



A PHARMACOLOGICAL APPROACH TOWARDS MECHANISMS OF CHRONIC STRESS INDUCING NEUROINFLAMMATION, DEPRESSION AND COGNITIVE IMPAIRMENT.

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ABSTRACT

Stress is a major contributor factor inducing depression and cognitive impairment. Up-to-date treatment is inefficient for depression with cognitive impairment due to poorly understood patho-physiological changes in chronic patients of stress. In this review, we present data of possible mechanism involved in chronic stress induced neuro behavioural changes like depressive, anxiety and memory impairment. Chronic stress increase levels of glucocorticoids, glutamate, and also evokes the pro inflammatory mediators such as interleukin 1 beta (IL-1 β), interleukin-6(IL-6), tumour necrosis factor α (TNF- α). These changes alter neurotransmitter levels and atrophy of dendrites CA1 and CA3 neurons in hippocampus causes like anxiety, depression and cognitive impairment. This article provides possible mechanism to novel pharmacological target for stress induced neuro inflammation, depression and cognitive impairment.

KEYWORDS: Stress, Neuroinflammation, Depression, Cognitive impairment.



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INTRODUCTION

Depression and Cognitive dysfunction is a common psychiatric disorder of chronic stress induced biological changes in brain.¹⁻³ WHO estimated 350 million people affected in different age groups. Although at present antidepressants are available for depressive disorder a failure of approximately 30% is noted in treating the such disorders.⁴ So, there is a eeries need to redefine the novel conceptual path-physiological pathway development of depression and cognitive impairment and to develop novel therapeutic applications. In this article, we review finding based on our understanding of chronic stress affecting on behavior and cognition through psychoneuroimmunology(PNI) causing to depression and cognitive dysfunction. Walter Cannon in 1915, pioneer described the reaction to stress as a threat with a release of the adrenergic neurotransmitters, driving the animal for the fighting or fleeing. The response, also called hyperarousal. In 1930's Selye has described⁵ three phases namely normal mechanism alarm, adaptation and exhaustion, primary phase of alarm correspond to release catecholamines, glucocorticoids and glutamate in many regions of brain and these acceleration is required for surviving. Normal activity and responsiveness of the stress systems is required for a sense of well-being, efficient task completion and appropriate social

interactions. Repeated stress may lead to physical, behavioural and /or neuropsychiatric symptoms like anxiety, depression and recognition impairment; reduction of dendritic spine and synaptic material CA1 and CA3 neurons in the hippocampus and prefrontal cortex, cardio vascular phenomena, diabetes mellitus type II and cardiovascular disease.⁵⁻⁷ Neuro behavioral changes in chronic stress are associated with neuro hormonal, immune and neuro chemical deviations.⁸ Chronic stress increases secretion of glucocorticoids and glutamate which contribute to atrophy dendrites in CA3 region,⁹ and also increases the pro inflammatory cytokines IL-1, IL-6, TNF.^{10,11} This alters levels of neurotransmitters mainly serotonin (5-HT), noradrenaline (NE) and its metabolites hydroxyindoleacetic acid (5HIAA), dopamine (DA)¹²⁻¹⁴ and cholinergic¹⁵ causing anxiety, depression with cognition impairment.^{9,12,14,16} Cytokines and elevated glucocorticoids potentiate the glutamate induced excitotoxicity and neurodegenerative disorders.^{9,10}

The aim of the present review is to highlight the role of glucocorticoids & cytokines altering the monoamino neurotransmitters and changes in morphology of hippocampus leading to stress- induced depression and cognition decline. This forms the basis for a possible drug discovery.(Figure 1).

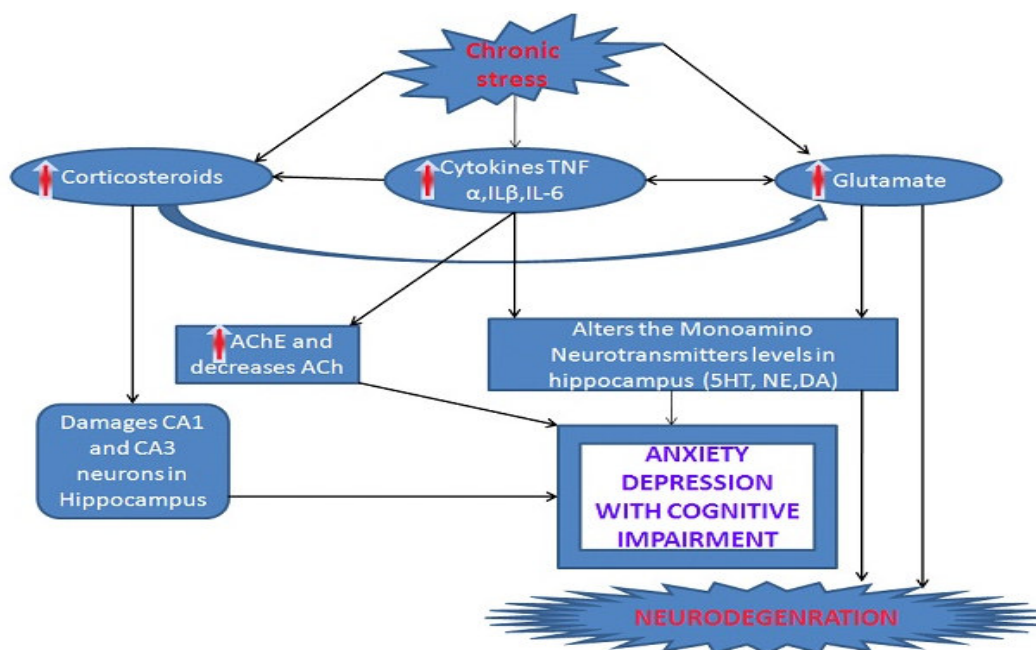


Figure 1

Chronic Stress induced cortisol /cytokines/ glutamate mediators in the brain.⁹⁻¹⁶
 [TNF = tumor necrosis factor alpha; IL 1β = interleukin 1beta; IL-6 = interleukin = 6; NE = noradrenaline; 5HT = serotonin; DA = dopamine. AChE = acetylcholinesterase; Ach = acetylcholine.]

STRESS AND GLUCOCORTICIDS ON HIPPOCAMPUS

When a situation is stressful, it stimulates hypothalamus and releases a corticotrophin releasing hormone (CRH). This CRH stimulates secretion of adrenocorticotrophic hormone (ACTH) from the pituitary gland. ACTH stimulates adrenal gland and it releases the

corticosteroids (called corticosterone in animals, and cortisol in humans) and catecholamines (adrenaline and nor adrenaline). These hormones also called as stress hormones.¹⁷ Corticosteroids reach every organ by way of circulation, which allows the coordination of most important brain regions having glucocorticoid receptors in hippocampus, amygdala and frontal lobes. Hippocampus neurons are involved in learning, memory

and body function to overcome stress, recovery and adaptation.¹⁸ This elevated glucocorticoids levels suppress the hypothalamic-pituitary- adrenal axis (HPA axis) activity at the level of the hypothalamus and pituitary. Hippocampus regulates the negative modulation of the HPA axis responsible for stress hormones through the hypothalamus. In chronic stress glucocorticoids and impaired hippocampal function contribute to disturbance of HPA axis.¹⁹ Many reports concluded that repeated stress stimulate hyperactivity of HPA axis, cause persistently elevated of glucocorticoid levels in the whole brain and impairment in the function of hippocampus which lead to behavioural changes, spatial learning and memory impairment as shown in animal studies²⁰⁻²³ and humans studies.²⁴ Rodents chronic restrain stress showed atrophy of CA3 pyramidal neurons in hippocampus which parallels to spatial memory impairments on the Y-maze in male rats,²⁵⁻²⁷ elevated anxiety like behavior in light/dark

exploration on elevated plus-maze test and open field test.²⁸⁻²⁹ Even chronic administration of corticosterone (CORT) in C57BL/J affected the behavior, learning and memory impairment shown on open field, elevated plus maze, Y maze and novel objective test.³⁰ Interestingly chronic stress induced cytokines in brain activates the HPA axis and increases release of glucocorticoids.³¹ Through this mechanism also may potentiate the glucocorticoids action on hippocampus and contributes to damage on CA3 neurons. Glucocorticoids the release of glutamate producing detrimental effects of chronic stress in hippocampus, amygdale and pre frontal cortex (PFC).³² There is also up regulation of N-methyl-D-aspartate (NMDA) receptors modifying inter gamma-Amino butyric acid (GABA) inhibitory tone which consequently leads to neuro behavioural changes, atrophy of apical dendrites of hippocampus and neurodegeneration.³³ (Figure 2).

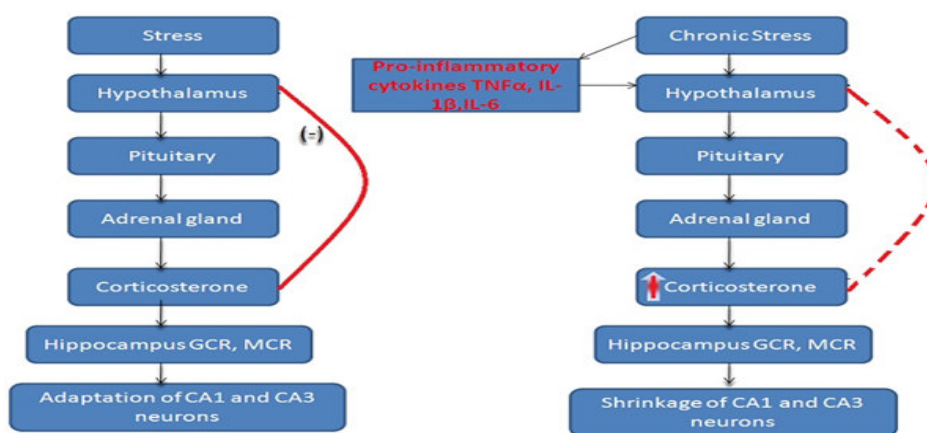


Figure 2
Chronic stress induced persistently elevated glucocorticoids lead to HPA axis dysfunction and hippocampus neuronal damage¹⁹⁻²³
 [HPA = hypothalamus pituitary axis; GRC = glucocorticoid receptor; MCR = mineralcorticoid receptor].

STRESS CYTOKINES

Like physical, psychological stress can inflame cytokines peripherally as well as in brain.³⁴⁻³⁷ Many Research findings have reported, repeated stressful condition elevates pro-inflammatory cytokines during childhood and as well as in adulthood have high possibility of mental illness.³⁸ In brain, the cytokines signaling may play most critical role in activation of microglia.³⁹ Activated microglia may evoke the expression of pro inflammatory cytokines such as interleukin 1 beta (IL-1 β), interleukin-6(IL-6), tumor necrosis factor α (TNFα), which influence the surrounding brain tissue.⁴⁰ These up regulation of cytokines associated with neuroendocrine, neurochemical systems might contribute to neuro behavioural disorders and neurodegeneration.⁴¹ In meta-analysis study of more than 300 studies about chronic stress, found an increased production of IL-6 and INF during the chronic stress, compared with control groups.⁴² Some researchers conducted studies in medical students on evaluation of examination stress

and tested patterns of pro inflammatory cytokines in the same subjects before and after the examination these result has shown in table 1. Another recent study (2015) shown hippocampus was the most frequent area affected. Increased IL-1β levels of between 20 and 200% (11/18 studies) in hippocampus has been reported by all 11 studies; 75% found psychological stress resulted in elevated IL-β activity³⁸. A longitudinal study compared long run effects of chronic stress measuring annual increase in serum IL-6 produced by caring for responsibilities.⁴³ Interestingly, pro inflammatory cytokines in response to psychological stress have shown exaggerated in patients with depression, consistent with findings that depressive symptoms are associated with amplified IL-6 response.⁴⁴ And also laboratory animals, a variety of psychological stress (Table-1). E.g. chronic restrain stress, induced pro-inflammatory cytokines,^{35,45-47} such as 1 beta(IL-1 β) , interleukin-6(IL-6), tumour necrosis factor α (TNFα) various brain regions involved in behavioural changes shown force swim test, open field exposure and elevated pluz maze.

Table 1
Studies investigating the involvement chronic of stress activating cytokines in animal models and humans.

Author	Year	Subject	Stress	Cytokine	Result
Dobbin <i>et al.</i> ,	1991	Medical students	Examination	Interferon- γ , IL-1 β	increased IL-1 β Decreased interferon- γ
Maes <i>et al.</i>	1998	Medical students	Examination	Interferon- γ , TNF- α , IL-4, IL-6, IL-10	Increased interferon- γ , TNF- α , IL-6, and IL-10;
Marshall <i>et al.</i>	1998	Medical students	Examination	Interferon- γ , IL-10	Decreased interferon- γ increased IL-10
José L.M. Madrigal <i>et al</i>	2002	Rats	Chronic restrain stress 21d \times 6hrs	TNF α & NF- κ B	Increased in hippocampus
Tianwei Guo <i>et al</i>	2014	Rats	Chronic restrain stress 21d \times 6hrs	IL-1 β , IL-6.	Increased IL-1beta and IL-6 expression levels in hippocampal CA3 region
Yuyan Cheng <i>et al</i>	2015	C57 BL/J Mouse	Foot shock stress	IL-1 β , IL-6, and TNF α	Increased IL-1 β , IL-6, and TNF α

[TNF = tumor necrosis factor alpha; IL 1 β = interleukin 1beta; IL-6 = interleukin = 6, NFKB = Nuclear factor- κ B]

Interestingly in healthy individual, cortisol eventually reduces the pro inflammatory cytokines production, But chronic stress induced excess of glucocorticoids in brain argue with microglia cells develop the resistant to effect of cortisol and unable to suppress the proinflammatory mediators.⁴⁸ Chronic stress can promote production of pro inflammatory cytokines IL-6, IL-1 β and TNF- α may Contribute to depression, learning and memory impairment (Figure 3).

CYTOKINES DEPRESSION AND COGNITIVE IMPAIRMENT

Numerous studies have reported chronic stress induced pro inflammatory cytokines in brain affects neuropsychiatric symptoms like anxiety and depression associated with cognitive impairment (Table 2), excitotoxicity and neurodegeneration. Cytokines including TNF- α , IL-1 β and IL-6 which mediate normal immune response was also shown as most certain markers in depression and cognitive impairment.^{49,50} The path physiological of behavioural changes in presences of cytokine alters the neurotransmitters levels such as serotonin, nor adrenaline, dopamine, acetylcholine and glutamate in hippocampus region and prefrontal cortex.⁵¹⁻⁵³ In rodent administration of IL-1 β cause decreased release and turnover of 5-HT, NE, DA, tryptophan in brain. It can also induce AChE expression and enhances the enzyme activity leading to acetylcholine deficit¹⁵. In addition, IL-1 β directly inhibits the acetylcholine release from hippocampus neurons has been reported. Increased Pro-inflammatory markers at rest were reported and also depressed subjects on

stress showed increase inflammatory responses. Three subject groups one with major depression and other with past history of stress when subjected to psychological stress responded with increased IL-6 in peripheral blood compared to control group.⁴⁴ One of the primary cytokine study on depressive disorder, comparing subgroups (suicidal-47; non-suicidal-17, controls-16), showed significant rise in serum pro-inflammatory markers in suicidal group than in non-suicidal and control group, which made this study to state TNF α and IL-6 as biomarkers of depressive disorder.⁵⁷ Meta-analysis of 1967 to 2008 studies reported depressive condition was positively associated with IL-1 β and IL-6 (IL-6, pb .001; IL-1, p= .03). Another recent meta-analysis of 24 studies also compared control with MDD patients and showed IL-6 significantly higher levels in serum MMD patients. Moreover, TNF α and IL-1 β leads to stimulate activation of the serotonin reuptake receptors, which increases uptake of serotonin via p38 MAPK signaling pathway.⁵⁸ In animal many studies reported stress induced neuroinflammation leading to depression, learning and memory impairment. Examples have shown in table2.

Table 2
Cognitive –Behaviour studies investing the involvement of cytokines in depression learning and memory processes.

Study	Species	Animal model	Cytokine	Behavior and Cognitive test	Findings
Jeffrey L. Voorhees <i>et al.</i> , 2013	C57 BL/J Mouse	Chronic restraint stress	IL-1 β , IL-6, TNF α	Force swim test	CRS activates Cytokines leading to depression
S. LIANG <i>et al.</i> , 2015	Rat	Chronic restraint stress	TNF	Objective recognition test, Objective placement test	TNF participates in hippocampal-dependent Memory. Neurochemical changes.
Wonil Lee <i>et al.</i> , 2015	Mice	Heat stress	IL-1 β , TNF α	Novel objective recognition, Y-Maze, step through passive avoidance	Heat stress significantly impaired learning and memory in mice
Avital <i>et al.</i> , 2003	Mouse	wt and IL-1rKO mice 129/ Sv Δ C57BL/6 background	IL-1	Morris water maze and contextual fear conditioning	IL-1 participates in hippocampus-dependent memory processes synaptic plasticity
Hryniewicz <i>et al.</i> (2007)	Mouse	wt and IL-6 Δ/Δ mice C57BL/6 background	IL-6	Novel object recognition task	IL-6 knockout mice displayed impaired recognition memory, suggesting that endogenous IL-6 plays a role in recognition memory
Baune <i>et al.</i> (2008)	C57BL/6 Mouse	TNF Δ/Δ , TNF R1 and R2	TNF	Barnes maze and novel object recognition task	Absence of TNF has detrimental effects on recognition performance, that is not receptor specific

[TNF = tumor necrosis factor alpha; IL 1 β = interleukin 1beta; IL-6 = interleukin = 6, NF- κ B = Nuclear factor- κ B]
 In transgenic mice model that IL-6 over expressed centrally also shown increased immobility behavior on the FST and TST similar to the animals that received intracranial injection IL-6.⁵⁹ In other study transgenic animals that over expressed pro inflammatory cytokines TNF- α and IL-6 has shown poor performance in recognition task.⁶⁰ Thus, while TNF- α signaling seems to be required for Physiological cognitive functioning,⁶¹ but elevated TNF- α signaling has been linked to related cognitive impairment Shown in experimental models of neuropsychiatric and neurodegenerative disorders.⁶²⁻⁶³ It is well documented that Cytokines including TNF- α induce the indoleamine 2, 3-dioxygenase (IDO), which leads to serotonin deprivation by converting tryptophan to kynurenine (KYN).

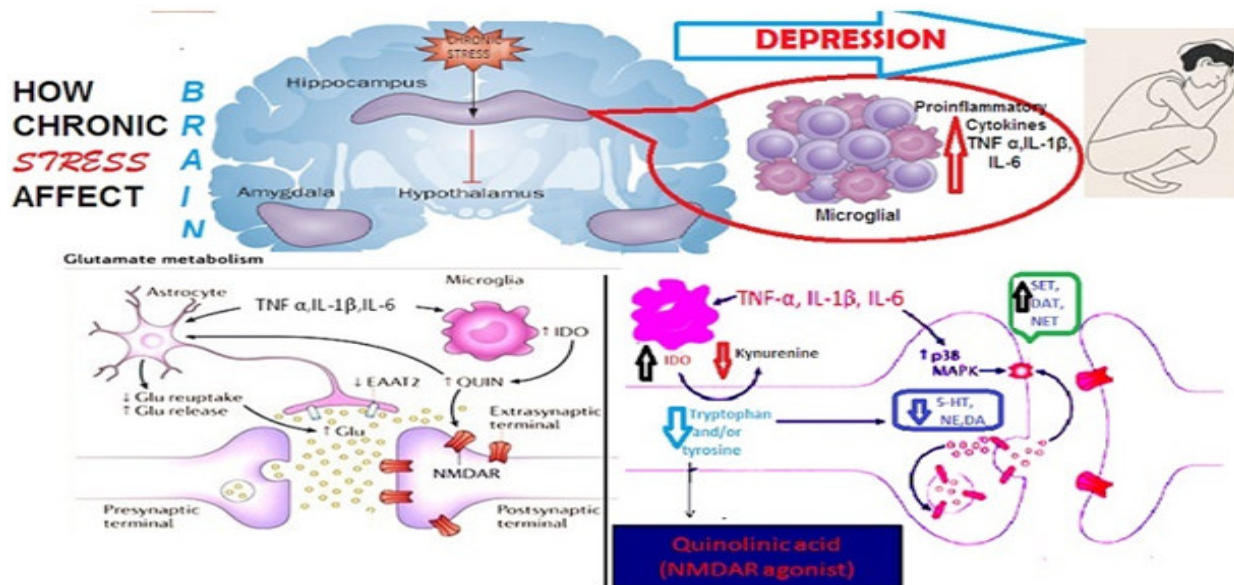


Figure 3

Chronic stress induced pro inflammatory cytokine in brain and it can alter neurotransmitters levels lead to anxiety and depression.

[TNF α = tumor necrosis factor alpha; IL 1 β = interleukin 1beta; IL-6 = interleukin = 6; NE = noradrenaline; 5HT = serotonin; DA = dopamine. AChE = acetylcholinesterase; Ach = acetylcholine; Glu = glutamate; SET = serotonin transporter; DAT = dopamine transporter; NET = noradrenaline transporter; IDO = indoleamine 2, 3-dioxygenase; QUIN = quinolinic acid; EAAT = excitatory amino acid transporters; NMDAR = N-methyl-D-aspartate receptor]

CYTOKINES INVOLVED KYNURINE PATHWAY

Microglial and astroglial cells induced indoleamine 2, 3-dioxygenase (IDO) is a rate limiting enzyme for tryptophan to kynurenine (KYN), serotonin and further serotonin catabolized to 5-hydroxyindoleacetic acid. TDO also metabolizing enzyme for tryptophan to KYN, One way KYN metabolized to 3-hydroxy kynurenine (3-OH-KYN) by kynurenine 3-monooxygenase (KMO) and in turn further metabolized to quinolinic acid; another way KYN metabolized to KYNA by kynurenine aminotransferase (KAT).⁶⁴ Chronic stress induced neuroinflammation cytokines like TNF- α , IL-1 β and IL-6 may enhance the IDO and KMO enzymes induction and lead to increased serotonin metabolism to 5-Hydroxyindoleacetic acid (5-HIAA) and KYN to quinolinic acid (NMDAR agonist). Due to these changes may result neuro behavioural changes, cognitive impairment, excitotoxicity and neurodegenerative disorders. Neuroinflammation can also alter glutamate metabolism, functions and inhibits transporters producing psychiatric impairments.⁶⁴⁻⁶⁶ CNS glutamate levels were amplified through different mechanism by pro-inflammatory cytokines which inhibits and oppose astroglial EAAT mediated glutamate reuptake function and cytokines increases microglial quinolinic acid synthesis which proved to promote synaptosomal glutamate release.^{13,67} Interestingly, mice were protected from stress-induced

depressive like behavior without affecting pro inflammatory response by reduced glutamate levels and IDO inhibition.^{44,69} This result support cytokines regulation of glutamate receptors levels as well as quinolinic acid through common pathway in stress induced neuroinflammation anxiety-like and depression. The drugs reducing glutamate, IDO levels may be applicable in stress induced neuroinflammation condition. (Figure 3)

FUTURE TREATMENT STRATEGIES AND CONCLUSION

It is strongly proved that there is a link between anxiety, depression and cognitive impairment in chronic stress induced neuro inflammation. Collectively, this review of drug discovery research support the theory that repeated stress induced neuroinflammation can alter neurotransmitters levels contributing to behavioural changes, learning and memory impairment. Moreover, approximately more than quarter of depressed patients fail to respond to present anti depressants treatments¹⁶ and these patients have been shown to exhibit elevated inflammatory cytokines.⁷⁰⁻⁷² Cognitive dysfunction in MDD is frequently sub optimally treated by conventional antidepressants, suggesting that clinical improvement may not equate to recovery.⁷³⁻⁷⁴ As a consequence, there is a compelling need for the development of novel neuroprotective and nootropic agents for MDD. An

intriguing adjunct to this line of reasoning is evidence demonstrating that traditional selective serotonin reuptake inhibitors have been to moderately decreasing the release of proinflammatory molecules from inflamed microglial⁷⁵ and that the typical time frame to the onset of therapeutics action for SRRIs corresponds closely to the time taken for the levels in the brain to reach the concentration at which they can inhibit inflamed microglia.⁷⁶⁻⁷⁷ But even clinical utilization of anti-inflammatory treatments in depression is still in research⁷⁸ and may benefit from the solution and understanding of the patho-physiological stage of cytokines within the brain might also provide vision into novel treatment strategies. Advancement of novel medication should aim in opposing depression and

cognitive impairment through down regulation harmful cytokines, correcting neurochemical, neuroendocrine systems and reversing the hippocampal morphological changes under the physiological & psychological stressors. Future research on pre-clinical studies are essential to clarifying understanding pathological mechanisms induced by stress which may be use for enhancing treatment strategies for depression and cognitive impairment.

CONFLICT OF INTEREST

Conflict of interest declared none.

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