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Decreased Norepinephrine Transporter Availability in Obesity: Positron Emission Tomography Imaging with (S,S)-[¹¹C]O-Methylreboxetine

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Abstract

Objectives—Noradrenergic dysfunction is implicated in obesity. The norepinephrine transporter (NET) regulates the synaptic availability of norepinephrine. However, NET availability has not been previously characterized *in vivo* in obese people using Positron Emission Tomography (PET) imaging. Here we report findings evaluating NET availability in individuals with obesity and matched lean (i.e., normal weight) comparison subjects.

Methods—Seventeen obese but otherwise healthy individuals with a mean±SD body mass index (BMI) of 34.7±2.6 and 17 lean individuals with a mean±SD BMI of 23.1±1.4 were studied using a High-Resolution Research Tomograph (HRRT) and (S,S)-[¹¹C]O-methylreboxetine ([¹¹C]-MRB), a radioligand selective for the NET. The regional brain NET binding potential (BP_{ND}) was estimated by the multilinear reference tissue model 2 (MRTM2) with the occipital cortex as a reference region. BP_{ND} for regions of interest were obtained with the Automated Anatomic Labeling (AAL) template registered to individual's structural MR scans.

Results—Obese individuals had lower NET BP_{ND} values in the thalamus ($p<0.038$, 27% reduction) including within the pulvinar ($p<0.083$, 30% reduction), but not in the hypothalamus, locus coeruleus or the raphe nuclei, compared to lean individuals. When age was included as a

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Disclosures

The authors report no conflicts of interest with the content of this manuscript.

covariate, the difference in NET BP_{ND} values remained significant in the thalamus ($p < 0.025$) and pulvinar ($p < 0.042$).

Conclusions—These results indicate that NET availability is decreased in the thalamus, including the pulvinar, in obese individuals. These findings further support data indicating noradrenergic dysfunction in obesity and suggest impaired NE clearance in obesity.

Keywords

[^{11}C]-MRB; norepinephrine; PET; human; obesity; BMI

Introduction

Obese individuals suffer adverse health effects including hypertension and Type-2 diabetes (Landsberg et al., 2013). The cost of obesity to society is tremendous due to illnesses associated with obesity and losses in productivity at work (Thorpe and Philyaw, 2012). In the United States, 36% of adults and 17% of children are obese according to Centers for Disease Control and Prevention (Flegal et al., 2012; Ogden et al., 2012). As prevalence estimates have been rising over time, understanding the biological factors underlying obesity could help advance prevention and treatment efforts.

While catecholaminergic dysfunction in obesity has largely focused on dopamine (Frascella et al., 2010; Kenny et al., 2011; Volkow et al., 2013; Wang et al., 2001), data also support noradrenergic contributions (Carlsson et al., 1979). Inhibition of either α_1 - or β_2 -noradrenergic receptors in the ventromedial/paraventricular hypothalamus reduces endogenous levels of norepinephrine (NE), decreasing food intake, while activation of α_2 -noradrenergic receptors of the lateral hypothalamus increases NE, increasing food intake (Bays et al., 2002; Levin et al., 1995; 1996). In people, intake of highly caloric diets increases noradrenergic turnover in peripheral tissues, leading to elevated resting plasma norepinephrine levels that may underlie increased excretion of norepinephrine and elevated rates of hypertension in obese versus lean people (Kotsis et al., 2010; Lee et al., 2001). These findings suggest an important role for the noradrenergic system in eating behaviors, obesity and obesity-related health conditions.

The concentration of NE at noradrenergic synapses is regulated by reuptake via the norepinephrine transporter (NET). The NET is expressed centrally in cortical and subcortical regions including the locus coeruleus, thalamus, hypothalamus, and hippocampus (Schroeter et al., 2000; Ding et al., 2010). Given their expression in brain regions proposed to underlie motivated behaviors (Chambers et al., 2003), NETs may contribute importantly to motivated behaviors underlying overeating in obesity. Additionally, the NET is targeted by therapeutic and abused drugs including stimulants and certain antidepressants (Hannestad et al., 2010; Gallezot et al., 2011), some of which may alter appetite and over time body mass, suggesting that the NET may represent an important target for medication development (Zhou, 2004).

We have previously demonstrated that the radioligand (S,S)-[^{11}C]O-methylreboxetine ([^{11}C]MRB) binds to the NET in the brain with higher specific binding and lower variability in non-specific binding than previous NET radioligands (Ding et al., 2005; Ding et al., 2006). This tracer has been employed successfully to assess occupancy of NET in clinical and preclinical studies (Hannestad et al., 2010; Gallezot et al., 2011) as well as to assess NET availability changes in cocaine-dependent individuals (Ding et al., 2010). To investigate NET availability in obesity, we compared [^{11}C]MRB binding potential values in seventeen obese and seventeen lean individuals, hypothesizing that we would observe between-group differences regions with high [^{11}C]MRB binding from our earlier work,

including the thalamus, hypothalamus, locus coeruleus, and the raphe nuclei (Ding et al., 2010; Gallezot et al., 2011; Hannestad et al., 2010).

Materials and Methods

Subjects

Thirty-four adults, including 17 obese (9 males, 32.1 ± 10.2 years of age) and 17 age- and gender-matched lean (9 males; 33.7 ± 11.5 years) individuals, participated in this study. The two groups differed both in weight (105.2 ± 12.7 vs. 66.7 ± 9.0 Kg; $p < 0.0001$) and BMI scores (34.7 ± 2.6 vs. 23.1 ± 1.4 ; $p < 0.0001$). All participants were screened to be free of major medical illness including past or present neurological and Axis-I psychiatric (First et al., 1995) conditions, denied current or past illicit substance use, and showed negative urine toxicology tests for stimulants, opioids, marijuana, and benzodiazepines at the time of the PET study. Participants were further required to be free of MRI contraindications based on the safety guidelines of Yale's Magnetic Resonance Research Center. All participants signed a written consent according to a protocol approved by the Yale Human Investigation Committee and the Yale-New Haven Hospital Radiation Safety Committee.

Magnetic Resonance (MR) Imaging

Participants were scanned on a Siemens 3-Tesla scanner (Trio; Siemens AG, Erlangen, Germany). Data for each participant consisted of a single high-resolution T1-weighted gradient-echo scan: 176 slices; 1 mm^3 isotropic voxels; field of view = $256 \times 256 \text{ mm}$; data acquisition matrix = 256×256 ; TR = 2530 ms; TE = 3.66 ms, bandwidth = 181 Hz/pixel; flip angle = 7°. The MR images were used for registration to an atlas to define regions of interest (ROIs).

Positron Emission Tomography (PET) imaging

The (S,S) enantiomer of the methyl analogue of reboxetine, 2-[alpha-(2-methoxyphenoxy)benzyl] morpholine was radiolabeled with carbon-11 ($[^{11}\text{C}]\text{MRB}$), as previously described (Ding et al., 2003). Subjects were scanned at the Yale PET Center on the High-Resolution Research Tomograph (HRRT) scanner. A 6-minute transmission scan was acquired using an orbiting ^{137}Cs point source prior to radiotracer injection for attenuation correction. One venous catheter was established in the forearm for a bolus injection of $[^{11}\text{C}]\text{MRB}$. A dose of $596 \pm 150 \text{ MBq}$ $[^{11}\text{C}]\text{MRB}$ with mass per weight of $0.024 \pm 0.017 \text{ }\mu\text{g/kg}$ and specific activity of $124 \pm 67 \text{ MBq/nmol}$ was delivered as a 2-minute bolus and the total scan time was 120 min. The acquisition of HRRT list-mode data began just prior to the initiation of the bolus injection delivered through a syringe pump (Harvard PHD 22/2000, Harvard Apparatus, Holliston, Massachusetts, United States). All scanning took place with the subjects in supine position and with an optical motion-tracking tool fastened to the subject's head (Vicra, NDI systems, Waterloo, Canada) via a swim cap.

The list mode data were reframed into a dynamic sequence of: $6 \times 30 \text{ sec}$, $3 \times 1 \text{ min}$, $2 \times 2 \text{ min}$, $22 \times 5 \text{ min}$. Dynamic images (207 slices and pixel size = $2 \times 2 \text{ mm}^2$) were reconstructed using ordered subset expectation maximization (OSEM, 2 iterations and 30 subsets) with corrections for measured attenuation, normalization, scatter, randoms, dead time, and event-by-event motion using the Motion-compensation OSEM List-mode Algorithm for Resolution-recovery Reconstruction (MOLAR) algorithm as previously described (Carson et al., 2003).

Image analyses

For registration, a summed PET image (0–10 min) was used for coregistration to the individual subject's MRI, which was linearly coregistered to a template MRI to determine the ROIs identified using the Automated Anatomical Labeling template (Tzourio-Mazoyer et al., 2002). The transformation was estimated based on normalized mutual information (FLIRT, <http://www.fmrib.ox.ac.uk/analysis/research/flirt/>). Regional [^{11}C]MRB uptake was quantified as binding potential (BP_{ND}), which is proportional to the density of available transporters for binding (Innis et al., 2007). The occipital cortex was used as a reference region as previously described (Hannestad et al., 2010). The estimates of BP_{ND} were obtained using the multilinear reference tissue model 2 (MRTM2; Ichise et al., 2003) that produces parametric BP_{ND} images, with the assumption that the nondisplaceable binding in the occipital cortex and target regions is similar.

We compared BP_{ND} values in the obese and lean groups using a two-tailed two-sample test for each of the regions of interest. Because age has been shown to influence [^{11}C]MRB binding (Ding et al., 2010), we also performed group comparison in a covariance analysis accounting for the differences in age between groups.

Results

The obese and lean individuals did not differ with regard to injected dose (578 ± 154 vs. 614 ± 148 MBq, $p=0.49$, two-tailed 2-sample t test) or injected mass per Kg body weight (0.025 ± 0.019 vs. 0.024 ± 0.015 $\mu\text{g/Kg}$; $p=0.86$).

NET binding potential (BP_{ND})

Consistent with our earlier studies, high uptake of [^{11}C]MRB was observed in regions rich in NET expression, including the thalamus, hypothalamus and the locus coeruleus and raphe nuclei in the midbrain (Ding et al., 2010). NET BP_{ND} estimates for obese and lean subjects are presented in Figure 1. Compared to lean participants, obese individuals had significantly lower NET BP_{ND} values in the thalamus (0.31 ± 0.14 vs. 0.43 ± 0.17 ; $p < 0.038$) and had lower NET BP_{ND} values in the pulvinar approaching significance (0.29 ± 0.19 vs. 0.41 ± 0.22 ; $p < 0.083$), but not in the hypothalamus, locus coeruleus or the raphe nuclei. Because NET availability decreased with age (Ding et al., 2010) and we found an age effect that was significant for the pulvinar ($p < 0.02$) and at trend level for the thalamus ($p < 0.10$), we accounted for the effects of age in a follow-up covariance analysis. The results showed that the difference in NET BP_{ND} values remained significant in the thalamus ($p < 0.025$) and reached significance in the pulvinar ($p < 0.042$). The other regions remained indistinguishable in NET BP_{ND} between groups. Figure 2 shows parametric images of a representative participant each from the obese and lean group.

Since most of the ROIs evaluated in our study are small structures, we considered potential biases in BP_{ND} estimates that may relate to the linear coregistration method used in delineating the ROIs. Thus, we reanalyzed the data using a nonlinear registration approach using the Bioimagesuite software (<http://www.bioimagesuite.org/>). The use of nonlinear transforms produced minor changes in the results. Compared to lean participants, obese individuals had significantly lower NET BP_{ND} values in the pulvinar (0.13 vs. 0.26 ; $p < 0.030$). The differences in thalamus were at trend level (0.20 vs. 0.29 ; $p < 0.067$). The other regions showed no significant differences in NET BP_{ND} between groups. With age correction, pulvinar and thalamus differences became more significant ($p < 0.024$ and 0.052 , respectively).

Discussion

Our findings partially confirmed our hypothesis that regional NET availability would differ between obese and lean individuals. Compared to lean people, obese people showed decreased NET binding potential in the thalamus and its pulvinar component after adjusting for age. However, differences in other regions were not observed. The thalamic and pulvinar results are consistent with earlier studies implicating noradrenergic dysfunction in maladaptive feeding and obesity, as discussed earlier. To our knowledge, this is the first *in vivo* imaging study of NET in obesity and the results directly demonstrate differences in NET availability related to obesity.

The thalamus, including its pulvinar component, have been described as relay stations in motivational neurocircuitry (Chambers et al., 2003; Saalman et al., 2012) and have been implicated in eating behaviors and obesity. For example, the thalamus becomes activated during pictures of high-versus low-calorie foods (Killgore et al., 2003). Glucose ingestion reduces cerebral blood flow in the hypothalamus and increases functional connectivity between the hypothalamus and thalamus, suggesting a role for these subcortical structures in regulating satiety and eating (Page et al., 2013). Restricted sleep increases cerebral responses to food cues in association with increased activity in the insula, striatum, thalamus, and prefrontal cortices (St-Onge et al., 2012). In obese but not lean individuals, food craving and insulin levels correlated positively with corticolimbic-striatal (including thalamic) activations during exposure to favorite-food and stress cues (Jastreboff et al., 2013). Furthermore, the relationship between insulin resistance and food craving in obese but not lean individuals was mediated by thalamic activation during exposure to favorite-food cues (Jastreboff et al., 2013). In an fMRI study of obese cancer survivors, behavioral lifestyle intervention decreased activation to high-calorie versus non-food cues in regions of reward and motivation circuitry, including the thalamus (Nock et al., 2012). Together, these studies suggest that the thalamus is involved in responses to food cues and intake that are altered in obese individuals and may contribute to excessive eating and obesity.

The current results contrast with those seen in cocaine dependence in which relatively increased [^{11}C]MRB was observed in the thalamus and its pulvinar component (Ding et al., 2010). While it is tempting to speculate that NE systems might regulate eating behaviors differently in cocaine dependence and obesity, future studies are needed to directly examine the roles of noradrenergic function with respect to specific aspects of each condition.

The present findings may also have implications for treatment development for obesity. For example, stimulant medications that target the NET and other biogenic aminergic transporters may reduce appetite and lead to weight loss, and the extent to which these effects might be mediated through thalamic mechanisms and modulated by other therapeutic drugs warrants consideration. Additionally, noradrenergic mechanisms have been implicated in obesity-related medical conditions like hypertension, and the extent to which the current findings might relate to hypertension in obesity deserve examination. Obesity is associated with mental-health disorders (Desai et al., 2009). As drugs targeting the NET have been shown to have efficacy in treating such conditions (e.g., depression), the current findings suggest possible mechanisms relating to their co-occurrence and a possible treatment target for medication development, although additional direct research is needed to explore this possibility.

For PET neuroreceptor/transporter imaging, a binding potential (BP_{ND}) in the range of 1–3, or higher, is desirable. [^{11}C]MRB, with its low binding potential due, in part, to the low concentration of NET, is currently the best available NET PET ligand. We have used [^{11}C]MRB successfully for multiple clinical and preclinical studies (Ding et al 2010,

Hannestad et al, 2010, Gallezot et al, 2011). It is important to note that, with low BP_{ND} values, between-group differences could be artificially introduced if there are between-group differences in the level of nondisplaceable binding, here obtained from the occipital cortex. However, such a bias would affect all regional values. Since the obesity effects were regionally specific (Figure 1), we cannot ascribe this difference to a between-group difference in nondisplaceable binding, although such group differences may have affected the magnitude and regional distribution of NET differences.

The current study has limitations. For example, although large for a PET study, the sample size is relatively small. Future studies employing larger samples might reveal important individual differences (e.g., gender) that have been linked to important aspects of eating behaviors and obesity. This is particularly important in light of a recent multicenter study that failed to replicate an association between BMI and dopamine transporter binding potential in the dorsal striatum (van de Giessen et al., 2013). Nonetheless, the groups are well matched on important characteristics, including gender and age, lending support to the potential generalizability of the findings. Second, we did not observe a difference in the hypothalamus, which has been implicated in noradrenergic dysfunction in association with obesity. The absence of a significant between-group in NET availability in the hypothalamus should be considered cautiously in that multiple factors (e.g., the small volume of the hypothalamus and the relatively low binding potential of [^{11}C]MRB) may preclude the identification of a significant between-group difference. Although [^{11}C]MRB is currently the most promising NET ligand available, future studies with PET ligands with improved affinity and specificity for the NET and involving larger numbers of subjects may help examine more definitively a role for noradrenergic function in the hypothalamus and other subnuclei of the thalamus in obesity.

In conclusion, we showed that the NET availability in the thalamus and pulvinar is decreased in obese, compared to lean, individuals. These results may provide a useful platform upon which to further investigate noradrenergic functions in obesity.

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References

1. Bays H, Dujovne C. Anti-obesity drug development. *Expert Opin Investig Drugs*. 2002; 11:1189–1204.
2. Carlsson, A. The impact of catecholamine research on medical science and practice. In: Usdin, E.; Kopin, I.; Barchas, J., editors. *Catecholamines: basic and clinic frontiers*. New York: Pergamon Press; 1979. p. 4-19.

3. Carson R, Barker W, Liow J, Johnson C. Design of a motion-compensation OSEM list-mode algorithm for resolution-recovery reconstruction for the HRRT. *IEEE Nucl Sci Symp.* 2003; 5:3181–3285.
4. Chambers RA, Taylor JR, Potenza MN. Developmental neurocircuitry of motivation in adolescence: A critical period of addiction vulnerability. *Am J Psychiatry.* 2003; 160:1041–1052. [PubMed: 12777258]
5. Desai RA, Manley MJ, Desai MM, Potenza MN. Gender differences in the association between body mass index and psychopathology. *CNS Spectrums.* 2009; 14:372–383. [PubMed: 19773713]
6. Ding YS, Lin KS, Garza V, Carter P, Alexoff D, Logan J, et al. Evaluation of a new norepinephrine transporter PET ligand in baboons, both in brain and peripheral organs. *Synapse.* 2003; 50:345–352. [PubMed: 14556239]
7. Ding YS, Lin KS, Logan J, Benveniste H, Carter P. Comparative evaluation of positron emission tomography radiotracers for imaging the norepinephrine transporter: (S, S) and (R, R) enantiomers of reboxetine analogs ([11C]methylreboxetine, 3-Cl-[11C]methylreboxetine and [18F]fluororeboxetine), (R)-[11C]nisoxetine, [11C] oxaprotiline and [11C]lortalamine. *J. Neurochem.* 2005; 94:337–351. [PubMed: 15998285]
8. Ding YS, Lin KS, Logan J. PET imaging of norepinephrine transporters. *Curr. Pharm. Des.* 2006; 12:3831–3845. [PubMed: 17073682]
9. Ding YS, Singhal T, Planeta-Wilson B, Gallezot JD, Nabulsi N, Labaree D, et al. PET imaging of the effects of age and cocaine on the norepinephrine transporter in the human brain using (S,S)-[(11C)O-methylreboxetine and HRRT. *Synapse.* 2010; 64:30–38. [PubMed: 19728366]
10. First, M.; Spitzer, R.; Williams, J.; Gibbon, M. Structured Clinical Interview for DSMIV (SCID). American Psychiatric Association; Washington DC: 1995.
11. Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of Obesity and Trends in the Distribution of Body Mass Index Among US Adults, 1999–2010. *J Am Med Assoc.* 2012; 307:491–497.
12. Frascella J, Potenza MN, Brown LL, Childress AR. Shared brain vulnerabilities open the way for nonsubstance addictions: carving addiction at a new joint? *Ann NY Acad Sci.* 2010; 1187:294–315. [PubMed: 20201859]
13. Gallezot JD, Weinzimmer D, Nabulsi N, Lin SF, Fowles K, Sandiego C, et al. Evaluation of [(11C)MRB for assessment of occupancy of norepinephrine transporters: Studies with atomoxetine in non-human primates. *Neuroimage.* 2011; 56:268–279. [PubMed: 20869448]
14. Hannestad J, Gallezot JD, Planeta-Wilson B, Lin SF, Williams WA, van Dyck CH, et al. Clinically relevant doses of methylphenidate significantly occupy norepinephrine transporters in humans in vivo. *Biol Psychiatry.* 2010; 68:854–860. [PubMed: 20691429]
15. Ichise M, Liow JS, Lu JQ, Takano A, Model K, Toyama H, et al. Linearized reference tissue parametric imaging methods: application to [11C]DASB positron emission tomography studies of the serotonin transporter in human brain. *J Cereb Blood Flow Metab.* 2003; 23:1096–1112. [PubMed: 12973026]
16. Innis RB, Cunningham VJ, Delforge J, Fujita M, Gjedde A, Gunn RN, et al. Consensus nomenclature for in vivo imaging of reversibly binding radioligands. *J Cereb Blood Flow Metab.* 2007; 27:1533–1539. [PubMed: 17519979]
17. Jastreboff AM, Sinha R, Lacadie C, Small DM, Sherwin RS, Potenza MN. Neural correlates of stress- and food cue-induced food craving in obesity: association with insulin levels. *Diabetes Care.* 2013; 36:394–402. [PubMed: 23069840]
18. Kenny PJ. Reward Mechanisms in Obesity: New Insights and Future Directions. *Neuron.* 2011; 69:664–679. [PubMed: 21338878]
19. Killgore WD, Young AD, Femia LA, Bogorodzki P, Rogowska J, Yurgelun-Todd DA. Cortical and limbic activation during viewing of high- versus low-calorie foods. *Neuroimage.* 2003; 19:1381–1394. [PubMed: 12948696]
20. Kotsis V, Stabouli S, Papakatsika S, Rizos Z, Parati G. Mechanisms of obesity-induced hypertension. *Hypertens Res.* 2010; 33:386–393. [PubMed: 20442753]
21. Lee ZS, Critchley JA, Tomlinson B, Young RP, Thomas GN, Cockram CS, Chan TY, Chan JC. Urinary epinephrine and norepinephrine interrelations with obesity, insulin, and the metabolic syndrome in Hong Kong Chinese. *Metabolism.* 2001; 50:135–143. [PubMed: 11229419]

22. Levin BE. Reduced norepinephrine turnover in organs and brains of obesity-prone rats. *Am J Physiol.* 1995; 268:R389–R394. [PubMed: 7864233]
23. Levin BE. Reduced paraventricular nucleus norepinephrine responsiveness in obesity-prone rats. *Am J Physiol.* 1996; 270:R456–R461. [PubMed: 8779879]
24. Landsberg L, Aronne LJ, Beilin LJ, Burke V, Igel LI, Lloyd-Jones D, Sowers J. Obesity-related hypertension: pathogenesis, cardiovascular risk, and treatment--a position paper of the The Obesity Society and The American Society of Hypertension. *Obesity (Silver Spring).* 2013; 21:8–24. [PubMed: 23401272]
25. Nock NL, Dimitropoulos A, Tkach J, Frasure H, von Gruenigen V. Reduction in neural activation to high-calorie food cues in obese endometrial cancer survivors after a behavioral lifestyle intervention: a pilot study. *BMC Neurosci.* 2012; 13:74. [PubMed: 22731395]
26. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of Obesity and Trends in Body Mass Index Among US Children and Adolescents, 1999–2010. *J Am Med Assoc.* 2012; 307:483–490.
27. Page KA, Chan O, Arora J, Belfort-Deaguiar R, Dzuira J, Roehmholdt B, Cline GW, Naik S, Sinha R, Constable RT, Sherwin RS. Effects of fructose vs glucose on regional cerebral blood flow in brain regions involved with appetite and reward pathways. *J Am Med Assoc.* 2013; 309:63–70.
28. Saalman YB, Pinski MA, Wang L, Li X, Kastner S. The pulvinar regulates information transmission between cortical areas based on attention demands. *Science.* 2012; 337:753–756. [PubMed: 22879517]
29. Schroeter S, Apparsundaram S, Wiley RG, Miner LH, Sesack SR, Blakely RD. Immunolocalization of the cocaine- and antidepressant-sensitive l-norepinephrine transporter. *J Comp Neurol.* 2000; 420:211–232. [PubMed: 10753308]
30. St-Onge MP, McReynolds A, Trivedi ZB, Roberts AL, Sy M, Hirsch J. Sleep restriction leads to increased activation of brain regions sensitive to food stimuli. *Am J Clin Nutr.* 2012; 95:818–824. [PubMed: 22357722]
31. Thorpe KE, Philyaw M. The medicalization of chronic disease and costs. *Annu Rev Public Health.* 2012; 33:409–423. [PubMed: 22224894]
32. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, et al. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage.* 2002; 15:273–289. [PubMed: 11771995]
33. van de Giessen E, Hesse S, Caan MW, Zientek F, Dickson JC, Tossici-Bolt L, Sera T, Asenbaum S, Guignard R, Akdemir UO, Knudsen GM, Nobili F, Pagani M, Vander Borgh T, Van Laere K, Varrone A, Tatsch K, Booij J, Sabri O. No association between striatal dopamine transporter binding and body mass index: a multi-center European study in healthy volunteers. *Neuroimage.* 2013; 64:61–67. [PubMed: 22982354]
34. Volkow ND, Wang GJ, Tomasi D, Baler RD. Obesity and addiction: neurobiological overlaps. *Obes Rev.* 2013; 14:2–18. [PubMed: 23016694]
35. Wang GJ, Volkow ND, Logan J, Pappas NR, Wong CT, Zhu W, et al. Brain dopamine and obesity. *Lancet.* 2001; 357:354–357. [PubMed: 11210998]
36. Zhou J. Norepinephrine transporter inhibitors and their therapeutic potential. *Drugs Future.* 2004; 29:1235–1244. [PubMed: 16871320]

Figure 1.

Norepinephrine transporter binding potential (BP_{ND}) estimates for regions of interest in lean (blue) and obese (green) participants. Histograms showed BP_{ND} in mean $\pm$ standard error. Compared to lean participants, obese participants demonstrated decreased BP_{ND} values in the thalamus (** $p < 0.038$) and pulvinar (* $p < 0.083$).

Figure 2.

Images of $[^{11}\text{C}]\text{MRB } BP_{\text{ND}}$ of a represent participant each from the lean and obese group, with reference to a structural image in axial, coronal, and sagittal sections. $[^{11}\text{C}]\text{MRB}$ binding is concentrated in the thalamus and midbrain. Compared to the lean participant, the obese participant showed decreased $[^{11}\text{C}]\text{MRB}$ binding.