Clinical Investigative Study

Change Over Time in Brain Serotonin Transporter Binding in Major Depression: Effects of Therapy Measured with [^{123}I]-ADAM SPECT

Jay D. Amsterdam, MD, Andrew B. Newberg, MD, Cory F. Newman, PhD, Justine Shults, PhD, Nancy Wintering, MSW, Irene Soeller, MSN, CRNP

From the Depression Research Unit, Department of Psychiatry, University of Pennsylvania School of Medicine, Philadelphia, PA (JDA, IS); Myrna Brind Center of Integrative Medicine, Thomas Jefferson University, Philadelphia, PA (ABN, NW); Department of Emergency Medicine and Radiology, Thomas Jefferson University, Philadelphia, PA (ABN); Center for Cognitive Therapy, Perelman School of Medicine at the University of Pennsylvania (CFN); Center for Clinical Epidemiology & Bio-statistics, University of Pennsylvania School of Medicine, Philadelphia, PA (JS).

ABSTRACT

Several studies have reported low brain serotonin transporter (SERT) binding in individuals with major depression. We hypothesized that the SERT standardized uptake ratio (SUR) values using [^{123}I]-ADAM single photon emission computed tomography would increase in depressed subjects who responded to cognitive behavior therapy (CBT) compared to CBT nonresponders. [^{123}I]-ADAM scans were acquired before and after 12 weeks of CBT from 20 depressed subjects and on two occasions 12 weeks apart from 10 nondepressed, healthy volunteers. The primary outcome measure was change over time in SUR values in the midbrain, medial temporal lobe, and basal ganglia regions. Depressed subjects demonstrated low pretreatment mean SUR values that significantly increased over time in the midbrain ($P = .011$), right medial temporal lobe ($P = .008$), and left medial temporal lobe ($P = .000$) regions. Treatment responders showed a significant increase over time in SUR values in left medial temporal lobe ($P = .029$) and right medial temporal lobe ($P = .007$) regions. Partial and nonresponder subjects also showed a significant increase over time in SUR values in the left medial temporal region ($P = .040$) (vs. healthy volunteers), but to a lesser degree. The findings suggest that low pretreatment SERT binding may increase over time in some depressed individuals who experience symptom improvement.

Keywords: SPECT, depression, serotonin transporter, treatment.

Acceptance: Received October 16, 2012, and in revised form January 2, 2013. Accepted for publication March 3, 2013.

Correspondence: Address correspondence to Andrew B. Newberg, MD, 925 Chestnut Street, Suite 120, Philadelphia, PA, 19107. E-mail: andrew.newberg@jefferson.edu.

This work was supported in part by National Institute of Health (NIH) grants MH-077580, AG-17524, DA-09469, NS-18509 and by the Jack Warsaw Fund for Research in Biological Psychiatry, Depression Research Unit, University of Pennsylvania Medical Center.

J Neuroimaging 2013;23:469-476.
DOI: 10.1111/jon.12035

Introduction

Several studies have demonstrated low serotonin transporter (SERT) binding in specific brain regions of depressed individuals.[1–9] For example, Malison et al[1] and Eggers et al[6] found low SERT binding in depressed subjects using [^{123}I]-β-CIT, a nonselective SERT and dopamine transporter radioligand using single photon emission computed tomography (SPECT). However, these observations have not been universally observed.[10–15] For example, Reivich et al[13] used the selective SERT radioligand, [^{11}C](+)McN5652 and positron emission tomography (PET) and found greater SERT binding in the temporal lobe region of depressed subjects (vs. healthy volunteers). In contrast, other investigators using [^{11}C](+)McN5652 have reported low SERT binding in depressed subjects.[5,15] In addition, Ruhé et al[8] reported low midbrain SERT binding in depressed males (vs. healthy volunteers) using [^{123}I] β-CIT SPECT; while Kalbitzer et al[16] found no difference in SERT binding in depressed (vs. healthy) women, and an increase in midbrain SERT binding in the winter (vs. other seasons).

We previously used the selective radioligand ^{123}I-labeled ((2-((dimethylamino)methyl) phenyl)thio)-5-iodophenylamine) ([^{123}I]-ADAM) to examine brain SERT binding in depressed individuals.[3] In a preliminary study of 7 depressed subjects and 6 healthy volunteers, we reported low midbrain SERT binding in depressed (vs. healthy) subjects ($P = .01$).[3] More recently, we replicated these findings in a new cohort of 20 depressed subjects versus 10 healthy volunteers[17] – although other [^{123}I]-ADAM studies have not substantiated these findings.[18,19]

The current study examines the change over time in SERT binding standardized uptake ratio (SUR) values before and after treatment with cognitive behavior therapy (CBT) in drug-free depressed subjects. We compared these results with SUR values obtained from untreated, healthy volunteers studied with other [^{123}I]-ADAM SPECT on two separate occasions. We

hypothesized that reduced SUR values would increase over time in treatment responders and would show little or no change over time in partial or nonresponders.

Materials and Methods

Informed Consent

Subjects provided written informed consent in accordance with the ethical standards of the Institutional Review Board (IRB) of the University of Pennsylvania. The study was conducted under IND #65,542 for [^{123}I]-ADAM using Good Clinical Practice guidelines with oversight by the local Office of Human Research and an independent Data & Safety Monitoring Board.

Subjects

Outpatient subjects ≥18 years old with a DSM IV-TR Axis I diagnosis of major depressive disorder (single or recurrent episode) were enrolled. Subjects were self-referred from IRB-approved media advertisements. The diagnosis was verified using the *Structured Clinical Interview for the DSM-IV-TR* format.[20] Subjects were drug free ≥ 12 months, and had a pre-treatment 17-item Hamilton Depression Rating (HAM-D)[21] total score ≥16. Subjects underwent a physical examination and laboratory evaluation, and were in good health without meaningful medical conditions or laboratory abnormalities. Women of child-bearing potential had a negative pregnancy test. Subjects were excluded from the study if they met any of the following criteria: participant in prior [^{123}I]-ADAM study; primary Axis I diagnosis other than major depressive disorder; history of mania or psychosis; actively suicidal; substance abuse or dependence within the preceding 3 months; positive screen for illicit drugs; unstable medical condition; pregnant or nursing; or history of transient ischemic attack, cerebral infarction, hypertensive encephalopathy, intracranial hemorrhage, closed head trauma with loss of consciousness, encephalitis, neurotoxin exposure, normal pressure hydrocephalus, brain tumor, basal ganglia disease, polyneuropathy, or unable to provide informed consent.

Healthy volunteers were recruited from IRB-approved media advertisements. The purpose of including this control group was to demonstrate the natural variability in [^{123}I]-ADAM uptake over time and to compare this value with the change over time in SERT binding observed in depressed subjects. Healthy subjects were ≥18 years old, had no current DSM IV-TR Axis I disorder (verified using the SCID format), and had a baseline total HAM-D score ≤6. None of the healthy volunteers had any clinically meaningful medical conditions or laboratory abnormalities.

Imaging Procedures

Depressed subjects underwent [^{123}I]-ADAM scanning sessions on two separate occasions approximately 12 weeks apart: prior to initiating CBT and within 2 weeks of completing CBT. Healthy volunteers also underwent two separate [^{123}I]-ADAM scanning sessions approximately 12 weeks apart. [Note–Two depressed subjects prematurely discontinued CBT and had their post-CBT scanning session performed at week 9 of the study. To comport with this time frame, 2 healthy volunteers also underwent their second scanning session at week 9 of the study].

At each scanning session, subjects were administered 18 drops of concentrated Lugol's solution in order to block ^{123}I uptake by the thyroid gland. [^{123}I]-ADAM 185 MBq (5 mCi) was injected through an intravenous catheter. Four hours after [^{123}I]-ADAM administration, SPECT images were acquired over 60 minutes. Prior kinetic modeling with [^{123}I]-ADAM indicated that the 4-hour delay in image acquisition allowed for the use of the reference region method for estimating SERT binding, without the need for arterial sampling.[22]

Image Analysis

SPECT images were analyzed using previously validated methods.[23] Images were reconstructed using a low pass filter and attenuation correction. All scans were resliced in the same plane using oblique reformatting. Manual demarcation of the region of interest (ROI) was then performed on the baseline scans focusing on the basal ganglia, midbrain, and medial temporal lobe regions–as these were the regions with low SERT binding from our prior ^{123}I]-ADAM studies. Standardized templates containing ROIs were fit on each scan using previously reported techniques.[3] These templates were originally developed using anatomically defined regions based on a magnetic resonance imaging atlas of ROIs. Within the x-y plane, the ROIs in the template are smaller than the actual structures they represent in order to minimize resolution-induced problems with ill-defined edges. To reduce the effects of volume averaging in the axial direction, the small ROIs were not placed on the slices that contained the upper most and lower most portions of the structures they represented. This limits the small ROIs to the central aspect of the structures they represented. The ROIs are therefore placed on the pretreatment scans within each brain structure in order to obtain the mean counts per voxel. ROIs were then directly placed onto the posttreatment scans since all scans were oriented and sliced in the same manner. All ROIs were placed by an expert in nuclear medicine image interpretation and analysis who was blinded to the diagnosis and treatment status.

The primary imaging outcome measure was the SUR value at 4 hours post [^{123}I]-ADAM injection, when the distribution of [^{123}I]-ADAM approached a near equilibrium state that reflected the ratio of k3/k4, which was related to [^{123}I]-ADAM binding potential. The SUR value was calculated as the ROI ÷ reference region where the reference region was the cerebellum which consists of nonspecific binding, as described previously.[22] [Note–Statistical Parametric Mapping (SPM) and other approaches to image analysis were considered. However, we chose the ROI technique because it has previously demonstrated highly accurate values in quantifying [^{123}I]-ADAM binding in humans.[3, 17, 22, 23] This procedure allowed us to compare [^{123}I]-ADAM uptake in the target regions to uptake in regions of nonspecific [^{123}I]-ADAM binding, and to calculate individual SUR values. Moreover, since the region of [^{123}I]-ADAM uptake is quite specific, we would have needed to use the ROI tool contained in the SPM program for our calculations. In addition, a voxel-by-voxel analysis would not have yielded additional

information because [^{123}I]-ADAM binds to only a limited number of brain structures].

CBT Procedures

Treatment was conducted by a senior therapist at the Center for Cognitive Therapy at the University of Pennsylvania. CBT was administered in a structured fashion according to Beck et al,[24] and consisted of a series of active directive sessions targeted at promoting behavioral activation and counteracting maladaptive cognitive biases. As CBT progressed, the emphasis shifted to identification and evaluation of underlying beliefs and schemas. There was an emphasis on cognitive-behavioral skills-training (including homework assignments) designed to allow individuals to gain more independent functioning as their own "therapists" by the end of treatment. These strategies were supplemented by techniques developed to prevent relapse following response to CBT.[25] Within this framework, CBT was provided in a flexible fashion as determined by the needs of the individual. Sessions were scheduled twice weekly during the initial 4 weeks (when possible) and weekly thereafter through week 12. Sessions typically lasted 50 minutes.

Outcome Measures

The primary outcome measure was the change over time in mean SUR values of the midbrain, medial temporal lobe, and basal ganglia regions in CBT responders versus healthy volunteers compared to CBT partial and nonresponders versus healthy volunteers. Response was defined as $\geq$50% reduction in baseline total HAM-D score. Partial and nonresponse was defined as $<$50% reduction in baseline total HAM-D score.

Statistical Procedures

Analyses were implemented with the realization that the limited sample size may only allow for the detection of large differences between groups. All analyses were conducted using Stata 11.0 (College Station, TX) with two-sided tests of hypotheses and a *P*-value $<$.05 as the criterion for statistical significance. Analyses included means, medians, ranges, and standard deviation (SD) of continuous covariates (eg, age) and SUR values. The "sktest" procedure in Stata was used to assess the normality of SUR values for each ROI. The intrasubject association of SUR values was estimated using the Spearman rank correlation coefficient test for each ROI.

T-tests and nonparametric Wilcoxon rank sum tests were used to compare the change over time in mean SUR values for depressed subjects and for depressed subjects versus healthy volunteers. ANOVA was used to compare the change over time in mean SUR values before and after CBT in responders versus partial and nonresponders (relative to the change over time in mean SUR values in healthy volunteers). Where significant differences occurred in the change over time in SUR values between depressed and healthy subjects, *post hoc* group comparisons were examined using the Scheffe multiple comparison test.

Sample Size Justification

Sample size calculations for the primary study outcome was conducted using Nquery Advisor sample size software and Diggle et al[26] to obtain estimates that could be used to power a larger follow-up study. Preliminary analyses yielded mean (SD) SUR values of 1.81 (.07) and 1.95 (.13) in depressed and healthy subjects, respectively. Assuming a common SD of .10 would yield an effect size difference of $|1.81\text{-}1.95|/.10 = 1.40$. A sample size of 20 depressed subjects versus 10 healthy volunteers would have 80% power to detect an effect size of 1.124 using a two-group *t*-test with a .05 two-sided significance level.

Table 1. Depressed Subjects' Demographic and Clinical Characteristics

Subject	Age	Gender	Age 1st Episode	Episode #*	Episode Duration**	Pre-CBT HAM-D	Post-CBT HAM-D
1	29	M	20	4	3	20	8
2	39	M	27	5	7	16	4
3	28	M	26	0	3	23	24
4	35	F	14	10	2	21	18
5	62	M	19	6	40	16	8
6	40	M	32	0	96	25	24
7	44	M	40	0	42	16	9
8	28	F	16	4	3	23	6
9	41	M	32	5	6	21	9
10	53	M	15	10	8	19	11
11	26	M	17	1	18	21	21
12	61	M	17	5	7	17	14
13	26	M	15	0	120	23	4
14	56	M	16	4	6	22	19
15	31	M	13	0	12	20	6
16	58	M	20	0	3	20	0
17	25	F	25	0	34	19	14
18	33	F	17	1	8	22	7
19	26	M	20	4	30	20	22
20	43	F	20	7	6	21	4
Mean	41.0		21.1	3.3	22.7	20.3	11.6
SD***	12.8		7.1	3.3	32.1	2.5	7.4
Range	25-63		14-40	0-10	2-120	16-25	4–24

*Episode # = Number of prior major depressive disorder episodes.
**Episode duration = Duration in months of the current major depressive disorder episode.
***SD = Standard deviation.

Results

Enrollment

We examined 20 depressed subjects and 10 healthy volunteers. There were no screen failures. Demographic and clinical characteristics of the subject cohorts are displayed in Tables 1 and 2. Ten depressed subjects (2 women) were drug naïve and 10 (5 women) previously received 3.0 (2.0) (range 1-10) antidepressant treatments over the course of their illness.

Baseline SUR Values

Depressed subjects demonstrated significantly lower SUR values for the midbrain ($P < .005$), right medial temporal lobe ($P < .0005$), left medial temporal lobe ($P < .004$), right basal ganglia ($P < .03$), and left basal ganglia ($P = .016$) regions (vs. healthy volunteers).[17] There was no effect of age, gender, illness duration, prior antidepressant drug exposure, or symptom severity on mean baseline SUR values.[17]

Table 2. Healthy Volunteers' Demographic and Clinical Characteristics

Subject	Age	Gender	HAM-D Score #1	HAM-D Score #2
1	34	F	2	2
2	53	F	0	0
3	56	F	0	0
4	40	M	0	0
5	48	M	1	1
6	26	M	0	0
7	36	M	0	0
8	62	M	0	0
9	47	M	0	0
10	46	M	0	0
Mean	44.8	-	.3	.3
SD	10.93	-	.7	.7
Range	20-62	-	0-1	0-2

Change in Mean SUR Values

Overall, depressed subjects demonstrated a significant increase in mean SUR values for the midbrain ($P = .011$), right medial temporal lobe ($P = .008$), and left medial temporal lobe ($P = .0001$) regions versus healthy volunteers (Table 3). Healthy volunteers demonstrated a modest (albeit nonsignificant) decrease over time in mean SUR values after repeated [^{123}I]-ADAM testing (Figure 1 and Table 3).

Change in Mean SUR Values Relative to Treatment Response

ANOVA demonstrated significant group differences over time in mean SUR values for the left medial temporal lobe ($P = .029$) and right medial temporal lobe ($P = .007$) regions, and a small (albeit nonsignificant) difference for the midbrain region ($P = .076$) (Table 4). Scheffe *post hoc* tests showed a significant increase over time in mean SUR values for treatment responders (vs. healthy volunteers) for the right medial temporal lobe ($P = .029$) and left medial temporal lobe ($P = .012$) regions. Scheffe test also showed a significant increase over time in mean SUR values for partial and nonresponders (vs. healthy volunteers) for the left medial temporal lobe region ($P = .040$) (Table 3). [Note–Some depressed subjects classified as partial and nonresponders demonstrated a clinically meaningful reduction in total HAM-D scores, but failed to achieve the criterion for "response"].

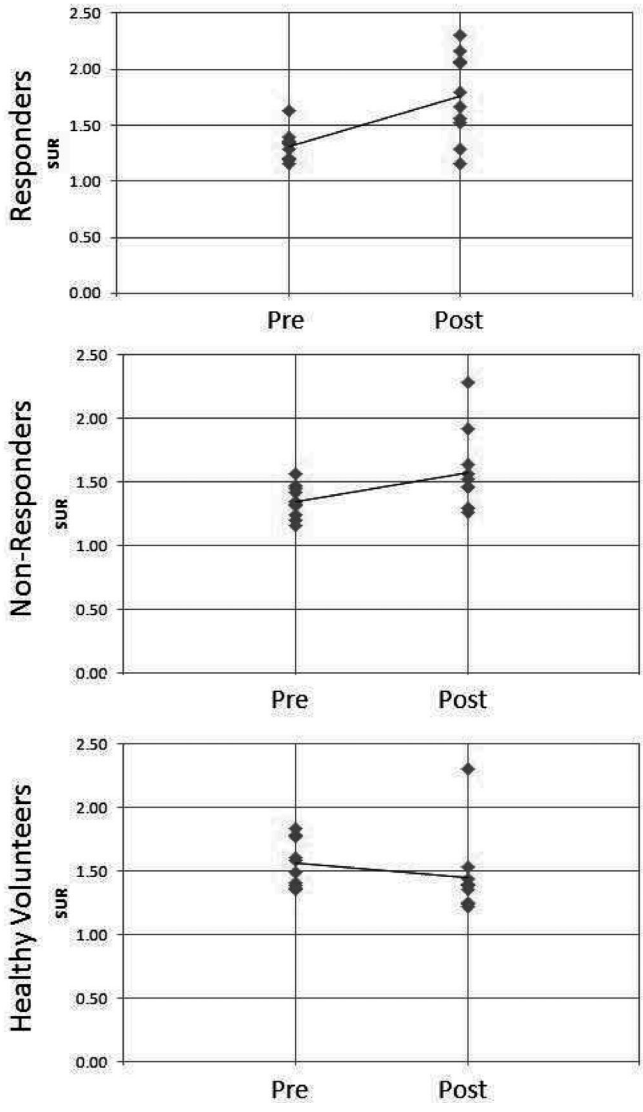

Fig 1. SUR values for the right medial temporal lobe for CBT responders, CBT nonresponders, and healthy volunteers.

Adverse Events

There were no serious adverse events. Five subjects did experience tingling at the site of [^{123}I]-ADAM injection. Thirteen subjects reported an unusual taste and 15 subjects reported

Table 3. Mean Change Over Time in SUR Values in all Depressed Subject Versus Healthy Volunteers

	Healthy Volunteers ($n = 10$)		Depressed Subjects ($n = 20$)		*T* test	Wilcoxon test
	SUR Change	95% CI	SUR Change	95% CI	Pr (T > t)	Pro >|z|
RBG †	−.035 (.159)	−.148; .079	.069 (.25)	−.049; .187	.123	.455
LBG †	.021 (.156)	−.091; .133	.098 (.20)	.004; .192	.150	.356
Midbrain	−.227 (.227)	−.390; −.065	.029 (.29)	−.107; .166	.011	.008
RMTL †	−.085 (.464)	−.417; .248	.33 (.40)	.147; .522	.008	.003
LMTL †	−.127 (.176)	−.253; −.001	.17 (.24)	.059; .285	.000	.002

†RBG = Right Basal Ganglia; LBG = Left Basal Ganglia; RMTL = Right Medial Temporal Lobe; LMTL = Left Medial Temporal Lobe.

Table 4. Mean (SD) Change in SUR Values in Responders and Nonresponders Versus Healthy Subjects

	Control ($n = 10$)	Nonresponder ($n = 10$)	Responder ($n = 10$)	F	P-value
RBG†	−.035 (.158)	−.001 (.226)	.139 (.267)	1.73	.196
LBG†	.021 (.156)	.081 (.188)	.114 (.222)	1.61	.196
Midbrain	−.227 (.227)	.026 (.361)	.033 (.223)	2.85	.076
RMTL†	−.085 (.464)	.222 (.369)	.448 (.418)	4.07	.029*
LMTL†	.127 (.176)	.144 (.233)	.200 (.259)	6.04	.007**,#

†RBG = Right Basal Ganglia; LBG = Left Basal Ganglia; RMTL = Right Medial Temporal Lobe; LMTL = Left Medial Temporal Lobe.

*Scheffe multiple comparison test showed a significant change over time in mean SUR values in CBT responders versus healthy volunteers for the right medial temporal lobe region ($P = .029$).

**Scheffe multiple comparison test showed a significant change over time in mean SUR values in CBT responders versus healthy volunteers for the left medial temporal lobe region ($P = .012$).

#Scheffe multiple comparison test showed a significant change over time in mean SUR values in CBT nonresponders versus healthy volunteers for the left medial temporal lobe region ($P = .040$).

unusual smell after ^{123}I-ADAM injection, which dissipated within 1 minute.

Discussion

We previously reported significantly lower baseline mean SERT binding levels in the midbrain, medial temporal lobe, and basal ganglia regions of drug-free depressed subjects (vs. healthy volunteers) using [^{123}I]-ADAM.[3,17] These findings support other studies showing low SERT binding in depressed subjects using other SERT radioligands (eg, [^{123}I]-β-CIT)[2,2,4–9]—although this has not been a universal observation.[11–14] In the current study, we examined the effects of treatment outcome on SERT binding in depressed subjects. We selected CBT as a nonpharmacological treatment intervention that would not directly affect SERT binding.

Several studies have examined the relationship of SERT binding to treatment response with selective serotonin reuptake inhibitor (SSRI) antidepressants. In general, these studies have reported a significant reduction in baseline SERT binding during SSRI treatment.[18,27] For example, Kugaya et al[11] used [^{123}I] β-CIT to examine the relationship between baseline SERT binding and response to fluoxetine therapy in 23 depressed subjects and found a significant relationship after 4 weeks of treatment ($\beta = 9.30$; $P = .028$), but not after 6 weeks of treatment ($\beta = 2.22$; $P = .42$). Similar results were reported in 10 depressed subjects treated with paroxetine.[11] Hsieh et al[28] used [^{123}I]-ADAM to examine SERT binding in 13 drug-free subjects whose depression had responded to SSRI treatment and found no significant difference in mean SUR values between euthymic depressed subjects (vs. 26 healthy volunteers). These investigators suggested that their observations provided indirect evidence that low baseline SERT binding increased (ie, "normalized") after response to treatment.

Other studies have examined the effects of psychotherapy on SERT binding in depression. For example, Viinamýki et al[29] used [^{123}I] β-CIT to examine the effect of dynamic psychotherapy on SERT binding in 2 depressed subjects. They reported low baseline SERT binding in the prefrontal cortex and thalamus that "normalized" after 1 year of psychotherapy (relative to nonpsychotherapy subjects). Martin et al[30] used [^{99m}Tc]-exametazime hexamethylpropyleneamine oxime SPECT to examine regional cerebral blood flow (rCBF) in 28 depressed subjects. They found an increase in rCBF in the basal ganglia region following response to either interpersonal psychotherapy or venlafaxine therapy. Increases in rCBF were observed in the temporal lobe region with venlafaxine and in the posterior cingulate gyrus with interpersonal psychotherapy. However, neither of these studies employed controlled methodology, and the response to pharmacotherapy was superior to interpersonal psychotherapy in both studies.

Finally, several studies used [^{18}F]-fluoro-deoxyglucose (FDG) PET to examine the effect of psychotherapy or pharmacotherapy on brain metabolism in depression. Brody et al[31] studied the relationship between baseline glucose metabolism and response to treatment with either interpersonal psychotherapy or paroxetine in 24 depressed subjects. They reported that low baseline prefrontal glucose metabolism predicted response to both treatment modalities. Goldapple et al[32] examined changes over time in glucose metabolism in 14 responders to CBT versus 13 responders to paroxetine. Paroxetine responders demonstrated an increase in glucose metabolism in the dorsolateral-prefrontal cortex and a reduction in glucose metabolism in the hippocampus, while CBT responders showed a reduction in glucose metabolism in the dorsolateral-prefrontal cortex and an increase in glucose metabolism in the hippocampus and dorsal cingulate regions. These investigators speculated that CBT produced a "top down" effect while antidepressants produced a "bottom up" effect, with initial change occurring in midbrain neurotransmitter activity.[32]

We speculate that the current [^{123}I]-ADAM observations may support the notion of Goldapple et al[32] of a "top-down" effect of CBT on SERT binding. The mechanism by which this physiological process occurs is not well understood. However, the SERT site is known to remove excess serotonin from the synaptic cleft,[17] and it is possible that the low SERT binding seen during depression may reflect lower brain serotonin levels via a compensatory SERT downregulation. Thus, low SERT binding in depression may reflect an overall low serotonin function in depression that "normalizes" during response to treatment. A comparative study of CBT and SSRI therapy with repeated [^{123}I]-ADAM scan sessions over time would be necessary to confirm a "top down" (vs. "bottom up") effect of CBT.

Several caveats should be considered when interpreting the current observations. For example, it is possible that the increase in low SERT binding in depressed subjects may have occurred independently of CBT. As no comparative treatment intervention (eg, SSRI) was included in the current study, it is possible that the observed increase in SERT binding occurred as a result of symptom reduction *per se* or from nonspecific aspects of treatment (ie, placebo effect).

The current study did not include comparison groups of depressed subjects who did not receive CBT and healthy volunteers who did receive CBT. While the inclusion of these

groups would have been of heuristic interest, we believe that their inclusion would have raised substantial ethical and procedural difficulties. For example, the inclusion of an untreated depressed subject group would have been unethical. Moreover, the inclusion of healthy volunteers "treated" with CBT would have raised ethical concerns such as exposing nondepressed, healthy subjects to a therapy specifically designed to treat depressive symptoms with no expected benefit or measurable outcome.

We also note that an increase in SERT binding after treatment occurred in both CBT responder and partial and nonresponder groups. This may have resulted from some subjects in the partial and nonresponder group having a clinically meaningful reduction in depressive symptoms and an increase in SERT binding–despite the fact that these subjects failed to achieve *a priori* criteria for "response." Similarly, it is possible that a larger difference in SERT binding between groups would have been more evident had a larger sample size been studied, or a different *a priori* criteria for "response" had been employed.

There was a modest, albeit nonsignificant, reduction over time in mean SUR values for healthy volunteers, and it is possible that this reduction in SERT binding contributed to the significance of the increase in SUR values seen in depressed subjects.

It is likely that the change over time in SERT binding occurred gradually and at varying rates among depressed subjects. Thus, the change over time in SERT binding in some depressed subjects may have lagged behind symptom improvement. As some depressed subjects were more severely ill than others, and some subjects did not receive a full course of CBT, it is also possible that some of these subjects may have had a more gradual increase in SUR values than other depressed subjects. It is also possible that the group differences would have been greater had a longer treatment course of CBT been applied.

Other factors may have contributed to variability in the SERT binding results. For example, there were differences in the time that elapsed between [^{123}I]-ADAM imaging sessions in 2 subjects. In addition, we did not control for possible seasonal effects of SERT binding.[8] Although the current study found no influence of age on mean SUR values,[17] other studies have reported an effect of age on SERT binding.[1,3]

It is possible that comorbid anxiety and/or prior exposure to antidepressant medication could have influenced SERT binding,[18,33] although an exclusion criterion was that patients could not have antidepressant medication for at least 12 months. In addition, differences in illness length, episode duration, symptom severity, environmental stress, sleep, carbohydrate intake, circadian rhythms, smoking, and alcohol use may also have influenced the current SERT binding results.[2,8,16,34–38]

Finally, it is possible that the current observations occurred by chance alone and were not related to treatment response or the degree of symptom improvement. Future placebo-controlled studies will be needed to determine whether or not treatment response is related to change over time in SERT binding in depression.

Conclusion

The findings of the current study suggest that low pretreatment SERT binding in depression may increase over time with treatment response. However, a limited subject sample size and large treatment response range hampered our ability to determine whether or not the increase over time in SERT binding in depressed subjects was due to treatment response *per se*. Future studies with larger sample sizes will be needed to better determine the relationship between SERT binding and treatment in patients with depression.

The authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analyses.

Grant Support: This work was supported in part by National Institute of Health (NIH) grants MH-077580, AG-17524, DA-09469, NS-18509 and by the Jack Warsaw Fund for Research in Biological Psychiatry, Depression Research Unit, University of Pennsylvania Medical Center.

Disclosures: Dr. Amsterdam received grant support from NIH grants MH077580, MH06099, MH060353, MH080097, and AT005074. He is not a member of any industry-sponsored advisory board or speaker's bureau, and has no financial interest in any pharmaceutical or medical device company. Dr. Newberg received grant support from NIH grant MH077580 and AG028688. He is not a member of any industry-sponsored scientific advisory board or speaker's bureau, and has no financial interest in any pharmaceutical or medical device company. Dr. Newman received grant support from NIH grant MH077580. He is not a member of any industry-sponsored scientific advisory board or speaker's bureau, and has no financial interest in any pharmaceutical or medical device company. Dr. Shults received grant support from NIH grant MH077580. She is not a member of any industry-sponsored advisory board or speaker's bureau, and has no financial interest in any pharmaceutical or medical device company. Nancy Wintering received grant support from NIH grant MH077580 and AG028688. She is not a member of any industry-sponsored advisory board or speaker's bureau, and has no financial interest in any pharmaceutical or medical device company. Irene Soeller received grant support from NIH grant MH077580. She is not a member of any industry-sponsored advisory board or speaker's bureau, and has no financial interest in any pharmaceutical or medical device company.

Contribution of Each Author to the Manuscript: Dr. Amsterdam designed and produced the study protocol, implemented the study procedures, recruited study subjects, oversaw study conduct, oversaw data monitoring and double data entry, assisted in data analysis, and prepared the initial and all subsequent drafts of the manuscript.

Dr. Newberg assisted in the design and writing of the study protocol, implemented and oversaw all aspects of the imaging procedures, oversaw imaging data entry and image analysis, assisted in data analysis, and assisted in the preparation of the initial and subsequent drafts of the manuscript.

Dr. Newman oversaw all aspects of cognitive therapy implementation and delivery, and assisted in the preparation of the initial and subsequent drafts of the manuscript.

Dr. Shults served as senior biostatistician on the project and oversaw all statistical analyses on the data. Dr. Shults was involved with the initial draft of the manuscript.

Ms. Wintering assisted in the image acquisition, management, and evaluation; the management of study subjects during the imaging sessions, and in the overall conduct of the study.

Ms. Soeller assisted in the recruitment of study subjects and in the overall conduct of the study.

References

1. Malison RT, Price LH, Berman R, et al. Reduced brain serotonin transporter availability in major depression as measured by [123I]-2 beta-carbomethoxy-3 beta-(4-iodophenyl)tropane and single photon emission computed tomography. *Biol Psychiatry* 1998;44:1090-1098.
2. Willeit M, Praschak-Rieder N, Neumeister A, et al. [123I]-beta-CIT SPECT imaging shows reduced brain serotonin transporter availability in drug-free depressed patients with seasonal affective disorder. *Biol Psychiatry* 2000;47:482-489.
3. Newberg AB, Amsterdam JD, Wintering N, et al. 123I ADAM binding to serotonin transporters in patients with major depression and healthy controls: a preliminary study. *J Nucl Med* 2005;46:993-997.
4. Lehto S, Tolmunen T, Joensuu M, et al. Midbrain binding of [123I]nor-beta-CIT in atypical depression. *Prog Neuropsychopharmacol Biol Psychiatry* 2006;30:1251-1255.
5. Parsey RV, Hastings RS, Oquendo MA, et al. Lower serotonin transporter binding potential in the human brain during major depressive episodes. *Am J Psychiatry* 2006;163:52-58.
6. Eggers B, Hermann W, Barthel H, et al. The degree of depression in Hamilton rating scale is correlated with the density of presynaptic serotonin transporters in 23 patients with Wilson's disease. *J Neurol* 2003;250:576-580.
7. Joensuu M, Tolmunen T, Saarinen PI, et al. Reduced midbrain serotonin transporter availability in drug-naïve patients with depression measured by SERT-specific [(123)I] nor-beta-CIT SPECT imaging. *Psychiatr Res* 2007;154:125-131.
8. Ruhé HG, Booij J, Reitsma JB, et al. Serotonin transporter binding with [123I]beta-CIT SPECT in major depressive disorder versus controls: effect of season and gender. *Eur J Nucl Med Molec Imaging* 2009;36:841-849.
9. Joensuu M, Lehto SM, Tolmunen T, et al. Serotonin-transporter-linked promoter region polymorphism and serotonin transporter binding in drug-naïve patients with major depression. *Psychiatr Clin Neurosci* 2010;64:387-393.
10. Lawrence KM, De Paermentier F, Lowther S, et al. Brain 5-hydroxytryptamine uptake sites labeled with [3H]paroxetine in antidepressant drug-treated depressed suicide victims and controls. *J Psychiatr Neurosci* 1997;22:185-191.
11. Kugaya A, Seneca NM, Snyder PJ, et al. Changes in human in vivo serotonin and dopamine transporter availabilities during chronic antidepressant administration. *Neuropsychopharmacol* 2003;28:413-420.
12. Meyer JH, Kapur S, Houle S, et al. Prefrontal cortex 5-HT2 receptors in depression, an [18F]setoperone PET imaging study. *Am J Psychiatry* 1999;56:1029-1034.
13. Reivich M, Amsterdam JD, Brunswick DJ, et al. PET brain imaging with [(11)C](+)McN5652 shows increased serotonin transporter availability in major depression. *J Affect Disord* 2004;82:321-327.
14. Staley JK, Sanacora G, Tamagnan G. Sex differences in diencephalons serotonin transporter availability in major depression. *Biol Psychiatry* 2005;59:40-47.
15. Ichimiya T, Suhara T, Sudo Y, et al. Serotonin transporter binding in patients with mood disorders, a PET study with [11C](+)McN5652. *Biol Psychiatry* 2002;51:715-722.
16. Kalbitzer J, Erritzoe D, Holst KK, et al. Seasonal changes in brain serotonin transporter binding in short serotonin transporter linked polymorphic region-allele carriers but not in long-allele homozygotes. *Biol Psychiatry* 2010;67:1033-1039.
17. Newberg AB, Amsterdam JD, Wintering N, et al. Reduced brain serotonin transporter density in major depressive disorder. *Psychiatr Res Neuroimag* 2012;202:161-167.
18. Catafau AM, Perez V, Plaza P, et al. Serotonin transporter occupancy induced by paroxetine in patients with major depression disorder, a (123)I-ADAM SPECT study. *Psychopharmacol (Berlin)* 2006;189:145-153.
19. Herold N, Uebelhack K, Franke L, et al. Imaging of serotonin transporters and its blockade by citalopram in patients with major depression using a novel SPECT ligand [123I]ADAM. *J Neural Trans* 2006;113:659-670.
20. First MB, Spitzer RL, Gibbon M, et al. *Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition With Psychotic Screen (SCID-I/P W/ PSY SCREEN).* New York, NY: Biometrics Research, New York State Psychiatric Institute, 2001.
21. Williams JBW. A structured interview guide for the Hamilton Depression Rating Scale. *Arch Gen Psychiatry* 1988;45:742-747.
22. Acton PD, Choi SR, Hou C, et al. Quantification of serotonin transporters in nonhuman primates using [(123)I]ADAM and SPECT. *J Nucl Med* 2001;42:1556-1562.
23. Newberg AB, Ploessl K, Mozley PD, et al. Biodistribution and imaging with (123)I-ADAM: a serotonin transporter imaging agent. *J Nucl Med* 2004;45:834-841.
24. Beck AT, Rush AJ, Shaw BF, et al. *Cognitive Therapy of Depression: A Treatment Manual.* New York, NY: Guilford Press, 1979.
25. Jarrett RB, Basco MR, Risser R, et al. Is there a role for continuation phase cognitive therapy for depressed outpatients? *J Consult Clin Psychol* 1998;66:1036-1040.
26. Diggle PJ, Liang KY, Zeger SL. *The Analysis of Longitudinal Data.* Oxford (UK): Oxford University Press, 1994.
27. Klein N, Sacher J, Geiss-Granadia T, et al. In vivo imaging of serotonin transporter occupancy by means of SPECT and [123I]ADAM in healthy subjects administered different doses of escitalopram or citalopram. *Psychopharmacol (Berlin)* 2006;188:263-272.
28. Hsieh PC, Lee IH, Yeh TL, et al. Distribution volume ratio of serotonin and dopamine transporters in euthymic patients with a history of major depression – a dual-isotope SPECT study. *Psychiatr Res* 2010;184:157-161.
29. Viinamýki H, Kuikka J, Tiihonen J, et al. Change in monoamine transporter density related to clinical recovery: a case-control study. *Nord J Psychiatry* 1998;52:39-44.
30. Martin SD, Martin E, Rai SS, et al. Brain blood flow changes in depressed patients treated with interpersonal psychotherapy or venlafaxine hydrochloride: preliminary findings. *Arch Gen Psychiatry* 2001;58:641-648.
31. Brody AL, Brody S, Saxena P, et al. Regional brain metabolic changes in patients with major depression treated with either paroxetine or interpersonal therapy. *Arch Gen Psychiatry* 2001;58:631-640.
32. Goldapple K, Segal Z, Garson C, et al. Modulation of cortical–limbic pathways in major depression: treatment specific effects of cognitive behavioral therapy compared to paroxetine. *Arch Gen Psychiatry* 2004;61:34-41.
33. Reimold M, Batra A, Knobel A, et al. Anxiety is associated with reduced central serotonin transporter availability in unmedicated patients with unipolar major depression: a [11C]DASB PET study. *Molec Psychiatry* 2008;13:606-613.

34. Uusitalo AL, Valkonen-Korhonen M, Helenius P, et al. Abnormal serotonin reuptake in an overtrained, insomnic and depressed team athlete. *International J Sports Med* 2004;25:150-153.
35. Lundgren JD, Amsterdam JD, Newberg A, et al. Differences in serotonin transporter binding affinity in patients with major depressive disorder and night eating syndrome. *Eating Weight Disord* 2009;14:45-50.
36. Erritzoe D, Frokjaer VG, Haahr MT, et al. Cerebral serotonin transporter binding is inversely related to body mass index. *Neuroimage* 2010;52:284-289.
37. Heinz A, Ragan P, Jones DW, et al. Reduced central serotonin transporters in alcoholism. *Am J Psychiatry* 1998;155:1544-1549.
38. Meyer JH, Houle S, Sagrati S, et al. Brain serotonin transporter binding potential measured with carbon 11-labeled DASB positron emission tomography: effects of major depressive episodes and severity of dysfunctional attitudes. *Arch General Psychiatry* 2004;61:1271-1279.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Supplemental Table S1 – Wilcoxon signed-rank test comparing the posttreatment to the pretreatment ADAM SURs for the entire depression group, responders, and nonresponders.