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Neuroreceptor imaging in depression

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ABSTRACT

The in vivo study of receptor binding potential in the human brain is made possible by positron emission tomography (PET) imaging. Here we review PET studies of neuroreceptor function in mood disorders — specifically, major depressive disorder (MDD) and bipolar disorder (BD). We concentrate on the most widely studied receptors of the serotonergic and dopaminergic systems. Specifically, the serotonin 1A (5-HT_{1A}), serotonin 2A (5-HT_{2A}), serotonin 1B (5-HT_{1B}), dopamine 1 (D1), and dopamine 2/3 (D2/3) receptors. We also review PET studies of the serotonin transporter (5-HTT), the dopamine transporter (DAT), monoamine oxidase A (MAO-A), and the muscarinic 2 receptor (M2). On the basis of the PET literature as well as supporting genetic studies, postmortem data, and preclinical models of depression, and several models of how monoaminergic function is altered in mood disorders are discussed with respect to inflammation, endocrine dysfunction, depression subtypes, and altered neurocircuitry.

Contents

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Introduction

Positron emission tomography (PET) makes use of the radioactive decay of positron-emitting nuclides to measure cerebral blood flow, metabolic activity or protein binding, in vivo. In vivo receptor function is best represented by the binding potential (BP), defined as the product of the density of receptors available to bind the radioligand (B_{avail}) and the affinity of the radioligand for its receptor ($1/K_D$), where K_D is the dissociation constant (Mintun et al., 1984). Stated differently, BP is the ratio of specifically bound to free tracer at equilibrium in a region of interest in the brain. In the context of PET, three different reference concentrations generally have been used to calculate this ratio and therefore there are three ways that the term "BP" is used in the PET literature.

The BP_F refers to the ratio at equilibrium of the concentration of specifically-bound radioligand in the brain to the concentration of free radioligand in the brain (Innis et al., 2007). In order to estimate the concentration of the unbound radioligand in the brain, the concentration of free radioligand in the plasma is measured from arterial blood samples obtained during the scan. Here the assumption is that under conditions of passive diffusion the concentration of free radioligand in the plasma equals the concentration of free radioligand in the brain. In practice, however, the free fraction of radioligand in the plasma cannot always be distinguished from protein-bound radioligand in the plasma. Thus a second method for assessing the BP involves calculation of BP_P: the ratio of specifically-bound radioligand in brain tissue to free plus protein-bound radioligand in plasma at equilibrium (Innis et al., 2007). In other words, BP_P is not corrected for the fraction of the tracer that is bound to plasma proteins. In mathematical terms, $BP_P = C_T - C_{ND}/C_P$ where C_T and C_{ND} denote mean radioactivity concentrations in the region of interest and reference region (see below), respectively, and C_P denotes the equilibrium concentration of radiotracer in the plasma.

The calculation of BP_F and BP_P necessitates arterial plasma sampling and tracer kinetic modeling and therefore the non-displaceable BP (BP_{ND}), which approximates BP_F and BP_P for certain radioligands, is usually used where possible. BP_{ND} is the ratio of free plus specifically-bound radiotracer to free plus nonspecifically bound (non-displaceable) radiotracer in brain tissue at equilibrium (Innis et al., 2007). BP_{ND} is calculated using a reference region, i.e. a region of the brain with negligible density of the receptor of interest. Thus BP_{ND} is the ratio of activity in a region where the target receptor protein is abundantly expressed to activity in a control region that is essentially devoid of the target receptor protein. A limitation of the BP_{ND} parameter is that a group difference can be driven by an abnormality in either the target tissue or the reference tissue. Here, the assumption is that the non-displaceable binding does not differ between the experimental and control subject samples.

In addition, the relative contributions of receptor density and receptor affinity to the BP parameter vary according to whether the radiotracer is an agonist or an antagonist. Antagonists bind with equal affinity to receptors in both high and low affinity states and thus largely measure receptor density while agonists bind preferentially to receptors in the high affinity state and are therefore sensitive to both receptor density and affinity. The majority of radioligands developed to date to measure receptor binding in the brain have been antagonists (Table 1).

Another potential measure of receptor or enzyme function is volume of distribution (V_T), which refers to the ratio of the concentration of the radioligand (at equilibrium) in the brain tissue (C_T) to the concentration of the radioligand in plasma (C_P) (Innis et al., 2007). V_T is used as a measure of receptor binding when no adequate reference region in the brain is available because of the ubiquity of the receptor under study. Because the total concentration of radioligand in the brain tissue (C_T) is composed of specifically bound (C_S), non-specifically bound (C_{NS}) and free radioligand (C_{FT}), the nomenclature V_S is used to signify that the volume of distribution reflects the ratio of the specifically-bound radiotracer in the brain to the concentration of the radiotracer in the plasma. V_S can be regarded as essentially equivalent to BP_F or BP_P (Innis et al., 2007).

In this review we focus on PET studies of neuroreceptor function in mood disorders — specifically, major depressive disorder (MDD) and bipolar disorder (BD). We concentrate on the most widely studied receptors of the serotonergic and dopaminergic systems: the serotonin 1A, serotonin 2A, dopamine 1, and dopamine 2/3 receptors. We also include studies of the serotonin transporter, the dopamine transporter, monoamine oxidase A (MAO-A), the serotonin 1B receptor, and the muscarinic 2 receptor. In the Results section, below, we present an overview of the findings for each receptor. In the Discussion section, we consider the possible reasons for the inconsistencies in the literature (where they exist) and refer to converging or diverging evidence from preclinical, postmortem, and genetic studies. Finally, we construct a simplified model of the role played by each receptor in affective illness and construct a heuristic integrated model of neuroreceptor function in mood disorders.

Methods

Relevant studies were identified through a MEDLINE search, National Library of Medicine, NIH (http://www.pubmed.gov) and cross-referenced papers in the field. Search terms used included the following: "PET", "bipolar disorder", "major depressive disorder", "5-HT_{1A}", "5-HT_{2A}", "5-HT_{1B}", "serotonin transporter", "monoamine oxidase A", "dopamine receptor", and "dopamine transporter". To our knowledge, all papers that compared mood disorder subjects to

Table 1
List of commonly used ligands.

Receptor	Radioligand	Chemical compound	Type
5-HT_{1A}	[^{11}C]WAY-100635	N-[2-[4-(2-methoxyphenyl)-1-piperazinyl] ethyl]-N-2-pyridinyl-trans-4-fluorocyclo-hexylcarboxamide	Antagonist
5-HT_{1B}	[^{11}C]P943.	*R*-1-[4-(2-methoxy-isopropyl)-phenyl]-3-[2-(4-methyl-piperazin-1-yl)benzyl]-pyrrolidin-2-one	Antagonist
5-HT_{2A}	[^{18}F]Altanserin	3-(2-(4-(4-Fluorobenzoyl)-1-piperidinyl)ethyl)-2,3-dihydro-2-thioxo-4(1H)-quinazolinone	Antagonist
5-HT_{2A}	[^{11}C]MDL	(R)-1-[2-(4-fluorophenyl)ethyl]-(4-(2,3-dimethoxyphenyl)-4-piperidinemethano)	Antagonist
5-HT_{2A}	[^{18}F]FESP	3-(2-Fluoroethyl)-8-[4-(4-fluorophenyl)-4-oxobutyl]-1-phenyl-1,3,8-triazaspiro[4.5] decan-4-one	Antagonist
5-HT_{2A}	[^{18}F]Setoperone	6-[2-[4-(4-Fluorobenzoyl)-1-piperidinyl]ethyl]-2,3-dihydro-7-methyl-5H-thiazolo[3,2a] pyrimidin-5-one	Antagonist
5-HTT	[^{11}C](+)McN5652	(6S,10bR)-1,2,3,5,6,10b-hexahydro-6-[4-(methylthio)phenyl]-pyrrolo[2,1-a] isoquinoline	Antagonist
5-HTT	[^{11}C]DASB	3-Amino-4-[[2-[(dimethylamino) methyl] phenyl]thio]benzonitrile	Antagonist
D1	[^{11}C]SCH 23390	8-Chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1H-3-benzazepin-7-ol	Antagonist
D1	[^{11}C]NNC-112	8-Chloro-7-hydroxy-3-methyl-5-(7-benzofuranyl)-2,3,4,5-tetrahydro-IH-3-benzazepine	Antagonist
D2/D3	[^{11}C]Raclopride	3,5-Dichloro-N-[[(2S)-1-ethyl-2-pyrrolidinyl] methyl]-2-hydroxy-6-methoxybenzamide	Antagonist
D2/D3	[^{18}F]Fallypride	Benzamide, 5-(3-fluoropropyl)-2,3-dimethexy-N-[(2S)-1-(2-propenyl)-2-pyrrolidinyl]methyl	Antagonist
D2/D3	[^{11}C]FLB-457	5-Bromo-N-[[(2S)-1-ethyl-2-pyrrolidinyl] methyl]-2,3-dimethoxybenzamide	Antagonist
D2/D4	[^{11}C]NMSP	8-[4-(4-Fluorophenyl)-4-oxobutyl]-2-methyl-4-phenyl-2,4,8-triazaspiro[4.5]decan-1-one	Antagonist
DAT	[^{11}C]CFT	[N-methyl-^{11}C]-2-b-carbomethoxy-3-b-(4-fluorophenyl)-tropane	Antagonist
DAT	[^{11}C]RTI-32	(−)-2β-Carbomethoxy-3β-(4-tolyl)tropane	Antagonist
MAO-A	[^{11}C]Harmine	7-Methoxy-1-methyl-9H-[3,4-b]indole	Antagonist
M2	[^{18}F]FP-TZTP	3-(3-(3-Flouropropyl)thio)-1,2,5-thiadiazol-4-yl)-1,2,5,6-tetrahydro-1-methylpyridine	Agonist

healthy controls using PET were included in the review. Single photon emission computerized tomography (SPECT) studies were not included in this review. Compared with SPECT, PET has modestly higher spatial resolution, and markedly greater sensitivity (i.e. signal-to-noise ratio) (Rahmim and Zaidi, 2008). Moreover, the number of radioligands available for assaying molecular targets of interest is substantially larger for PET.

Results

Serotonin 1A

The serotonin 1A (5-HT_{1A}) literature pertaining to mood disorders is summarized in Table 2. Studies of MDD patients that have used BP_{ND} as a measure of receptor function have consistently found a decrease in 5-HT_{1A} receptor binding in the raphe as well as limbic and cortical regions (Bhagwagar et al., 2004; Drevets et al., 2000, 2007; Sargent et al., 2000) — although one study of late-life depression reported a reduction in the raphe but not in other regions, Meltzer et al (2004) and Mickey et al. (2008a) found no difference in BP_{ND} in MDD patients versus healthy controls. Similarly, Hirvonen et al. (2008a) reported reduced 5-HT_{1A} BP_P in the cortex and hippocampus, but not the raphe of drug-naïve MDD patients. In addition, a mixed sample of women with post-partum MDD and BD showed reduced BP_P in the subgenual and pregenual anterior cingulate, lateral orbital, and mesiotemporal cortices (Moses-Kolko et al., 2008). Finally, depressed patients with BD and MDD subjects with a family history of BD also had lower 5-HT_{1A} BP_{ND} than controls in the raphe and mesiotemporal cortex (Drevets et al., 1999, 2007). Consistent with these data Nugent et al. (in press) observed reductions in both the BP_F and the BP_{ND} in depressed bipolar disordered subjects relative to controls.

In contrast, other researchers, notably the Columbia group, reported increased 5-HT_{1A} BP_F both pre-synaptically and post-synaptically in remitted and depressed patients with MDD (Miller et al., 2009a; Parsey et al., 2010) as well as in patients with BD (Sullivan et al., 2009). In these studies the BP_{ND} was either unchanged or significantly *reduced* in patients with mood disorders.

In addition, in patients with temporal lobe epilepsy (TLE) the depression ratings were inversely correlated with 5-HT_{1A} receptor distribution volume in the hippocampus of Theodore et al. (2007). While subjects with TLE showed decreased 5-HT_{1A} receptor binding in the epileptic focus itself, comorbid MDD was associated with a significantly more pronounced reduction in 5-HT_{1A} receptor binding in TLE patients relative both to healthy controls and to non-depressed TLE patients, and extending into limbic brain areas outside the epileptic focus (Hasler et al., 2007). In a later study, the same group replicated the inverse association between depression ratings and hippocampal binding (Theodore et al., 2012).

The apparent divergence in findings in mood disorders is addressed in the Discussion section, but it is noteworthy that the inconsistency seen in the literature regarding 5-HT_{1A} receptor binding extends to PET studies of other neuroreceptor species in primary mood disorders as well.

Serotonin 2A

The serotonin 2A (5-HT_{2A}) literature is summarized in Table 3. The data are contradictory with increases, decreases and no changes in 5-HT_{2A} binding reported. Because the radioligands, [^{18}F]FESP and [^{18}F]setoperone also bind to D2 receptors, studies applying these radioligands are limited to examining the cortex which has a relatively low concentration of D2 receptors. In contrast, [^{18}F]altanserin shows good affinity and specificity for the 5-HT_{2A} receptor (Sadzot et al., 1995) but produces lipophilic metabolites which necessitate additional modeling.

In the only [^{18}F]FESP study to date, Messa et al. (2003) found a reduction in BP_{ND} in anti-depressant drug naïve MDD patients in all cortical regions and the anterior cingulate cortex (ACC). Nevertheless, many of these patients were taking benzodiazepines at the time of the study. MDD patients have also been reported to show decreased [^{18}F]altanserin binding in the orbitoinsular cortex (Biver et al., 1997) and hippocampus (Mintun et al., 2004). Similarly, using [^{18}F] setoperone, Attar-Levy et al. (1999) and Yatham et al. (2000) reported decreased BP_{ND} in the frontal cortex, and in the frontal, temporal, parietal and occipital cortices, respectively. In contrast, Meyer et al. (2003) reported an increase in [^{18}F]setoperone binding in Brodmann's area 9 (BA9) in MDD patients who showed elevations in the personality trait, "dysfunctional attitude". In a previous study, the same group had reported that treatment of MDD with paroxetine decreased [^{18}F] setoperone binding in the cortex of 20–30 year-old patients — putatively a result of the downregulation of 5-HT_{2A} receptors (Meyer et al., 2001a). Finally, a study with the radioligand, [^{11}C]MDL showed increased BP_P in the frontal, parietal and occipital cortices of remitted MDD patients (Bhagwagar et al., 2006). Bhagwagar et al. (2006) also replicated the positive association between dysfunctional attitudes and 5-HT_{2A} receptor BP reported by Meyer et al. (2003). As we discuss below, the conflicting results may partially result from the use of medicated subjects in a number of studies mentioned above.

Table 2
5-HT_{1A} receptor imaging studies in mood disorders.

Study	Sample	Age	Method	Presynaptic	Postsynaptic
Drevets et al. (1999)[a]	12 MDD 8 HC	35.8 ± 9.7 35.3 ± 13.5	Simplified reference tissue model (cerebellum)	↓ BP_{ND} raphe (27%)	↓ BP_{ND} MTC (42%)
Sargent et al. (2000)	15 Unmedicated MDD 20 Medicated MDD 18 HC	37.7 ± 1.7 43.1 ± 14.8 36.4 ± 8.3	Simplified reference tissue model (cerebellum)	↓ BP_{ND} raphe (20%)	↓ BP_{ND} MTC (OFC, dACC, VLPFC, DLPFC and insula in both MDD groups
Bhagwagar et al. (2004)	14 MDD 18 HC	48 ± 14.9 43.2 ± 13	Simplified reference tissue model (cerebellum)	NS	↓ BP_{ND} broad areas of cortex (17%), including ACC, hippocampus, amygdala, frontomedial cortex
Meltzer et al. (2004)	17 MDD 17 HC	71.4 ± 5.9 70 ± 6.7	Distribution volume by graphical analysis with plasma input function	↓ BP_P raphe (±38%)	NS
Parsey et al., (2006b)[b]	13 MDD Remitters 9 MDD Non-remitters 43 HC	39.9 ± 10.4 42.9 ± 14.9 38.2 ± 15.0	Distribution volume by compartmental model with plasma input function	NS	↑ BP_P non-remitters: ACC, hippocampus, DLPFC, VLPFC and other cortical regions
Drevets et al. (2007)[a]	16 MDD 8 HC	32 ± 10 32 ± 12	Simplified reference tissue model (cerebellum)	↓ BP_{ND} raphe (43%)	↓ BP_{ND} MTC (26%)
Hirvonen et al. (2008a)	21 MDD 15 HC	40.1 ± 9 32.6 ± 7.7	Two-tissue compartmental model with cerebellar white matter reference tissue	NS (↓) BP_P	↓ (9%–25%) BP_P in diverse regions including amygdala, hippocampus, ACC, and mPFC
Mickey et al. (2008)	14 MDD 17 HC	38 ± 11 34 ± 12	Distribution volume by graphical analysis with reference tissue	NS	NS
Moses-Kolko et al. (2008)	9 PPD 7 HC	26.9 ± 7.9 33.0 ± 3.9	Simplified reference tissue model (cerebellum)	NS (↓ 10%)	↓ BP_{ND} (20%–28%) sgACC, pgACC, MTC; OFC
Miller et al. (2009a)[b]	15 rMDD 13 MDD 51 HC	31.8 ± 10.9 35.9 ± 12.3 37.4 ± 14.5	Distribution volume by compartmental model with plasma input function	↑ BP_F ↓ BP_{ND} NS BP_P	↑ BP_F ↓ BP_{ND} NS BP_P
Sullivan et al. (2009)	32 BD 47 HC	38.4 ± 9.7 38.1 ± 14.7	Distribution volume by compartmental model with plasma input function	↑ BP_F in males Raphe (102%) NS (BP_{ND})	↑ BP_F in males (29-50%) in diverse regions including amygdala, hippocampus, ACC, mPFC, OFC, and insula NS (BP_{ND})
Parsey et al. (2010)	22 MDD 9 HC	40.6 ± 13.1 37.4 ± 14.4	Distribution volume by compartmental model with plasma input function	↑ BP_F ↑ V_T ↓ BP_{ND}	↑ BP_F ↑ V_T ↓ BP_{ND} in diverse regions including amygdala, hippocampus, ACC, mPFC, OFC, and insula
Sargent et al. (2010)	8 BD 8 HC	45 ± 8 49 ± 8	Simplified reference tissue model (cerebellum)	NS	NS

Note: all studies used the radioligand, [carbonyl-11C]WAY-100635. ACC = anterior cingulate cortex; BD = bipolar disorder; DLPFC = dorsolateral prefrontal cortex; HC = healthy control; MDD = major depressive disorder; mPFC = medial prefrontal cortex; MTC = mesiotemporal cortex; NA = not applicable; NR = not reported; NS = not significant; OFC = orbitofrontal cortex; pgACC = pregenual ACC; PPD = postpartum depression; rMDD = remitted MDD and VLPFC = ventrolateral prefrontal cortex.
[a] Samples overlapped between these studies.
[b] Samples overlapped between these studies.

Table 3
5-HT_{2A} receptor imaging studies in mood disorders.

Study	Sample	Age	Medication status	Radioligand	Method	Result
Biver et al. (1997)	8 MDD 22 HC	48 ± 10 38 ± 12	Unmedicated 10 + days	[18F]altanserin	Ratio model during equilibrium	↓ BP right orbitoinsular cortex
Attar-Levy et al. (1999)	7 MDD 7 HC	40 ± 11 38 ± 10	Unmedicated 1 + year	[18F]setoperone	Ratio model during equilibrium	↓ BP frontal cortex
(Meltzer et al. (1999)	11 MDD 10 HC	65 ± 6 70 ± 5	Unmedicated	[18F]altanserin	Distribution volume by graphical analysis with plasma input function	NS
Meyer et al. (1999)	14 MDD 19 HC	32 ± 6 32 ± 7	Unmedicated 6 + months	[18F]setoperone	Ratio model during equilibrium	NS
Yatham et al. (2000)	20 MDD 20 HC	40 ± 10 38 ± 13	Unmedicated 2 + weeks	[18F]setoperone	Ratio model during equilibrium	↓ BP_{ND} in all regions of the cortex
Messa et al. (2003)	19 untreated MDD 15 treated MDD 20 HC	39 37 36	Naïve/SSRI	[18F]FESP	Binding index (the ratio of tracer uptake in cortex relative to that in cerebellum)	↓ BP_{ND} in naïve MDD frontal, temporal, occipital cortices, + ACC
Meyer et al. (2003)	22 MDD 22 HC	18–44	Unmedicated 4 + weeks	[18F]setoperone	Ratio model during equilibrium	↑ BP in BA9 in MDD with high dysfunctional attitude
Mintun et al. (2004)	46 MDD 29 HC	50 ± 6 46 ± 15	Unmedicated for 4 + weeks	[18F]altanserin	Distribution volume by compartmental model with plasma input function	↓ V_T in hippocampus. Trend perigenual ACC
Bhagwagar et al. (2006)	20 remitted MDD 20 HC	39 ± 12 43 ± 14	Unmedicated 6 + months	[11C]MDL	Distribution volume by graphical analysis with plasma input function	↑ BP_P frontal, parietal, occipital cortex

Table 4
5-HTT imaging studies in mood disorders.

Study	Sample	Age	Medication status	Radioligand	Method	Result
Ichimiya et al. (2002)	7 MDD 6 BD 21 HC	44.1 ± 13.5 41.7 ± 8.8 42.3 ± 14.5	Unmedicated 6 + weeks	[11C] (+)McN5652	Graphical reference tissue model (cerebellum)	↑ BP_{ND} in thalamus in patients (22%) but not midbrain
Meyer et al. (2004)	20 MDD 20 HC	35 ± 11 35 ± 11	Unmedicated 3 + months	[11C]DASB	Graphical reference tissue model (cerebellum)	NS
Reivich et al. (2004)	4 MDD 4 HC	22–56 23–59	Unmedicated five elimination half-lives of drug	[11C] (+)McN5652	Distribution volume by compartmental model with plasma input function	↑ BP_P left frontal cortex, right cingulate cortex
Cannon et al. (2006b)	18 BD 37 HC	30 ± 9 32 ± 9	Unmedicated 3 + weeks	[11C]DASB	Multilinear reference tissue model (cerebellum)	↑ BP_{ND} in thalamus, dorsal cingulate cortex, mPFC and insula ↓ BP in raphe
Parsey et al. (2006a)	25 MDD 43 HC	38.0 ± 13.4 38.8 ± 15.9	Unmedicated 2 + weeks	[11C] (+)McN5652	Distribution volume by graphical analysis with plasma input function	↓ BP_P in amygdala (20%) and midbrain (20%) in AD-naive MDD sample
Bhagwagar et al. (2007)	24 Remitted MDD 24 HC	38.9 ± 11.9 35.7 ± 9.8	Unmedicated 23 + months	[11C]DASB	Distribution volume by graphical analysis with plasma input function	NS
Cannon et al. (2007)	18 MDD 34 HC	35 ± 8.9 33 ± 8.4	Unmedicated 3 + weeks	[11C]DASB	Multilinear reference tissue model (cerebellum)	↑ BP_{ND} in thalamus (27%), insula (15%), anteroventral striatum (12%), pgACC (16%), PAG (22%)
Oquendo et al. (2007)	18 BD 41 HC	39.3 ± 16.0 38.1 ± 9.7	Unmedicated 2 + weeks	[11C] (+)McN5652	Distribution volume by graphical analysis with plasma input function	↓ BP_P (16–26%) in midbrain, putamen, amygdala, thalamus, and ACC
Miller et al. (2008)	7 MDD remitters 12 MDD non-remitters 41 HC	38.9 ± 11.4 41.7 ± 15.1 39.0 ± 16.1	Unmedicated 2 + weeks	[11C] (+)McN5652	Distribution volume by graphical analysis with plasma input function	↓ BP_P in non-remitters in midbrain, amygdala and ACC
Reimold et al. (2008)	10 MDD 19 HC	48.3 ± 9.7 44.2 ± 10.1	Unmedicated five elimination half-lives of drug	[11C]DASB	Multilinear reference tissue model (cerebellum)	↓ BP_{ND} in thalamus
Frokjaer et al. (2009)	9 HR 11 LR	32.2 ± 4.2 32.4 ± 5.0	Naive	[11C]DASB	Multilinear reference tissue model (cerebellum)	↓ BP_{ND} in DLPFC (35%) and trend towards significance in ACC (15%) in HR
Miller et al. (2009b)	15 MDD with past trauma 13 MDD without trauma 43 HC	39.1 ± 16.1 39.2 ± 11.4 38.8 ± 15.9	Unmedicated 2 + weeks	[11C] (+)McN5652	Distribution volume by graphical analysis with plasma input function	↓ BP_P in anterior cingulate, hippocampus, amygdala, putamen, midbrain, thalamus in abused MDD
Reimold et al. (2011)	10 MDD 20 HC	48.3 ± 9.7 44.2 ± 9.8	Unmedicated five elimination half-lives of drug	[11C]DASB	Multilinear reference tissue model (cerebellum)	↓ BP_{ND} in thalamus, which was associated with higher cortisol levels after DEX/CRF
Selvaraj et al. (2011)	12 MDD 24 HC	42.1 ± 11.6 42.4 ± 11.4	Medication free 4–240 months	[11C]DASB	Distribution volume by graphical analysis with plasma input function	↓ BP_{ND} in brain stem, thalamus ↓ BP_P in brain stem, thalamus, caudate, putamen, and ACC

Note: ACC = anterior cingulate cortex; BD = bipolar disorder; DEX/CRF = dexamethasone/cortisol releasing factor; DLPFC = dorsolateral prefrontal cortex; HC = healthy control; HIV = human immunodeficiency virus; HR = high risk; LR = low risk; MDD = major depressive disorder; mPFC = medial prefrontal cortex; NS = not significant; PCC = posterior cingulate cortex; and PD = Parkinson's disease.

Serotonin 1B

The 5-HT_{1B} receptor is a presynaptic autoreceptor or heteroreceptor which inhibits serotonin and other monoamine neurotransmitter release (Svenningsson et al., 2006). Murrough et al. (2011) recently reported a 20% decrease in 5-HT_{1B} receptor BP_{ND} in the ventral striatum and ventral pallidum of treatment-naïve patients with MDD.

Serotonin transporter

The serotonin transporter (5-HTT) literature is summarized in Table 4. Since the [^{11}C](+)McN5652 radioligand shows non-specific binding (Buck et al., 2000), we focus here on the results of studies using the [^{11}C]DASB radioligand which has a greater ratio of specific to non-specific binding, and therefore allows for the measurement of BP in cortical as well as subcortical brain regions (Meyer, 2007).

Our group previously reported increased 5-HTT BP_{ND} in unmedicated MDD patients in the thalamus, periaqueductal gray matter (PAG), insula, and striatum (Cannon et al., 2007). The [^{11}C]DASB binding was significantly correlated with the severity of depression and anxiety. In currently depressed patients with BD, we also found increased 5-HTT BP_{ND} in the thalamus, dorsal ACC, medial PFC, and insula as well as decreased 5-HTT BP_{ND} in the raphe (Cannon et al., 2006b). In currently remitted subjects with MDD, in contrast, Bhagwagar et al. (2007) failed to identify significant abnormalities in 5-HTT binding in regions including the amygdala, ACC, hippocampus, and thalamus. Although no difference in 5-HTT binding was detected by Meyer et al. (2004) in MDD patients versus healthy controls, scores on the Dysfunctional Attitude Scale were correlated positively with the 5-HTT binding in the PFC, ACC, putamen and thalamus.

Another group reported decreases in 5-HTT BP_{ND} and BP_P in MDD. Reimold et al. (2008) reported reduced thalamic BP_{ND} as well as a negative correlation between 5-HTT availability in the thalamus and amygdala, and depression and anxiety ratings. More recently they reported a decrease in BP_{ND} in a combined group of OCD and MDD subjects versus controls (but not MDD patients versus controls) in the thalamus. The decrease in BP_{ND} was associated with higher levels of cortisol after administration of DEX/CRF in the combined patient group (Reimold et al., 2011).

Dopamine 1 receptor

The literature search yielded three PET studies of the D1 receptor (Table 6). All three studies used a simplified reference tissue model to analyze the data, and reported decreases in D1 BP_{ND} in depressed samples. Using [^{11}C]SCH 23390, Suhara et al. (1992) found a decrease in BP_{ND} in the frontal cortex (but not the striatum) in BD patients who were only unmedicated for 2 or more days prior to the scan. However, [^{11}C]SCH 23390 displays relatively poor specificity which compromises the reliability of the D_1 receptor measurement in extrastriatal areas such as the frontal cortex where the density of these receptors is significantly lower than in the striatum. Dougherty et al. (2006) reported a 13% reduction in [^{11}C]SCH 23390 binding in the striatum of MDD patients with anger attacks. The authors interpret their data as indicative of a downregulation of D1 receptors in response to elevated dopamine concentrations associated with anger and aggression. Potentially consistent with this result, we found the mean D1 receptor binding, measured with [^{11}C]NNC-112, to be 14% lower in the left middle caudate of MDD subjects compared with healthy controls (Cannon et al., 2009). No significant difference was found in other striatal regions, the amygdala, insula, or ACC. However, because the density of the D1 and 5-HT_{2A} receptors are comparable in the insula and ACC, these results may be confounded by the fact that [^{11}C]NNC-112 is only 2–3 fold more selective for the D1 receptor than the 5-HT_{2A} receptor.

Dopamine 2 receptor

In two early studies which made use of the D2 receptor family radioligand, [^{11}C]NMSP, increased B_{max} was reported in the caudate of unmedicated BD patients with psychosis (Pearlson et al., 1995; Wong et al., 1997). More recent studies have used D2/D3 receptor radioligands such as [^{11}C]raclopride or [^{11}C]FLB-457. No differences in extrastriatal D2/3 binding were found using [^{11}C]FLB-457 in medicated patients with MDD (Montgomery et al., 2007; Saijo et al., 2010). However, Saijo et al. (2010) reported that D2/3 receptor binding decreased in the ACC of depressed patients after electroconvulsive therapy. No difference in [^{11}C]raclopride binding between manic patients with BD and healthy controls was found by Yatham et al. (2002). Similarly, Hirvonen et al. (2008b) found no significant differences in BP_{ND} between antidepressant-naïve MDD patients and controls, although they did report a non-significant 4% reduction in BP_{ND} in the ventral striatum in MDD. On the other hand, a group of unmedicated MDD patients with motor retardation displayed increased BP_{ND} in the caudate and striatum compared with healthy controls (Meyer et al., 2006b), although this finding was not confirmed by the results obtained in a smaller, medicated sample (Montgomery et al., 2007).

Dopamine transporter

Two studies examined dopamine transporter (DAT) function in the context of PET imaging (Table 5). Meyer et al. (2001b) found a 14% reduction in BP_{ND} in the striatum of unmedicated patients with MDD, and Anand et al. (2011) reported decreased BP_{ND} in the caudate, but not the putamen of BD patients relative to healthy controls.

Monoamine oxidase-A

Studies of MAO-A in depression are summarized in Table 6. MAO-A metabolizes serotonin, norepinephrine, and dopamine. In patients with MDD, Meyer et al. (2006a) reported an increase in V_S averaging 34% in widespread brain regions including the PFC, ACC, caudate, putamen, and hippocampus. Interestingly, this finding was replicated in an independent group of depressed MDD subjects who also showed greater MAO-A V_T compared with controls after SSRI treatment (Meyer et al., 2009). Moreover, remitted patients who later had a recurrence of major depression had higher MAO-A V_T in the PFC and ACC than those patients who did not relapse.

Muscarinic 2 receptor

Cannon et al. (2006a) found that M2 receptor binding was decreased in the ACC of patients with BD compared with patients with MDD and healthy controls. Although this is the only published study of the M2 receptor in BD, as we point out below, this is an important finding to pursue because of its relationship with variation in the M2 receptor gene (CHRM2).

Discussion

Serotonin 1A

While the weight of evidence is suggestive of decreased postsynaptic 5-HT_{1A} receptor binding in mood disorders, other researchers, notably the Columbia group have hypothesized that both presynaptic and postsynaptic 5-HT_{1A} receptor binding is in fact elevated in mood disorders and have replicated their finding in independent samples (reviewed in Shrestha et al., 2012). These authors argue that reports of decreased BP_{ND} are biased by use of the cerebellar gray matter as a reference region, and reported that when cerebellar white matter was used as the reference region, BP_{ND} was significantly higher in remitted MDD subjects relative to controls (Miller et al., 2009a). In contrast,

Table 5
Dopamine receptor imaging studies in mood disorders.

Study	Sample	Age	Medication/nicotine	Receptor	Radioligand	Method	Result
Suhara et al. (1992)	10 BD	30–63	Unmedicated 2 + days	D1	[11C]SCH 23,390	Reference tissue model (cerebellum)	↓ BP_{ND} in frontal cortex but not striatum
	21 HC	20–72	Not reported				
Dougherty et al. (2006)	10 MDD with anger attacks	43.1 ± 7.3	Unmedicated 3 + weeks	D1	[11C]SCH 23,390	Compartmental modeling (cerebellum)	↓ BP_{ND} in striatum
	10 HC	41.6 ± 6.4	Not reported				
Cannon et al. (2009)	18 MDD	31 ± 11	Unmedicated 3 + weeks	D1	[11C]NNC-112	Simplified reference tissue model (cerebellum)	↓ BP_{ND} in left middle caudate
	19 HC	31 ± 8.5	Smokers excluded				
Pearlson et al. (1995)	7 BD (psychotic)	40 ± 14	Unmedicated 6 + months	D2/4	[11C]NMSP	Blocked versus non-blocked calculation of receptor density (Bmax)	↑ B_{max} in caudate in psychotic BD
	7 BD (non-psychotic)	41 ± 13	Not stated				
	14 HC	28 ± 13					
Yatham et al. (2002)	13 BD (manic)	33 ± 12	Naïve	D2/3	[11C]Raclopride	Ratio method (cerebellum)	NS
	14 HC	31 ± 11	Not stated				
Meyer et al. (2006b)	21 MDD	35 ± 10	Unmedicated 26 + weeks	D2/3	[11C]Raclopride	Simplified reference tissue model (cerebellum)	↑ BP_{ND} in caudate and striatum
	21 HC	34 ± 11	Smokers excluded				
Montgomery et al. (2007)	7 MDD	44.1 ± 8.7	Medicated	D2/3	[11C]FLB-457	Distribution volume by compartmental model with plasma input function	NS
	7 HC	35.7 ± 10.9	Mixed smokers and non-smokers				
Montgomery et al. (2007)	8 MDD	42.6 ± 8.9	Medicated	D2/3	[11C]Raclopride	Simplified reference tissue model (cerebellum)	↓ BP_{ND} in medicated patients in dorsal but not ventral striatum
	8 HC	38.6 ± 10.3	2 smokers, 14 non-smokers				
Hirvonen et al. (2008b)	25 MDD	40.2 ± 9.0	Naïve	D2/3	[11C]Raclopride	Simplified reference tissue model (cerebellum)	NS
	19 HC	39.4 ± 10.5	5 MDD smokers				
Meyer et al. (2001b)	9 MDD	35 ± 8	Unmedicated 3 + months	DAT	[11C]RTI-32	Simplified reference tissue model (cerebellum)	↓ BP_{ND} in striatum
	23 HC	37 ± 10	Smokers excluded				
Anand et al. (2011)	11 BD	27.3 ± 9.7	Unmedicated 2 + weeks	DAT	[11C]CFT	Simplified reference tissue model (cerebellum)	↓ BP_{ND} in caudate but not ventral striatum
	13 HC	27.5 ± 7.3	Smokers included but smoking status not associated with BP_{ND}				

when cerebellar gray matter (which has extremely low concentrations of 5-HT_{1A} receptors) was used as a reference region, the BP_{ND} was significantly lower in the patient group, suggesting that group differences in cerebellar gray matter binding exist. Nevertheless, the region-of-interest defined in the cerebellar gray matter in this study was positioned too closely to the gray matter of the occipital and temporal cortices, and thus was confounded by the spilling in of radioactivity from the latter structures (Links et al., 1996; Mazziotta et al., 1981). Moreover, some of the studies that reported reductions in binding in depression indeed defined their reference ROI in the cerebellar white matter (e.g., Meltzer et al., 2004), and more recently reported studies that defined the cerebellar ROI in the white matter found reductions in both BP_{ND} and BP_F in depressed samples with MDD (Carlson et al., 2008) and BD (Nugent et al. in press).

Secondly, tracer kinetic modeling is based on the assumption that the ratio of k_1/k_2 is identical in the target and reference regions. However, this assumption is questionable when cerebellar white matter is used as a reference region because cerebral blood flow (k1) is significantly higher in gray matter than in white matter, and k2 is difficult to measure accurately.

Thirdly, the calculation of BP_{ND} assumes no between group differences in the free fraction of ligand in the nondisplaceable compartment, f_{ND}. Yet, Sullivan et al. (2009) report a significant between-group difference in f_P – the fraction of ligand that is bound to plasma proteins – thus implying a between group difference in f_{ND}. A difference in f_P has not been found in more recent studies of depressed subjects studied using either 5-HT_{1A} radioligands or radioligands for other receptors.

It has also been argued that BP_F is the "gold standard" measure of receptor binding and therefore results obtained using BP_{ND} as an outcome measure are inaccurate (Parsey et al., 2010; Shrestha et al., 2012). However, two independent groups have reported reductions in cortical, hippocampal, and raphe 5-HT_{1A} receptor binding using arterial sampling and full tracer kinetic modeling (Hirvonen et al., 2008a; Meltzer et al., 2004; Moses-Kolko et al., 2008). We further

Table 6
MAO-A imaging studies in mood disorders.

Study	Sample	Age	Medication Status	Radioligand	Method	Result
Meyer et al. (2006a)	17 MDD	34 ± 8	Unmedicated 5 + months	[11C]Harmine	Logan method with a plasma arterial input	↑ V_S in PFC, temporal cortex, ACC, PCC, thalamus, caudate, putamen, hippocampus, midbrain
	17 HC	34 ± 8				
Meyer et al. (2009)	16 MDD	32 ± 8	Unmedicated 7 + months	[11C]Harmine	Logan method with a plasma arterial input	↑ V_T in both MDD and rMDD patients in multiple brain regions.
	18 rMDD	31 ± 8				↑ V_T persisted after SSRI treatment
	28 HC	32 ± 8				
Bacher et al. (2011)	24 HC smokers withdrawn from nicotine	36 ± 7	Unmedicated	[11C]Harmine	Logan method with a plasma arterial input	Depressive symptoms associated with abstinence correlated positively with V_T in PFC and ACC

recently tested the hypothesis that 5-HT_{1A} activity will be elevated if BP_F or BP_P is calculated instead of BP_{ND}. We found reductions in BP_P in the ACC, anterior insula, and medial temporal cortex (but not the raphe) in depressed patients with BD (Carlson et al., 2008; Nugent et al. in press). Furthermore, we found no group difference in f_P.

Theoretically, the discrepancies in the direction of abnormalities of 5-HT_{1A} binding in depressed subjects versus controls in the Columbia series relative to those from other laboratories may reflect biological heterogeneity across the depressed samples, as opposed to technical differences in the measurement of receptor specific radiotracer binding. This possibility appears compatible with the discrepancies in the 5-HTT binding in MDD reported across these laboratories, despite their having applied similar methods for measuring 5-HTT BP_{ND}. For example, we recently found that BP_P was inversely correlated with trough plasma cortisol levels in the mesiotemporal cortex (Nugent et al. in press). However, not all patients with MDD display hypothalamic–pituitary–adrenal (HPA) axis abnormalities. The Drevets series participants suffered from familial, primary, recurrent mood disorders and as a group showed abnormally elevated stress plasma cortisol concentrations (Drevets et al., 1999, 2007), while other studies have included patients with depression secondary to other medical conditions. Moreover, glucocorticoids have been shown to exert opposing effects on central serotonergic transmission depending on their concentration. Levels of glucocorticoids at the lower end of the normal diurnal range (corresponding to the trough) stimulated serotonergic neurotransmission whereas glucocorticoid concentrations at the mid-point of the normal diurnal range suppressed serotonergic neurotransmission (Judge et al., 2004). Nevertheless, overwhelming evidence indicated that elevated concentrations of glucocorticoid hormones, particularly within the context of repeated stress, lead to a reduction in 5-HT_{1A} receptor expression (reviewed in Savitz et al., 2009).

The hypothesis that 5-HT_{1A} receptor function is reduced in mood disorders receives support from a recent PET study of previously healthy subjects exposed to a severe recent stressor. Compared with non-stressed subjects, stressed subjects displayed reduced BP_{ND} in the ACC, insula and hippocampus, with a trend toward significance in the amygdala, DLPFC, parietal cortex, temporal cortex, and raphe (Jovanovic et al., 2011). In addition, non-human primate studies provide support to the PET studies that have reported a reduction in 5-HT_{1A} BP_{ND}. Reduced 5-HT_{1A} receptor distribution volume/BP_P was found in the raphe nuclei, amygdala, hippocampus, and ACC in a PET study of subordinate cynomolgus monkeys who showed behavioral signs of depression after exposure to social defeat (Shively et al., 2006). In another study, parentally-deprived monkeys were found to have reduced hippocampal WAY-100635 binding, and mRNA expression relative to their normally-reared siblings (although 5-HT_{1A} receptor binding was actually increased in the dentate gyrus and CA3 field in males) (Law et al., 2008).

Reports of decreased 5-HT_{1A} receptor binding in mood disorders are also potentially consistent with a combined PET and fMRI study of 20 healthy individuals that examined the correlation between 5-HT_{1A} receptor binding measured using [^{11}C]WAY100635 and threat-related amygdala activity measured using an fMRI task (Fisher et al., 2006). A reduction in 5-HT_{1A} BP in the raphe was associated with increased BOLD amygdala response to threatening faces (Fisher et al., 2006), a replicated biomarker of MDD (Savitz and Drevets, 2009). Moreover, decreasing amygdala 5-HT_{1A} BP was associated with increasing amygdala reactivity to threatening faces (Fisher et al., 2006).

Genetic studies provide additional support to the hypothesis that post-synaptic 5-HT_{1A} receptor function is reduced in depression. The G allele of the rs6295 HTR1A polymorphism, which has been postulated to decrease expression of the postsynaptic 5-HT_{1A} receptor, (but increase the expression of the 5-HT_{1A} autoreceptor), was found to be over-represented in MDD and is associated with suicidality (Albert and Francois, 2010; Lemonde et al., 2003). In addition, the short, putative risk allele for depression of the serotonin transporter gene promoter polymorphism (5-HTTLPR) was associated with reduced 5-HT_{1A} receptor binding in 18 different regions of interest, including the raphe, hippocampus, amygdala, and PFC (David et al., 2005). In an epigenetic study, increased methylation of the promoter region of the 5-HT_{1A} receptor gene, indicative of decreased 5-HT_{1A} receptor expression, was found in the PFC region of subjects who had committed suicide (Albert et al., 2008).

As reviewed in Savitz et al. (2009), the postmortem MDD literature is largely indicative of reduced 5-HT_{1A} receptor mRNA, binding and/or numbers in the ventrolateral prefrontal cortex and the temporal polar cortex (Bowen et al., 1989), caudal aspects of the dorsal raphe (Arango et al., 2001; Boldrini et al., 2008), dorsolateral prefrontal cortex (DLPFC) and hippocampus (Lopez-Figueroa et al., 2004), BA10 of the prefrontal cortex (PFC) in females (Szewczyk et al., 2008), hippocampus (Lopez et al., 1998), and orbitofrontal cortex (OFC) (Anisman et al., 2008).

Nevertheless, other reports of increased 5-HT_{1A} receptor density and/or binding in mood disorders suggest that the direction of abnormality with respect to healthy controls may differ on the basis of co-morbid conditions, concurrent medications or anatomical region. Arango et al. (1995) reported that the binding of a 5-HT_{1A} receptor agonist was increased in MDD in the ventrolateral PFC. However, they later found that the elevation was attributable to depressed cases with co-morbid alcoholism. Non-alcoholic depressed cases showed no difference compared to controls in agonist binding (V. Arango, personal communication). Gray et al. (2006) reported increased [^{3}H]8-OH-DPAT binding in the cortex (BA 9, 10, 40 and 46) of a sample of BD I subjects, half of whom were treated with lithium before death. Notably a prospective study of the effect of mood stabilizer treatment in BD showed that lithium and divalproex treatment increased the post-synaptic 5-HT_{1A} receptor binding in several regions, reversing the baseline reduction in binding evident in the same subjects (Nugent et al. in press). Other groups have reported increased 5-HT_{1A} receptor density in the dorsal raphe but these findings appear specific to rostral, ventrolateral and dorsal subnuclei (Boldrini et al., 2008; Stockmeier et al., 1998). In contrast, Boldrini et al. (2008) reported *lower* 5-HT_{1A} receptor binding in the caudal sub-nucleus of the raphe.

Preclinical studies are also indicative of a decrease in postsynaptic 5-HT_{1A} receptor function although the functional status of the 5-HT_{1A} autoreceptor is more equivocal. Inactivation of 5-HT_{1A} postsynaptic receptors in the frontal cortex during development, but not in adulthood, produces analogs of anxiety in adult mice (Gross et al., 2002). Consistent with this study, mice genetically-engineered to overexpress the 5-HT_{1A} receptor in the cortex and hippocampus show an antidepressant-like effect when subjected to the forced-swim test, a rodent model of depression (Gunther et al., 2011). Similarly, mice engineered to under-express the post-synaptic 5-HT_{1A} receptor show increased depression-related behavior (Richardson-Jones et al., 2009). Using autoradiography and radioimmunoassays in a rodent model of epilepsy-associated depression, Pineda et al. (2011) reported an increase in corticosterone levels concomitant with an increase in 5-HT_{1A} autoreceptor activity and a reduction in hippocampal 5-HT_{1A} receptor function. Pharmacological activation of the hippocampal 5-HT_{1A} receptor ameliorated the depressive behavior.

The mechanism of action of antidepressant medications provides further evidence that depression is associated with decreased serotonergic signaling at the postsynaptic 5-HT_{1A} receptor. Tricyclic antidepressants putatively enhance the sensitivity of the post-synaptic 5-HT_{1A} receptor and thus tonic serotonergic transmission via their effect on the 5-HT_{1A} receptor-associated G proteins (Blier and Bouchard, 1994; Rossi et al., 2006). Moreover, the increased sensitivity of post-synaptic 5-HT_{1A} receptors also occurs in limbic structures following administration of electroconvulsive shock (ECS) (Ishihara and Sasa, 1999) and the selective norepinephrine reuptake inhibitor, reboxetine (Szabo and Blier, 2001). On the other hand, some data suggest that the 5-HT_{1A} autoreceptor may be upregulated

or sensitized in depression. For example, SSRIs are hypothesized to enhance serotonergic neurotransmission by desensitizing 5-HT_{1A} autoreceptors in the raphe thereby increasing postsynaptic 5-HT_{1A} receptor signaling (Blier et al., 1987, 1998).

Interim summary

The 5-HT_{1A} literature is in disagreement over whether serotonergic signaling at 5-HT_{1A} receptors is increased or decreased in mood disorders. Based on the imaging, postmortem, genetic, and preclinical literature discussed above the predominant weight of evidence favors the hypothesis that postsynaptic 5-HT_{1A} receptor binding or density in the mesiotemporal cortex is reduced in depression — although this finding may be specific to individuals who show elevations in circulating cortisol levels. We also hypothesize that the discrepancy in the direction of 5-HT_{1A} autoreceptor binding may be related to functional differences in subregions of raphe that cannot be detected with the current resolution of PET. As mentioned above, postmortem studies have suggested that 5-HT_{1A} receptor binding is increased in the rostral, ventrolateral and dorsal subnuclei of the raphe but decreased in the caudal subnucleus of the raphe (Boldrini et al., 2008; Stockmeier et al., 1998).

A simplified model of 5-HT_{1A} receptor dysfunction in mood disorders

The 5-HT_{1A} receptor is concentrated in the raphe in the form of an autoreceptor that exerts inhibitory effects on serotonin synthesis and release, as well as in the corticolimbic region in the form of either receptors that inhibit pyramidal cell firing activity or heteroreceptors. Theoretically, chronic stress-related serotonin release may downregulate or desensitize postsynaptic 5-HT_{1A} receptors, explaining the reduction in 5-HT_{1A} receptor numbers or binding often reported at postmortem and in PET imaging studies. The reduction in 5-HT_{1A} receptor function may result in part from stress-induced secretion of corticosteroids which in animal models downregulate the genetic expression of postsynaptic 5-HT_{1A} receptors (reviewed in Savitz et al., 2009). Antidepressant medications putatively enhance serotonergic signaling at the postsynaptic receptor either by desensitizing the somatodendritic autoreceptor or by facilitating the activation of G proteins associated with the postsynaptic 5-HT_{1A} receptor.

Serotonin 2A

A review of Table 3 raises the possibility that reports of decreased 5-HT_{2A} receptor binding in mood disorders may have been confounded by the effects of antidepressant treatment which has been shown to downregulate the 5-HT_{2A} receptor (Meyer et al., 2001a). In three studies reporting decreased 5-HT_{2A} receptor binding, patients were unmedicated for 1–4 weeks prior to imaging while Bhagwagar et al. (2006) reported increased cortical BP_P in patients who were unmedicated for at least 6 months prior to imaging. Other confounding factors may be comorbid alcohol abuse and obesity, which are more prevalent in mood disorders than in the general population. A family history of alcohol abuse has been associated with reduced 5-HT_{2A} receptor binding in the PFC at postmortem (Underwood et al., 2008) while cortical 5-HT_{2A} receptor binding was positively associated with body mass index (BMI) in an [^{18}F]altanserin PET study (Erritzoe et al., 2009).

Given the lack of clarity in PET studies of the 5-HT_{2A} receptor in mood disorders, it may also be instructive to examine mood disorder-related subphenotypes. At least four studies have examined the association between mood disorder-associated personality traits and 5-HT_{2A} receptor binding potential in healthy individuals. "Neuroticism", a personality trait associated with increased risk for depression, also was associated with increased BP_P in the entorhinal cortex, superior and inferior frontal cortices, and posterior cingulate cortex (Frokjaer et al., 2008), and in a follow-up study, individuals with a family-history of MDD or BD showed a positive association between "neuroticism" and 5-HT_{2A} receptor binding in the OFC, ACC, entorhinal cortex, and hippocampus (Frokjaer et al., 2010). Similarly, hippocampal BP_P measured with [^{18}F]altanserin was found to be positively correlated with the personality trait, "negativism" in females (Soloff et al., 2010). In contrast, an inverse relationship between [^{18}F]FESP binding and "harm avoidance" was found in regions such as the inferior frontal gyrus, middle and inferior temporal gyrus, ACC, and hypothalamus (Moresco et al., 2002).

In contrast to the results of most PET studies, the postmortem literature is generally indicative of increased 5-HT_{2A} receptor density in mood disorders although many negative findings have been published (reviewed in Stockmeier, 2003). Increased 5-HT_{2A} receptor levels have been reported in BA8/9 (Stanley and Mann, 1983; Turecki et al., 1999), BA9 (Arango et al., 1990), BA9 and amygdala (Hrdina et al., 1993), BA9/10/11 (Arranz et al., 1994), BA8/9 and hippocampus (Pandey et al., 2002), frontopolar cortex and amygdala (Anisman et al., 2008) and BA10 (Shelton et al., 2009).

Potentially consistent with the reports of increased 5-HT_{2A} receptor function in mood disorders at postmortem, preclinical studies demonstrate that antidepressant medication reduces the density of 5-HT_{2A} receptors in rodents (Carr and Lucki, 2011). Similarly, activation of 5-HT_{2A} receptor in the limbic forebrain increases anxious behavior while blocking the 5-HT_{2A} receptor reduces anxiety, perhaps explaining why the HTR2A knock-out produces a low-anxiety behavioral phenotype in mice (Weisstaub et al., 2006).

Interim summary

Although there are five extant reports of decreased 5-HT_{2A} receptor binding in mood disordered samples assessed using PET imaging, the personality, postmortem, and preclinical literature suggest that the 5-HT_{2A} receptor may be upregulated in certain populations of patients with mood disorders.

A simplified model of 5-HT_{2A} receptor dysfunction in mood disorders

The 5-HT_{2A} receptor is predominantly located on cortical glutamatergic pyramidal neurons and γ-aminobutyric acid (GABA) interneurons (Santana et al., 2004). At least in rodents, chronic corticosterone administration increases cortical 5-HT_{2A} receptor expression and induces the development of behavioral analogs of depression (Fernandes et al., 1997; Kuroda et al., 1992). Similarly, in mice over-expressing the glucocorticoid receptor (GR), 5-HT_{2A} receptor levels and 5-HT_{2A} receptor binding was increased in the hippocampus (Trajkovska et al., 2009). More recently, Magalhaes et al. (2010) reported that administration of CRF into the prefrontal cortex of mice induced behavioral analogs of anxiety in conjunction with increased cell surface expression and signaling at the 5-HT_2 receptor. The 5-HT_{2A} receptor is also found in the paraventricular nucleus of the hypothalamus, where it exerts an excitatory effect, facilitating the secretion of cortisol releasing factor (CRF) during stress (Zhang et al., 2002). While short-term glucocorticoid activity also increases 5-HT_{2A} receptor expression in the hypothalamus, prolonged elevations in circulating glucocorticoids may desensitize the 5-HT_{2A} receptor, preventing further activation of the HPA axis (Lee et al., 2009).

Conceivably, elevations in circulating levels of cortisol may explain the increased 5-HT_{2A} receptor BP observed in some PET studies. The fact that not all depressed patients show glucocorticoid resistance may partly explain the divergent findings in the literature. Theoretically, antidepressant medications that increase serotonergic signaling at the 5-HT_{1A} receptor or antagonize the 5-HT_{2A} receptor may overcome the serotonin signaling abnormality and downregulate or desensitize corticolimbic 5-HT_{2A} receptors. Potentially consistent with this hypothesis, chronic administration of selective serotonin reuptake inhibitors (SSRI) has been shown to decrease 5-HT_{2A} receptor

binding in rodents that were exposed to stress (Gunther et al., 2008; Syvalahti et al., 2006; Yamauchi et al., 2006).

Serotonin 1B

Supporting evidence for the reduction in 5-HT_{1B} function in MDD emanates from both preclinical and postmortem data. Svenningsson et al. (2006) focused on p11, a protein which potentiates 5-HT_{1B} function by impacting the intracellular trafficking and cell surface expression of 5-HT_{1B}. The authors found that antidepressant medication increased the level of p11 in the forebrain while mice that overexpressed p11 showed similar behavioral characteristics to the antidepressant-treated mice. Consistent with these data, p11 knockout mice showed behavioral analogs of depression including a decreased responsiveness to sucrose. Moreover, Svenningsson et al. (2006) reported both reduced mRNA and protein expression of p11 in the ACC of people who had suffered from MDD. Consistent with these data, Anisman et al. (2008) reported a reduction in 5-HT_{1B} mRNA expression in the frontopolar cortex, OFC and hippocampus of patients who had committed suicide. P11 expression was also decreased in the amygdala, hippocampus, OFC, and frontopolar cortex (Anisman et al., 2008).

Serotonin transporter

Evidence for 5-HTT binding in mood disorders has been mixed with both increases, decreases and negative findings reported (reviewed in Savitz and Drevets, 2009). In addition to the type of radioligand, a number of potential confounds may contribute the discrepancy in results across studies. For instance, Praschak-Rieder et al. (2008) observed that 5-HTT BP correlated negatively with daily hours of sunshine with higher BP in the fall and winter months compared with spring and summer. BMI is another potential confound as the 5-HTT BP_{ND} is negatively correlated with BMI in the caudate, putamen and thalamus (Erritzoe et al., 2010).

PET imaging studies of depression-related phenotypes generally support the hypothesis that 5-HTT binding is increased in patients with mood disorders. Neuroticism was found to be associated with higher thalamic BP in humans (Takano et al., 2007) while 5-HTT availability in the amygdala was positively associated with anxious temperament in rhesus monkeys (Oler et al., 2009). In addition, Boileau et al. (2008) detected increased 5-HTT BP_{ND} in the dorsolateral PFC in clinically depressed patients with Parkinson's disease (PD), and another study similarly reported increased 5-HTT BP_P in several regions, including the amygdala, hypothalamus, raphe, and posterior cingulate cortex in depressed versus non-depressed PD patients (Politis et al., 2010). HIV positive patients with depression also showed increased BP_{ND} in regions such as the midbrain, thalamus, putamen, caudate, and ACC compared with HIV positive patients without depression (Hammoud et al., 2010). Participants in these PD and HIV studies were unmedicated and in some cases antidepressant medication-naive.

Rats that display various behavioral analogs of depression show increased hippocampal serotonin levels (Keck et al., 2005) as well as elevated 5-HTT density and serotonin concentrations (Grecksch et al., 1997). Since CRF has been shown to increase serotonin release in rodents, one possible explanation for the increase in 5-HTT binding is a stress-induced compensatory upregulation of 5-HTT expression in response to the elevation in serotonergic transmission. Alternatively, an increase in 5-HTT binding may result from increased 5-HTT trafficking from the cytosol to the membrane (Blakely et al., 1998). Radiotracers tend to show greater affinity for receptors situated on the cell membrane compared with the cytosol (Laruelle et al., 1988) — although this divergence in affinity has not been characterized for DASB.

The postulated increase in 5-HTT activity receives additional support from the psychoneuroimmunology literature. Zhu et al. (2010) showed that intraperitoneal injection of lipopolysaccharide (LPS) induced behavioral despair by enhancing brain 5-HTT activity through IL-1R and p38 MAPK pathways. A previous in vitro study showed that IL1-B administration increases the affinity of the 5-HTT for serotonin (Zhu et al., 2006).

On the other hand, there is contradictory evidence suggesting that 5-HTT function is reduced in mood disorders. Frokjaer et al. (2009) found that healthy individuals who were at high risk of developing MDD by virtue of having a co-twin with the disorder, displayed reduced 5-HTT BP_{ND} in the DLPFC and the ACC compared with low-risk individuals. Nevertheless, in the absence of a longitudinal study, one cannot be sure which "high-risk" individuals are truly vulnerable to developing depression, and which individuals are resilient.

Consistent with the PET imaging studies that have reported a mood disorder-associated reduction in 5-HTT BP, a review of the postmortem literature concluded that studies using selective 5-HTT ligands report either reductions or no changes in 5-HTT levels in the cerebral cortex (Stockmeier, 2003). More recent studies support this conclusion. While no change in 5-HTT mRNA expression was reported in the dorsal raphe (Anisman et al., 2008), a decrease in the density of serotonin-synthesizing neurons, often together with a reduction in 5-HTT binding, was found in the dorsal and ventral PFCs (Underwood et al., 2011), and the dorsal raphe (Arango et al., 2001; Baumann et al., 2002).

Lower 5-HTT BP might reflect a downregulation of 5-HTT in response to lower intrasynaptic levels of serotonin, a loss of raphe serotonergic projections to corticolimbic regions, or a decrease in SLC6A4 gene expression (Frokjaer et al., 2009). The reduction in the cerebrospinal fluid (CSF) concentration of the serotonin metabolite, 5-hydroxyindoleacetic acid (5-HIAA), that is found in mood disorder patients with a history of suicidal behavior (Asberg, 1997; Mann and Currier, 2007) could be interpreted as being consistent with a decrease in serotonergic transmission. However, not all studies of mood disorder patients find reductions in 5-HIAA — see for example Barton et al. (2008). The effect appears to be more strongly related to impulsivity and violence than depression, per se. In addition, a reduction in serotonin turnover could also be interpreted as reflecting greater 5-HTT-mediated reuptake and vesicular packaging of intrasynaptic serotonin which decreases the breakdown of serotonin by monoamine oxidase A. Consistent with this possibility, Heinz et al. (1998) found that reduced concentrations of 5-HIAA were associated with increased brainstem 5-HTT BP.

At first glance, the fact that the short, low-activity allele of the promoter polymorphism of the 5-HTT gene (5-HTTLPR) putatively predisposes to depression in the context of stress (Caspi et al., 2003; Karg et al., 2011), appears to be congruent with reports of reduced 5-HTT BP in mood disorders.

Nevertheless, the in vivo effect of the 5-HTTLPR variant on 5-HTT expression is somewhat controversial. While three studies reported that subjects homozygous for the long allele displayed increased 5-HTT binding in the putamen (Praschak-Rieder et al., 2007), midbrain (Reimold et al., 2007), and caudate (Kalbitzer et al., 2010), in contrast, (Parsey et al., 2006a) and (Murthy et al., 2010) found no effect of the 5-HTTLPR variant on [^{11}C]McN5652 and [^{11}C]DASB binding, respectively. Similarly, [^{11}C]DASB binding was not significantly affected by 5-HTTLPR genotype in rhesus monkeys (Christian et al., 2009). In their review of the literature, Willeit and Praschak-Rieder (2010) conclude that 5-HTTLPR does have an effect on in vivo 5-HTT binding when subjects are genotyped for the so-called triallelic polymorphism,[1] however, the effect is weakened by factors such as ligand quality, psychiatric diagnosis and seasonality.

Even if the short, "risk" allele is associated with reduced 5-HTT binding, this effect is not necessarily incompatible with increased 5-HTT function in depression. Firstly, although the short allele of the 5-HTTLPR polymorphism appears to predispose to depression in the

[1] A SNP in the long 5-HTTLPR variant results in two additional alleles, LA and LG. LG is functionally similar to the short 5-HTTLPR allele.

context of psychological stress, the short allele may actually be protective in the absence of psychosocial adversity (Homberg and Lesch, 2011; Van den Hove et al., 2011). Secondly, the impact of the 5-HTTLPR polymorphism on 5-HTT function may be more significant prenatally or during childhood (Sibille and Lewis, 2006) where conceivably an abnormal increase in serotonergic signaling can exert detrimental effects on cell migration, neurogenesis and apoptosis.

Interim summary

The PET 5-HTT data in mood disorders are mixed. Nevertheless, based on imaging studies of depression-related phenotypes, the preclinical, and the neuroimmunology literatures, we hypothesize that 5-HTT function is increased in depression.

A simplified hypothesis of serotonin transporter dysfunction in mood disorders

Increased serotonergic transmission in response to depression-related elevations in CRF and/or inflammation conceivably results in an increase in 5-HTT function leading to chronic overactivity of the 5-HTT and decreased serotonergic neurotransmission. Future research in preclinical models of depression may elucidate whether elevated 5-HTT activity is an acute response to the increase in serotonergic neurotransmission associated with a stressor or whether exposure to a stressor can result in a chronic upregulation of the 5-HTT.

The D1 receptor

PET assessments of D1 receptor binding have emphasized the striatum due to the relatively low specific-to-nonspecific binding in extra-striatal tissues. The extant PET data are suggestive of a decrease in D1 receptor availability in the striatum. Postmortem studies, in contrast, have focused on extrastriatal regions. The percentage of D1-expressing neurons together with D1 mRNA expression was reported to be increased by 25% in the CA3 region of the hippocampus (Pantazopoulos et al., 2004) in BD subjects versus controls, but to not differ from controls in the amygdala of MDD subjects (Xiang et al., 2008).

The hypothesis that the D1 receptor function is decreased in the striatum of depressed patients receives some support from a rat model of anhedonia. Anhedonic rats show a decreased dopaminergic response in the nucleus accumbens (NAc) to palatable food concurrent with decreased sensitivity of the D1 receptor (Scheggi et al., 2011). Further, in rhesus monkeys, electroconvulsive therapy (ECT) resulted in increased dopaminergic neurotransmission in the striatum together with transient increases in D1 receptor binding (Landau et al., 2011).

The D2/3 receptor

The preclinical literature suggested the hypothesis that D2/3 receptor binding would be increased in depression. Rats exposed to chronic social stress show increased D2, but not D1, receptor binding in the striatum (Lucas et al., 2004), and both maternal deprivation and chronic mild stress lead to an increase in D2 mRNA expression in the striatum (Zhu et al., 2011). Moreover, dopamine receptor agonists exert antidepressant effects in rodent models of depression via activation of the D2/3 receptor (Basso et al., 2005).

Two postmortem receptor binding studies have found no difference in basal ganglia D2 receptor binding between suicide victims and controls (Allard and Norlen, 2001; Bowden et al., 1997). On the other hand, Klimek et al. (2002) initially reported increased D2 receptor binding in the amygdalae of depressed patients, but were subsequently unable to replicate this finding (Xiang et al., 2008).

Imaging studies of mood disorder-related phenotypes provide mixed evidence for increased D2/3 receptor function in MDD. Enhanced BOLD response of the amygdala to unpleasant pictures, a potential biomarker of depression, was found to correlate negatively with [^{18}F]fallypride BP_{ND} in the striatum but positively with [^{18}F]fallypride BP_{ND} in the amygdala, insula, and ACC (Kobiella et al., 2010). Kestler et al. (2000) reported a positive correlation between [11C]raclopride binding in the striatum and Depression score on the NEO PI-R personality inventory. In contrast, a more recent high-resolution PET study found an inverse relationship between the depression-related personality trait, "harm avoidance", and D2/3 distribution volume in the dorsal caudate and putamen in healthy individuals (Kim et al., 2011). Notably, the inverse correlation between harm avoidance and D2/3 receptor availability was found in the dorsal association and sensorimotor regions of the striatum where D2 receptor signaling has been associated with psychomotor activity, rather than the ventral striatum where D2 receptor signaling has been more closely related to reward and motivation.

One potential confound which is not always addressed in the literature is smoking status. Nicotine can influence D2/3 receptor binding in the ventral striatum. For example, in the Kobiella et al.'s (2010) study cited above, smokers showed an attenuated amygdala BOLD response to unpleasant stimuli compared with non-smokers. In the Kim et al.'s (2011) study, which showed a negative correlation between harm avoidance and D2/3 distribution volume in the dorsal caudate and putamen, 20% of the subjects were smokers. Meyer et al. (2006b), who reported increased D2/3 BP_{ND} in the caudate and striatum in depression excluded smokers from their study. However, other groups reporting reduced D2/3 receptor binding or non-significant results have generally included smokers in their studies or have not provided details regarding smoking status (Table 5).

Interim summary

The functional status of the D2/3 receptor in depression is unclear. Discrepant findings in the literature may partly relate to incomplete control of nicotine use and to the sensitivity of some PET radioligands to endogenous dopamine concentrations (i.e., [^{11}C]raclopride and [^{18}F]fallypride). Conceivably the use of such D2/3 receptor ligands in paradigms that assess dopamine release in response to unpredictable reward may provide more reproducible results across studies.

The dopamine transporter

The only two PET studies that have examined DAT function in mood disorders are indicative of a decrease in BP_{ND} in the striatum. Consistent with these data, rhesus monkeys subjected to ECT showed increases in DAT and vesicular monoamine transporter binding post-ECT that returned to normal within 6 weeks (Landau et al., 2011). Striatal DAT levels have not to our knowledge been examined in postmortem patients but reduced concentrations of DAT were found in the central and basal nuclei of the amygdala in postmortem MDD cases (Klimek et al., 2002).

A simplified model of dopamine receptor and DAT dysfunction in mood disorders

Dopamine receptor function varies across different brain regions. Although the D1 receptor is preferentially localized to GABAergic neurons in the PFC (Smiley and Goldman-Rakic, 1993), here we limit our discussion to the striatum since most PET studies have focused exclusively on this brain region. The PET literature has also been limited to BP measurement under resting state conditions and we note that the heuristic model of dopamine receptor function outlined below may differ with respect to dopamine release in response to unpredicted reward or other types of reward learning paradigms.

Preclinical models in rodents have emphasized the shell region of the NAc, part of the ventral striatum, as playing an important role in

regulating goal-directed behavior in the context of a reward. In primates, however, the cells that manifest the histochemical and connectional features of the NAc shell region are distributed throughout the anteroventral striatum (accumbens area, ventromedial caudate, anteroventral putamen; reviewed in Drevets et al., 1999). The ventral striatum receives excitatory glutamatergic projections from the PFC, the amygdala, and the subiculum, as well as modulatory dopaminergic projections from the ventral tegmental area (VTA) (Sesack and Grace, 2010). Both the excitatory afferents and the modulatory dopaminergic afferents synapse onto the spines of GABAergic medium spiny neurons which express both D1 and D2 receptors (Surmeier et al., 2007). D2 receptor signaling inhibits NAc activity, while D1 receptor signaling enhances NAc function (Sesack and Grace, 2010). Dopamine neurons switch to phasic burst firing when exposed to stimuli that signal a reward. Because D1 receptors are in a low-affinity state compared with D2 receptors, they are primarily activated by phasic reward-related dopamine-release (Schultz, 2010). In contrast, low levels of dopamine primarily activate high-affinity D2 receptors (Schultz, 2010). It could therefore be speculated that the decrease in D1 receptor BP is associated with the deficit in motivated behavior characteristic of some types of depression. The putative decrease in DAT BP, may reflect the impact of inflammation (see below) and/or a compensatory response to decreased dopaminergic signaling in the ventral striatum. In support of this hypothesis, DAT decreases in density after chronic dopamine depletion (Gordon et al., 1996). In other words, at least some types of depression may be associated with low basal levels of intrasynaptic dopamine. Conceivably these individuals may be predisposed to a greater reward-associated dopamine release, and consequently a heightened vulnerability to addiction.

Nevertheless, we note that the biological role played by dopamine receptors in reward and anhedonia is likely to be complex. For example, one complicating factor is that D1 and D2 receptors can form a heteromer in the ventral striatum, which allows dopamine to enhance the expression of BDNF together with the maturation, differentiation and growth of neurons (Hasbi et al., 2009). Somewhat counterintuitively, the D1–D2 heteromer was found to be upregulated in the striatum of MDD subjects compared with control subjects studied postmortem. Notably, disruption of the complex exerted antidepressant effects in rats undergoing the forced-swim test (Pei et al., 2010). The effect of the D1–D2 receptor complex on measurements of BP in the context of PET imaging is currently unknown.

Monoamine oxidase-A

The evidence for increased MAO-A density in depression receives indirect support from a PET study of healthy smokers who were acutely withdrawn from nicotine. Withdrawal from nicotine was associated with an increase in V_T in the PFC and ACC, and the depressive symptoms associated with smoking abstinence were positively correlated with V_T (Bacher et al., 2011). The same group also recently reported that the early post-partum period is associated with an increase (≈40%) in MAO-A V_T in the PFC, ACC, temporal cortex, thalamus, putamen, hippocampus, and midbrain, perhaps contributing to the pathogenesis of post-partum depression (Sacher et al., 2010). In a somewhat contradictory result, a personality trait derived from the NEO neuroticism scale (which the authors have labeled as anger–hostility) was negatively correlated with MAO-A V_T in the PFC in healthy individuals (Soliman et al., 2011).

In an early quantitative autoradiography study of postmortem samples with MDD, Ordway et al. (1999) failed to detect a significant difference in MAO-A binding in the locus coeruleus and raphe between MDD subjects and healthy controls. A recent postmortem study showed that R1, a transcriptional repressor of MAO-A was decreased by 30–38% in the PFC of medicated and unmedicated individuals with MDD (Johnson et al., 2011). Further, MAO-A activity was increased by 40% in the unmedicated MDD sample (Johnson et al., 2011). This result is consistent with a previous report of reduced R1 in the OFC of violent suicide victims (Thalmeier et al., 2008).

A simplified hypothesis of MAO-A dysfunction in mood disorders

Meyer et al. (2006a) hypothesize that the elevated density of MAO-A in depression is the primary driver of the reduction in monoaminergic signaling. The functional status of the individual monoamine transporters (i.e. 5-HTT, DAT, and NET) then exerts a secondary influence on specific extracellular monoamine levels, and together with MAO-A, determine the severity and symptom profiles of the depressive episode. The same group later reported an elevation in MAO-A in remitted depressed patients as well as an elevation in MAO-A in depressed MDD patients treated with SSRI medication, suggesting that increased MAO-A density is a trait marker of MDD (Meyer et al., 2009).

The muscarinic 2 receptor

[^{18}F]FP-TZTP is an agonist and binds to M2 autoreceptors in the high-affinity state. This property of [18F]FP-TZTP makes its binding sensitive to endogenous acetylcholine which may desensitize the M2 receptor or compete with [^{18}F]FP-TZTP for the M2 receptor (Cannon et al., 2006a). Thus the finding of decreased M2 receptor binding in BD is supported by observations that administration of the acetylcholinesterase inhibitor, physostigmine, can worsen depressive symptoms (Cannon et al., 2006a). Furthermore, the antimuscarinic drug, scopolamine, was shown to exert antidepressant effects in currently depressed patients with MDD or BD (Furey and Drevets, 2006) (Drevets and Furey, 2010).

The finding that M2 receptor binding is decreased in patients with BD also receives support from a genetic study which demonstrated a disjunction in the effects of a SNP (rs324650) in the M2 gene (CHRM2) on [^{18}F]FP-TZTP binding in patients with BD versus healthy controls (Cannon et al., 2011). In the healthy control group, the thymine (T) allele was associated with greater M2 receptor binding whereas in the BD group, the T allele was associated with a reduction in M2 receptor binding.

A heuristic model of extant neuroreceptor imaging data

Preclinical data show that IL1β administration increases the affinity of the 5-HTT for serotonin (Zhu et al., 2006). The same group also showed that intraperitoneal injection of lipopolysaccharide (LPS) induced behavioral despair by enhancing brain 5-HTT activity through IL-1R and p38 MAPK pathways (Zhu et al., 2010). Consistent with these data, the selective serotonin reuptake inhibitors (SSRIs), paroxetine and sertraline, inhibited the generation of nitric oxide (NO) and tumor necrosis factor (TNF) from activated microglial cells (Horikawa et al., 2010).

Cytokines such as IFNα also decrease concentrations of CNS dopamine (Capuron and Miller, 2011). Reports are conflicting as to whether this decrease in dopamine is correlated with an upregulation of DAT as reported by Moron et al. (2003) or a downregulation of DAT as reported by Lai et al. (2009). LPS-induced cytokine production by macrophages is enhanced in DAT-knockout mice (Kavelaars et al., 2005). Further, Wang et al. (2009) showed that a single injection of LPS in pregnant rats on gestation day 10 when dopamine and serotonin neurons first emerge, causes significant loss of neurons in the substantia nigra and dorsal raphe, respectively. In a follow-up study, the offspring of the LPS-exposed rats showed increased anxiety-like behavior along with a significant decrease in dopamine in the NAc and decrease in serotonin in the medial PFC and ventral hippocampus (Lin et al., 2012). The putative inflammation-associated reduction in dopamine concentration may also be a result of an inflammation-induced breakdown of tetrahydrobiopterin (BH4), an enzyme co-factor for tyrosine hydroxylase, which

converts tyrosine to L-DOPA and is the rate limiting enzyme in DA synthesis (Capuron and Miller, 2011).

Consistent with the data suggesting an inflammation-related increase in 5-HTT activity and a decrease in tyrosine hydroxylase function, LPS-induced tumor necrosis factor alpha (TNF) expression was almost completely inhibited by the MAO-A/B inhibitor, phenelzine, in rodents (Ekuni et al., 2009) while the MAO-A inhibitor moclobemide was demonstrated to inhibit the production of TNF and IL8 in healthy volunteers as well as to enhance the LPS-stimulated production of the anti-inflammatory cytokine IL10 (Lin et al., 2000). Conceivably therefore, inflammation may partly account for the changes in 5-HTT, DAT, and MAO-A function reported in PET studies of depression.[2]

The relationship between inflammation and glucocorticoid signaling is complex (Miller et al., 1999) and beyond the scope of this review. Nevertheless, inflammation may impact neuroreceptor function via its effects on the endocrine system. Regardless of the nature of the relationship between inflammation and endocrine dysregulation, stress, which is associated with mood disorders, is known to impact glucocorticoid signaling.

As reviewed above, stress-induced secretion of corticosteroids may lead to the downregulation of 5-HT_{1A} postsynaptic receptor expression and possibly also to 5-HT_{1A} autoreceptor function in the raphe. In contrast, 5-HT_{2A} receptors may be upregulated by glucocorticoid hypersecretion, facilitating the secretion of cortisol releasing factor (CRF) during stress and contributing to the chronic elevation of circulating cortisol levels. Consistent with reports of increased MAO-A binding in depression, elderly rats administered dexamethasone were reported to show a 300% increase in MAO-A density in the brain (Slotkin et al., 1998). Similarly, increased serotonergic neurotransmission in response to stress and/or depression-related inflammation may result in a chronic increase in 5-HTT function, contributing to decreased serotonergic signaling at the postsynaptic 5-HT_{1A} receptor. Conceivably, the anhedonia and motivational deficits characteristic of depression may result from decreased dopaminergic signaling in the ventral striatum concurrent with reduced tyrosine hydroxylase, DAT and/or D1 receptor function.

Conclusion and future directions

PET neuroreceptor imaging has revolutionized our understanding of psychiatric illness by allowing for the in vivo study of specific proteins in the brain. The current focus on serotonin and dopamine receptor and transporter proteins is likely to expand in the future as new radioligands are developed. Multi-modal imaging studies that combine fMRI and PET data may offer new insights into the pathophysiology of mood disorders. This approach has been implemented successfully in healthy individuals (Fisher et al., 2006, 2009; Kienast et al., 2008; Rhodes et al., 2007; Takahashi et al., 2010).

The results obtained for a particular receptor also may be affected by the activity of an interacting receptor. For example, Fisher et al. (2011) reported that PFC 5-HT_{1A} binding moderates the effect of 5-HT_{2A} binding on the hemodynamic response of the amygdala to threatening faces. Thus future studies should attempt to obtain data from multiple receptors in the same cohort of volunteers. Studies that integrate receptor function with endocrine or immune data may also produce important new leads. Finally, the need exists for longitudinal PET studies which would allow changes in neuroreceptor function to be coupled to clinical state. Identification of the genetic correlates of receptor function in the context of PET imaging is also important but acquiring the necessary statistical power is a challenge given the expense and invasiveness of PET.

[2] We note parenthetically that BMI, which has been shown to impact 5-HT_{2A} receptor binding and 5-HTT binding, correlates positively with inflammation.

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Conflict of interest

Wayne Drevets, M.D. has consulted for Johnson & Johnson, Pfizer, Myriad/RBM and Eisai. Jonathan Savitz, Ph.D. has no financial disclosure to make.

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