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Applying Neuroimaging Ligands to Study Major Depressive Disorder

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The recent increase in radioligands available for neuroimaging major depressive disorder has led to advancements in our understanding of the pathophysiology of this illness and improved antidepressant development. Major depressive disorder can be defined as an illness of recurrent major depressive episodes of persistently low mood, dysregulated sleep, appetite and weight, anhedonia, cognitive impairment, and suicidality. The main target sites investigated with radioligand neuroimaging include receptor sites that regulate in response to lowered monoamine levels, targets related to removal of monoamines, uptake of ligands related to regional brain function, and target sites of antidepressants.
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A recent set of neuroimaging studies has built on the original monoamine hypothesis of major depression by adding several concepts: heterogeneity of monoamine loss for multiple monoamines,[1-3] excessive clearance of monoamines through greater monoamine transporter binding,[4-6] and excessive metabolism of monoamines.[7] This information may be translated into treatment development because it predicts that targeting multiple monoamines will, on average, be more therapeutic; that particular symptoms will associate with responsiveness for raising specific monoamines; and that interfering with specific mechanisms of monoamine loss will be helpful in reversing symptoms of major depressive episodes (MDEs). Another line of investigation into major depressive disorder (MDD) and anxiety disorders suggests that 5-HT_{1A} receptor binding is low in this spectrum, which may have implications for the treatment refractoriness of MDD with comorbid anxiety disorders.[8-14]

Abnormal patterns of ^{18}F-fluorodeoxyglucose (FDG) uptake and ^{15}O-H_2O can identify changes in function in several sets of processes during MDE, including the generation of sad affect, cognitive changes, and greater functioning of compensatory mechanisms and circuits (the latter of which can differentiate between treatment responders and nonresponders[15,16]). These studies have practical application in guiding the location choice (such as selection of subgenual cingulate) for deep brain stimulation for treatment-resistant MDD.[16]

In the field of MDD research, neuroimaging of antidepressant occupancy is advanced because the occupancy for most commonly prescribed antidepressants has been established.[17-28] Most investigations have centered on the serotonin transporter (5-HTT) site, and most of the remaining investigations focus on DAT and 5-HT_{1A} occupancy.[17-26] Selective serotonin reuptake inhibitor doses associated with a differential response from placebo typically achieve 80% occupancy.[17,18] The discovery of this threshold heavily impacts development of new serotonin transporter binding antidepressants, which aim for an 80% occupancy. Low occupancy of dopamine reuptake inhibitors[19-21,24] and 5-HT_{1A} autoreceptor inhibitor medications[25-28] at the higher end of the tolerated dosing range suggest an opportunity to develop higher occupancy treatments for these targets. Future ligand development will likely target other nonmonoaminergic pathologies associated with MDD with great potential to understand how these pathologies relate to clinical symptoms, course of illness and effect of novel treatments.

Neuroimaging Contributions to Monoamine Regulation in MDD

Before the contributions of neuroimaging, the monoamine hypothesis of MDD was that some monoamines, likely serotonin and norepinephrine, were low in MDD.[29] There were several lines of evidence to suggest that major monoamines (serotonin, norepinephrine, dopamine) may be dysregulated in MDD: depletion of monoamines is associated with a lowering of mood, particularly in people who are vulnerable to

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Table 1 Comparison of Radioligands for Imaging of 5-HT_{2A} Receptors in Humans

	^{18}F-Setoperone PET*	^{11}C-MDL 100907 PET†	^{18}F-Altanserin PET‡
Selectivity: based upon displaceability	Selective in cortex. Specific binding in cortex completely displaced by 5-HT_{2A} antagonist in humans.[44] Cortex-specific binding displaced completely by 5-HT_2 antagonists across species[45-48]	Selective in cortex, not selective in putamen. In humans, putamen, had 22% occupancy when other regions had 70% occupancy after mirtazapine.[49] Specific binding in cortex completely displaced in animals with 5-HT_2 antagonists[50,51]	Cortex displaced near 100% with ketanserin in humans[52] and highly displaceable with 5-HT_2 antagonists in rodent.[53] Striatum binding unaffected by D_2 antagonist in rodent[53]
Selectivity: based upon in vitro affinity and relative density of receptors	Selective in cortex: high in vitro affinity for 5-HT_{2A} receptor; and low affinity for other receptors except D_2—modest D_2 affinity rules out striatum measure[54-56,58]	High in vitro affinity for 5-HT_{2A} receptor, and low affinity for some other receptors types[51,57,58]—undisplaceable signal in striatum not identified[49]	Likely selective in all brain regions -high affinity in vitro to 5-HT_{2A} receptor and low affinity for other receptor types[59]
Reversibility	Very good with peak at 10-30 minutes in cortex[46,60]	Modest with peak at 50-90 minutes in cortex[49,61]	Good with peak at approx 30 minutes in cortex[62,63]
Brain uptake	High[45-47]	High[49,61]	High[62,63]
Specific binding to free and nonspecific binding ratio	Average cortex 5-HT_{2A} BP_{ND} approx. 2 between ages 18 to 40[1,46,60]	Average cortex 5-HT_{2A} BP_{ND} approx. 2 in application study of mean age 40[3]	Very good: average cortex 5-HT_{2A} BP_{ND} approx. 3 for sample between ages 33 to 67[64]
Metabolites cross blood–brain barrier?	No[65]	Unlikely[49]	Yes,[52,66] consider bolus and infusion paradigm to address
Reliability of 5-HT_{2A} BP	Excellent[67]	Unavailable	Excellent in cortex, adequate in subcortical regions[64]

*For ^{18}F-setoperone, the main strengths are selectivity in cortex for 5-HT_{2A} receptors, reversibility, and excellent reliability. Its main limitation is that the striatum measure is not selective.

†^{11}C-MDL 100907 is best used as a cortex radiotracer. For ^{11}C-MDL 100907, its main limitations are moderate reversibility and a non-displaceable signal in striatum.

‡For ^{18}F-altanserin, the main strengths are a high specific binding to free and non-specific binding ratio. Its main limitations are that there are metabolites that cross the blood–brain barrier.[52,66]

MDD.[30-32] Most antidepressants increase the level of monoamines; therefore, chronic raising of monoamines is associated with reversal of major depressive episodes.[33] In addition, there is a reasonably frequent rate of receptor binding abnormalities observed in postmortem studies of suicide and MDD that is consistent with chronically lowered monoamines.[34-43] These events collectively support the concept that monoamines may be low in most brain regions during MDEs of MDD.

A recent set of neuroimaging studies have built on the monoamine hypothesis of MDE of MDD by adding several concepts: heterogeneity of monoamine loss,[1,2] excessive clearance of monoamines through greater monoamine transporter binding,[4,5] and excessive metabolism of monoamines.[7]

Heterogeneity of Monoamine Loss

In the traditional monoamine model of MDD, extracellular serotonin loss is present in untreated individuals. Although one cannot measure extracellular serotonin directly, one may measure an index of regional 5-HT_{2A} receptor density, such as 5-HT_{2A} binding potential (BP) or 5-HT_{2A} BP_{ND} (an index of specific binding relative to free and nonspecific binding). (See Table 1[3,44-67] for a list of 5-HT_{2A} radiotracers applied in humans.[68]) 5-HT_{2A} density has an inverse relationship to extracellular serotonin such that binding increases when extracellular serotonin is chronically lowered.[69-72] Therefore, if the traditional monoamine model of MDE were valid, increased 5-HT_{2A} BP_{ND} would occur in regions such as the prefrontal cortex in during MDE. Authors of a review of 5-HT_{2A} imaging studies of MDE before 2003 found a reduction in those with recent antidepressant use and no change in those with no recent antidepressant use (Table 2).[3,68,73-80] The latter findings of no change in 5-HT_{2A} BP_{ND} would suggest either abandoning the monoamine model or modifying it.

Heterogeneous Extracellular Serotonin Loss in Cortex

One hypothesized modification of the monoamine model is that monoamine loss during MDD is heterogenous and that

Table 2 Imaging Studies of 5-HT_{2A} Receptors in Major Depressive Disorder (updated from Meyer[68])

Study	Method	Number of Subjects	Medication-Free Status	Result
D'Haenen et al[73]	^{123}I-ketanserin SPECT	19 depressed, 10 healthy	7 days	Greater in parietal cortex
Biver et al[74]	^{18}F-altanserin PET	8 depressed, 22 healthy	10 days	Lower in orbitofrontal cortex
Attar Levy et al[75]	^{18}F-setoperone PET	7 depressed, 7 healthy	Taking benzodiazepines	Lower in prefrontal cortex
Meyer et al[76]	^{18}F-setoperone PET	14 depressed, 14 healthy	3 months plus 5 half lives	No difference
Meltzer et al[77]	^{18}F-altanserin PET	11 depressed, 11 healthy	"untreated"	No difference
Yatham et al[78]	^{18}F-setoperone PET	20 depressed, 20 healthy	2 weeks	Decrease in cortex
Messa et al[79]	^{18}F-setoperone PET	19 depressed, 19 healthy	Taking benzodiazepines	Decrease in cortex
Meyer et al[1]*	^{18}F-setoperone PET	22 depressed, 22 healthy	6 months	Positive association with dysfunctional attitude severity in cortex
Mintun et al[80]†	^{18}F-altanserin PET	46 depressed, 29 healthy	4 weeks	Decrease in hippocampus
Bhagwagar et al[3]	^{11}C-MDL 100907	20 recovered depressed, 20 healthy	6 months	Positive association with dysfunctional attitude severity in prefrontal cortex; elevation in most cortex regions

*Subjects enrolled in the study by Meyer et al[76] (1999) were also included in the expanded study by Meyer et al[1] (2003) of 5-HT_{2A} receptors and dysfunctional attitudes in subjects with depression as well as subjects with borderline personality disorder.
†Findings largely appear driven by a single healthy subject with very high 5-HT_{2A} BP.

the loss is greatest in those with the most severe symptoms. The first investigations of this revision of the monoamine model began with prefrontal cortex 5-HT_{2A} BP_{ND} measurement and its relationship to specific symptoms. It was hypothesized that increases in 5-HT_{2A} BP_{ND} would only occur in MDE with greater symptom severity (when extracellular serotonin would be theoretically lower[1]).

The symptom chosen was pessimism, as measured with the dysfunctional attitudes scale (DAS)[81] because increasing the level of extracellular serotonin abruptly (via intravenous d-fenfluramine administration) in healthy humans shifted perspective toward optimism as measured by the DAS.[1] The DAS[81] is a sensitive measure for detecting pessimistic thinking in the midst of MDE[82-84] that has very good internal consistency (Cronbach's $\alpha = 0.85$ to 0.87)[85,86] and high test–retest reliability.[81,86] The interpretation of this shift toward optimism after d-fenfluramine was that one of the cognitive functions of extracellular serotonin in humans is to reduce pessimism.[1]

In support of the hypothesis, a strong correlation was observed between severity of dysfunctional attitudes (pessimism) and elevation in cortex 5-HT_{2A} BP_{ND}. Moreover, cortex 5-HT_{2A} BP_{ND} was significantly elevated in subjects with MDE and severe pessimism.[1] For example, in the prefrontal cortex region centered on Brodman's area 9, 5-HT_{2A} BP_{ND} was increased 29% in depression subjects with dysfunctional attitude scores higher (more pessimistic) than the median for the group (Fig. 1). A recent study by Bhagwagar and coworkers replicated this relationship between dysfunctional attitudes severity and prefrontal cortex 5-HT_{2A} BP_{ND} in recovered depressed subjects.[3] These findings support a model of heterogeneous extracellular serotonin loss in prefrontal cortex in MDD.

Heterogeneous Extracellular Dopamine Loss in Striatum

Evidence for a model of heterogenous putamen dopamine loss and motor retardation was subsequently investigated in nonsmoking, medication-free subjects with MDE and MDD. Motor retardation is a known symptom during MDE that is present to a variable extent[3,87] and motor speed is measurable with a neuropsychological test called the finger tapping test.[87,88] The disease model of reduced putamen dopamine neurotransmission and subsequent motor retardation is well established in a number of other illnesses (eg, Parkinson's disease, multisystem atrophy, progressive supranuclear palsy).[89-92] ^{11}C-raclopride is a positron emission tomography (PET) radiotracer that is selective for D_2 type receptors,[93-96] and the index of D_2 type receptors found with this method (D_2 BP_{ND}), is inversely proportional to extracellular dopamine levels in acute and chronic paradigms of dopamine depletion.[96-99]

The main findings of this study of striatal D_2 BP_{ND} and motor retardation were that the caudate and putamen D_2 BP_{ND} were increased in the depressed group as compared with the healthy group and that greater putamen D_2 BP_{ND} was significantly correlated with more severe motor retardation in the depressed group (Fig. 2).[2] The findings support a specific role for striatal dopamine loss during de-

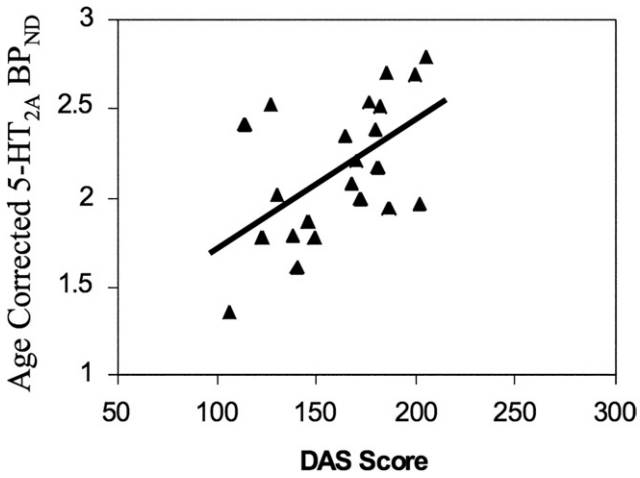

Figure 1 5-HT_{2A} binding potential in prefrontal cortex is associated with dysfunctional attitudes in depressed subjects. Age-corrected 5-HT_{2A} receptor binding potential (5-HT_{2A} BP) within bilateral prefrontal cortex (Brodmann's area 9) in depressed subjects was plotted against the DAS score. When controlling for age, the correlation coefficient between 5-HT_{2A} BP and DAS was 0.56, $P = 0.009$. The age-corrected 5-HT_{2A} BP was calculated by applying a linear regression with predictor variables age and DAS to the 5-HT_{2A} BP. The slope of the line for the age predictor was used to normalize each subject's 5-HT_{2A} BP to that expected for a 30-year-old subject. (Updated and reprinted with permission from Meyer et al.[1])

pression, especially when motor retardation is present. They extend support for the concept of heterogeneous monoamine loss with the greatest loss in the most symptomatic individuals.

Excessive Clearance of Monoamines Via Monoamine Transporters

If extracellular monoamines are lowered during MDEs, then abnormal monoamine transporter function should be considered a potential contributing mechanism. There are at least 4 plausible models to explain how indices of monoamine transporter binding could be altered in a disease that lowers brain monoamines.[68] These are referred to here as models 1 through 4. Model 1 is a lesion model that reduces monoamine releasing neurons. In a lesion model, reductions in binding occur. Model 2 is a model of secondary change in transporter binding consequent to monoamine lowering via a different process. Model 3 is increased clearance of extracellular monoamine via greater monoamine transporter density. In model 3, greater available monoamine transporter binding leads to greater clearance of monoamines from extracellular locations. Model 4 is endogenous displacement and is dependent on the properties of the radioligand. Endogenous displacement is the property of a few radioligands to express different binding after short term manipulations of their endogenous neurotransmitter. Abnormalities in monoamine transporter binding during major depressive episodes may be discussed in the context of these models.

A particular issue with model 2 is that available evidence suggests that the different monoamine transporters do not regulate in the same fashion after chronic depletion of their endogenous monoamine. Acute reductions in serotonin have repeatedly shown reductions in 5-HTT mRNA.[100-102] However, longer-term reductions or elevations in serotonin typi-

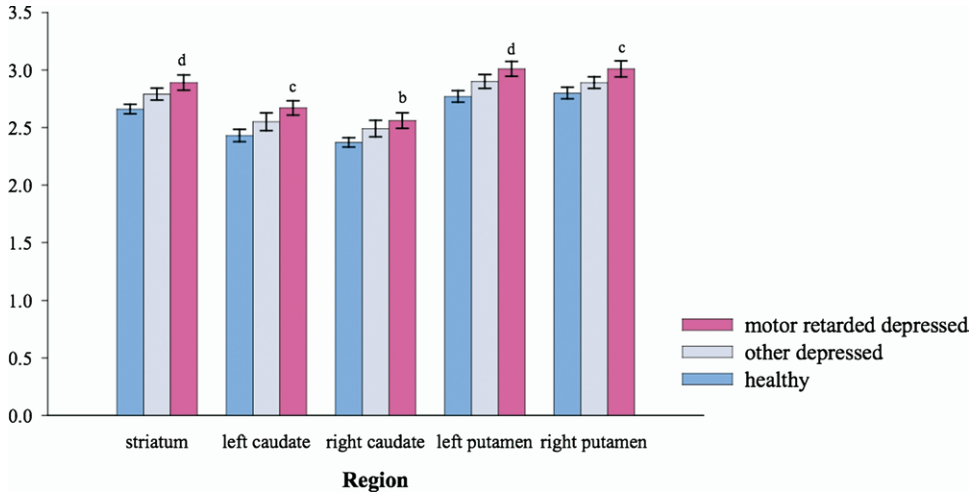

Figure 2 Striatal D_2 receptor binding potential in motor retarded depressed (n = 10), other depressed (n = 11) and healthy subjects (n = 21). Mean and standard error are shown. The motor retarded depressed group was selected based on slower scores on the finger tapping test. The motor retarded group had significantly slower scores as compared with healthy subjects (t29 = 3.37, $P = 0.002$, 47.0 taps/10 seconds versus 37.34 taps/10 seconds). Subjects' D2 BP values were normalized to a 30-year-old subject using the slope of the age-related decline. $^{b}P \leq 0.05$, independent sample t-test; $^{c}P \leq 0.01$, independent sample t-test; $^{d}P \leq 0.005$, independent sample t-test. (Reprinted with permission from Meyer et al.[2])

Table 3 Comparison of Radioligands for Imaging of 5-HTT in Humans[68]

	^{123}I-β-CIT SPECT	^{11}C-(+)McN5652 PET	^{11}C-DASB PET	^{123}I-ADAM SPECT
Selectivity	Nonselective—near 1:1 affinity for 5-HTT to DAT[123,124]	Likely selective 10:1 to 100:1 affinity for 5-HTT over NET[125,126]	Highly selective 1000:1 affinity for 5-HTT over NET or DAT*[127,128]	Highly selective 1000:1 affinity for 5-HTT over NET or DAT[129,130]
Displaceability of specific binding	Incomplete[131,132]	In most, but not all, reports[22,23,133]	Highly displaceable[17,18,127,128,134]	Highly displaceable[129,130,135]
Reversibility†	Good[136,137]	Not adequate to adequate, depending upon region‡[133,138,139]	Adequate in midbrain, good to very good in other regions[140-142]	Adequate in midbrain[135,143]
Brain uptake	Adequate[136,137]	Good[133,138]	Very good[140-142]	Adequate[135,143]
Specific binding to free and nonspecific binding ratio†	Good[136,137]	Not adequate in some regions; adequate in thalamus[138,144]	Adequate to very good‡[140,142]	Not adequate in most regions; adequate in midbrain[135,143]
Reliability of 5-HTT BP†	Not measured	Modest[23]	Very good to excellent[17,145]	Most regions reasonable[143]
5-HTT BP measurable in multiple regions?	Brainstem only[136,137]	Measurable in thalamus,[138] not measurable in cortex[133,139]	Yes[140,142]	Measurable in midbrain; unclear for other regions[135,143]

*^{11}C-DASB is also highly selective for 5-HTT over a number of other targets tested in vitro.[128]
†For humans (radiotracer performance differs across species).
‡Depending upon brain region.

cally show no effect on regional 5-HTT density.[103-105] In contrast, for dopamine transporters in striatum, the evidence to support a relationship between long-term reductions in extracellular dopamine and a lowering of striatal dopamine transporter density is fairly strong.[106-109] Norepinephrine density in most brain regions decreases in density after chronic norepinephrine depletion.[110]

Serotonin Transporter Binding During Major Depressive Episodes

Neuroimaging studies of the serotonin transporter offer the opportunity to measure an index of 5-HTT density, the 5-HTT BP_{ND}, in the midst of a depressive episode that was a significant barrier for most postmortem studies of 5-HTT density. There are only 2 postmortem investigations of 5-HTT density in subjects with recent symptoms of depressive episodes.[111,112] In these investigations, no changes in 5-HTT density were found in the dorsal raphe or the locus coeruleus. Other postmortem investigations of 5-HTT density sampled subjects with a history of a depressive episode and these investigations usually studied the prefrontal cortex and/or dorsal raphe nucleus. Findings ranged from decreased 5-HTT density[113-117] to no difference in 5-HTT density.[118-122] In several of these studies, subjects were medication free,[115,118,119] and for many of these investigations, average postmortem delays were less than a day.[111-113,115,117,121] For greater detail the reader is referred to the review of Stockmeier.[40] Other sampling issues that may influence postmortem investigations are effects of additionally sampling patients with bipolar disorder and possible differences between early- versus late-onset MDD.

Recent advances in radioligand development, particularly with the advent of ^{11}C-DASB, have led to a series of investigations of 5-HTT BP in MDD. (See Table 3[17,18,22,23,68,123-145] for a description of new radiotracers and Table 4[4,6,68,146-150] for a list of neuroimaging investigations.) The first application of ^{11}C-DASB PET imaging to MDD sampled 20 subjects with MDE and 20 healthy controls.[4] Subjects were medication free for at least 3 months, and they had no other comorbid axis I illnesses, did not smoke, and had early-onset depression. There was no evidence for a difference in 5-HTT BP_{ND} during MDE of early-onset MDD. However, MDE subjects with severely pessimistic dysfunctional attitudes had significantly greater levels of 5-HTT BP_{ND}, compared with healthy subjects in brain regions sampling serotonin nerve terminals (prefrontal cortex, anterior cingulate, thalamus, bilateral caudate, bilateral putamen). On average, 5-HTT BP_{ND} was 21% greater in these regions in MDE subjects with severely pessimistic dysfunctional attitudes. Moreover, within the MDE group, greater 5-HTT BP_{ND} was strongly associated with more negativistic dysfunctional attitudes in the same brain regions (Fig. 3). The interpretation was that serotonin transporters have an important role in influencing extracellular serotonin during MDEs: Greater regional 5-HTT levels can provide greater vulnerability to low extracellular 5-HT and symptoms of extremely negativistic dysfunctional atti-

Table 4 Imaging Investigations of the Serotonin Transporter in Untreated MDEs (Updated From Meyer[68])

Study	Ligand	No.	Illnesses	Medication Use?	Main Finding
Malison et al, 1998[146]	^{123}I-β-CIT SPECT	15 MDE, 15 healthy	MDD and/or comorbid disorders	6 Medication naïve, 9 medication free for 3 weeks	Lower BP in brainstem
Ichimiya et al, 2002[147]	^{11}C (+)McN5652 PET	7 MDE,* 15 healthy	MDD only (pooled with BD only)	All Medication free for >6 weeks	↑ 5-HTT BP in thalamus no change in midbrain in pool of MDD and BD subjects
Meyer et al, 2004[4]	^{11}C-DASB PET	20 MDE, 20 healthy	MDD only	All medication free for >3 months and 14 also antidepressant naive	No change in 5-HTT BP in MDE; in MDE with severe pessimism, greater 5-HTT BP in all regions except midbrain
Newberg et al, 2005[148]	^{123}I-ADAM SPECT	7 MDE, 6 healthy	MDD only	All medication free for >two weeks and 2 antidepressant naive	No change in 5-HTT BP in thalamus and striatum; lower 5-HTT BP in midbrain
Parsey et al, 2006[149]	^{11}C (+)McN5652 PET	25 MDE, 43 healthy	MDD, n = 19 with comorbid anxiety disorders	All potentially exposed to benzodiazepines; All antidepressant free for >2 weeks and 12 antidepressant naïve	No change in putamen, thalamus, hippocampus, or anterior cingulate ↓ 5-HTT BP in midbrain and amygdala†
Herold et al, 2006[150]	^{123}I-ADAM SPECT	21 MDE, 13 healthy	MDD only	All medication free for >2 months;	Trend towards greater midbrain 5-HTT BP
Cannon et al, 2007[6]	^{11}C-DASB PET	18 MDE, 34 healthy	MDD; 7 with history of panic attacks	Antidepressant free for >3 weeks (8 for fluoxetine)	Greater 5-HTT BP in thalamus, striatum, insula

*Ichimiya et al[147] sampled 21 mood disordered subjects, of which 14 had bipolar disorder.
†Findings were natural log transformed before analysis after a quantity was added.

tudes. This interpretation, in subjects with high levels of pessimism during MDE, corresponds to model number 3 (see the section "Excessive Clearance of Monoamines via Monoamine Transporters"). Because ^{11}C-DASB is insensitive to tryptophan depletion in humans, model number 4 is unlikely.[68,145,151]

In general, neuroimaging studies that (1) apply methodologies sampling of subjects who are medication free for longer than 2 months, (2) sample subjects who do not have comorbid axis I disorders, or (3) apply ^{11}C-DASB tend to find either no change in regional 5-HTT BP or an increase in regional 5-HTT BP (Table 4).[4,6,147,150] Investigations that sample subjects with comorbid axis I psychiatric disorders, or subjects with recent antidepressant use, or do not apply a selective radiotracer are more likely to report a reduction in regional 5-HTT BP.[146,148,149]

Dopamine Transporter Binding During MDD

Most dopamine transporter imaging radioligands applied in depression, such as ^{11}C-RTI-32, ^{123}I-FP-CIT, and ^{99m}Tc-TRODAT-1, have high selectivity, high specific binding relative to free and nonspecific binding, but are modestly reversible.[152-154] ^{123}I-β-CIT has reversible time activity curves within the time of scanning, but its measure of specific binding in striatum has a modest contribution from serotonin transporter binding. (This estimate is based on the similar affinity of ^{123}I-β-CIT for dopamine and serotonin transporters[123,124] and the relative density of these sites in the striatum.[155-158])

A novel radiotracer, ^{11}C-PE2I, demonstrates reversibility, selectivity, and high specific binding relative to free and nonspecific binding.[159-161] Metabolites that cross the blood–brain barrier have been identified in rodents,[162] but it is possible that these metabolites will not be present in humans.

There is a postmortem study of dopamine transporter binding during major depressive episodes that reported reductions in binding in basal and lateral amygdaloid nuclei.[42] In the same study, greater D_2 type receptor binding were present in the same amygdaloid nuclei, leading to the interpretation that dopamine levels were depleted in these regions within the amygdalae of depressed subjects.

Most neuroimaging investigations have focused on striatum and apply gray matter of cerebellum (or prefrontal cortex) as a reference tissue. Among investigations applying data in this manner, some commonality of findings is present: Those conducted in samples which were medication free for longer time periods tend to find reductions in striatal DAT binding,[5,163,164] whereas those in subjects who have recently taken antidepressants tend to find elevations in striatal DAT binding.[24,165] In unmedicated depressed subjects, it could be argued that model 1 (lesion) or model 2 (downregulation in response to another monoamine lowering process) are important.

Clarification of these models was possible through additional investigations in which the relationship between finger tapping speed and putamen DAT BP was assessed during

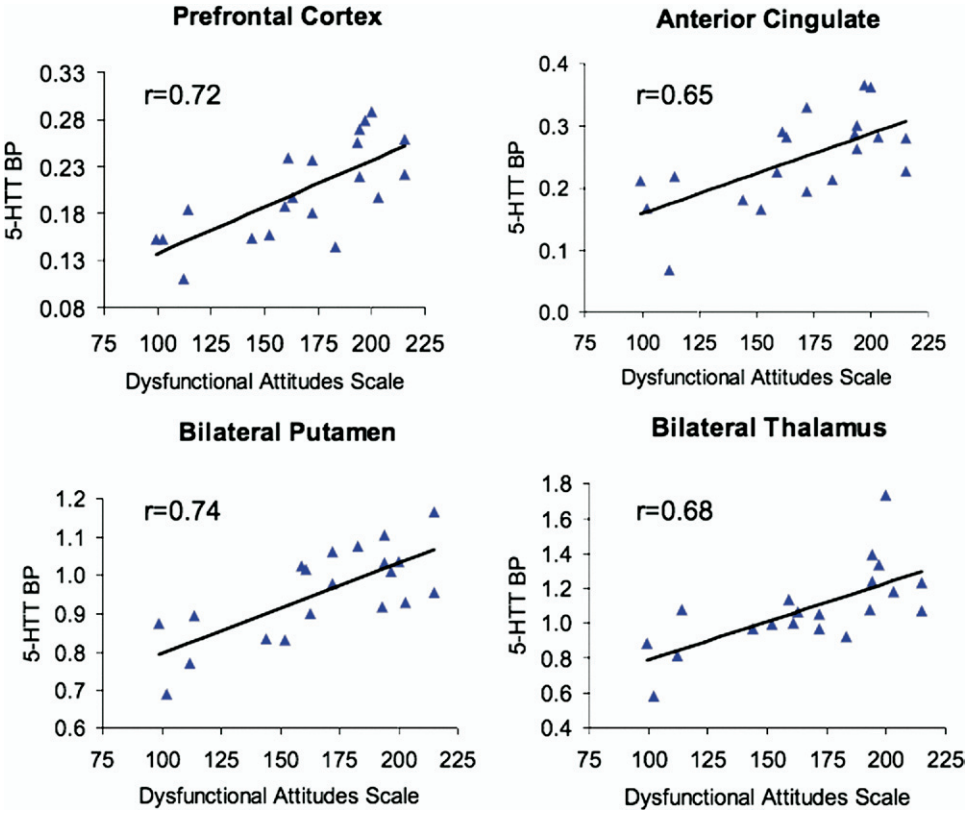

Figure 3 Correlations between dysfunctional attitudes (DAS) and serotonin transporter binding potential (5-HTT BP) in some of the larger regions in depressed subjects. Highly significant correlations were found for the prefrontal cortex ($P = 0.0004$), anterior cingulate ($P = 0.002$), bilateral putamen ($P = 0.0002$), and bilateral thalamus ($P = 0.001$). (Reprinted from Meyer et al,[4] with permission from the American Medical Association.) (Color version of figure is available online.)

MDE. A strong, negative correlation between the 2 measures was found (Fig. 4). Subjects' performances on the finger tapping test are impaired when dopamine concentrations are low (as indirectly measured by D_2 BP[2,166] or ^{18}F-DOPA uptake[167,168]) and when depressive episodes are present.[87] The data can be interpreted to argue that patients without motor retardation have lower DAT BP and demonstrate a compensatory protective mechanism[5]: When dopamine is chronically low in striatum, downregulation of DAT occurs.[106-109] Reduced DAT levels decrease the clearance of extracellular dopamine.[169] Compared with the usual healthy state, the compensated state has near similar (or mildly reduced) extracellular striatal dopamine concentrations with downregulated DAT. This process whereby DAT BP is decreased protects some patients from showing motor slowing. These data argue for involvement of two models: model 2 (downregulation in response to another monoamine lowering process) and model 3 (relatively greater DAT BP is associated with greater symptom burden).

Excessive Monoamine Metabolism During MDEs

Other major influences on extracellular monoamines besides monoamine transporter function include monoamine synthesis and metabolism processes. Decreased monoamine synthesis is unlikely during untreated MDE because postmortem investigations of monoamine synthesis enzymes in monoamine nuclei tend to find no change or modestly increased levels in most brain regions in subjects with MDD.[170-172] Neuroimaging investigations attempting to determine whether monoamine precursor uptake is reduced in untreated depression are inconclusive as the samples collected are associated with recent antidepressant use.[173,174]

Monoamine oxidase A regulates levels of all 3 major monoamines (serotonin, norepinephrine, dopamine) in the brain.[175] Postmortem studies have not fully addressed the question as to whether brain MAO-A is abnormal during major depressive episodes because each investigation had at least two limitations that may influence results,[7,176-181] including complete nonspecificity of technique for MAO-A versus monoamine oxidase B, enrollment of subjects who recently took medication, unclear diagnosis of suicide victims, small sample size, or lack of differentiation between early-onset depression and late-onset depression. Differentiation of the more common early-onset depression (before age 40) versus late-onset depression is important when evaluating indices of monoamine metabolism because dysregulation of monoamines in late onset depression is suspected of being attributable to lesions and/or degenerative disease.[182-185]

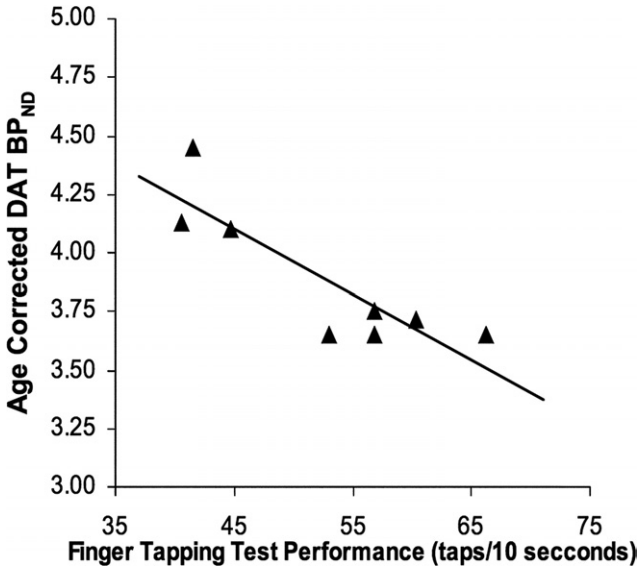

Figure 4 Correlation between age-corrected, striatal, dopamine transporter binding potential, and performance on the finger tapping test ($r = -0.86$, $P = 0.006$). (Reprinted from Meyer et al[5] with permission from Lippincott Williams & Wilkins.)

Radioligands to measure an index of MAO-A levels for neuroimaging include ^{11}C-clorgyline, deuterium-labeled ^{11}C-clorgyline, ^{11}C-harmine, and ^{11}C-befloxatone.[186-191] The latter 2 have a considerable advantage in terms of having more rapid kinetics and greater reversibility. ^{11}C-harmine has also been modeled in humans and possesses high affinity for the MAO-A site, selectivity, excellent specific binding relative to free and nonspecific binding ratios, high brain uptake, and is therefore the lead radiotracer for quantitating brain MAO-A binding in humans.[7,188,190,192,193]

There is one study of MAO-A binding in MDE, and MAO-A DVs, an index of MAO-A density, was elevated throughout the brain on average by 34% (2 standard deviations; Fig. 5).[7] Elevated brain MAO-A density during major depressive episodes when combined with previous neuroimaging results in medication free depressed subjects[1,2,4,5] (ie, no medication for 3 months or more) leads to an advanced monoamine theory (Fig. 6) as follows[7]: During a major depressive episode, elevated MAO-A increases the metabolism of monoamines. Then, individual monoamine transporter densities have a secondary influence on particular extracellular monoamine levels. If the monoamine transporter density for a particular monoamine is low, the effect of greater monoamine metabolism on extracellular monoamine levels is somewhat attenuated resulting in a moderate monoamine loss. Longstanding moderate loss of a particular monoamine in specific brain regions eventually results in a moderate severity of particular symptoms. If the monoamine transporter density for a particular monoamine is not low during a MDE, then the extracellular concentration of the monoamine is severely reduced and symptoms associated with chronic regional loss of that particular monoamine eventually become severe. To summarize, elevated MAO-A can be considered a general monoamine lowering process (with no relationship to particular symptoms) and the regional density of monoamine transporters can be considered a selective influence on particular monoamines (with a strong relationship with particular symptoms).[1,2,4,5,7]

Clinical Implications of a New Monoamine Theory

This modern model views both excessive MAO-A levels and relatively greater monoamine transporter density as being major contributors to regional monoamine loss.[1,2,4,5,7] This has implications for designing future treatments and matching treatments to illness. If it is assumed that greater

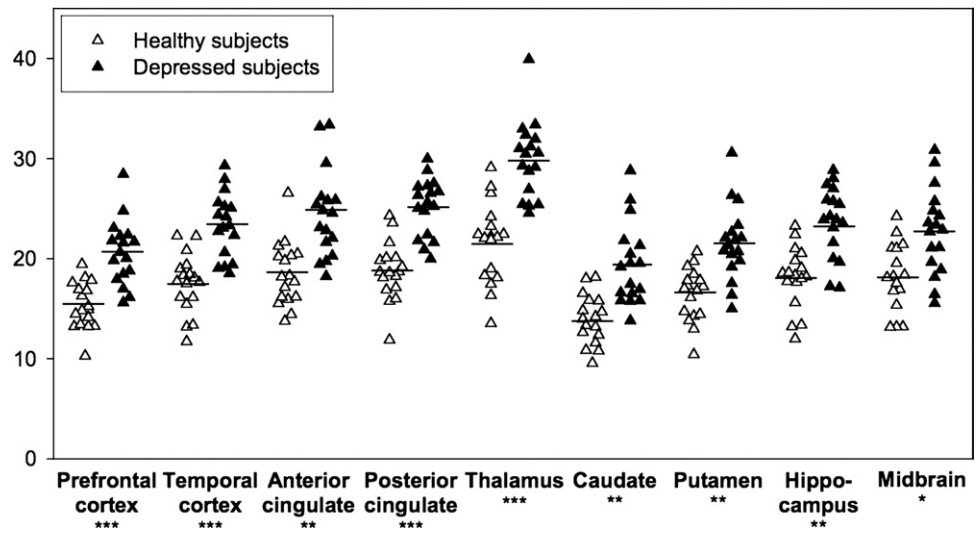

Figure 5 Comparison of MAO-A DVs between depressed and healthy subjects. On average, MAO-A DVs was increased by 34%, or 2 standard deviations, in depressed individuals. Differences between groups were highly significant in each region. *$P = 0.001$, ** $P < 0.0001$, *** $P < 0.00001$. (Reprinted from Meyer et al,[7] with permission from the American Medical Association.)

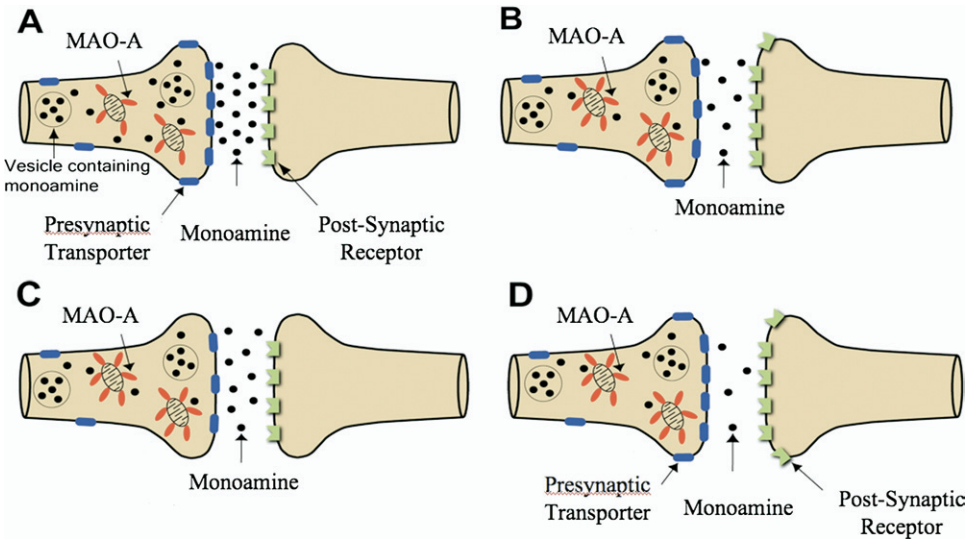

Figure 6 Modernization of Monoamine Theory of Depression. (A) Description of monoamine release in a synapse in a healthy person. (B) During a major depressive episode, monoamine oxidase A (MAO-A) density is elevated resulting in greater metabolism of monoamines such as serotonin, norepinephrine, and dopamine in the brain. Outcomes range from (C) to (D). (C) If the monoamine transporter density for a particular monoamine is low during a major depressive episode, the effect of elevated MAO-A upon reducing that particular monoamine in extracellular space is somewhat attenuated resulting in a moderate loss of monoamine. This eventually results in a moderate severity of symptoms associated with chronic loss of that particular monoamine. (D) If the monoamine transporter density for a particular monoamine is not low during a major depressive episode, then there is no protection against the effect of elevated MAO-A. The extracellular concentration of the monoamine is severely reduced and symptoms associated with chronic loss of that particular monoamine eventually become severe. Some post-synaptic receptors increase in density when their endogenous monoamine is chronically low. MAO-A is mostly found in norepinephrine releasing neurons, but is reported to be detectable in other cells such as serotonin releasing neurons and glia. Even so, MAO-A metabolizes serotonin, norepinephrine, and dopamine in vivo.

intervention on disease pathology leads to greater therapeutic effect, the model would predict that raising all three monoamines, would on average, increase the likelihood of response relative to a treatment that raises a single monoamine. It would also predict that the optimal match of subjects to treatment would relate to their symptom profiles. For example, symptoms associated with loss of particular monoamines would be expected to predict response to antidepressants that raise these monoamines. Conversely, presence of symptoms correlated with monoamine loss not directly targeted by an antidepressant would predict nonresponse. For example, it would be predicted that a depressed individual with symptoms corresponding to loss of dopamine would be less likely to respond to a serotonin reuptake inhibitor (which was reported in one recent investigation[194]).

Serotonin$_{1A}$ Receptor Imaging in MDD (With Anxiety)

There are several ^{11}C-WAY-100635 PET studies reporting greater 5-HT$_{1A}$ BP in most brain regions during major depressive episodes and persistence of this reduction during remission.[8-10] There is one exception to this result[11] and it may be that the selection of white matter as a reference region, logarithmic transformation of data and/or sampling characteristics account for the outlying result.

With regards to sampling issues, comorbid anxiety and/or anxiety disorders may be particularly important. During MDEs, anxiety and/or anxiety disorders are often present, and there is very good evidence to suggest that anxiety and/or anxiety disorders have a strong link to reductions in regional 5-HT$_{1A}$ BP: In an ^{18}F-trans-4-fluoro-N-2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl]-N-(2-pyridyl) cyclohexanecarboxamide (^{18}F-FCWAY) study of panic disorder (with comorbid MDD in almost half the cases), substantial reductions in 5-HT$_{1A}$ BP in anterior cingulate, posterior cingulate, and raphe regions were reported.[12] (Quantitation with this radiotracer is suitable for medial regions but not peripheral brain regions because of bone uptake of radioactive signal.) In social anxiety disorder, reductions in 5-HT$_{1A}$ BP in most brain regions (insula, anterior cingulate cortex, medial orbitofrontal cortex, amygdala, midbrain) were also reported.[13] In healthy individuals, there is an inverse correlation between anxiety levels and 5-HT$_{1A}$ BP in cortical and subcortical brain regions,[14] and there is an inverse correlation between personality variables related to worry regarding social desirability and 5-HT$_{1A}$ BP in cortical and subcortical brain regions.[195]

Investigations of Abnormally Functioning Brain Structures in MDD Via ^{18}F-FDG and ^{15}O-H_2O Uptake Measurement

Most neurobiological theories of depression propose that neurochemical and/or cognitive changes affect the function of particular brain structures. A line of investigation consistent with this perspective includes studies of FDG and ^{15}O-H_2O uptake in MDD because regional uptake of these radiotracers is often sensitive to changes in the function of particular brain regions. Abnormal patterns of ^{18}F-FDG uptake can be conceptualized as primarily relating to processes which reflect abnormal function during MDE. One is greater generation of sad affect which may relate to excessive activity of some components of the limbic system. A second is cognitive changes, which may relate to reduced activity of cortical structures. A third is greater functioning of compensatory mechanisms and circuits which can differ between treatment responders and nonresponders.[15,16]

Abnormalities during MDE include reductions in FDG uptake and/or ^{15}O-H_2O blood flow to structures that participate in cognition, attention and execution of decision making tasks such as dorsolateral and dorsomedial prefrontal cortex,[196-198] dorsal anterior cingulate cortex,[198,199] and caudate.[198-200] Changes in FDG uptake and/or ^{15}O-H_2O blood flow uptake are commonly observed in brain structures related to generation, and processing of affect such as subgenual cingulate cortex, anterior cingulate cortex, ventrolateral prefrontal cortex, amygdala, thalamus, and orbitofrontal cortex.[198,200-203] Variations in the direction of the abnormal change in radiotracer uptake in MDE groups as compared with healthy is often related to subgroupings of MDE such as treatment resistant and treatment responsive subgroups, and subgroups with volume loss.[15,16]

These investigations are often with the patient in a "resting state" with eyes shut. With the advent of bold functional magnetic resonance imaging, it has become clear that patterns of difference between depressed and healthy subjects are influenced by task choice and/or genotype.[204-207] However, prevailing patterns of change in FDG uptake can be viewed as representing predominant changes in regional function and have had practical application in guiding location choice (such as selection of subgenual cingulate) for techniques such as deep brain stimulation for treatment resistant subjects.[16]

In geriatric depression, particularly late-onset depression, where pathology of onset is likely related to lesions and loss of glia and neurons,[183,185] FDG uptake may be used to elicit neurochemically specific abnormalities. In such studies a challenge is given to stimulate release of a monoamine and changes in FDG uptake are evaluated.[185] Studies conducted in geriatric depression with a citalopram challenge have shown a differential lateralized pattern of acute metabolic effects in the patients who have a s allele of the serotonin transporter in contrast to comparison subjects.[208] Further investigations with other monoamine specific challenges may elicit abnormalities specific to subtypes of late-onset depression.

Improving Antidepressant Development Through Antidepressant Occupancy Studies

Quantitating brain penetration of antidepressants to the target sites has considerable practical application in developing antidepressants and can inform prescribing practices. Antidepressant occupancy can be defined as the percent change in specific binding index in the antidepressant treated condition relative to the untreated condition. It can be viewed as an index of brain penetration of antidepressants. Before the development of occupancy measurement, it was assumed that plasma levels may predict brain occupancy, but there are active transport mechanisms that remove medications from the brain and lipophilicity influences brain penetration of medications.[18] In the field of MDD, occupancy application is advanced relative to most areas of medicine since the occupancy for most commonly prescribed antidepressants has been established within the typically prescribed dosing range.[17,18] Most investigations have centered on the 5-HTT site, and the majority of the remaining investigations focus on DAT and 5-HT_{1A} occupancy.[17-26]

5-HTT Occupancy Studies

In 2001, the first selective serotonin reuptake inhibitor (SSRI) occupancy study with ^{11}C-DASB PET reported an 80% occupancy in multiple regions after 4 weeks of treatment with doses of paroxetine and citalopram that are clinically distinguishable from placebo.[17] This result has been replicated in brain regions of reasonable size with other SSRIs, such as fluvoxamine,[22] fluoxetine,[18] sertraline,[18] and venlafaxine (Figs. 7 and 8).[18] Although these SSRI have a 100-

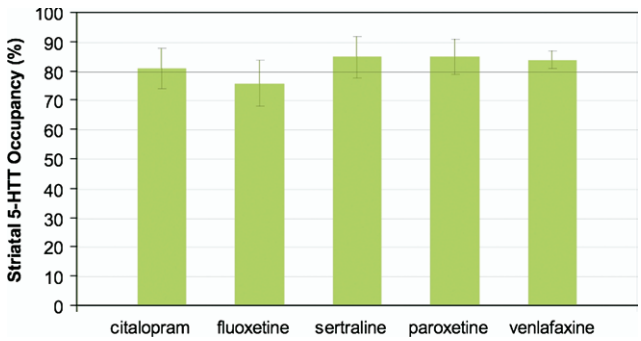

Figure 7 5-HTT occupancy at minimum therapeutic dose. Mean striatal serotonin transporter (5-HTT) occupancy for 5 selective serotonin reuptake inhibitors after 4 weeks of minimum therapeutic dosing. The vertical ranges represent SD. Subjects received citalopram 20-40 mg (n = 7), fluoxetine 20 mg (n = 4), sertraline 50 mg (n = 3), paroxetine 20 mg (n = 7), or venlafaxine XR 75 mg (n = 4). (Reprinted with permission from Meyer et al.[18]) (Color version of figure is available online.)

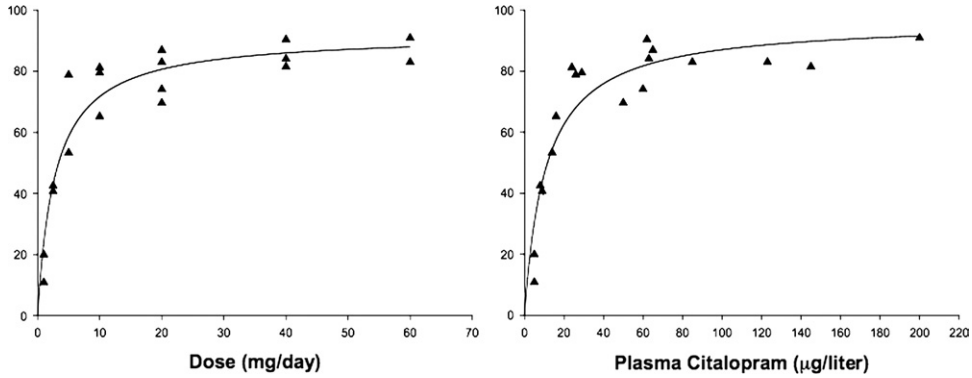

Figure 8 Relationship between striatal 5-HTT occupancy and dose or plasma concentration of citalopram. The data were fit using an equation of form f(x) = a*x/(b+x). The relationship between dose and occupancy was highly significant (f(x) = 92*x/(b+x), $F_{1,16} = 127$, $P < 0.0001$). The relationship between plasma level and occupancy was highly significant (f(x) = 96*x/(b+x), $F_{1,16} = 103$, $P < 0.0001$). (Reprinted with permission from Meyer et al.[17])

fold range in affinity for the serotonin transporter, an 80% striatal 5-HTT occupancy occurs at minimum clinical dose. Moreover, the in vitro EC_{50} does not correlate with affinity.[9] This demonstrates that, although affinity is an essential piece of information regarding an antidepressant, it cannot predict occupancy, even when plasma levels are known.[18] Given the association between the clinically relevant dose and 5-HTT occupancy for the SSRIs, it is now generally believed that an 80% 5-HTT occupancy is a therapeutic threshold for new antidepressants. This technique can be applied in a practical fashion during phase I trials to assess whether potential new antidepressant drugs are adequately brain penetrant and to guide dosing selection for subsequent phase II clinical trials.

5-HTT occupancy has been evaluated at a number of different doses for 5 commonly prescribed SSRIs.[17,18,209] Both dose and especially plasma level have a very strong relationship to 5-HTT occupancy: There is increasing occupancy with increasing dose (and plasma level), with plateauing at the greater doses and greater plasma levels (see Fig. 8). This has several important clinical implications. First, it is unlikely that inadequate 5-HTT occupancy explains treatment resistance, because one may raise the dose of the SSRI to obtain adequate plasma levels. Second, in clinical circumstances, 5-HTT imaging may not need to be completed to estimate 5-HTT occupancy. Instead, one may use the plasma level and the figures of plasma level versus occupancy in the main publication[18] to estimate the 5-HTT occupancy of any SSRI. Third, given the plateauing of occupancy in the clinical dosing range, none of the SSRI antidepressants demonstrate a 5-HTT occupancy exceeding 90%. This suggests that there is an opportunity to develop SSRI antidepressants with higher 5-HTT occupancy.[209]

DAT Occupancy Studies

Bupropion is an antidepressant which, based on its affinity profile, may be considered a dopamine reuptake inhibitor with modest affinity.[210,211] Occupancy studies in striatum report a reasonably consistent range of values between zero and 25%.[19-21,24] Given the low occupancy, it may be helpful to develop higher occupancy DAT inhibiting antidepressants.

5-HT_{1A} Occupancy Studies

Autoreceptor inhibition has been described as a mechanism of delayed response and nonresponse to SSRI.[211] Consequently, 5-HT_{1A} antagonists have been added to SSRI as a means to hasten antidepressant actions with detectable effects, but this is not done in routine clinical practice.[212] Investigations of pindolol and other 5-HT_{1A} antagonists have shown that the doses used in these augmenting studies correspond to low levels of 5-HT_{1A} occupancy in superior raphe nuclei and that occupancy at undesirable sites in cortex is also present.[25-28] Therefore, clinical trials have not yet been applied in a manner so as to optimize the autoreceptor inhibition of 5-HT_{1A} antagonists and future antidepressant development should focus on interventions that maximize 5-HT_{1A} autoreceptor inhibition and minimize 5-HT_{1A} antagonism in cortex.

Replicability Issues of Neuroimaging Investigations in MDD

Replication of occupancy findings has been robust.[17-27] However, replication of findings in disease states is best identified when sampling methodology and radioligand characteristics are considered.[1-16,24,68,73-80,146-150,163-165] Sampling issues that influence replicability across sites include duration of medication/antidepressant free status (with greater homogeneity of findings when medication free status exceeds two months), and comorbidity. It is anticipated that age of onset will be an important issue in future studies since there are distinct structural MRI abnormalities and patterns of cell loss in late-onset MDD.[183-185] Another important sampling issue is based on heterogeneity of symptom expression in MDD (A major depressive episode is defined as having the presence of at least five of nine symptoms[213]). Because MDD has a heter-

ogeneous expression of symptoms, quantitation of symptom severity related to the target of interest is necessary to further improve replicability across studies.[1-7] Samples with similar severity of target related symptoms are expected to demonstrate similar findings whereas samples with dissimilar severity of target related symptoms are unlikely to have similar findings. Radioligand selectivity, as assessed by the relative affinity of specific binding in vitro and the relative density of these target sites within specific regions in vivo,[68] is also a key issue for some investigations. Increasingly these sampling issues and radioligand characteristics are being considered, and thus it is likely that replications across settings will continue to improve.

Future Radioligand Development for Investigating MDD

It is likely that some of the immediate new radioligand development will relate to monoamine targets but that more of the future radiotracer development will be in other areas. Some postmortem investigations in untreated depressed subjects report a reduction in norepinephrine transporter density,[41] and many antidepressants target the norepinephrine transporter,[210,214] so there is great interest in measuring an index of norepinephrine transporter density in vivo. Developments have not yet yielded a radioligand that is highly sensitive to changes in available norepinephrine transporter binding. A promising radioligand in humans is ^{11}C-(S,S) 2-[(2-methoxyphenoxy)phenylmethyl]morpholine or ^{11}C-(S,S) O-methylreboxetine.[215,216] It demonstrates selectivity in animal displacement studies, but it has a few limitations in humans such as modest specific binding relative to free and nonspecific binding and a variable level of free and nonspecific binding between individuals.[215-217]

New key directions for future radioligand development are related to other pathophysiological aspects of MDD such as excessive secretion of glucocorticoids, aberrant signal transduction and markers of cell loss.[218] Radioligands for these targets are mostly in the development stage but some show promise.[219-221] The most common reason why current candidate compounds in these areas frequently have limited success is poor brain uptake or excessive lipophilicity.[222,223] However, similar challenges were overcome in the past for radiotracers for other target sites and it is anticipated that as new compounds are created for medicinal purposes, some of the more brain penetrant compounds will eventually be modified into valid radiotracers.

Conclusions

Radioligand neuroimaging has advanced the monoamine theory of MDD to a concept of chronic loss of particular monoamines, such as serotonin, norepinephrine, and dopamine, which occurs to a greater extent when particular symptoms are more severe.[1,2] The use of neuroimaging has also identified mechanisms of monoamine loss, including greater monoamine metabolism[7] and excessive monoamine transporter density in the presence of monoamine depleting processes.[4,5]

This information may be translated into treatment development: (1) It predicts that targeting multiple monoamines will, on average, be more therapeutic; (2) It predicts that particular symptoms will associate with responsiveness for raising specific monoamines; and (3) It predicts that interfering with specific mechanisms of monoamine loss will be helpful in reversing symptoms of major depressive episodes.

Reductions in 5-HT$_{1A}$ binding associated with MDD are most likely related to comorbid anxiety and/or anxiety disorders, which may be clinically relevant because comorbid anxiety disorders are associated with treatment refractoriness.[8-10,12,13]

Patterns of ^{18}F-FDG and ^{15}O-H_2O uptake in MDD tend to demonstrate overactivity of regions that generate mood and underactivity of regions related to cognition.[15,16] Activations associated with nonresponse are candidate targets for treatment such as deep brain stimulation for treatment resistant individuals.[16]

Dosing of selective serotonin reuptake inhibitors associated with a differential response from placebo typically achieve 80% occupancy.[17,18] This information now guides development of new serotonin transporter binding antidepressants which aim for an 80% occupancy. The extremely strong relationship between plasma levels and occupancy may be applied by clinicians to estimate occupancy based on plasma levels, in situations of nonresponse.

Low occupancy of dopamine reuptake inhibitors[19-21,24] and 5-HT$_{1A}$ autoreceptor inhibitor medications[25,27,28] at the higher end of the tolerated dosing range suggest there is an opportunity to develop higher occupancy treatments for these targets.

Future ligand development will likely target other nonmonoaminergic pathophysiologies associated with major depressive disorder such as excessive secretion of glucocorticoids, aberrant signal transduction and markers of cell loss, with the potential to better understand how these pathologies relate to clinical symptoms, course of illness and effect of novel treatments.

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