908045]
15. McBride WJ, et al. Regional serotonin1A receptors in the CNS of alcohol-preferring and -nonpreferring rats. *Pharmacol Biochem Behav* 1994;49(1):7–12. [PubMed: 7816892]
16. Advani T, Hensler JG, Koek W. Effect of early rearing conditions on alcohol drinking and 5-HT1A receptor function in C57BL/6J mice. *Int J Neuropsychopharmacol* 2007;10(5):595–607. [PubMed: 17134528]
17. Cloninger CR. Neurogenetic adaptive mechanisms in alcohol. *Science* 1987;236:410–416. [PubMed: 2882604]
18. Maisto SA, et al. Comparison of two techniques to obtain retrospective reports of drinking behavior from alcohol abusers. *Addict Behav* 1982;7(1):33–8. [PubMed: 7080882]
19. Skinner HA, Allen BA. Alcohol dependence syndrome: measurement and validation. *J Abnorm Psychol* 1982;91(3):199–209. [PubMed: 7096790]
20. Frankle WG, et al. Serotonin 1A receptor availability in patients with schizophrenia and schizoaffective disorder: a positron emission tomography imaging study with [11C]WAY 100635. *Psychopharmacology (Berl)* 2006;189(2):155–64. [PubMed: 16953380]
21. Frankle WG, et al. Estimation of serotonin transporter parameters with 11C-DASB in healthy humans: reproducibility and comparison of methods. *J Nucl Med* 2006;47(5):815–26. [PubMed: 16644752]
22. Slifstein M, Laruelle M. Models and methods for derivation of in vivo neuroreceptor parameters with PET and SPECT reversible radiotracers. *Nuclear Medicine and Biology* 2001;28(5):595–608. [PubMed: 11516703]
23. Innis RB, et al. Consensus nomenclature for in vivo imaging of reversibly binding radioligands. *J Cereb Blood Flow Metab* 2007;27(9):1533–9. [PubMed: 17519979]
24. Smith AD, Weiss F. Ethanol exposure differentially alters central monoamine neurotransmission in alcohol-preferring versus -nonpreferring rats. *J Pharmacol Exp Ther* 1999;288(3):1223–8. [PubMed: 10027862]
25. Katner SN, Weiss F. Neurochemical characteristics associated with ethanol preference in selected alcohol-preferring and -nonpreferring rats: a quantitative microdialysis study. *Alcohol Clin Exp Res* 2001;25(2):198–205. [PubMed: 11236833]
26. Thielen RJ, et al. Ethanol-stimulated serotonin release in the ventral hippocampus: an absence of rapid tolerance for the alcohol-preferring P rat and insensitivity in the alcohol-nonpreferring NP rat. *Pharmacol Biochem Behav* 2002;71(1–2):111–7. [PubMed: 11812514]
27. Mantere T, et al. Serotonin transporter distribution and density in the cerebral cortex of alcoholic and nonalcoholic comparison subjects: a whole-hemisphere autoradiography study. *Am J Psychiatry* 2002;159(4):599–606. [PubMed: 11925298]
28. Storvik M, et al. Lower serotonin transporter binding in caudate in alcoholics. *Synapse* 2006;59(3):144–51. [PubMed: 16358330]
29. Storvik M, et al. Amygdala serotonin transporters in alcoholics measured by whole hemisphere autoradiography. *Synapse* 2007;61(8):629–36. [PubMed: 17476685]

30. Storvik M, et al. Correlation between the SERT binding densities in hypothalamus and amygdala in Cloninger type 1 and 2 alcoholics. *Alcohol Alcohol* 2008;43(1):25–30. [PubMed: 18039673]
31. Heinz A, et al. Relationship between cortisol and serotonin metabolites and transporters in alcoholism [correction of alcoholism]. *Pharmacopsychiatry* 2002;35(4):127–34. [PubMed: 12163982]
32. Heinz A, et al. A relationship between serotonin transporter genotype and in vivo protein expression and alcohol neurotoxicity. *Biol Psychiatry* 2000;47(7):643–9. [PubMed: 10745057]
33. Wilson AA, et al. In vitro and in vivo characterisation of [11C]-DASB: a probe for in vivo measurements of the serotonin transporter by positron emission tomography. *Nucl Med Biol* 2002;29(5):509–15. [PubMed: 12088720]
34. Reimold M, et al. Midbrain serotonin transporter binding potential measured with [11C]DASB is affected by serotonin transporter genotype. *J Neural Transm* 2007;114(5):635–9. [PubMed: 17225932]
35. Praschak-Rieder N, et al. Novel 5-HTTLPR allele associates with higher serotonin transporter binding in putamen: a [(11)C] DASB positron emission tomography study. *Biol Psychiatry* 2007;62(4):327–31. [PubMed: 17210141]
36. Talbot PS, et al. Effects of reduced endogenous 5-HT on the in vivo binding of the serotonin transporter radioligand 11C-DASB in healthy humans. *Synapse* 2005;55(3):164–75. [PubMed: 15605360]
37. Milak MS, et al. Effects of tryptophan depletion on the binding of [11C]-DASB to the serotonin transporter in baboons: response to acute serotonin deficiency. *Biol Psychiatry* 2005;57(1):102–6. [PubMed: 15607307]

Figure 1.

[¹¹C]DASB binding potential (BPP, g/ml) in the regions of interest. Solid bars are healthy control subjects, clear bars are the alcohol dependent subjects. No significant difference was seen between the two groups. Abbreviations are: RN: raphe nuclei; MPFC: medial prefrontal cortex; SPFC: subgenual prefrontal cortex; AC: anterior cingulate; AMY: amygdala; HIP: hippocampus; PHG: parahippocampal gyrus; EC: entorhinal cortex; INS: insula; THL: thalamus; VST: ventral striatum; prCA: precommissural dorsal caudate; prPT: precommissural dorsal putamen; pCA: postcommissural dorsal putamen; pPT: postcommissural dorsal putamen; STR: striatum.

Figure 2.

[¹¹C]WAY100635 binding potential (BPP, g/ml) in the regions of interest. Solid bars are healthy control subjects, clear bars are the alcohol dependent subjects. No significant difference was seen between the two groups. Values are mean $\pm$ SD, n = 13 per group. Values are mean $\pm$ SD, n = 12 per group. Abbreviations are: HC: healthy control; AD: alcohol dependent; RN: raphe nuclei; MPFC: medial prefrontal cortex; SPFC: subgenual prefrontal cortex; DPFC: dorsolateral prefrontal cortex; OFC: orbitofrontal cortex; AC: anterior cingulate; AMY: amygdala; HIP: hippocampus; PHG: parahippocampal gyrus; EC: entorhinal cortex; INS: insula; TC: temporal cortex; OC: occipital cortex; PC: parietal cortex.

Table 1

Subject Demographics

Parameter	[11C]DASB			[11C]WAY 100635		
	HC	ALD	p	HC	ALD	p
n (Male/Female)	12 (10M/2F)	12 (10M/2F)	-	13 (11M/2F)	13 (11M/2F)	-
Age (mean ± SD, years)	35 ± 8	33 ± 6	0.60	36 ± 8	36 ± 6	0.90
Ethnicity	1AA/3H/8C	2AA/3H/7C	-	1AA/2H/10C	3AA/3H/7C	-
Smoking status (N, S, Ex)	5N, 6S, 1Ex	6N, 6S, 0Ex	-	4N, 8S, 1Ex	4N, 8S, 1Ex	-
Smoking (cig/day)	12 ± 5 (5N)	13 ± 5	0.80	13 ± 5	12 ± 6	0.80

Abbreviations: AA: African-American; H: Hispanic; C: Caucasian ; cig/day cigarettes per day

Table 2

PET scan parameters

Parameter	¹¹ C]DASB				¹¹ C]WAY 100635			
	HC	ALD	p		HC	ALD	p	
Injected dose (mCi)	13.5 ± 3.1	13.1 ± 2.4	0.72		8.3 ± 3.0	7.4 ± 2.7	0.42	
Specific Activity (Ci/mmoles)	1242.9 ± 789.8	1530.1 ± 1218.1	0.50		1570.7 ± 625.7	1889.5 ± 860.6	0.29	
Injected mass (µg)	4.0 ± 2.6	4.1 ± 2.2	0.87		2.6 ± 1.8	1.8 ± 1.0	0.20	
Clearance (L h ⁻¹)	166.0 ± 58.8	202.5 ± 87.7	0.24		136.9 ± 36.0	169.6 ± 81.5	0.20	
Plasma f ₁ (%)	8.2 ± 1.3	8.4 ± 2.0	0.80		6.6 ± 1.8	7.3 ± 2.2	0.36	
VT _{CER} (mL g ⁻¹)	10.4 ± 1.2	9.6 ± 1.5	0.20		0.5 ± 0.3	0.5 ± 0.2	0.39	

Abbreviations: Plasma f₁: plasma free fraction; VT_{CER}: cerebellum volume of distribution.

Table 3

Baseline [¹¹C]DASB BP_{ND} (unitless)

Region of interest	HC	ALD
Raphe Nuclei	2.0 ± 0.7	1.7 ± 0.6
Medial Prefrontal Cortex	0.1 ± 0.1	0.1 ± 0.1
Subgenual Prefrontal Cortex	0.3 ± 0.2	0.3 ± 0.3
Anterior Cingulate	0.3 ± 0.1	0.4 ± 0.4
Amygdala	1.0 ± 0.4	1.0 ± 0.2
Hippocampus	0.3 ± 0.2	0.3 ± 0.1
Parahippocampus	0.2 ± 0.1	0.2 ± 0.1
Entorhinal cortex	0.5 ± 0.3	0.6 ± 0.3
Insula	0.6 ± 0.2	0.5 ± 0.2
Thalamus	1.0 ± 0.2	1.0 ± 0.2
Ventral Striatum	1.4 ± 0.4	1.3 ± 0.3
Pre- Dorsal Caudate	0.8 ± 0.2	0.8 ± 0.2
Pre- Dorsal Putamen	1.3 ± 0.3	1.3 ± 0.3
Post- Caudate	0.3 ± 0.1	0.3 ± 0.1
Post-Putamen	1.0 ± 0.3	1.1 ± 0.3
Striatum	1.0 ± 0.3	1.0 ± 0.2

No significant differences were seen between the two groups. Values are mean ± SD, n = 12 per group.

Abbreviations: HC: healthy control subjects; ALD: alcohol dependent subjects.

Table 4 $[^{11}\text{C}]\text{WAY BP}_{\text{ND}}$ (unitless)

Region of interest	HC	ALD
Raphe Nuclei	2.7 ± 0.7	2.6 ± 1.3
Medial Prefrontal Cortex	7.0 ± 1.7	6.3 ± 1.6
Subgenual Prefrontal cortex	7.8 ± 2.0	7.5 ± 2.6
Dorsolateral Prefrontal Cortex	5.8 ± 1.4	5.6 ± 1.4
Orbito-frontal Cortex	5.7 ± 1.6	5.1 ± 1.5
Anterior Cingulate	7.9 ± 1.9	7.3 ± 1.9
Amygdala	6.5 ± 1.7	7.3 ± 3.2
Hippocampus	9.2 ± 2.6	9.9 ± 4.7
Parahippocampus	9.9 ± 2.5	9.0 ± 3.0
Entorhinal Cortex	11.4 ± 2.6	12.0 ± 3.3
Insula	1.0 ± 2.2	9.1 ± 2.2
Temporal Cortex	8.8 ± 1.8	8.2 ± 1.8
Occipital Cortex	4.7 ± 1.3	4.3 ± 1.3
Parietal Cortex	5.4 ± 1.3	5.0 ± 1.4

No significant differences were seen between the two groups. Values are mean ± SD, n = 13 per group. Abbreviations: HC: healthy control subjects; ALD: alcohol dependent subjects.