Neurobiology of Chronic Stress-Related Psychiatric Disorders: Evidence from Molecular Imaging Studies

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Abstract

Chronic stress accounts for billions of dollars of economic loss annually in the United States alone, and is recognized as a major source of disability and mortality worldwide. Robust evidence suggests that chronic stress plays a significant role in the onset of severe and impairing psychiatric conditions, including major depressive disorder, bipolar disorder, and posttraumatic stress disorder. Application of molecular imaging techniques such as positron emission tomography and single photon emission computed tomography in recent years has begun to provide insight into the molecular mechanisms by which chronic stress confers risk for these disorders. The present paper provides a comprehensive review and synthesis of all positron emission tomography and single photon emission computed tomography imaging publications focused on the examination of molecular targets in individuals with major depressive disorder, posttraumatic stress disorder, or bipolar disorder to date. Critical discussion of discrepant findings and broad strengths and weaknesses of the current body of literature is provided. Recommended future directions for the field of molecular imaging to further elucidate the neurobiological substrates of chronic stress-related disorders are also discussed. This article is part of the inaugural issue for the journal focused on various aspects of chronic stress.

Introduction

The experience of chronic psychological stress is associated with a variety of serious physical, financial, and emotional consequences at both individual and societal levels.[1] The World Health Organization has labeled stress as a "worldwide epidemic" in recognition of the magnitude of its deleterious effects.[2] The American Institute of Stress estimates that the effects of chronic stress cost US companies over 300 billion dollars annually.[3] More gravely, stress and resultant changes in affect are associated with increased morbidity and mortality,[4] including increased rates of mental illness and suicide.[5] Robust evidence has linked the experience of chronic stress to onset of major depressive disorder (MDD), which is the leading cause of disability worldwide.[1,6,7] Likewise, onset of bipolar (BD) and posttraumatic stress (PTSD) disorders, both of which are associated with substantial emotional, physical, and financial burden,[8,9] has been linked to chronic stress. Unfortunately, the molecular mechanisms by which chronic stress confers risk for mental health problems are poorly understood, hindering the development of critical interventions to resolve and prevent chronic stress-related disorders.

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Application of Positron Emission Tomography and Single Photon Emission

Computed tomography (SPECT) has begun to provide information concerning how the brain changes following chronic stress on a molecular level. Positron emission tomography (PET) and SPECT molecular imaging techniques allow for the quantification of biochemical processes, including those known to play a pivotal role in the pathophysiology of psychiatric disorders in the living human brain.[10] Both techniques rely on the injection of a "radiotracer," a physiologically active compound with affinity for a specific target, which has been tagged with a small amount of radioactive isotope. This review is part of the journal's inaugural issue, which is designed to comprehensively describe the neurobiological and neuroclinical effects of chronic stress. The role of this review is to summarize the existing molecular imaging work in psychiatric conditions known to be associated with chronic stress—MDD, BD, and PTSD—and recommend directions for future research.

Methods

Separate searches of the PubMed database were conducted for each disorder. In each case, the following standard prompts were used: "positron emission tomography" OR "PET" OR "single photon emission computed tomography" OR "SPECT" OR "single photon emission tomography" OR "SPET"). Distinct specifiers were then added for each of the three disorders: AND ("depression" OR "MDD"), AND ("bipolar disorder" OR "mania"), AND ("posttraumatic stress disorder" OR "PTSD"). Searches for MDD, BD, and PTSD initially yielded 2, 302, 447, and 158 PubMed article results, respectively. Studies were included in this review if they satisfied the following criteria: (1) articles focused on the use of PET or SPECT techniques, (2) articles describing original research, (3) articles presenting in vivo results in human participants, and (4) articles focused on the imaging of specific molecule/receptor types (i.e. excluding glucose metabolism and cerebral blood flow). Following careful review, 126 MDD, 22 BD, and 15 PTSD articles were retained.

Results

Major Depressive Disorder

A substantial body of research supports the assertion that stress, both chronic and acute, is causally related to the onset of MDD.[11] Recent research suggests that exposure to chronic or "every day" stress in financial, occupational, or personal settings alone, or in combination with acute stress exposure is more powerfully predictive of MDD than acute stress exposure alone.[12–14] While short-term stress can be adaptive, prolonged, or chronic exposure to stress can lead to long-term dysregulation of many physiological and neurochemical processes. PET and SPECT research has provided more precise insight into the nature of the chronic stress-related alterations associated with the onset and persistence of MDD (Table 1).

The majority of existing PET and SPECT research in MDD populations has focused on the functioning of two monoaminergic neurotransmitters: serotonin and dopamine. Focus on monoamine functioning in depression resulted in part from the monoaminergic hypothesis,[97] which postulates that alterations in the function of monoaminergic neurotransmission play a causal role in the development of MDD.

Serotonin. Between 1991 and 2016, 71 molecular imaging studies meeting the criteria specified above were published. Strong evidence supports the role of the serotonergic (5HT) system, which plays a role in the regulation of sleep, stress responses, and affective cognition[98] in the development and continuation of depressive symptoms.[99] However, the exact nature of the relationship between 5HT functioning and MDD is still under debate. Both preclinical and postmortem evidence suggests that serotonergic dysfunction and specifically deficits in serotonin are central to the pathophysiology of MDD.[100,101] In line with such findings, evidence from PET work suggests lower serotonin synthesis in MDD individuals relative to healthy control,[15–19] and that treatment with selective serotonin reuptake inhibitor (SSRI) resulted in increased serotonin synthesis.[16]

The serotonin transporter (SERT) plays a key role in modulation of brain 5HT levels via reuptake into presynaptic neurons,[98] and is the primary target of action for many commonly prescribed antidepressant medications.[102] Interest in SERT has been motivated in part by evidence suggesting that expression of the *SERT* gene (5HTT) may moderate emotional and behavioral responses to stress,[103] such that individuals displaying a specific 5HTT polymorphism (associated with decreased serotonergic functioning in preclinical studies[103,104]) were more likely to develop MDD and suicidal behavior following stress.[105] Evidence from a recent SPECT study similarly found lower SERT availability in the thalamus and that high levels of life stress interacted to predict depressive symptom severity, suggesting that SERT may play a specific role in the development of depression following chronic stress.[106] Miller et al.[25] observed lower SERT availability across brain regions in individuals reporting a history of child abuse who went on to develop MDD, but not PTSD, relative to MDD individuals without an abuse history. Further, support for the relationship between SERT and stress comes from an

Table 1. Radiotracers used for in vivo molecular imaging in individuals with major depressive disorder.

Molecular target (receptor) MDD	Radiotracer (full name)	Abbreviation(s)	Main findings
Serotonin synthesis	a-[11C]methyl-L-tryptophan	a-[11C]- MTrp	↓Serotonin synthesis in MDD[15–17]
	5-hydroxytryptophan (5-HTP) labelled with 11C in the ß position	[ß-11C]5-HTP	↓Serotonin synthesis in MDD[18,19]
Serotonin transporter (SERT)	(3-amino-4-(2-dimethylami-nomethyl-phenylsulfanyl)-benzonitrile)	[11C]DASB	↓SERT availability in MDD;[20–22] mixed findings[23,24]
	(11)C-(+)-6ß -(4Methylthiophenyl)-1,2,3,5,6alpha,10ß hexahydropyrrolo [2,1-a] isoquinoline	[11C]McN5652	↓SERT availability in MDD;[25,26] ↑SERT availability in MDD[27,28]
	[123I] 2-((2-((dimethylamino)methyl) phenyl) thio)-5-iodophenylamine (aDaM)	[123I]-ADAM	↓SERT availability in MDD;[29–,32] ↑mid-brain SERT availability in suicide attempters[33]
	N, N-dimethyl-2-(2-amino-4-[18F]fluorophenylthio)benzylamine (4-[18F]-aDaM)	(4-[18F]-ADAM)	Suicidal ideation positively correlated with SERT availability[34]
	Carbon-11 labeled 2β-carbomethoxy-3β-[4′-((Z)-2-iodoethenyl)phenyl]nortropane	[11C]-ZIENT PET	↓SERT availability in MDD suicide attempters[35]
Serotonin 1A (5HT1A) receptors	carbon11–labeledN-(2-1-4-2-methoxyphe-nyl)-1piperazinyl)ethyl))- N-(2-pyridyl)-cyclohexanecarboxamide	[11C]WAY-100635	↑5HT1A availability in MDD[26,36–40]; ↓5HT1A availability in MDD[41–48]
	No-carrier-added 4-(2′-methoxyphenyl)-1-[2′-(N-2-pyridinyl)-p-[18F] fluorobenzamido]ethylpiperazine)	[18F]MPPF	↓5HT1A availability in MDD[49]
			(cont.)
Serotonin 1B (5HT1B) receptors	(R-1-[4-(2-methoxy-isopropyl)-phenyl]-3-[2-(4-methyl-piperazin-1-yl)benzyl]-pyrrolidin-2-one)	[11C]P943	↓5HT1B availability in MDD[50]
	(5-methyl-8-(4-methyl-piperazin-1-yl)-4-oxo-4H-chromene-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide)	[11C]AZ10419369	↓5HT1B availability in MDD;[51] ↓5HT1B availability in MDD following therapy[52]
Serotonin 2A (5HT2A) receptors	123iodinated 4-amino-N-1-[3-(4-fluorophenoxy)propyl]-4-methyl-4-piperidinyl] 5-iodo-2-methoxybenzamide	123I-5-I-R91150	↓5HT2A availability in MDD[53]
	[18F]altanserin		↓5HT2A availability in MDD[54,55]
	((R)-(+)-4 -(l-hydroxy-1-(2,3-dimethoxyphenyl)methyl)-N -2-(4-fluorophenylethyl)piperidine) labeled with 11C	[11C]MDL 100,907	↑5HT2A availability in individuals with a history of MDD[56]
	[18F]fluoroethylspiperone	[18F]FESP	↓5HT2A availability in drug-naïve MDD, not different from HC in SSRI responders[57]
	[18F]setoperone		↓5HT2A availability in MDD;[58,59] ↑5HT2A availability in MDD[60,61]
Serotonin receptor type 4 (5HT4)		[11C]SB207145	↓5HT4 availability in healthy individuals with family history of MDD[62]
SERT/dopamine trans-porter (DAT)	123I-labelled 2β-carbomethoxy-3 β-(4-iodophenyl)-tropane	[123I]I-ß-CIT	↓SERT/DAT availability in MDD[63–66]
		[123I]nor-ß-CIT	↓SERT/DAT availability in MDD[67,68]
	(2β-carbomethoxy-3β-(4- iodophenyl)-tropane	[123I-labeled β -CIT	Mixed results[69,64]
Dopamine synthesis	[18F]fluorodopa	[18F]DOPA	↓Dopamine synthesis[70]

(continued)

Table 1. Continued

Molecular target (receptor) MDD	Radiotracer (full name)	Abbreviation(s)	Main findings
Doapmine synthesis (cont)	¹¹C-labeled 3,4-Dihydroxy-phenyl-L-alanine	L-[¹¹C]DOPA	↓Dopamine synthesis[102]
Dopamine transpoter (DAT)	((99 m)Tc-[2[[2-[[[3-(4-chlorophenyl)-8-methyl-8-azabicyclo[3,2,1]-oct-2-yl]-methyl](2-mercaptoethyl) amino]ethyl] amino]ethane-thiolato(3-)-N2,N2′,S2,S2]oxo-[1R-(exo-exo)]]))	[99mTc] TRODAT-1	↓DAT availability in MDD[71–76]
	[¹²³I]N-fluoropropyl-carbomethoxy-3β-(4-iodophenyl)tropane	[¹¹C]RTI-32 PET	↓DAT availability in MDD[77]
			↓DAT availability in MDD[78]
Dopamine type 2/3 receptors (D2/3)	[¹²³I]iodo-benzamide	([¹²³I]IBZM)	↑D 2/3 availability in MDD;[62,79] No differences in D 2/3 availability between MDD and HC[80,74,81,82]
	[¹²³I]epidepride		↑D 2/3 availability in MDD[68]
	((S)-N-((1-ethyl-2-pyrrolidinyl)methyl)-5- bromo-2,3-dimethoxybenzamide)	[¹¹C]FLB 457	No differences in D 2/3 availability between MDD and HC[83]
	[¹¹C]raclopride	[¹¹C]RAC	↑D1 availability in MDD[24]
Dopamine Type 1 Receptors (D1)	8-chloro-7-hydroxy-3-methyl-5-(7-benzofuranyl)-2,3,4,5-tetrahydro-1H-3-benzazepine)	[¹¹C]NNC-112	↓D1 availability in MDD[84]
	((R)-(+)-8-chloro-2,3,4,5-tetrahydro-3- methyl-5-phenyl-1H-3-benzazepin-7-ol)	[¹¹C]SCH 23,390	↓D1 availability in MDD with anger[85]
Metabotropic glutamate receptors type 5 (mGluR5)	(3-(6-methyl-pyridin-2-ylethynyl)-cyclohex-2-enone-O-(11) C-methyl-oxime)	[¹¹C]ABP688	↓mGluR5 availability in MDD[86,87]
		[¹⁸F]FPEB	No differences in mGluR5 availability between MDD and HC[88]
Translocator protein (TSPO)		[¹¹C]PBR28	No differences in TSPO availability between MDD (mild symptom severity) and HC[89]
	fluorine F 18–labeled N-(2-(2-fluoroethoxy)benzyl)-N-(4-phenoxypyridin-3-yl)acetamide	([¹⁸F]FEPPA)	↑TSPO availability in MDD[90,91]
MAO-A		([¹¹C]harmine)	↑MAO-A availability in MDD[92,93]
β-Amyloid	F-florbetapir		↑ β-Amyloid availability in MDD[94]
	N-Methyl-[¹¹C]-2-(4′methyaminophenyl)-6-hydroxybenzothiasole	[¹¹C]PIB-PET	β-Amyloid availability correlated with MDD severity[95]
β2*-nAChR	(¹²³I-IA); [¹²³I]-5-iodo-3-[2(S)-azetidinylmethoxy]pyridine	[¹²³I]5-I-A-85380	No differences in β2*-nAChR between MDD and HC[96]

Note. MDD, major depressive disorder; PET, positron emission tomography; MAO, monoamine oxidase; HC, healthy control.

experimental study of HPA axis dysfunction, as measured by the dexamethasone suppression test,[107] showing an association with reduction in SERT levels. Evidence points to lower SERT availability in multiple brain areas, most commonly the thalamus,[20,29] and midbrain[21,22,30,31,67] or brainstem,[63,69] areas responsible for regulation of sleep/wake cycles which are frequently disrupted in MDD.

Importantly, SERT levels appear to be related to antidepressant treatment outcome and illness progression.[32,108,109,110,111] Increase in midbrain SERT availability is associated with depressive symptom remission following antidepressant treatment,[109,111,112] and Amsterdam et al.[110] showed a significant increase in both midbrain and medial temporal lobe SERT availability in treatment responders following 12 weeks of cognitive behavioral therapy. Conversely, in participants whose MDD symptoms did not remit following a year of antidepressant use, lower SERT availability was detected in several brain regions in individuals with MDD relative to healthy controls.[27]

Of note, in vivo evidence for low SERT in MDD is strong but not universal. Some studies have reported no significant differences in SERT availability between MDD and healthy control groups,[23,28,64,113,114] while others reported higher SERT availability in individuals with MDD relative to controls.[65,113,115] No clear explanation for these discrepant findings is available, though low sample size due to cost in PET and SPECT studies, difficulty in recruiting these patients, and cross-sample variability (e.g. symptom severity, sex, race, medication) likely play a role. Notably, characteristics of some specific radiotracers may have biased findings in some cases. For example, both SPECT tracers, [^{123}I]nor-β-CIT and [^{123}I]β-CIT, have been shown to bind not only to SERT but to norepinephrine (NET) and dopamine (DAT) transporters.[116] Thus, depending on the region, quantification of SERT might represent SERT and DAT/NET densities.

A large focus in the serotonergic literature has also been the 5HT1A receptor, which is a post-synaptic G-coupled protein receptor and the most common serotonergic receptor in the brain.[105] The 5HT1A receptor is located both in brain areas with projections from the raphe nuclei (RN), where the serotonergic system is centralized,[117] and in the RN itself. Preclinical research has shown that animals with higher numbers of 5HT1A receptors are more vulnerable to stress[118] and display more "depressive" behavior (e.g. helplessness[119]). Similarly, some postmortem studies have shown higher 5HT1A density in select brain regions (e.g. midbrain dorsal RN) of individuals with MDD relative to healthy controls.[49] Based on evidence from other modalities, it is reasonable to hypothesize observation of similarly increased 5HT1A availability in vivo.

To date all published 5HT1A studies have used PET, with all but one using the 5HT1A radiotracer [^{11}C]WAY-100635 with somewhat mixed findings. Unlike cited preclinical and postmortem studies, there does not appear to be a consensus on whether 5HT1A is up or downregulated in depression: about half the published studies observed lower 5HT1A availability in MDD participants across various brain regions,[41–46] whereas the other half found evidence for higher levels of 5HT1A in MDD, particularly in treatment-resistant individuals,[26,36–39,47,48,120,121] and with only one study reporting no 5HT1A differences between MDD participants and controls.[40] Interestingly, downregulation in 5HT1A appears to be associated with treatment response following SSRI treatment.[39,121]

Importantly, a specific, testable explanation for the observed variability in 5HT1A findings has been proposed. In molecular imaging, there are various ways to quantify receptor availability, one of which is by the use of a reference tissue, which should be a region that is devoid of the target molecule (commonly the cerebellum).

This method has been implemented in the studies that report lower 5HT1A availability in MDD; however, it appears that the cerebellum is not devoid of 5HT1A and there is evidence of lower cerebellar 5HT1A availability in the control relative to the MDD groups,[98] which would bias the results and lead to an underestimation of the true 5HT1A density in MDD. Illustrating this point, Hesselgrave and Parsey[122] showed that the same data set showed lower 5HT1A availability in MDD when analyses were completed using the cerebellum as reference, and the opposite finding when the outcome measure was a blood derived input function. It has also been suggested that 5HT1A level varies temporally over the course of MDD, possibly in part as a function of antidepressant exposure.[122] At present, all that can be concluded is that the preponderance of evidence suggests 5HT1A is elevated in MDD.

Like 5HT1A, the 5HT1B receptor is an autoreceptor present in the terminal regions of serotonergic neurons and plays a role in regulating, specifically decreasing when activated, the amount of serotonin in the synapse.[98] Both clinical[123] and preclinical[124] studies have shown that 5HT1B agonists have antidepressant properties, suggesting that unlike 5HT1A, lower levels of 5HT1B may be associated with MDD symptom experience. Although limited, evidence is somewhat consistent with this hypothesis with two reports of lower 5HT1B availability in the ventral striatum and pallidum[50] and the anterior cingulate cortex (ACC), subgenual prefrontal cortex (PFC), and hippocampus,[51] respectively, but another report of lower 5HT1B availability in the dorsal brainstem following cognitive behavioral therapy for MDD.[52]

The 5HT2A receptor has received significant molecular imaging research attention, largely because SSRIs are known to act directly on 5HT2A receptors, leading to receptor downregulation.[125] Importantly, the 5HT2A receptor has proven responsive to stress exposure; 5HT2A levels have been shown to increase following exposure to chronic stress in preclinical studies.[126,127] Depressive behavior following stress has also been shown to increase in response to 5HT2A agonists,[128,129] further implicating upregulated 5HT2A in the pathophysiology of MDD. In vivo molecular imaging studies, however, have shown mixed results. There are several reports of downregulated[53–55,57,58,60] 5HT2A in MDD across several brain regions. However, there are also studies of no significant differences between untreated MDD participants and controls,[59,130] and two showed higher levels of 5HT2A in the basal ganglia[131] and frontal, parietal, and occipital cortices[56] of unmedicated MDD participants relative to controls. The reports of higher 5HT2A density in MDD are in agreement with studies showing a reduction in cortical 5HT2A availability following treatment with tricyclic antidepressants.[61,130] In attempting to account for mixed findings concerning

5HT2A in MDD, Ruhe et al.[98] suggested that individuals with MDD may have lower 5HT2A availability in the hippocampus due to HPA axis dysregulation and higher 5HT2A availability in other areas (e.g. the frontal cortex), a pattern that has been shown in animals exposed to chronic stress. However, this proposed explanation has not yet been directly tested.[132]

Finally, a single PET study investigated the relationship between MDD risk and availability of the 5HT4 receptor,[62] which has been implicated in recent preclinical studies as a potential target for rapidly acting antidepressant agents.[133] The authors reported that healthy individuals with a family history of MDD have lower 5HT4 availability in the striatum, which was inversely correlated with the number of first degree relatives with MDD. These findings implicate the 5HT4 receptor as a potential target subserving familial risk for MDD, though replication and exploration of this receptor system in individuals with MDD is warranted.

Dopamine. Another monoaminergic neurotransmitter implicated in the pathophysiology of MDD is dopamine, which is known to be associated with emotion regulation, attention, motivation, and reward.[134] Dopaminergic circuits contribute to the regulation of concentration and memory functioning, as well as the ability to experience pleasure, all of which are impaired in MDD.[135] Dopaminergic dysfunction (i.e. reduced D2 receptor function), specifically in the nucleus accumbens, has also been linked directly to the experience of chronic stress, and subsequent development of depressive symptoms (anhedonia) in preclinical studies.[80,136]

As with serotonin, early molecular imaging of the dopamine system sought to examine the neurotransmitter's synthesis in the brain, speculating in part based on results from clinical studies,[137] that less dopamine synthesis would be observed in depressed individuals.[98] This was verified by some PET studies in limited brain regions.[19,138] A much larger number of studies have examined the functioning of dopamine transmitters (DAT) in MDD but have produced incongruent results. Specifically, genetic research has suggested that a DAT gene polymorphism, which increases DAT availability, is associated with higher risk for MDD.[70,139] Several postmortem studies, however, have observed lower brain-wide DAT availability in MDD individuals. Findings in the molecular imaging literature are similarly mixed. Although there are reports of higher DAT availability in the striatum,[71,140] basal ganglia,[72] and other brain areas[73] of MDD participants, others reported no significant differences between MDD and healthy control (HC),[74,75] and three reported lower DAT availability in MDD in the striatum.[76,78,141] Furthermore, Meyer et al.[76] reported that a downregulation in DAT availability was related to more severe depressive symptoms. However,

they did not detect a significant change in DAT availability before and after bupropion antidepressant therapy,[76] suggesting that bupropion treatment did not appear to target this system or this system may not be significantly involved in MDD pathophysiology.

Measuring DAT with SPECT has also yielded some mixed results.[28,63,67–69,77,108,109] However, not all of these studies characterized their results as indicative of DAT availability because, as noted above, SPECT DAT tracers are recognized to have affinity for SERT and NET as well. Results of these studies should therefore be interpreted with caution. Furthermore, Camardese et al.[66] highlighted the heterogeneity in presentation of MDD symptoms that can meet diagnosis and the potential effects of pharmacological treatment history and drug abuse as potential confounds affecting the observed variability in findings. As with SERT, inconsistent findings make it difficult to form a conclusion concerning the relationship between DAT and MDD at present.

The majority of neuroimaging studies investigating dopamine receptor availability have focused primarily on D2/D3 receptors, in part due to these receptors being targets for antidepressant and antipsychotic therapy.[136] Evidence from other modalities implicates possible downregulation of D2/3 receptors in MDD. Epigenetic studies have presented evidence for a link between chronic stress, D2 downregulation, and the development of depression.[66] Similarly, preclinical studies have shown downregulation of D3 in animals experiencing stress and depression. However, of the 14 studies which have examined D2/3 availability using PET and SPECT in individuals with MDD, all but 3 failed to observe differences in both medicated[44,81,142,143] and unmedicated[26,43,73,79,142] MDD participants relative to HCs. The remaining three showed higher D2/3 availability in MDD in the striatum,[82,131] and in the case of Lehto et al.,[77] a positive correlation between MDD symptom severity and D2/3 availability in the temporal cortex. However, although in vivo evidence suggests no specific D2/3 dysregulation in MDD, alterations treatment with SSRIs appears to influence D2/3 availability. For example, Montgomery et al.[24] reported lower D2/3 availability in the striatum of MDD participants using SSRIs, while two other studies observed increased D2/3 in the basal ganglia[136] and striatum[83] of SSRI treatment responders but not non-responders. Of note, while only two published studies have examined the D1 receptor in vivo in MDD, both found lower D1 availability in the striatum of MDD relative to control groups.[85,144]

Glutamate. More recently, there has been a major focus on the glutamatergic system in MDD. Glutamate is the primary excitatory neurotransmitter in the brain, with 80%–90% of synapses in the human brain being glutamatergic. Dysfunction of the glutamate system is thought

to play a role in MDD[84] and there is currently an intensive focus on the glutamate system as a target for novel treatments for MDD.[84] Part of this focus has been on metabotropic glutamate receptors (mGluRs), G-protein-coupled receptors that mediate neuromodulatory effects of glutamate.[145] Indeed, mGluR5 antagonists have consistently shown antidepressant effects in animal models of depression.[146–151] Lower levels of mGluR5 protein expression was also found in postmortem PFC tissue of individuals with MDD;[152] however, another study did not detect differences using autoradiography.[86] To date, there are four PET imaging studies that report on mGluR5 availability in MDD. Two smaller scale studies found lower levels of mGluR5 in various brain regions of those with unmedicated MDD including the PFC, ACC, and insula.[152,153] A recent PET study focusing on late-life MDD found no differences in mGluR5 availability between older adults with MDD and matched controls.[87] Similarly, a recent study by our group found no differences in mGluR5 availability in a large group of unmedicated MDD individuals compared to HCs. As part of the same study, we used MRS to assess measures of glutamate and found a negative correlation between mGluR5 availability and MRS measures of glutamate in the ACC.[154] It is possible, therefore, that higher levels of glutamate are associated with a downregulation of mGluR5 in MDD. Furthermore, we recently observed that rapid downregulation of mGluR5 is associated with a reduction of somatic anxiety symptoms in MDD participants, suggesting this might be a treatment target for anxiety in MDD.[153] Further work will be required to definitively determine whether mGluR5 is a viable treatment target for symptoms of MDD.

Inflammation. Convergent evidence indicates that inflammation plays a significant role in MDD.[88,155,156] Inflammatory mechanisms have been proposed to underlie the link between chronic stress and depression,[33] and meta-analyses have confirmed elevated inflammatory markers in individuals with MDD.[157–160] However, the specific role of inflammation in the brain is less clear. It is possible to measure neuroinflammation with PET and radioligands that bind to the translocator protein (TSPO), which is upregulated on activated microglia, the immune cells of the brain.[161] To date, there are two published PET studies investigating TSPO in depression. The first found no difference in TSPO availability between depressed individuals with symptoms of mild severity and controls.[162] The second larger study showed elevated microglial activation in medication-free depression of moderate to severe severity, specifically in the PFC, ACC, and insula.[89] This finding has recently been replicated in a similar sample of medication-free depressed individuals.[90] Interestingly, this study found elevated TSPO in depressed individuals with versus without current suicidal thinking, suggesting a role for neuroinflammation in suicidal ideation specifically. Indeed, the heterogeneity in MDD symptomatology may play a role in the expression of neuroinflammation in MDD and account for divergent findings. PET and the 40+ existing TSPO radioligands provide a unique opportunity for clarifying the role of neuroinflammation in the pathophysiology of MDD and evaluating the use of anti-inflammatory medications in treating its symptoms.

Other Neurotransmitters. In addition to those reviewed above, PET and SPECT have been used to measure other systems such as monoamine oxidase (MAO-A), β-Amyloid, nicotinic acetylcholine receptors (β₂*-nAChR), and γ-aminobutyric acid (GABA)—benzodiazepine receptors (GABA_A-BZR). MAO-A is an enzyme known to be responsible for the regulation of brain monoamine levels.[91] Higher MAO-A availability is observed in MDD participants relative to HC,[91,92] which would be in line with the studies showing lower monoamine neurotransmission in MDD.

β-Amyloid deposition in the brain, which is associated with the development of dementia, has been shown to correlate with history of lifetime MDD episode in postmortem work.[93] A single PET study by Wu et al.[93] showed higher β-Amyloid levels in depressed, but cognitively normal, older adults relative to age-matched HCs in multiple brain regions. A recent study by Yasuno et al.[94] looking at older adults without clinical MDD also reported a positive correlation between β-Amyloid availability averaged across the brain and depressive symptom severity. The cholinergic system has long been identified to be dysregulated in MDD,[95,163–166] with the hypothesis of excesses in acetylcholine levels contributing to the experiences of depression. Specific to the neuroimaging literature, the β₂*-nAChR has been identified as potentially relevant to MDD symptom expression,[167] although clinical trials with targets to downregulate β₂*-nAChR did not prove efficacious for treatment of MDD. Combined in vivo/postmortem study from our group verified that β₂*-nAChR does not appear to be dysregulated in MDD; however, elevations in acetylcholine levels might indeed play a role in depression.[168] Finally, a single study examined GABA_A-BZR availability in MDD and found no differences in availability between MDD and control groups.[96]

PET and SPECT Literature: Suicidal behavior. Importantly, while suicidal behavior is most frequently investigated as an associated feature of MDD, evidence from clinical research suggests the existence of meaningful neurobiological differences between suicide attempters and non-attempters.[169] For example, platelet studies showed that suicidal individuals had higher number for 5HT2A binding sites compared both to MDD

non-attempters and HCs.[169] Similarly, variation in the DRD2 gene affecting D2 receptor expression has been consistently associated with risk for suicidal behavior, but not for MDD.[35] To date, seven published studies, all focused on the serotonergic system, have explicitly examined associations with current or historical suicidal behavior (ideation or attempt). Five studies focused on SERT availability in MDD participants with suicidal behavior with interesting if mixed results. For example, Yeh et al. observed a positive correlation between SERT availability and suicidal ideation across brain regions[33] while two other studies observed lower SERT availability in the midbrain[170] and putamen[170] of MDD participants with a history of suicide attempts compared to both healthy controls and MDD non-attempters. In combination, these findings suggest that lower midbrain SERT availability might distinguish between MDD individuals with and without risk for suicide. Notably, Oquendo et al.[171] failed to confirm midbrain SERT availability as a predictor of attempts in a recent longitudinal study. They did, however, observe that increased 5HT1A availability in the RN predicted both suicidal ideation and lethality of suicidal behavior.[171] In a cross-sectional study, Sullivan et al. also found that 5HT1A availability in the RN correlated positively with the lethality of attempt.[90] Thus, 5HT1A availability in the RN serve as a marker for suicide risk. Of note, a single PET study in high-lethality suicide attempters across psychiatric diagnoses found lower serotonin synthesis in the orbital and ventromedial PFC of attempters relative to HCs.[172] These promising results underscore the need for more molecular imaging work in suicidal individuals.

Bipolar Disorder

Relationship Between BD and Chronic Stress. Stress is also thought to play a significant role in the development of bipolar disorder (BD). Stress can trigger the first manic/hypomanic episode, predict episode recurrence, and lead to less favorable outcomes.[173–177] Thus, there is significant interest in stress as a target for treatment and prevention strategies in BD. Molecular imaging can provide invaluable information on the molecular mechanisms underlying the link between stress and BD. To date, 22 PET and SPECT studies have been performed in BD (Table 2), and like MDD, the majority (n=14) have focused on the serotonergic system.

PET and SPECT Literature: BD

Serotonin. Serotoninergic function has long been thought to be central to the development of bipolar disorder.[58] Prange et al.[195] proposed what they termed the "permissive hypothesis of 5HT function" in bipolar disorder, which stated that deficient serotonergic functioning underlies bipolar disorder, and that manic and depressive episodes specifically would be marked by low 5HT. Supporting this proposal, a recent meta-analysis confirmed two gene SNPs related to the production of tryptophan hydroxylase-2, a rate-limiting enzyme for 5HT in the brain, are consistently associated with the development of bipolar disorder.[196] However, existing PET and SPECT imaging evidence has not yet substantiated the permissive hypothesis. It appears that there is a variability in SERT availability across mood states in BD.[98] During euthymia, there is lower SERT availability consistently measured across studies.[179–182,184,197] During depression, studies appear to diverge in their findings, with reports of no differences in SERT availability in BD compared to HC,[184] lower SERT availability in thalamus, putamen, amygdala of depressed BD participants,[34] and higher SERT availability in the thalamus compared to MDD participants, but lower availability in the RN relative to controls.[178] No studies investigating SERT availability in manic BD participants have been published to date.

Both 5HT1A and 5HT2A are target receptors for medications used to treat BD (e.g. lamotrigine[198] and ziprasidone,[199] respectively). Further, genetic studies have found that the presence of specific SNPs in the 5HT1A gene predict both MDD and BD,[200] suggesting a possible similar pattern of 5HT1A upregulation in both disorders. By contrast, a postmortem study observed decreased 5HT2A mRNA levels in the hippocampal region of BD individuals relative to MDD and HC.[201] Quantitation of 5HT1A and 5HT2A receptors in BD in vivo has led to divergence in findings,[187,188,202] including lower and higher receptor availability during depression, and no differences during euthymia.[187] 5HT2A availability has been examined in bipolar mania only, with observations of lower availability relative to HC in all cortical regions,[185] and no alterations in 5HT2A availability following three to five weeks treatment with mood stabilizers.[186] More research across mood states is needed to increase understanding of the potential involvement of both receptors in BD. Of note, researchers have observed that while serotonin modulation plays a role in antidepressant action in bipolar depression, based on examination of the most effective agents for BD depression, it is not sufficient for symptom relief.[198] It is therefore crucial that molecular imaging research in BD examine other receptor systems.

Dopamine. Dopaminergic dysfunction is also implicated in the development and expression of BD.[98] Researchers have suggested that increased dopaminergic function underlies mania, while the opposite is true for depressive episodes in BD.[203] Many antipsychotic drugs are commonly prescribed to treat mania block dopamine receptors, decreasing levels of dopamine in the brain.[204]

Table 2. Radiotracers used for in vivo molecular imaging in individuals with bipolar disorder.

Molecular target (receptor) BD	Radiotracer (full name)	Abbreviation(s)	Major findings
SERT (serotonin transporter)	trans-1,2,3,5,6,10- -hexahydro-6-[4-(methylthio) phenyl]pyrrolo-[2,1-a]-isoquinoline	[^{11}C](+)-McNeil 5652	↓SERT availability in BD[178]
	[^{11}C]-3-amino-4-(2-dimethylaminomethyl- phenylsulfanyl)-benzonitrile	[^{11}C]DASB	Mixed findings[65,34]
	[(123)I]-2-((2-((dimethylamino)methyl)- phenyl)thio)- 5-iodophenylamine	[^{123}I]-ADAM	↓SERT availability in euthymic BD[179–184]
Serotonin 2A receptor (5HT2A)	[^{18}F]-setoperone		Mixed findings[185,186]
Serotonin type 1A receptor (5HT1A)	[N-(2-(4-(2-methoxyphenyl)-1-piperaziny- l)ethyl)-N-(2- pyridinyl) cyclohexane carboxamide]	[Carbonyl-C-11]WAY- 100635	No differences in 5HT2A availability in euthymic BD;[187] ↑5HT2A availability in BD depression[123]
	[^{18}F]trans- 4-fluoro-N-(2-[4-(2-methoxyphenyl) piperazino]-ethyl)-N- (2-pyridyl) cyclohexanecarboxamid	[^{18}F]FCWAY	↓5HT2A availability in BD depression[188]
Dopamine transporter (DAT)	((99 m)Tc-[2[[2-[[[3-(4-chlorophenyl)-8- methyl-8-azabicyclo[3,2,1]-oct-2-yl]- methyl](2-mercaptoethyl) amino]ethy- l]amino]ethane-thiolato(3-)- N2,N2′,S2,S2]oxo-[1R-(exo-exo)]]))	[99mTc]TRODAT-1	↑DAT availability in depressed[189] and euthymic BD[190]
	[O-methyl-^{11}C]b -CFT	[^{11}C]CFT	↓DAT availability in BD across mood states
Dopamine type 2 teceptor (D2)	[^{11}C]raclopride.	[^{11}C]RAC	No differences in D2 availability in manic BD[191]
Translocator protein (TSPO)	[1-(2-chlorophenyl)-N-methyl-N-(1-methyl propyl)-3-isoquinoline carboxamide]	[^{11}C]-(R)-PK11195	↑TSPO availability in euthymic BD
β2*-nAChR	5-iodo-3-(2(S) azetidinylmethoxy) pyridine	[^{123}I]5IA	No differences in β2*-nAChR availabil- ity between depressed BD, euthymic BD, and HC[192]
Muscarinic type 2 (M2) receptor	(fluorodopa F 18 [3-(3-[3-fluoroprop- ly]thio)-1,2,5-thiadiazol-4-yl]-1,2,5,6-tet- rahydro-1- methylpyridine)	[^{18}F]FP-TZTP	↓M2 availability in depressed BD[193,194]

Note. BP, bipolar disorder.

Indeed drugs known to increase levels of dopamine (e.g. some tricyclic antidepressants) have also been shown to induce mania in BD individuals.[205,206] Two postmortem studies have observed upregulation of D2 in the dlPFC of BD.[207,208] However, to date, only one molecular imaging study has examined D2 in BD during mania, finding no differences in D2 receptor availability in the striatum of manic BD participants relative to HCs.[191] The remainder of molecular imaging studies have focused on DAT, dysfunction of which, genetic research suggests, is associated with risk for BD.[209,210] Interestingly, DAT findings in BD diverge based on imaging modality used. More specifically, two studies using SPECT and [^{99m}Tc]TRODAT-1 (a non-selective DAT tracer[98]) observed higher DAT availability in the striatum of both depressed[189] and euthymic[190] BD participants relative to HC. By contrast, using PET and a DAT select- ive tracer ([^{11}C]CFT), Anand et al.[208] observed lower striatal DAT in BD across mood states relative to HC. As with serotonin, more research is needed to further clarify the relationship between dopaminergic neuro- transmission and BD.

Inflammation. Mounting evidence suggests that inflam- mation plays a key role in BD as well as MDD.[211] For example, pro-inflammatory cytokines have been shown to be elevated in the blood of BD individuals, during periods of mania, depression, and euthymia, suggesting that

low-grade inflammation may be a trait marker of BD.[212] Preliminary evidence suggests the presence of inflammation in the brain as well as the periphery in BD, with one postmortem study showing upregulation of markers of neuroinflammation in the frontal cortex in BD.[213] One study has investigated neuroinflammation in vivo using PET to date. Using $[^{11}C](R)PK11195$, Haarman et al. reported elevated TSPO levels in the right hippocampus of euthymic-medicated BD participants compared to controls.[214] Whether these medications impact neuroinflammation and whether level of measurable neuroinflammation differs across mood states remains to be determined.

Other Neurotransmitters. Cholinergic neurotransmitter systems have also been implicated in the pathophysiology of BD.[193] Both muscarinic agonists and acetylcholinesterase inhibitors increase cholinergic neurotransmission, and have been shown to increase depressive and decrease manic symptoms.[193] They have also been found to elicit erratic emotional responding—similar to that manifested in BD—when administered to HCs.[215] Additionally, CHRM2, which encodes for muscarinic receptors (M2) is one of several candidate genes shown to be expressed more in the ACC of BD individuals relative to HC in a recent postmortem study. Three molecular imaging studies have examined the availability of muscarinic (mACh) and nicotinic (nACh) receptors in BD. Cannon et al. first showed lower M2 availability in the ACC of depressed BD participants relative to HC.[193] They then showed that variation in the gene that encodes for M2, specifically, presence of the TT allele, was associated with lower M2 availability in the ACC of BD participants, and with more severe lifetime BD symptoms.[194] However, we did not find lower β_2*-nAChR in depressed BD participants compared to euthymic BD and HC individuals, although variability in ACh levels between depression and euthymia may interfere with receptor availability quantification.[192] Alterations in ACh levels were not taken into account in the Cannon et al. studies; therefore, the role of the cholinergic receptors in the pathophysiology of BD needs further research.

Posttraumatic Stress Disorder

Relationship Between PTSD and Chronic Stress. PTSD is a psychiatric condition, which by definition occurs in direct response to acute stress exposure (i.e. exposure to trauma). However, while approximately 80% of individuals will be exposed to a traumatic event capable of conferring PTSD (per the DSM-5[6,21]), only 8%–15% of the general population will go on to develop PTSD.[8] One reliable predictor of developing PTSD following trauma exposure is historical exposure to chronic stress.[217] As with MDD and BD, molecular imaging has the potential to provide crucial insights into the pathophysiology of PTSD and specifically its relationship to chronic stress (Table 3).

PET and SPECT Literature: PTSD

Serotonin. As was the case with MDD and BD, altered serotonergic function has been implicated in the development of PTSD.[203] More specifically, in contrast to reductions observed in MDD models, preclinical studies have reported increased 5HT synthesis in PTSD in multiple brain regions.[231–233] As in MDD, presence of the short SERT gene allele is a risk factor for PTSD, although a recent meta-analysis suggests that risk only extends to highly trauma exposed individuals.[234] Published imaging data suggest lower SERT availability in PTSD as well as correlations between SERT and severity of PTSD-related symptomatology.[218–220]

Focusing on presynaptic serotonin receptors, preclinical evidence suggests that alterations in 5HT1A function are associated with attentional bias to threat-related stimuli,[235] and exposure to stress reduces functioning of the 5HT1B receptor.[236] In line with preclinical findings, Sullivan et al.[222] observed upregulation of 5HT1A in the amygdala, RN, and all cortical regions of individuals with PTSD with and without comorbid MDD relative to HCs. Of note, an earlier study by Bonne et al.[221] observed no differences in 5HT1A availability in PTSD participants. However, Sullivan et al.[222] argued that characteristics of the PET tracer used and issues with the analytic approach used might have contributed to the Bonne's null result. Further, consistent with preclinical evidence, there is a finding of lower 5HT1B availability in trauma-exposed control participants relative to HCs with no previous trauma exposure.[50] Earlier age of trauma exposure appears to be associated with both lower 5HT1B availability and PTSD symptom severity, suggesting that 5HT1B availability may be affected by trauma exposure, particularly during development.

Dopamine. Dopaminergic hyper-functioning has also been implicated in the development of PTSD, and specifically in the experience of hyperarousal symptoms.[237] More specifically, a DAT gene polymorphism has been shown to be associated with risk for developing PTSD following trauma exposure.[238] In keeping, researchers found higher availability of DAT in the striatum of PTSD participants relative to trauma-exposed control subjects.[223]

GABA$_A$-BZR. Evidence has shown that exposure to trauma/acute stress is associated with reduction in GABA$_A$ benzodiazepine receptor (GABA$_A$-BZR) density,[239] which plays an important role in modulating nervous stress response in the central nervous system.[225]

Table 3. Radiotracers used for in vivo molecular imaging in individuals with posttraumatic stress disorder.

Molecular target (receptor)	Radiotracer (full name)	Abbreviation(s)	Studies utilizing this tracer in vivo
Neurokinin 1 Receptor (NK1)	(2 S,3 S)-N-[[2-[11C]Methoxy-5-[5-(trifluoro-methyl)tetrazol-1-yl]phenyl]methyl]-2-phenyl-piperidin-3-amine	[^{11}C]GR205171	
Serotonin transporter (SERT)	[^{11}C]2-(2-(Dimethylaminomethyl)phenylthio)-5-fluoromethylphenylamine	[^{11}C]AFM	↓SERT availability in MDD[218]
	[^{11}C]-3-amino-4-(2-dimethylaminomethylphe-nylsulfanyl)-benzonitrile	[^{11}C]DASB	↓SERT availability in MDD[219,220]
Serotonin 1B receptor (5HT1B)	(R-1-[4-(2-methoxy-isopropyl)-phenyl]-3-[2-(4-methyl-piperazin-1-yl)benzyl]-pyrrolidin-2-one)	[^{11}C]P943	↓5HT1B in trauma exposed HC[50]
Serotonin 1A receptor (5HT1A)	carbon11–labeledN-(2-(1-(4-(2-methoxy-phenyl)-1piperazinyl)ethyl))-N-(2-pyridyl)-cyclohexanecarboxamide	[carbonyl-C-^{11}]WAY-100635	↑5HT1A availability in MDD[221]
	(N-{2-[4-(2-methoxyphenyl)piperazino]}-N-(2-pyridinyl)trans-4-fluorocyclohexanecarboxamide)	[^{18}F]CWAY	No differences in 5HT1A availability in MDD[222]
Dopamine transporter (DAT)	((99 m)Tc-[2[[2-[[[3-(4-chlorophenyl)-8-methyl-8-azabicyclo[3,2,1]-oct-2-yl]-methyl](2-mercaptoethyl) amino]ethyl]ami-no]ethane-thiolato(3-)-N2,N2′,S2,S2]oxo-[1R-(exo-exo)]))	[99mTC]-TRODAT-1	↑DAT availability in PTSD[223]
GABA$_A$-BZR	[^{123}I]iomazenil		↑ GABAA-BZR availability in PTSD[224]
	[^{11}C]flumazenil		↑ GABAA-BZR availability in PTSD[225]
Cannabinoid receptor 1 (CB1)	([^{11}C]JHU75528)	[^{11}C]OMAR	↑CB1 availability in PTSD[226,227]
Norepinephrine Transporter (NET)	[^{11}C]methylreboxetine	([^{11}C]MRB)	↓NET availability in PTSD relative to HC, but not trauma controls[228]
ß2*-nAChR	(^{123}I-5-IA; [^{123}I]-5-iodo-3-[2(S)-azetidinylmethoxy]pyridine)	[^{123}I]5-IA-85380 ([^{123}I]5-IA)	↑ ß2*-nAChR availability in PTSD[229]
K- Opioid Receptor		[^{11}C]LY2795050	↓KOR availability associated with severity of loss symptoms in trauma survivors

In vivo quantification is in line with the animal studies reporting lower PFC GABA$_A$-BZR availability in individuals with combat-related or nonrelated PTSD relative to HCs.[224,225]

Other Neurotransmitters. Other neurotransmitters have also been examined in trauma-related psychopathology: cannabinoid receptor 1 (CB1), NET, β_2*-nAChR, and mGluR5. In line with preclinical reports of an association between chronic stress and altered CB1,[240,241] Neumeister et al.[226] reported elevated CB1 availability brain-wide in PTSD participants relative to both trauma-exposed controls and HCs. In an research domain criteria approach to examine the pathophysiology of PTSD, we reported that trauma and PTSD-related symptomology was associated with higher amygdalar CB1 availability.[227] NET has also been implicated in the development of anxiety-related disorders like PTSD.[242] A single PET study by Pietrzak et al.[243] found lower NET availability in PTSD in the locus coeruleus relative to healthy controls. However, no significant differences in NET availability were observed in the trauma-exposed control group (compared to PTSD and HC groups).[228] β_2*-nAChRs availability, which has been

implicated in regulation of memory and arousal which function abnormally in PTSD,[244] appears to be upregulated in the mesiotemporal cortex of PTSD individuals relative to HCs. This receptor also appears to be implicated in the re-experiencing symptoms in PTSD.[229] Finally, mGluR5 has emerged as a target of interest in PTSD[245] due to its role in fear conditioning and emotion regulation. In a recent pilot study, we observed increased mGluR5 availability in PTSD participants relative to HC across cortical regions. MGluR5 availability was also correlated with severity of PTSD avoidance symptoms. The cause of this dysregulation is not clear; however, postmortem examination and preclinical data suggest deficits in glucocorticoid functioning may be impacting mGluR5 density. Based on this preliminary evidence, CB1, NET, β2*-nACh, and mGluR5 may all play roles in the pathophysiology of PTSD; however, the limited numbers of studies preclude firm conclusions.

Discussion

In the last 20 years, molecular imaging has made a substantial contribution to the understanding of the neurobiological alterations underlying chronic stress-related disorders. The reviewed studies have enriched our understanding of how and why existing psychotherapeutic agents affect neurotransmitter function and have implicated novel targets for optimizing treatment efficacy.[246] To begin, they have confirmed the presence of in vivo alterations in serotonergic and dopaminergic functioning in at least some subgroups of MDD, BD, and PTSD individuals and provided preliminary evidence that other neurotransmitter systems play a role in these disorders.[247] Areas of overlap between molecular imaging evidence and other research modalities (e.g. lower SERT in MDD) lend confidence to assertions concerning the role of some receptors and psychiatric diagnoses. Areas of discrepancy, however, encourage critical examination of explanations for such incongruity like that proposed and tested by Hesselgrave and Parsey[122] to explain discrepant in vivo 5HT1A results in MDD.

While PET and SPECT have been confirmed as powerful and highly useful clinical research tools,[228] as it stands, the molecular imaging literature on MDD, BD, and PTSD raises as many questions as it answers. One exciting novel application of molecular imaging with the potential to reduce variability in findings is transdiagnostic research. As noted, the experience of chronic stress conveys risk for complex and highly comorbid psychiatric diagnoses (e.g. MDD and PTSD). Heterogeneous symptom presentation within wide and overlapping diagnostic categories makes the systematic study of these disorders by obtaining a "representative sample" extremely challenging. Transdiagnostic designs could eliminate a significant source of error by basing analyses on the presence or absence of a specific symptoms in lieu of diagnosis (i.e. using research domain criteria[248]). In a recent example, Pietrzak et al.[249] examined the availability of Kappa-opioid receptors (KORs) in individuals with a range of trauma-related pathology (including MDD and PTSD). Instead of examining the relationship between diagnostic status and receptor density, they used principal components analysis to group symptoms into transdiagnostic "threat" and "loss" categories, and observed that low KOR availability in the amygdalar-ACC-ventral striatal circuit was associated with severe loss, but not threat symptoms, suggesting the use of molecular imaging to investigate the relationship between receptor availability and transdiagnostic aspects of chronic stress-related psychopathology may be an important next step.

In summary, molecular imaging has provided unique insight into the neurobiological underpinnings of chronic stress-related disorders. Despite inconsistencies in specific findings, the wide-reaching impact of chronic stress, and subsequent disorders like MDD, BD, and PTSD, is evident. The ability to confirm preclinical and postmortem findings, and to quantify the action of pharmacological agents in vivo has allowed for identification of biomarkers to improve risk assessment, progress toward optimization of pharmacotherapy, and identification of promising new treatment targets.

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