



Molecular Neuroimaging in Posttraumatic Stress Disorder

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Over the past decade, an increasing number of neuroimaging studies have provided insight into the neurobiological mechanisms of posttraumatic stress disorder (PTSD). In particular, molecular neuroimaging techniques have been employed in examining metabolic and neurochemical processes in PTSD. This article reviews molecular neuroimaging studies in PTSD and focuses on findings using three imaging modalities including positron emission tomography (PET), single photon emission computed tomography (SPECT), and magnetic resonance spectroscopy (MRS). Although there were some inconsistencies in the findings, patients with PTSD showed altered cerebral metabolism and perfusion, receptor bindings, and metabolite profiles in the limbic regions, medial prefrontal cortex, and temporal cortex. Studies that have investigated brain correlates of treatment response are also reviewed. Lastly, the limitations of the molecular neuroimaging studies and potential future research directions are discussed.

Key words: Posttraumatic stress disorder (PTSD), Molecular neuroimaging, Positron emission tomography (PET), Single photon emission computed tomography (SPECT), Magnetic resonance spectroscopy (MRS)

INTRODUCTION

Posttraumatic stress disorder (PTSD) is a debilitating psychiatric disorder that is characterized by intrusion symptoms, avoidance, negative alterations in cognitions and mood, and heightened arousal and reactivity following a traumatic event [1]. A growing number of structural and functional neuroimaging studies have been conducted to investigate the pathophysiology of PTSD over

the past decade. Advances in molecular imaging have allowed non-invasive methods to visualize and measure biochemical processes in human brain *in vivo*. Moreover, various molecular imaging modalities have been applied to elucidate molecular and neurochemical mechanisms of PTSD.

The purpose of this article is to critically review molecular neuroimaging of PTSD in humans. The term molecular neuroimaging refers to the use of imaging methods to quantitatively measure and visualize biological processes at the molecular and cellular levels in the living brain [2]. The present review focuses on three imaging modalities including positron emission tomography (PET), single photon emission computed tomography (SPECT), and proton (¹H) magnetic resonance spectroscopy (MRS). The review is divided into three main

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sections based on the imaging modality and further divided into subsections according to the molecular targets including cerebral perfusion, metabolism, neuroreceptors, and metabolites, as well as the types of experimental interventions or paradigms that were employed.

POSITRON EMISSION TOMOGRAPHY

PET is a commonly used molecular imaging technique which generates three-dimensional functional maps of neural activity such as regional cerebral metabolism or blood flow. It acquires signals during registrations of two photons at 180-degree angles and visualizes concentrations and positions of the radiotracers in certain brain areas [3]. It has advantages of relatively evident signal changes, selectivity and availability of various tracers, and heightened sensitivity compared to other functional neuroimaging modalities. For instance, PET allows pronounced signal changes (10%) in the brain, whereas 1~2% of signal changes are detected using functional magnetic resonance imaging (fMRI). However, PET has some disadvantages such as low temporal resolution compared to fMRI [4]. All PET studies reviewed in this article are presented in Table 1.

PET STUDIES OF REGIONAL CEREBRAL METABOLISM

Resting state paradigms

PET studies that employed resting state paradigms are the most straightforward methods to investigate baseline cerebral metabolism and neurobiological underpinnings of PTSD. Use of a tracer called [¹⁸F]fluorodeoxyglucose (FDG) in PET studies has allowed measurement of relative glucose uptake in certain brain regions as an indirect measure of neural activity.

Two previous PET studies of PTSD have assessed regional cerebral metabolic rate for glucose (rCMRglu) at resting state. One study using FDG revealed greater rCMRglu in the temporal, occipital, and fusiform cortices, as well as cerebellum and lower rCMRglu in the insula, cingulate gyri, and hippocampus [5]. A twin study using FDG PET reported that increased metabolic rate may be a predisposing factor for PTSD development after trauma exposure rather than acquired characteristics. Veterans with PTSD and their co-twins showed augmented resting metabolic activity in the dorsal anterior cingulate cortex (dACC) and mid-cingulate cortex (MCC) as compared with non-PTSD veterans and their co-twins. In addition, resting metabolic rate of the dACC/MCC in those unexposed to combat was associated with PTSD symptom severity of their respective combat – exposed twin pairs, suggesting its genetic predisposition to pathogenesis [6].

Symptom provocation paradigms

Symptom provocation is the most widely used paradigm in PET studies to trigger symptomatic states and elicit activities in brain regions associated with symptom manifestation. Neural activities in response to symptom provocation are compared between PTSD patients and healthy controls in order to investigate the neurobiological substrates underlying PTSD pathophysiology. Several paradigms that target fear response mechanisms, in which the amygdala is mainly involved, have been commonly used.

Glucose metabolic changes in response to administration of yohimbine, an α_2 -antagonist which stimulates brain adrenaline release and induces anxiety symptoms, were measured in a FDG PET study. After yohimbine administration, Vietnam veterans with PTSD exhibited anxiety symptoms and showed diminished metabolic rates in the orbitofrontal cortex (OFC), parietal cortex, and temporal cortex including the hippocampus. In contrast, healthy controls showed increased metabolic rates in the prefrontal cortex including the OFC without development of any anxiety symptoms after the administration [7]. These findings suggest that development of anxiety symptoms is related to lower metabolic rate in the higher cognitive regions including the OFC, parietal cortex, and hippocampus.

PET STUDIES OF REGIONAL CEREBRAL BLOOD FLOW

Symptom provocation paradigms

Sensory stimuli

Several PET studies of PTSD have applied trauma-related sensory stimuli (sounds, pictures, and smells) to elicit activities in brain regions related to clinical presentation of PTSD. Vietnam veterans with PTSD, who were presented with combat sounds and pictures, showed elevated regional cerebral blood flow (rCBF) in the precentral and inferior parietal cortex, posterior cingulate cortex, and lingual gyrus, all of which are involved in processing of memory, emotion, and visual information, and lower rCBF in the medial prefrontal cortex (mPFC) including the anterior cingulate cortex (ACC), compared to those without PTSD [8]. A [¹⁵O]CO₂ PET study revealed relatively increased rCBF in the ventral anterior cingulate gyrus and right amygdala in the Vietnam veterans with PTSD during exposure to combat-related visual images compared to neutral images [9]. These activation patterns may underlie re-experiencing symptoms, involving mental imagery of traumatic experiences. Increased rCBF in the right sensorimotor cortex and right amygdala was also found during traumatic sound vs. neutral sound presentation in veterans with PTSD [10]. Furthermore, veterans with PTSD, who were

Table 1. PET studies in patients with PTSD

PET studies of regional cerebral metabolism						
Study	Condition	PTSD	Control	Increased/ decreased	Brain regions	
Mollina et al. (2007) [5]	Resting	15	6 (non-PTSD)	↑ rCMRglu ↓ rCMRglu (1), (2) > (3), (4)	Temporal, occipital, fusiform cortices, and cerebellum Insula, cingulate gyri, and hippocampus dACC and MCC	
Shin et al. (2009) [6]	Resting	(1) 14 (2) 19 (non-PTSD)	(3) 14 (co-twin HC) (4) 19 (co-twin HC)			
Bremner et al. (1997) [7]	Symptom provocation	10	10 (HC)	↓ Metabolism	OFC, parietal cortex, and temporal cortex including the hippocampus	
PET studies of regional cerebral blood flow						
Study	Condition	Paradigm	PTSD	Control	Increased/ decreased	Brain regions
Bremner et al. (1999) [8]	Symptom provocation	Sensory stimuli	10	10 (non-PTSD)	↑	Posterior cingulate, precentral/inferior parietal cortex, and lingual gyrus
Shin et al. (1997) [9]	Symptom provocation	Sensory stimuli	7	7 (non-PTSD)	↓	mPFC including ACC
Pissiota et al. (2002) [10]	Symptom provocation	Sensory stimuli	17	-	↑	Ventral ACC and right amygdala
Vermetten et al. (2007) [11]	Symptom provocation	Sensory stimuli	8	8 (non-PTSD)	↓	Broca's area
Bremner et al. (1999) [12]	Symptom provocation	Script-driven imagery	10	10 (non-PTSD)	↑	Right sensorimotor cortex and right amygdala
Shin et al. (1999) [13]	Symptom provocation	Script-driven imagery	8	8 (non-PTSD)	↑	Amygdala, insula, mPFC, and ACC
Britton et al. (2005) [14]	Symptom provocation	Script-driven imagery	16	15 (non-PTSD) 14 (HC)	↓	Lateral PFC
Shin et al. (2004) [15]	Symptom provocation	Script-driven imagery	17	19 (non-PTSD)	↑	Motor and posterior cingulate cortices
Rauch et al. (1996) [16]	Symptom provocation	Script-driven imagery	8 (traumatic scripts)	8 (PTSD) (neutral scripts)	↓	mPFC (particularly ACC), hippocampus, and visual association cortex [All trauma exposed group (PTSD+non-PTSD)]
Osuch et al. (2001) [17]	Symptom provocation	Script-driven imagery	12	-	↓	OFC and anterior temporal poles Left inferior frontal gyrus rACC
Bremner et al. (2005) [19]	Symptom provocation	Fear conditioning	8	11 (non-PTSD)	↑	Amygdala Medial frontal gyrus Right limbic and paralimbic regions and visual cortex Left inferior frontal and middle temporal cortices Brainstem, lingual, bilateral insula, right putamen, left hippocampal/parahippocampal, somatosensory, and cerebellar regions DLPFC, right fusiform gyrus, and right MTC Left amygdala ACC

Table 1. Continued

PET studies of regional cerebral blood flow						
Study	Condition	Paradigm	PTSD	Control	Increased/decreased	Brain regions
Giloba et al. (2004) [20]	Symptom provocation	Functional connectivity	14	12 (non-PTSD)	Effective connectivity	Amygdala on visual cortex, subcallosal gyrus, and AC
Semple et al. (1993) [21]	Active task	Emotion-unrelated	6	7 (HC)	↑	OFC
Semple et al. (1996) [22]	Active task	Emotion-unrelated	8	8 (HC)	↓ Perfusion ratio	Left/right hippocampus
Semple et al. (2000) [23]	Active task	Emotion-unrelated	7	6 (HC)	↓	Parietal cortex
Shin et al. (2004) [24]	Active task	Emotion-unrelated	8	8 (non-PTSD)	↑	Right amygdala, left parahippocampal gyrus, and occipital cortex
Bremner et al. (2003) [25]	Active task	Emotion-unrelated	10	12 (non-PTSD) 11 (HC)	↓	Frontal cortex including ACC
Shaw et al. (2002) [26]	Active task	Functional connectivity	10	10 (HC)	↑	Left precentral gyrus, bilateral inferior parietal lobes
Bremner et al. (2003) [27]	Active task	Emotion-related	10	11 (HC)	↓	Fronto-temporal regions
Bremner et al. (2004) [28]	Active task	Emotion-related	12	9 (non-PTSD)	↑	Left middle frontal gyrus, visual association cortex, left IPC, and PCC
					↓	mPFC, left hippocampus, and inferior temporal gyrus/fusiform gyrus
					↓	ACC
PET studies of labeled ligand						
Study	Neuroreceptor/transporter	PTSD	Control	Control	Increased/decreased	Brain regions
Frick et al. (2016) [35]	5-HT transporters	16	16 (HC)		↓ Expressions	Insula, putamen, thalamus, and lateral orbitofrontal gyrus
Liberzon et al. (2007) [29]	Micro-opioid receptors	16	14 (non-PTSD) 14 (HC)		↓ Binding potentials	ACC and amygdala
Pietrzak et al. (2014) [30]	Kappa-opioid receptors	35 (30 trauma-exposed, 5 HC)	-		↓ Receptors	Amygdala-ACC-ventral striatal neural circuit
Neumeister et al. (2013) [31]	Brain cannabinoid CB1 receptor	25	12 (non-PTSD) 23 (HC)		↑ Receptors	ACC, amygdala, OFC
Sullivan et al. (2013) [32]	5-HT(1A) receptors	20	49 (HC)		↑ Bindings	Amygdala and brainstem raphe nuclei
Bonne et al. (2005) [33]	5-HT(1A) receptors	12	11 (HC)		-	Not significant

Table 1. Continued

PET studies of labeled ligand					
Study	Neuroreceptor/ transporter	PTSD	Control	Increased/ decreased	Brain regions
Pietrzak et al.(2013) [34]	5-HT(1B) receptors	49	-	↑ 5-HT1B heteroreceptors ↓ Receptors	Pallidum and hippocampus - associated with anxious arousal symptoms Hippocampus - associated with behavioral inhibition and numbing symptoms Locus coeruleus
Pietrzak et al.(2013) [36]	NET	22	16 (non-PTSD) 18 (HC)	↓ Transporters	Cortex, hippocampus and thalamus
Geuze et al.(2008) [37]	GABA(A) receptors	9	7 (non-PTSD)	↓ Bindings	

The ↑ symbol indicates an increase, and ↓ a decrease.

5-HT; 5-hydroxytryptamine (serotonin); AC, anterior cingulate cortex; ACC, anterior cingulate gyrus; CATs, catecholamines; dACC, dorsal anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; GM, gray matter; HC, healthy controls; IPC, inferior parietal cortex; MCC, medial cingulate cortex; mPFC, medial prefrontal cortex; MTC, medial temporal cortex; ET, norepinephrine transporter; OFC, orbitofrontal cortex; PCC, posterior cingulate cortex; PET, positron emission tomography; PFC, prefrontal cortex; PTSD, posttraumatic disorder; rACC, rostral anterior cingulate cortex; rCMRglu, resting cerebral metabolic rate for glucose.

exposed to diesel smell reminiscent of traumatic experiences, demonstrated enhanced rCBF in the prefronto-limbic regions including the amygdala, insula, and mPFC, particularly the ACC, and diminished rCBF in the lateral prefrontal cortex relative to non-PTSD veterans, suggestive of alterations in memory and olfactory processing related to PTSD [11].

Script-driven imagery

Script-driven imagery, in which participants listened to either their trauma-related-autobiographical scripts or neutral scripts in the scanner, has been frequently used as a traumatic reminder in PET studies of PTSD.

Two PET studies have examined rCBF differences among sexually abused PTSD women, sexually abused non-PTSD women, and healthy women in response to traumatic vs. neutral scripts [12, 13]. Bremner et al. revealed that the PTSD group had significantly reduced rCBF in the mPFC particularly the ACC, hippocampus, and visual association cortex, and increased perfusion in the motor and posterior cingulate cortices relative to the trauma-exposed non-PTSD group [12]. In a PET study using [¹⁵O]CO₂, both trauma-exposed groups with and without PTSD showed elevated rCBF in the anterior paralimbic regions in response to traumatic vs. neutral conditions. However, the PTSD group relative to non-PTSD group demonstrated reduced perfusion in the anterior cingulate, left inferior frontal, and parahippocampal gyri, and greater perfusion increases in the OFC and anterior temporal pole [13]. These findings implicate that the deactivation of the cognitive areas such as the frontal cortex and hippocampus, resulting in dysfunctional emotion control, is a biological underpinning responsible for PTSD pathophysiology. This interpretation could be further supported by a PET study using [¹⁵O]H₂O [14]. While veterans with and without PTSD as well as healthy noncombat individuals all exhibited mPFC deactivation, veterans with PTSD showed greater deactivation of the rostral ACC relative to the comparison groups.

In line with these findings, increased rCBF in the amygdala and diminished perfusion in the medial frontal gyrus were reported in combat veterans with PTSD who were exposed to traumatic script vs. neutral script [15]. Consistently, the PTSD group exhibited increased rCBF in the right limbic and paralimbic regions, as well as the visual cortex. Alterations in these brain regions were respectively associated with symptoms of emotional distress and re-experiencing during exposure to traumatic script vs. neutral script. Blood flow of the left inferior frontal and middle temporal cortices was relatively reduced in the PTSD group [16]. In another PET study using script-driven imagery, flashback intensity of PTSD patients was positively associated with rCBF in the brain

areas involved in visuospatial cue-processing, memory, and motor control including the brain stem, bilateral insula, left hippocampal and parahippocampal, lingual, somatosensory, and cerebellar areas and negatively with rCBF in the bilateral dorsolateral prefrontal cortex (DLPFC), right fusiform gyrus, and right medial temporal cortex [17]. This inverse correlation between flashback intensity and rCBF in the DLPFC suggests dysfunctional activity of the DLPFC in PTSD patients. Interestingly, a longitudinal neuroimaging study on recovering PTSD patients found that as patients recover from PTSD, they showed greater DLPFC thickness relative to controls and the thickness eventually normalized during the recovery period [18].

Fear conditioning

Bremner et al. investigated the neural correlates during fear conditioning, fear extinction, and habituation in sexual abuse-related PTSD patients in a PET study using [^{15}O]H $_2\text{O}$ [19]. PTSD patients showed greater rCBF in the left amygdala during fear acquisition and decreased ACC activation during extinction, relative to healthy controls. The amygdala and ACC have been suggested for their respective roles in acquisition and extinction of fear responses related to PTSD. More specifically, in PTSD subjects, fear acquisition was associated with increased activation in the bilateral superior temporal gyrus, bilateral inferior frontal gyrus, and posterior cingulate and reduced activation in the bilateral inferior frontal gyrus, bilateral superior temporal gyrus, posterior cingulate, and cerebellum. Within the PTSD group, fear extinction was related with dysfunction in the mPFC (ACC, subcallosal gyrus, OFC) and visual association cortex. Importantly, decreased perfusion in the mPFC during fear extinction was associated with heightened anxiety within the PTSD group.

These findings are consistent with the neurobiological model of PTSD implying the key role of the mPFC dysregulation over the hyperactive amygdala during acute threat in the pathophysiology of PTSD. A negative correlation found between elevated amygdalar blood flow during fear acquisition and decreased rCBF in the mPFC during fear extinction further supports this model of hyperactive amygdala and hypoactive mPFC in PTSD.

Functional connectivity

Functional connectivity analysis examines efficiency of functional coupling among brain regions, as indicated by balanced activation patterns within the brain network. PTSD literature has suggested alterations in the brain network related to higher cognitive and emotional processing. A functional connectivity analysis of PET study using [^{15}O]H $_2\text{O}$ demonstrated that civilian trauma-related PTSD patients showed alterations in the emotional

control network during traumatic vs. neutral scripts relative to the trauma-exposed non-PTSD individuals. The altered functional connectivity pattern was characterized by predominant influences of the amygdala over brain regions associated with higher-order and autonomic processing of visual memory (ACC, visual cortex, and subcallosal gyrus). Memory retrieval networks showed no differences in their connectivity patterns between PTSD and non-PTSD groups [20].

Cognitive tasks

Participating in cognitive tasks elicits predicted responses in brain regions associated with memory and emotional processing. Several PET studies have investigated the neural correlates of dysfunctional memory and emotional regulation in PTSD, using cognitive tasks that often include traumatic reminders. Findings of decreased activation in the mPFC have been replicated in PTSD patients during cognitive tasks. However, the hippocampus showed inconsistent activation patterns depending on whether the tasks involve emotional words related to trauma or not.

Non-emotional cognitive tasks

Sampele and colleagues examined rCBF pattern during auditory continuous performance tasks (ACPT) in three PET studies [21-23]. The earlier PET studies using H $_2\text{O}_{15}$ reported that war veterans with PTSD during the ACPT task showed relatively higher blood flow in the OFC and lower rCBF in the hippocampus and parietal cortex [21, 22].

These findings were not entirely replicated by a more recent PET study using [^{15}O] butanol. War veterans with PTSD, while performing ACPT task, had relatively elevated rCBF in the right amygdala, left parahippocampal gyrus, and occipital cortex and reduced rCBF in the frontal cortex, including the ACC, relative to the comparison group [23]. Similarly, firefighters with PTSD compared to those without PTSD showed higher rCBF in the left amygdala and bilateral hippocampus during explicit retrieval of non-emotional words, in a PET study using a word-stem completion task. Within the PTSD group, a positive association was found between PTSD symptom severity and rCBF in the hippocampus and parahippocampus [24].

These findings of the hyperactive hippocampus during cognitive tasks were not replicated in a PET (H $_2\text{O}_{15}$) study using the hippocampal-based verbal declarative memory task (paragraph-encoding task) [25]. PTSD patients with childhood sexual abuse history, relative to the trauma-exposed non-PTSD group, demonstrated the left hippocampal deactivation, along with lower rCBF in the OFC and cerebellum.

Shaw et al., using an n-back working memory task, reported

alterations in memory network connectivity in PTSD patients, specifically characterized by hyperactivation in the left precentral gyrus and bilateral inferior parietal lobes and hypoactivation in the fronto-temporal regions including the bilateral middle frontal gyri, inferior medial frontal lobe, and right inferior temporal gyrus [26].

Emotional-cognitive tasks

PET (H_2O_{15}) studies have examined the neural responses of female PTSD patients with sexual abuse history during the cognitive tasks including the traumatic reminders (words such as 'rape' or 'mutilate'). Dysfunction in brain regions related to memory and emotion has been suggested as PTSD-specific neural substrates [27, 28].

Specifically, the PTSD group, relative to the non-PTSD comparison group, had lower rCBF in the mPFC (ACC and OFC), left hippocampus, and inferior temporal gyrus/fusiform gyrus and increased perfusion in the left middle frontal gyrus, visual association cortex, left inferior parietal cortex, and posterior cingulate cortex during the performance of an emotional word retrieval task [27].

Another [^{15}O]H₂O PET study using the emotional Stroop task further adds evidence in support of the ACC dysfunction as neural correlates underlying PTSD pathophysiology. Women with PTSD showed decreased rCBF in the ACC, while performing the emotional Stroop task (naming the color of the word, 'rape'), but not during the classical Stroop task [28].

PET STUDIES OF LABELED LIGAND

Neuroreceptor imaging studies using PET have investigated alterations in regional populations and binding potentials of receptors related to PTSD. Availability of brain opioid receptor and serotonergic receptor in the medial temporal areas and ACC has received particular attention in PET studies due to their implicated roles in modulation of fear and anxiety stress, respectively.

Opioids

A PET study using [^{11}C]carfentanil as a tracer has provided neurobiological evidence for the role of opioid system in the development of PTSD [29]. The combat-related PTSD patients showed lower micro-opioid receptor binding potential in the ACC, implying dysfunctional stress coping. In contrast, the combat-exposed non-PTSD individuals showed decreases in micro-opioid receptor-binding potential of the amygdala and increases in that of the OFC. Both veterans with and without PTSD relative to healthy controls showed greater binding potential in the OFC and lower

binding potential in the dorsal frontal and insular cortex, nucleus accumbens, and amygdala. In addition, lower *in vivo* kappa-opioid receptor availability in the amygdala-ACC-ventral striatal neural circuit of trauma-exposed individuals was associated with their trauma-related loss symptoms [30]. Veterans with PTSD showed heightened concentrations of cannabinoid type 1 (CB₁) receptor in the ACC, OFC, and amygdala relative to healthy controls, leading to upregulation of glucocorticoid system, increased norepinephrine projections to the amygdala, and hyperconsolidation of traumatic memories. Atypical signaling mediated by elevated brain CB₁ receptor along with lower anandamide and cortisol levels of PTSD veterans could be implicated as a promising biomarker related to PTSD etiology [31].

Serotonin

A PET study with [^{11}C]WAY-100635 reported higher serotonin-1A (5-HT_{1A}) binding in the forebrain and brainstem of patients with PTSD relative to healthy controls, which could be regarded as a potential brain biomarker for stress exposure. PTSD patients with and without comorbid major depression showed higher *in vivo* 5-HT_{1A} binding in the amygdala and brain stem raphe nuclei, leading to less release of serotonin and then mood imbalance [32]. However, this was challenged by non-significant findings of 5-HT_{1A} receptor concentrations related to PTSD [33].

In a [^{11}C]P943 PET study, PTSD-related anxious arousal symptoms could potentially be explained by increased serotonin-1A (5-HT_{1B}) heteroreceptors in the pallidum and hippocampus, which may influence the glutamatergic activity. Decreased 5-HT_{1B} receptors in the hippocampus were associated with behavioral inhibition and numbing symptoms in PTSD patients partly due to the imbalance between excitatory and inhibitory neurotransmission and modulation of gamma aminobutyric acidergic outputs [34]. Furthermore, a lower degree of overlapping expression of both serotonin transporters and neurokinin-1 receptors in the insula, putamen, thalamus, and lateral orbitofrontal gyrus of PTSD patients was correlated with greater PTSD symptom severity in a PET study using multi-tracers including [^{11}C]-3-amino-4 and [^{11}C]GR205171 [35].

Others

Veterans with chronic PTSD relatively showed a reduction in norepinephrine transporter availability in the locus coeruleus, which was positively associated with the severity of hypervigilance symptoms [36]. Another PET study reported lower [^{11}C]flumazenil binding in the hippocampus and thalamus in combat veterans with PTSD, indicating diminished function of benzodiazepine/gamma aminobutyric acid-A (GABA_A) receptor related to PTSD

pathology [37].

SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY

SPECT is a molecular imaging modality which uses tracers labeled with gamma-emitting radioactive isotopes [38]. Although SPECT offers poorer spatial resolution relative to PET, it is widely used due to its comparatively less sophisticated and inexpensive methodology [39]. Accordingly, a number of studies have employed SPECT in investigating molecular pathophysiology of PTSD. Using SPECT, cerebral perfusion and neuroreceptor density have been measured as the metabolic activities and neurochemistry related to PTSD. Moreover, SPECT has been used for evaluation of the neural mechanisms underlying the responses to pharmacological and psychotherapy treatments. All SPECT studies included in this review are presented in Table 2.

SPECT STUDIES OF REGIONAL CEREBRAL BLOOD FLOW

Resting state paradigms

Most SPECT studies on PTSD have examined alterations in rCBF, which are measured by the uptake of radioactive tracer in certain brain areas and often interpreted as an indirect measure of brain activity. Using resting state paradigms, several studies have used SPECT to investigate regional cerebral perfusion in patients with PTSD.

In a SPECT study using technetium-99m hexamethylpropylenamine oxime (Tc-99m HMPAO), PTSD patients showed an increase in rCBF in the anterior and posterior cingulate cortices, right temporal and parietal cortices, right caudate/putamen region, and left orbital and hippocampal regions compared with healthy controls during resting conditions [40]. When the analysis was restricted to medication-free PTSD patients compared with controls, an increase in rCBF was found only in the ACC, caudate/putamen regions, and right orbital cortex.

Using a different radioactive tracer of technetium-99m ethyl cysteinate dimer (Tc-99m ECD), Chung et al. replicated some of the results of Sachinvala [40] such as increased rCBF in the ACC and hippocampus related to PTSD [41]. Additionally, this study reported an increase of cerebral perfusion in the parahippocampal gyrus, isthmus of cingulate gyrus, and rhinencephalon and a decrease in the left frontal precentral, inferior temporal, and parietal angular gyri. Overall, the results from both studies suggest the involvement of the limbic areas in the pathophysiology of PTSD. Moreover, alterations of cerebral blood perfusion in the limbic regions in PTSD patients are consistent with the previous findings [9, 11, 16, 23, 42].

Elevated rCBF was found in the cerebellum of PTSD patients compared with both trauma-exposed and unexposed healthy controls in a SPECT study using Tc-99 HMPAO [43]. Moreover, PTSD patients exhibited an increase in cerebral perfusion in the left inferior lateral temporal lobe and left supramarginal gyrus to the postcentral gyrus compared with trauma-exposed controls, as well as an increase in the right precentral, superior temporal, inferior temporal, and fusiform gyri compared with trauma-unexposed controls. In another study using Tc-99 HMPAO, an increased level of cerebral perfusion was found in the right superior parietal lobe and a decrease in the right thalamus compared to healthy controls [44]. The authors suggest that the decreased thalamic rCBF may be a coping strategy to reduce re-experiencing symptoms by eluding the process of information that are related to the traumatic event. The role of the thalamus in sensory gating related to the traumatic event has been further supported by a recent study examining dynamic changes in amygdalar connectivity to the thalamus during recovery from PTSD [45].

Interestingly, two SPECT studies have reported interhemispheric asymmetry of cerebral perfusion in PTSD patients. Specifically, PTSD patients showed higher cerebral blood flow in the left hemisphere than in the right, most notably in the temporoparietal region [46] and in the projection area of the ventral basal ganglia [47].

Symptom provocation paradigms

In symptom provocation paradigms, individuals are exposed to certain stimuli to elicit trauma-related symptoms. A few SPECT studies of PTSD have been performed using auditory stimulus such as combat sounds or personalized trauma scripts. In veterans with combat related trauma, an elevated level of rCBF was observed in the mPFC, left amygdala, and left nucleus accumbens during exposure to combat sounds [42, 48]. One of the veterans from the study experienced a full-blown flashback following exposure to combat sounds. This case was not included in the final analysis and was reported separately in a different study [49]. During his flashback, the veteran showed greater uptake in subcortical regions compared with cortical regions, particularly in the thalamus, suggesting corticothalamic dysfunction as possibly playing a role in flashbacks. In another SPECT study with Tc-99 HMPAO, Lindauer et al. used script driven imagery to examine rCBF in police officers with PTSD in comparison to trauma-exposed controls [50]. In the traumatic versus neutral conditions, rCBF increase was found in the right cuneus and decrease in the medial frontal gyrus.

Two of these SPECT studies using symptom provocation

Table 2. SPECT studies in patients with PTSD

SPECT studies of regional cerebral blood flow					
Study	Condition	PTSD	Control	Increased/ decreased	Brain regions
Sachinvala et al. (2000) [40]	Resting	17	8 (HC)	↑	Bilateral AC/PC regions, the right temporal and parietal regions, the right caudate/putamen region, and the left orbital and hippocampal regions Restricted to drug-free PTSD: caudate/putamen regions, anterior cingulate cortex, and the right orbital cortex
Chung et al. (2006) [41]	Resting	23	64 (HC)	↑	Limbic regions
Liberzon et al. (1999) [42]	Symptom provocation	14	14 (HC) 14 (non-PTSD)	↓	Superior frontal gyrus and parietal/temporal regions
Bonne et al. (2003) [43]	Resting	11	11 (HC) 17 (non-PTSD)	↑	Left amygdala and left nucleus accumbens
Kim et al. (2007) [44]	Resting	19	19 (HC)	↑	Cerebellum
Mirzaei et al. (2001) [46]	Resting	8	8 (HC)	↑	Right superior parietal lobe
Pavic et al. (2003) [47]	Resting	25	-	↓	Right thalamus
Zubieta et al. (1999) [48]	Symptom provocation	12	12 (HC) 11 (non-PTSD)	↑	Left > right in the temporoparietal region in PTSD group
Liberzon et al. (1996) [49]	Symptom provocation	1	-	↑	Interhemispheric asymmetry
Lindauer et al. (2004) [50]	Symptom provocation	15	15 (non-PTSD)	↑	Interhemispheric asymmetry
				↓	Left > right in projection area of ventral basal ganglia in 13 of 25 participants
				↑	Medial prefrontal cortex
				↑	Subcortical regions, particularly the thalamus, during a flashback
				↑	Right cuneus
				↓	Medial frontal gyrus
SPECT studies examining treatment responses*					
Study	Therapy	PTSD	Control	Increased/ decreased	Brain regions
Seedat et al. (2004) [53]	Pharmacotherapy	11	-	↓	Left medial temporal cortex
Peres et al. (2007) [54]	Psychotherapy	16	11 (non-PTSD)	↑	Parietal lobes, left hippocampus, thalamus, and left prefrontal cortex
Lindauer et al. (2008) [55]	Psychotherapy	20	15 (non-PTSD)	↓	Right middle frontal gyrus
Levin et al. (1999) [56]	Psychotherapy	6	-	↑	Anterior cingulate gyrus and left frontal lobe in 4 of 6 patients
Lansing et al. (2005) [57]	Psychotherapy	6	-	↑	Left inferior frontal gyrus
Pagani et al. (2007) [58]	Psychotherapy	15	27 (non-PTSD)	↓	Bilateral occipital lobe, left parietal lobe, and right precentral frontal lobe
				↑	Orbitofrontal cortex and temporal pole, extended to the lateral temporal cortex and to the hypothalamus

Table 2. Continued

SPECT studies of labeled ligand					
Study	Neuroreceptor/ transporter	PTSD	Control	Increased/ decreased	Brain regions
Bremner et al. (2000) [59]	BZD receptor binding	13	13 (HC)	↓	Prefrontal cortex
Fujita et al. (2004) [60]	BZD receptors	19	19 (HC)	-	No regional differences
Hoexter et al. (2012) [61]	DAT density	21	21 (non-PTSD)	↑	Bilateral striatal DAT

The ↑ symbol indicates an increase, and ↓ a decrease.

*Only post-treatment findings are included.

AC, anterior cingulate; BZD, benzodiazepine; DAT, dopamine transporter; HC, healthy controls; PC, posterior cingulate; PTSD, posttraumatic disorder; SPECT, single photon emission computed tomography.

paradigms reported inconsistent findings on the mPFC [48, 50]. A large body of literature on PTSD suggests that the mPFC plays a critical role in pathogenesis of PTSD. Dysfunctions in the mPFC may lead to failed suppression of fear responses. While some PET and SPECT studies have confirmed this view [8, 12-14, 27, 50], other studies have found no significant findings [10, 17, 43, 46] and some studies even found hyperactivation [9, 16, 40, 48].

SPECT STUDIES EXAMINING TREATMENT RESPONSES

Neuroimaging studies have been used to evaluate the neuroanatomical correlates of therapeutic efficacy of various treatments. Thus far, several treatment approaches have been applied and found as being effective in treating PTSD [51]. These treatments include pharmacological therapies such as serotonin selective reuptake inhibitor (SSRI) medications, as well as psychological therapies such as cognitive behavioral therapy (CBT) and eye movement desensitization and reprocessing (EMDR). In recent years, several SPECT studies have examined the effects of pharmacological and psychological treatments on regional cerebral activity in PTSD patients.

Pharmacotherapy

The most commonly studied pharmacological treatment for PTSD involves SSRI medications [52]. Seedat et al. conducted a SPECT Tc-99 HMPAO study in patients who were treated with SSRI, citalopram, for 8 weeks [53]. SPECT data were obtained twice before and after the treatment to examine the effects of SSRI on rCBF. The study reported that PTSD patients who were treated with SSRI showed significant deactivation in the left medial temporal cortex. The authors suggest that reduced activity in the medial temporal cortex may be due to SSRI-induced effects and then improvement of PTSD symptoms. This finding of normalization of the temporo-limbic dysregulation with treatment in PTSD patients is consistent with some of the previous studies [7, 13, 16, 46].

Psychotherapy

The effectiveness of psychotherapies including CBT and EMDR in treating patients with PTSD has been validated in a number of studies [51]. A SPECT study using Tc-99m ECD have investigated the effects of exposure-based and cognitive restructuring therapy on the brain in individuals who have subthreshold PTSD compared with those without treatment [54]. In the post-treatment scan using personalized script driven imagery, increased activity was found in the left prefrontal cortex, left hippocampus, thalamus, and parietal lobes during memory retrieval. The authors

suggest that increased rCBF in these areas may reflect better inhibition of the amygdala, better processing of trauma-related spatial and temporal information, and more efficient integrative functions.

In another SPECT study using script driven imagery, PTSD patients were observed after 16 weeks of brief eclectic psychotherapy compared to those on the waiting list and trauma-exposed controls [55]. Before psychotherapy, PTSD patients showed greater rCBF in the right insula and right superior/middle frontal gyrus compared with controls. After psychotherapy, patients who received treatment showed lowered rCBF in the right middle frontal gyrus compared with patients who were put on the waiting list. Reduced activation in the medial frontal gyrus following the treatment has not been in line with the existing literature. The authors explain that possible reasons for this discrepancy include differences in patient populations, paradigms, and study design.

Three SPECT studies were performed to investigate the effects of EMDR in PTSD patients. Levin et al. acquired scans before and after 3 sessions of EMDR treatment using script driven imagery paradigm in a single patient [56]. In the post-treatment scan compared to pre-treatment scan, increased activation was observed in the anterior cingulate gyrus and left frontal lobe during retrieval of the traumatic memory. The authors reported that these changes were consistent in 4 of 6 patients from their ongoing study. Using technetium-99m exametazime, police officers with PTSD were scanned before and after EMDR treatment [57]. During scanning, the patients performed a standardized concentration task to simulate their daily functioning. In post-treatment scan, increased rCBF was found in the left frontal lobe, most notably in the inferior frontal gyrus, and decreased rCBF was observed in the right thalamus, precentral gyrus of the right frontal lobe, postcentral gyrus of the left parietal lobe, and occipital lobe.

In another SPECT Tc-99 HMPAO study examining the effects of EMDR treatment, baseline examinations revealed greater rCBF in the OFC, temporal pole, and medial temporal cortex, notably in the uncus, during script driven imagery paradigm [58]. After the treatment, increased rCBF remained significant in the OFC and temporal pole which extended to the lateral temporal cortex and to the hypothalamus. All three studies that investigated the effects of EMDR reported an increase in rCBF in the left frontal cortex. The authors attributed these discrepancies among the studies to differences in sample size, trauma type, or inclusion of a control group.

SPECT STUDIES OF LABELED LIGAND

To date, a small number of neuroreceptor imaging studies with SPECT have investigated the neurochemical mechanisms underlying PTSD. These studies examined binding potentials for benzodiazepines [59, 60] and dopamine transporters [61] in patients with PTSD.

Benzodiazepine

Animals that have been exposed to excessive stress showed a decrease in benzodiazepine receptor binding in the frontal cortex [62]. Moreover, given the clinical efficacy of benzodiazepine-type medications in treating anxiety symptoms in PTSD, decreased benzodiazepine receptor binding in the frontal cortex may play a role in the maintenance of PTSD symptoms. Using a SPECT imaging technique with [¹²³I]iomazenil, the binding potential of central benzodiazepine receptors were examined [59]. The authors found a lower distribution volume of benzodiazepine receptors in the prefrontal cortex (Brodmann's area 9) among 13 Vietnam War veterans with PTSD compared with healthy controls. However, another study using the same imaging modality with [¹²³I]iomazenil did not confirm this finding in 19 Gulf War veterans with PTSD [60]. The authors from the latter study explained that the differences in severity of symptoms, duration of illness, and choice of control group may account for the inconsistent findings.

Dopamine

A growing number of evidence has suggested that hyperdopaminergic activity may underlie the molecular mechanisms involved in the development and maintenance of PTSD, especially with regard to arousal symptoms [63-66]. In a SPECT study with technetium-99m TRODAT-1, the dopamine transporter binding potential was measured in the striatum as the region of interest in patients with PTSD [61]. The results of the study reported that PTSD patients showed greater dopamine transporter density in the bilateral striatum compared to trauma-exposed individuals without PTSD.

MAGNETIC RESONANCE SPECTROSCOPY

Magnetic resonance spectroscopy (MRS) is a non-invasive brain imaging method for measuring the concentration of neurochemical metabolites in the living brain. While MRS can be used to measure a variety of nuclei and isotopes such as proton (¹H), carbon (¹³C), fluorine (¹⁹F), phosphorus (³¹P), and lithium (⁷Li), ¹H- and ³¹P-MRS are most commonly used because they are abundant in brain tissue and allow analysis of a variety of

metabolites [67]. This review focuses on studies using ^1H -MRS since there have not been studies using ^{31}P -MRS in PTSD patients. The major neurochemical metabolites that can be measured by ^1H -MRS include N-acetylaspartate (NAA), choline-containing compounds (Cho), creatine and phosphocreatine (Cr), gamma aminobutyric acid (GABA), and glutamate-glutamine complex (Glx). Each metabolite shows a distinct peak in the ^1H -MRS [68]. In the normal brain, the major peaks are from N-acetyl groups of NAA (2.1 ppm), Cr (3.02 ppm), and Cho (3.22 ppm) and minor peaks include Glx (2.1~2.4 ppm) and myoinositol (Ino) (3.55 ppm). Therefore, alterations in these major peaks may implicate changes in neurochemical metabolites that are associated with psychiatric disorders. All MRS studies reviewed in this article are presented in Table 3.

MRS STUDIES OF NEUROCHEMICAL METABOLITES

In previous ^1H -MRS studies on PTSD patients, the concentration and ratio of major neurochemical metabolite peaks, such as NAA level, NAA/Cr ratio, and Cho/Cr ratio, were studied. Cr is often used as a denominator in signal ratio because Cr is in chemical equilibrium and comparatively unaffected by neurodegenerative processes [68]. GABA levels have also been examined using editing techniques such as MEGA-PRESS that allows for detecting brain GABA independently from other metabolites with overlapping resonances [69]. In most of the ^1H -MRS studies of PTSD, the ACC and temporal lobe structures including the hippocampus, which play an important role in the development and maintenance of PTSD symptoms, were investigated as regions of interest (ROIs) [70-74].

N-acetylaspartate

NAA is an excitatory neurotransmitter which contributes to neuronal integrity [75]. NAA is also considered to be an indicator of neuronal density [76]. A number of studies have found that NAA reductions are associated with brain pathologies [77-80] or psychiatric disorders [81-83]. Specifically, NAA reductions have been observed in patients with PTSD relative to healthy controls [75, 84-86].

Reduced NAA levels [84-87] and NAA/Cr ratios [75, 88-91] in PTSD patients have been detected in the hippocampus. This may be partly due to PTSD-related hippocampal damage. In line with these findings, NAA/Cr ratio reductions were also found in the medial temporal lobe structures of patients with PTSD [76]. Moreover, reductions of NAA levels or NAA/Cr ratios in the hippocampus were related to PTSD symptom severity. Specifically, the NAA/Cr ratio was negatively correlated with the total scores

of the Clinician-Administered PTSD Scale (CAPS), as well as the symptom cluster scores (re-experiencing, avoidance, and hyperarousal) of the CAPS [92]. Likewise, it has been reported that NAA levels of the bilateral hippocampus were negatively correlated with re-experiencing symptom severity in PTSD patients [86]. In contrast, another study showed that the NAA/Cr ratio in the medial temporal lobe, where the hippocampus is located, was positively correlated with re-experiencing symptom severity in patients with PTSD [93]. However, this finding was not replicated in a different study on similar participants [94].

The ACC has received attention in PTSD research, considering its role in processing of anxiety and extinction of conditioned fear responses. Although there are inconsistent findings [95], most previous ^1H -MRS studies have reported that the NAA/Cr ratio in the ACC was lower in PTSD patients than healthy controls [75, 86, 89, 91, 96].

Choline

Cho signal has been known as an indicator of cellular density [68]. A few ^1H -MRS studies have been performed to investigate alterations in Cho concentrations related to PTSD. The Cho/Cr ratio was increased in the bilateral hippocampus [89], ACC [95], and cingulate gyrus [91] of PTSD patients as compared with healthy controls. In addition, higher Cho/Cr ratio was associated with more severe PTSD symptoms measured using the CAPS [92]. However, Bo et al. did not find significant differences in Cho/Cr ratio or Cho levels between PTSD patients and healthy controls [87].

Gamma-aminobutyric acid and Glutamate-glutamine complex

As GABA is an inhibitory neurotransmitter and modulates neuronal excitability [37], alterations in GABA levels have been implicated in the pathophysiology of anxiety disorders, including PTSD [97]. Partly due to relatively low concentration of GABA in the human brain and its overlapping resonance with other metabolites, specific acquisition methodology with increased field strength of MRI scanners [98] as well as special editing techniques such as MEGA-PRESS [99] or MEGA-sLASER [100] may be required to accurately measure GABA levels. Therefore, only a few studies have been performed to examine GABA levels in patients with PTSD so far. A higher GABA level was found in the DLPFC and ACC of patients with PTSD relative to healthy controls [101]. The authors interpreted this results as enhanced inhibitory neurotransmission to reduce PTSD symptoms. In contrast, GABA levels were lowered in the insula [102], parieto-occipital cortex [96], and medial temporal cortex [96] of patients with PTSD than

Table 3. ¹H-MRS studies in patients with PTSD

Study	Method	PTSD	Control	ROI	Main findings
N-acetylaspartate					
De Bellis et al. (2000) [75]	NAA/Cr ratio	11	11 (HC)	ACC	↓ in the ACC
Freeman et al. (1998) [76]	NAA/Cr ratio	21	8 (non-PTSD)	TLS	↓ in the right medial TLS
Schuff et al. (2001) [84]	NAA	18	19 (HC)	Hippocampus	↓ about 23% in the bilateral hippocampus
Ham et al. (2007) [86]	NAA	26	25 (HC)	ACC	↓ in the ACC
					Negatively related with re-experience symptom scores
Bo et al. (2006) [87]	NAA	17	17 (HC)	Hippocampus	↓ in the bilateral hippocampus
Mohanakrishnan Menon et al. (2003) [88]	NAA/Cr ratio	14	7 (non-PTSD)	Hippocampus	Negatively related with re-experience symptom scores
				Hippocampus	↓ in the bilateral hippocampus
				Hippocampus	↓ in the left hippocampus
Mahmutyazicioğlu et al. (2005) [89]	NAA/Cr ratio	10	6 (HC)	ACC	↓ in the ACC
Li et al. (2006) [90]	NAA/Cr ratio	12	12 (non-PTSD)	Hippocampus	↓ in the bilateral hippocampus
Guo et al. (2012) [91]	NAA/Cr ratio	50	50 (HC)	Hippocampus	↓ in the left hippocampus
				ACG	↓ in the ACG
Shu et al. (2013) [92]	NAA/Cr ratio	11	11 (HC)	Hippocampus	↓ in the bilateral hippocampus
				Hippocampus	↓ in the bilateral hippocampus
Brown et al. (2003) [93]	NAA/Cr ratio	9	12 POWs (non-PTSD)	MTL	Negatively related with re-experience, avoidance, and hyper-arousal symptom scores
				MTL	↓ in the left MTL
Freeman et al. (2006) [94]	NAA/Cr ratio	10	10 POWs (non-PTSD)	Hippocampus	Strongly correlated with re-experiencing symptom scores in PTSD group
				Hippocampus	Not significant
Seedat et al. (2005) [95]	NAA/Cr ratio	16	11 (HC)	ACC	Not significant
				Occipital GM	
Meyerhoff et al. (2014) [96]	NAA	27	18 (non-PTSD)	ACC	↓ in the ACC
Choline					
Bo et al. (2006) [87]	Cho	17	17 (HC)	Hippocampus	Not significant
Mahmutyazicioğlu et al. (2005) [89]	Cho	10	6 (HC)	ACC	Not significant
Guo et al. (2012) [91]	Cho/Cr ratio	50	50 (HC)	Hippocampus	↑ in the bilateral hippocampus
				ACG	↑ in the ACG
Shu et al. (2013) [92]	Cho/Cr ratio	11	11 (HC)	Hippocampus	Not significant
Seedat et al. (2005) [95]	Cho/Cr ratio	16	11 (HC)	Hippocampus	Positively related with re-experience symptom scores
				ACC	↑ in the ACC

Table 3. Continued

Study	Method	PTSD	Control	ROI	Main findings
Gamma-aminobutyric acid and Glutamate-glutamine complex					
Meyerhoff et al. (2014) [96]	GABA Glu	27	18 (non-PTSD)	POC, MTC MTC	↓ in the POC and MTC ↑ in the MTC
Michels et al. (2014) [101]	GABA	12	17 (non-PTSD)	ACC	↑ in the ACC
Rosso et al. (2014) [102]	GABA	13	13 (HC)	DLPFC Insula	↑ in the DLPFC ↓ in the insula
Yang et al. (2015) [101]	Glx/Cr ratio	10	21 (HC) 23 (remitted PTSD)	Dorsal ACC ACC	Not significant PTSD < remitted PTSD < HC

The ↑ symbol indicates an increase, and ↓ a decrease.

Abbreviations: ACC, anterior cingulate cortex; ACG, anterior cingulate gyrus; Cho, choline; Cr, creatine; DLPFC, dorsolateral prefrontal cortex; GABA, gamma aminobutyric acid; Glu, glutamate; Glx, glutamate-glutamine complex; GM, gray matter; HC, healthy controls; 1H-MRS, Proton magnetic resonance spectroscopy; MTC, medial temporal cortex; MTL, medial temporal lobe; NAA, N-acetylaspartate; POC, parieto-occipital cortex; POWs, former prisoners of war; PTSD, posttraumatic disorder; ROI, region of interest; TLS, temporal lobe structure.

healthy controls. Although the number of studies was limited, a recent meta-analysis has reported no significant alterations in GABA levels related to PTSD [69].

As an excitatory neurotransmitter, Glx signal has been related to encoding of fear memory in anxiety disorders [96, 103]. The level of Glx signal was higher in the medial temporal cortex of PTSD patients relative to healthy controls [96]. This may be normalized with recovery of PTSD symptoms [103]. Since only a few previous ¹H-MRS studies have investigated GABA or Glx in PTSD patients, more studies are needed to reveal the role of GABA or Glx in PTSD pathophysiology.

CONCLUSION

Taken together, molecular neuroimaging research reviewed in this article revealed alterations of cerebral metabolism and perfusion, ligand bindings, and metabolite concentrations in the limbic regions, mPFC, and temporal cortex in patients with PTSD. Although it is generally agreed that increased brain activity in the limbic regions and decreased activity in the mPFC are involved in the pathophysiology of PTSD, several inconsistent results have been reported due to the fact that the molecular mechanisms of PTSD are complex and multifaceted. Moreover, differences in sample size, trauma type, severity and/or duration of illness, medication use, comorbid conditions, inclusion of control group, and experimental paradigms have been considered as possible reasons for the discrepancies in the findings. Alternatively, future studies may consider a larger longitudinal study with various trauma types including both trauma-exposed and non-exposed control groups. Furthermore, a multimodal molecular neuroimaging study could potentially integrate the strengths while overcoming the limitations of individual modalities, offering a comprehensive view of neurobiological mechanisms underlying PTSD.

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