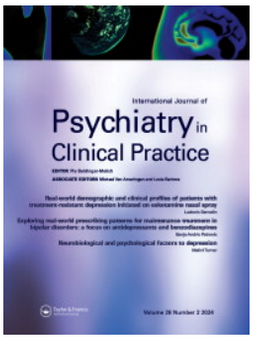

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REVIEW ARTICLE

Neurobiological and psychological factors to depression

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ABSTRACT

Major Depressive Disorder (MDD) is a common condition with complex psychological and biological background. While its aetiology is still unclear, chronic stress stands amongst major risk factors to MDD pathogenesis. When researching on MDD, it is necessary to be familiar with the neurobiological effects of several prominent contributors to the chronic stress factor experienced across hypothalamic-pituitary-adrenal (HPA) axis, neurotransmission, immune system reflexivity, and genetic alterations. Bi-directional flow of MDD pathogenesis suggests that psychological factors produce biological effects. Here, a summary of how the MDD expresses its mechanisms of action across an overactive HPA axis, the negative impacts of reduced neurotransmitter functions, the inflammatory responses and their gene x environment interactions. This paper builds on these conceptual factors and their input towards the MDD symptomatology with a purpose of synthesising the current findings and create an integrated view of the MDD pathogenesis. Finally, relevant treatment implications will be summarised, along with recommendations to a multimodal clinical practice.

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Depression; neurobiological pathways; chronic stress; neurotransmission; inflammation; gene x environment interaction

Introduction

MDD is a debilitating mental condition with serious consequences, making it a major contributor to the global burden of disease (James et al., 2017), characterised by a number of dysfunctions in the ability to emotional regulation, motivation, cognition, memory and neurovegetative symptomatology, making it standing second across mental health problems, globally (Vigo et al., 2016) and a predominant cause of disability (Friedrich, 2017). MDD pathophysiology is initiated after a prolonged over-reactivity to both external and internal stimuli, involving all the abovementioned levels (Dean & Keshavan, 2017). From this perspectiveit is prudent to consider some earlier works such as those of McGonagle and Kessler (1990), Connor and Leonard (1998) or Nestler et al. (2002), where the deliberation on these repetitive factors has been taken into the account to further the chronic stress as the chief cause to MDD pathogenesis (Keller et al., 2017; Ko et al., 2014). MDD is a mood disorder with behavioural patterns related to chronic stress, triggered by various stimuli (Menke, 2019). As any emotional activity is based on behavioural, autonomic and endocrine responses (Charles et al., 2020), similarly, stress is regulated by a complex network of psychoneuroimmune signalling that involve various responses across the central nervous system (CNS) with behaviours of thinking, feeling and willing linked to physiological expression of defence against abnormal cellular division such as inflammation and troublesome genetic expression. The biological and psychological expressions of MDD are interconnected and a more accurate understanding to the applied treatment of MDD may be built upon linking specific psychological expressions with their neurobiological pathways (Sharpley & Bitsika, 2013). With that in mind, this review discusses the interaction of chronic or cumulative stress with depression pathogenesis, examining stress responses, neurotransmission, inflammatory factors, and genetic input.

Method

This literature review began on 25 March 2022 and continued till 25 March 2023, using the Boolean phrasing with the key words: (major depressive disorder OR depression) AND (neurobiology) AND (stress OR "psychological stress" OR "chronic stress") AND (neurotransmission) AND (immun* OR inflamma*) AND (gene* OR environment). The search included depression because the literature uses these two terms interchangeably. The key search terms were applied across PubMed and Google Scholar and included journal articles published in English between January 2002 and January 2023. The author of this paper conducted the search with a primary focus on clinical studies, systematic and narrative reviews excluding grey literature and website publications to increase validity and credibility of this review. Due to single authorship, to and reduce potential bias and to improve the strength of the supplied evidence, prior to publication, this paper has been reviewed by four professionals with both clinical and research-based expertise across neuroscience and mood disorders.

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Chronic stress interaction with HPA axis and monoamines in MDD

Current research suggests that chronic stress links the psychological with neural as well as environmental with hormonal responses *via hypothalamus-pituitary-adrenal* (HPA) axis, with expression of depressive symptomatology (Keller et al., 2017; Mikulska et al., 2021). To maintain homeostasis, the interaction of nervous and endocrine systems mediate the stress response *via* the peripheral and immune signalling of corticotropin-releasing hormone (CRH) from the HPA axis (Seki et al., 2018). As HPA axis is the primary system associated with MDD hyper-responsiveness to stress (Galbally et al., 2020; Starr & Huang, 2019), chronic stress significantly contributes towards an increased glucocorticoid exchange across HPA axis (Ko et al., 2014). Serum concentration of CRH depend on the levels of activity of the hippocampal glucocorticoid receptors (Conrad, 2005). Since those are regulated by their negative feedback to the hypothalamic *paraventricular nucleus* (PVN), their signalling either stimulates or inhibits amygdala activity with regards to cognition (Sharpley, 2017), producing either hyper-vigilance or psychomotor retardation. As hormonal regulation almost entirely depends on the glucocorticoids secreted from PVN after being stimulated by adrenocorticotropic hormone (ACTH) (Carlson, 2014), glucocorticoids and particularly cortisol, are strongly implicated in the resistance to stress and in the regulation of metabolic functions (Charles et al., 2020).Therefore, the disrupted cortisol regulation with expressions of both hyper- and hypo-secretions, are amongst the most investigated MDD areas of pathogenesis (Pellegrino et al., 2013; Sharpley, 2017). Glucocorticoid imbalances results in extended autonomic and neuroendocrine disturbances (Drevets et al., 2008), observed across more than 50% of MDD patients (Duman & Aghajanian, 2012).

The cascade of hormonal release is shown in Figure 1 begins with the psychological and environmental stress triggering PVN towards activation of CRH, across the PVN-CRH pathway. Homeostatic mechanisms elevate production of cortisol to protect against excess organism stress reactivity (Pellegrino et al., 2013) however, persistently overactive PVN-CRH pathway decreases mitochondrial oxidation, lowering levels of adenosine triphosphate, and producing hypo-cognition and fatigue (Beurel & Nemeroff, 2014; Mikulska et al., 2021). CRH signals the anterior pituitary gland release *adrenocorticotropic hormone* (ACTH), involved in facilitation of cortisol release from the adrenal cortex (Carlson, 2014). CRH signals to posterior pituitary produce the hormone vasopressin that is mainly involved in MDD inflammatory responses (Beurel & Nemeroff, 2014).

Optimal noradrenaline release is central in response to stress as part of *locus coeruleus* pathway (Seki et al., 2018). Overactive HPA axis on the PVN-locus coeruleus pathway was associated with hypercortisolaemia, resulting in disrupted cognition (Keller et al., 2017) as well as hippocampal atrophy (Pellegrino et al., 2013), due to the negative feedback of glucocorticoid receptors resulting in decreased learning capacity (Pittenger & Duman, 2008). The increased signalling of HPA axis leads to enhancement of the amygdala's synaptic plasticity (Swartz et al., 2017). The homeostatic mechanism however, will compensate with an increased production of brain-derived neurotrophic factor (BDNF) across hippocampus and in the amygdala (Kuhn et al., 2014), leading to MDD adaptation (Masi & Brovedani, 2011), with amygdala-generated threat responses expressing behavioural withdrawals (Robson et al., 2017) and impaired social functioning (Duman, 2009).

The neurons linking PVN and CRH are highly responsive to stress coping as well as in regulation of *escape* behaviours (Daviu et al., 2020). An increased production of ACTH from the anterior pituitary has been found in primary adrenal insufficiencies and its enforced pathway during MDD enhances further production of cortisol (Choi et al., 2019). As CRH is a significant target of negative feedback by glucocorticoids, it is highly sensitive to their input, making it a major regulator of HPA axis (Nandam et al., 2020). Under chronic stress conditions, CRH innervations display an increased neural plasticity, raising the cellular excitability and diminishing their inhibitory activity (Herman & Tasker, 2016). The structural changes induced by a chronic stress hyperdrive reduce the efficacy of the local glucocorticoid feedback, lowering glucocorticoid receptor's resistance and leading to disordered production of cortisol (Sarapultsev et al., 2020). Since cortisol is major glucocorticoid on the PVN-CRH pathway, the homeostatic mechanism will translate its hyper-production into inflammatory conditions (Jeanneteau et al., 2012) and on the PVN-locus coeruleus pathway – as a reduction of BDNF expression (Suri & Vaidya, 2013) (see Figure 1), both leading to reduced psychomotor activity and increased psychosomatic symptomatology.

The chronic stress perpetuates CRH hyperactivity of this pathway, driving it to inflammatory and somatic MDD effects (Nandam et al., 2019). CRH-posterior pituitary gland activation triggers extra release of vasopressin, a peptide hormone acting in synergy with CRH in increasing the production of ACTH and cortisol (Bao et al., 2008). Vasopressin is known to increase loss of neural tissue and increase water retention, thereby increasing organism's inflammatory responses (Szmydynger-Chodobska et al., 2010). An example of one such inflammatory responses are the high levels of vasopressin found post-mortem in the plasma and brain of clinically depressed patients (Müller et al., 2000) along with other symptomatic changes displaying an activation of pro-inflammatory cytokines (Swartz et al., 2017), towards MDD somatic symptomatology (Sharpley & Bitsika, 2013).

During stress response, the SNS is activated with neurons in the brain stem signalling the adrenal medulla for the release of both adrenaline and hormone noradrenaline (Carlson, 2014). During stress, noradrenaline additionally acts as a neurotransmitter, sent from *locus coeruleus* to the hypothalamus as well as the dorsolateral prefrontal cortex (dlPFC), to initiate normal nervous system responses (Moret & Briley, 2011) (see Figure 1). Under chronic stress conditions, noradrenaline participation in HPA axis overstimulates ventral noradrenergic bundle pathway and the increased cortisol production from PVN reduces dlPFC signalling (Drevets et al., 2008), resulting in reduced ability to cognition.

Altered neurotransmission in MDD

As previously mentioned, noradrenaline functions as a neurotransmitter, regulating attention, cognition and working memory (Castellano et al., 2016). In the SNS, noradrenaline plays an essential role in *fight or flight* arousal response (Gouws et al., 2022) *via* its relationship with corticotropin-releasing hormone (CRH), and as part of HPA axis (see Figure 1). During normal stress response, stimuli activate *locus coeruleus* in the brain stem, resulting in increased noradrenaline production across HPA axis (Seki et al., 2018). Under chronic stress, noradrenaline in HPA axis overactivates the dorsal noradrenergic bundle pathway and reduces dlPFC signalling (Moret & Briley, 2011), implicated in downregulated capacity to attention, psychomotor retardation, and low working memory (Mikulska et al., 2021) as shown in Figure 2.

Under normal conditions, noradrenaline regulates the SNS autonomic functions such as breathing and heartbeat *via* the nuclei of medulla oblongata, pons and midbrain (Kiernan, 1998). During chronic stress, noradrenaline ventral noradrenergic bundle

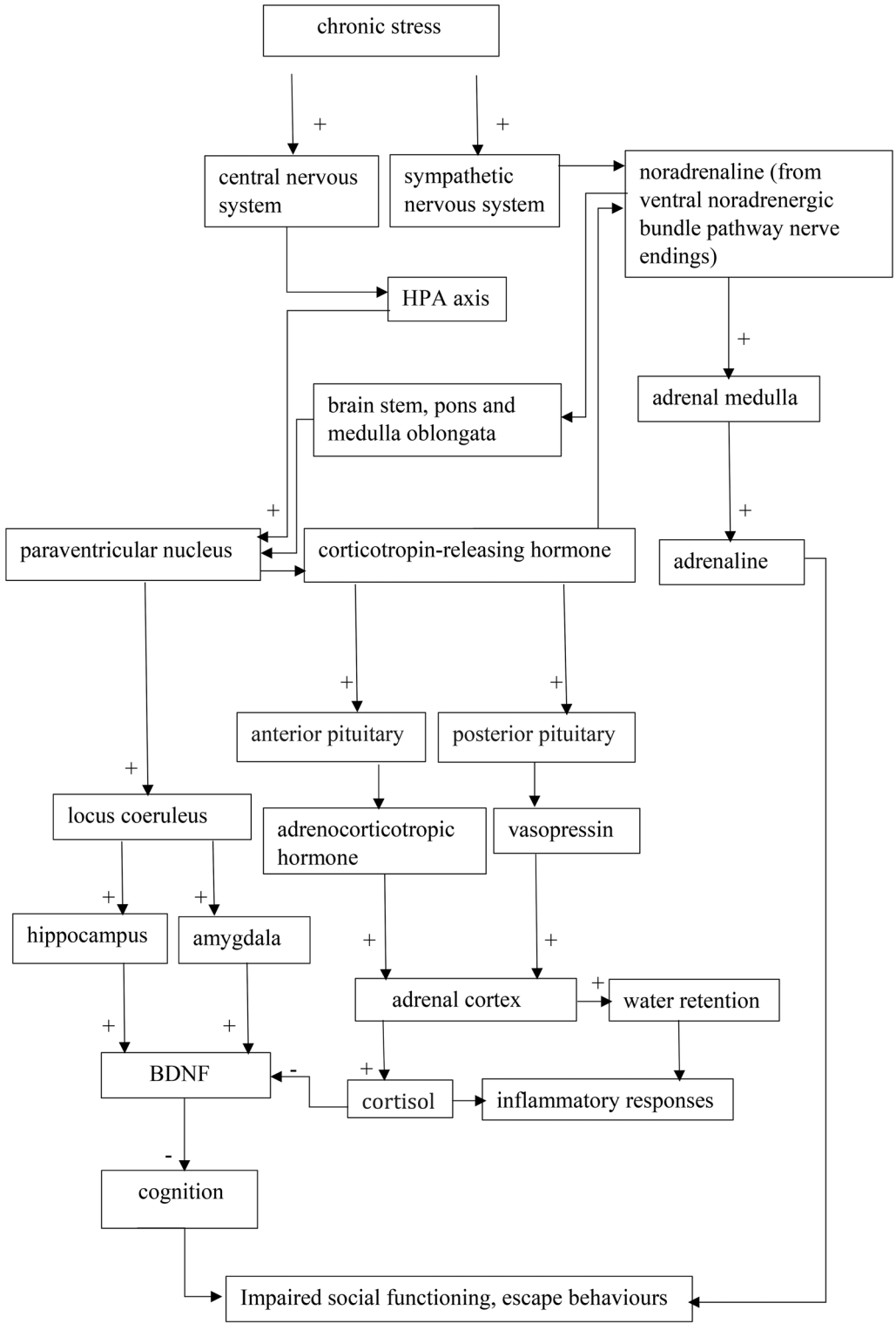

Figure 1. Chronic stress interactions with hypothalamus – pituitary – adrenal (HPA) axis (+ = hyperfunction; – = hypofunction).

pathway dysfunctions in HPA axis overactivate cortisol production (as shown on Figure 2), significantly reducing the secretion of noradrenaline (Koga et al., 2020) and leading to depressed mood (Drevets et al., 2008). It is also the ventral noradrenergic bundle pathway that interacts with MDD inflammatory profile, inducing fatigue and low energy levels (Kerr et al., 2012; Seki et al., 2018).

Serotonin neurons originate in *raphe nuclei* of the brain stem operating *via* two ascending bundles and one descending bundle (Kiernan, 1998). The two ascending bundles contain the dorsal periventricular axons and the ventral tegmental axons that intersect in the PVN of hypothalamus, continuing with signals to the medial forebrain bundle (mFB) (Leu-Semenescu et al., 2010). The dorsal periventricular axons are involved in circadian rhythms such as sleep mechanism and ventral tegmental axons are related to the hippocampal emotional association responses (Berumen et al., 2012). The descending bundle connections to vagal nerve facilitate brain-gut communication

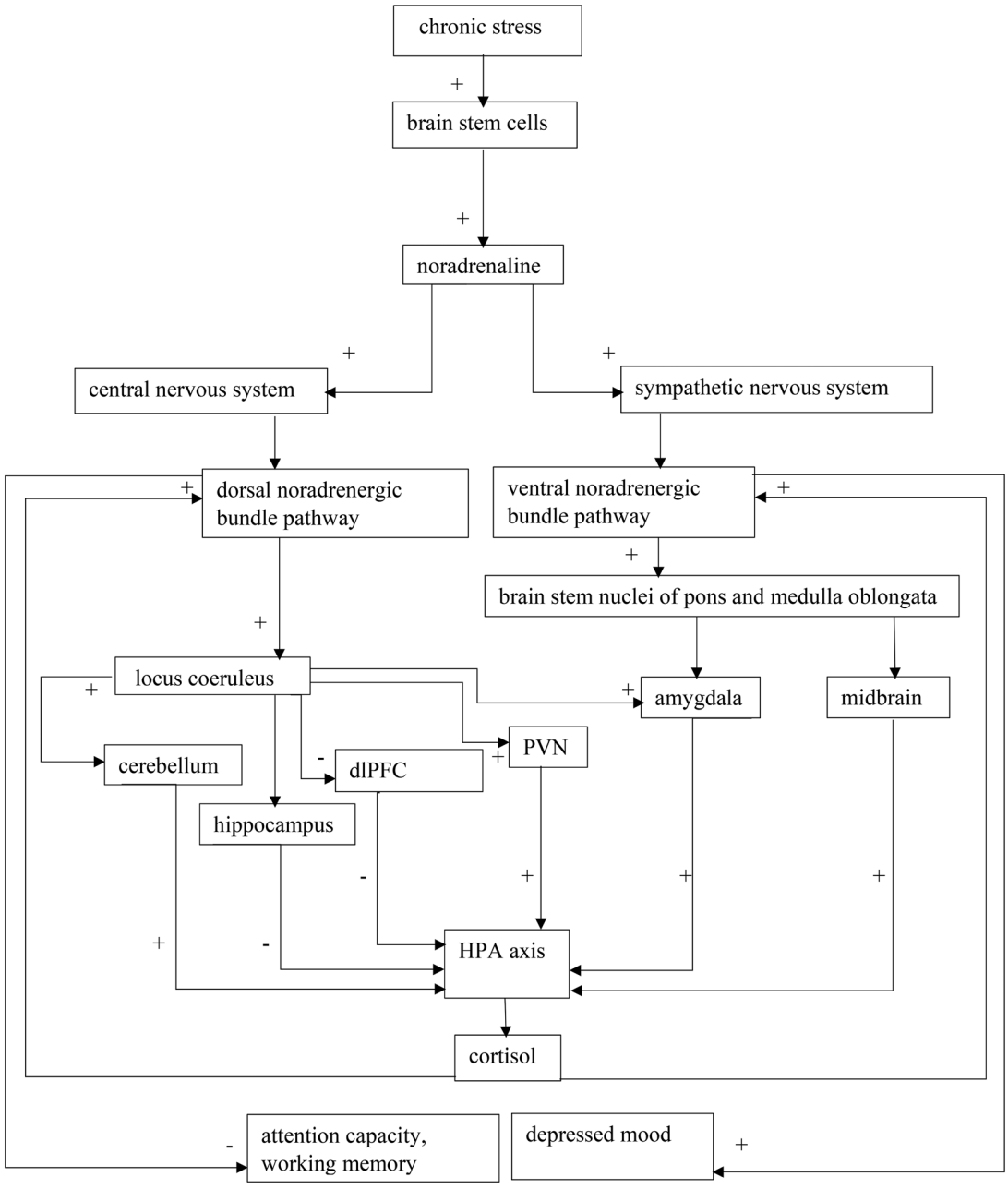

Figure 2. Noradrenaline function during chronic stress (+ = hyperfunction; – = hypofunction; PVN (paraventricular nucleus), dorsolateral pre-frontal cortex (dlPFC).

(Breit et al., 2018) and are of pain modulating properties (Crossman & Neary, 1995), as shown in Figure 3.

Serotonin influences a number of core behavioural and somatic functions and its reduced neurotransmission results in depressed mood (Drevets et al., 2008) (see Figure 3) For example, reduced signals from the dorsal periventricular axons to medial forebrain bundle results in less synaptic neuroplasticity (Koponen et al., 2005) following an exacerbation of sleep disturbances and reduced capacity for emotional processing (Leu-Semenescu et al., 2010). Further, reduced serotonin activity leads to downregulated vagal nerve signalling, initiating brain's nociceptive reflexes (Osiecki & Meeke, 2005), effecting lowered plasma tryptophan levels that result in increase of pro-inflammatory responses (Cowen & Browning, 2015). Apart from triggering depressed mood symptoms (Jenkins et al., 2016), this pathway initiated inflammatory responses further discussed in Immune System Factors (see Figure 5).

Dopamine signals across the mesocortical pathway (MsCortP), mesolimbic pathway (MsLimbP), and nigrostriatal pathway (NStrP) are all involved in MDD pathology as shown in Figure 4. Both MsCortP and MsLimbP originate in ventral tegmental area (VTA) (Wise, 2009), most prominently – pedunculopontine tegmental nucleus (PPTg), involved in reward responses (Hong & Hikosaka, 2014), with reference to MDD anhedonia. The NStrP originates in substantia nigra pars compacta (SNpC) and its function overlaps with the pathway with VTA signalling (Morikawa & Paladini, 2011). In normal conditions, PPTg sends efferents to MsCortP and receives afferents from prefrontal cortex (PFC), supporting cognition towards a behavioural decision-making and reinforcing action selection and learning (Seamans & Yang, 2004). Reduced dopamine expression leads to low attention and reduced short-term memory, particularly expressed in dlPFC, hypofunctional in MDD (Drevets, 2007).

As MsLimbP is involved in reward-based behaviours (Belujon & Grace, 2017), reduced firing from PPTg towards ventrolateral

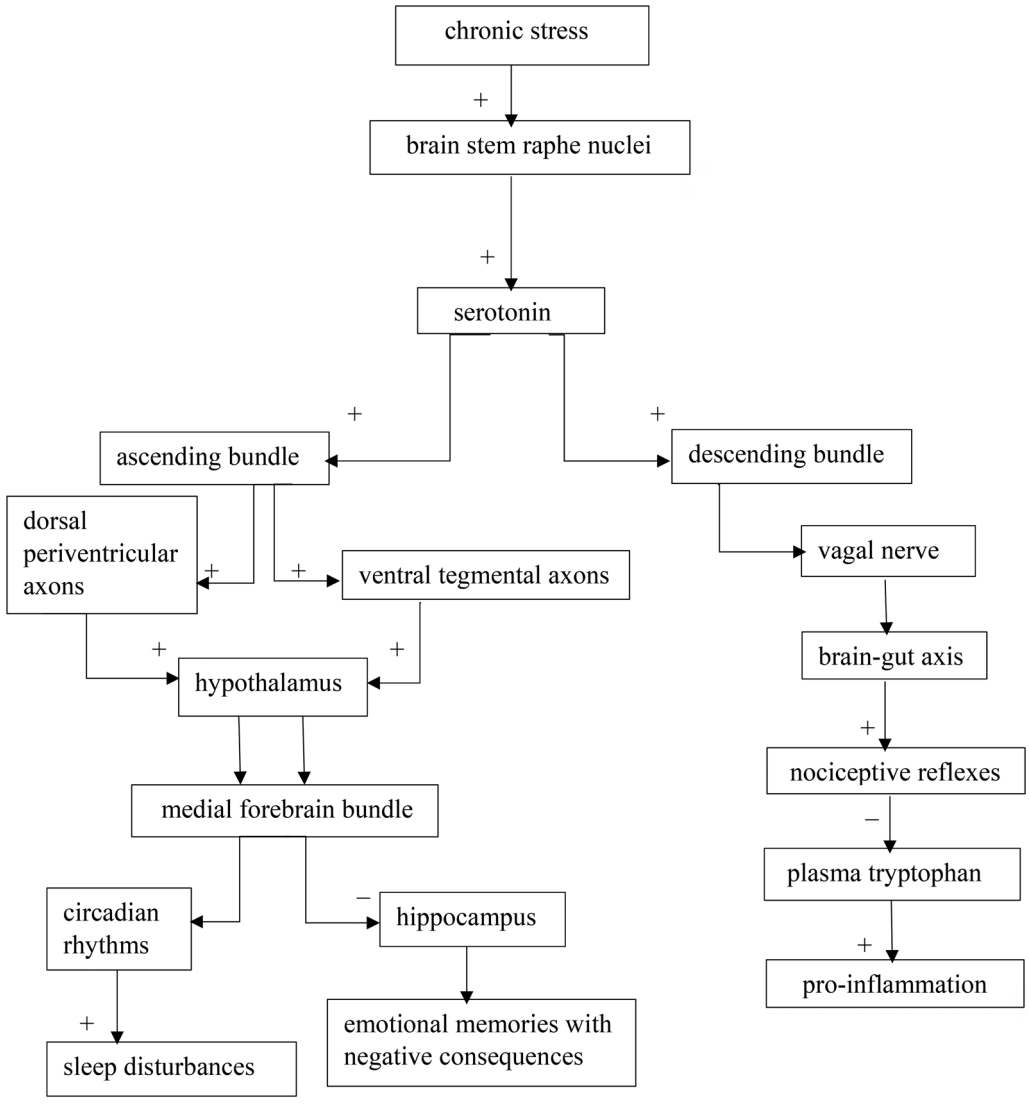

Figure 3. Serotonin function during chronic stress (+ = hyperfunction; – = hypofunction).

basal ganglia (vsBG) downregulates reward-seeking behaviours, leading to anhedonia (Morikawa & Paladini, 2011). Downregulated afferents from NAc towards mPFC account for MDD emotional deficiencies and lack of self-control (Belujon & Grace, 2017). In NStrP, SNpC sends reduced dopaminergic afferents to dsStriatum; a hypoactive dsStriatum generates disruptions in motor control regulation in dlPFC (Forbes et al., 2009), bringing symptoms of physical fatigue and low energy (Kerr et al., 2012) (see Figure 4). PPTg function in the MsLimbP overlaps with that in the NstrP and results in additionally reduced firing towards dsStriatum, resulting in avoidance learning, as part of MDD social deficiencies (Bains & Abdijadid, 2021; Fernández-Theoduloz et al., 2019).

Factoring the immune system inflammatory responses to MDD development

MDD-associated immune processes display a significant rise of pro-inflammatory cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α) (Gądek-Michalska et al., 2013) as well as C-reactive proteins (McFarland et al., 2019), and the outline of these inflammatory pathways could critically modify the MDD further pathogenesis. As MDD has been found to occur as a comorbidity across already physically ill patients (Valkanova et al., 2013), establishing an understanding of the bi-directional relationship between inflammatory processes and MDD pathogenesis is of significant importance (Beurel et al., 2020). The relationship between physiological condition's severity and the concomitant stress as a psychogenic factor (Sharpley, 2017) amplify both inflammatory and stress responses, often mediating a clinical condition, known as a *sickness behaviour* (Aubert et al., 1995). Low grade inflammation forms a significant factor in MDD profile, often resulting in incomplete recovery and a frequent relapse (Leonard, 2014). Brain inflammatory responses were amongst the chief causes for the cellular damages in chronic stress disorders (Gądek-Michalska et al., 2013). Since stress responses over a persistent antigen challenge have a rather spending effect on the immune system, the comorbidity of MDD was hypothesised to be a form of maladaptive pathway of cytokine-induced sickness (Sharpley, 2017). Explorations of this *sickness behaviour* found it to be triggered by IL-1α, IL-1β, TNF-α and IL-6 (Dantzer et al., 2008); co-incidentally, MDD symptomatology was related to the same biomarkers (Stieglitz et al., 2015). Biologically, IL-1 acts on the PVN to cause fever and reduce locomotor activity and TNF-α increases endogenous pyrogens production, resulting in fever responses (Walter et al., 2016). The

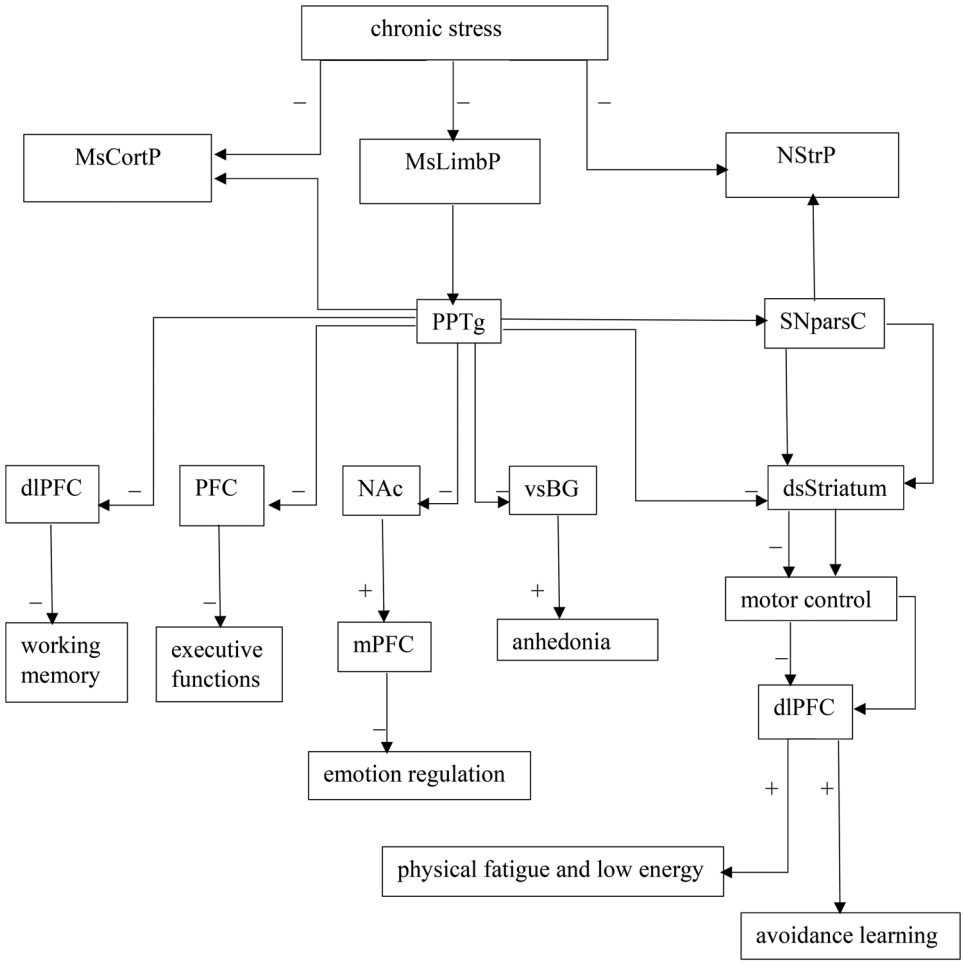

Figure 4. Dopamine function during chronic stress (+ = hyperfunction; – = hypofunction; MsCortP (mesocortical pathway), MsLimbP (mesolimbic pathway), and NStrP (nigrostriatal pathway), VTA (ventral tegmental area), PPTg (pedunculopontine tegmental nucleus), SNparsC (substantia nigra pars compacta), dlPFC (dorsolateral prefrontal cortex), PFC (prefrontal cortex), NAc (nucleus accumbens), vsBG (ventrolateral basal ganglia), dsStriatum (dorsal striatum), mPFC (medial prefrontal cortex).

inflammatory pathway involving IL-1 receptors, is further triggered by pro-inflammatory cytokines, resulting in production of prostaglandins – another potent inflammatory mediator that disrupts neuronal growth and inhibits neuroplasticity in PFC and hippocampus (Gądek-Michalska et al., 2013). Consistent with the displayed symptomatology, an initial differential diagnosis between the rise of pro-inflammatory cytokines in sickness behaviour and MDD picture could be difficult as both disorders had symptoms of physical and social environment withdrawal, comorbid with pain, fatigue, and anhedonia (Dantzer et al., 2008). Consequently, such *sickness behaviour* might not be an uncommon factor to take into consideration across MDD immune system profile.

The inflammatory processes in MDD are triggered by chronic internal and external stress stimuli, facilitated by cell-mediated immune factors (Sharpley, 2017). Cellular responses begin with activation of T-cells by a specific antigen receptor, following proliferation and differentiation to initiate cell-mediated and antibody-mediated immune responses. This interaction is shown in Figure 5. Cell-mediated immune response is of interest to MDD pathology as it involves T-cells selective proliferation, affecting the organism's adequate immune protection, causing the inflammation (Audet & Anisman, 2013). Pro-inflammatory cytokines mediate the body's response by coordinating inflammatory responses to various pathogens (Dantzer et al., 2008), increasing the actions of microglia, monocytes and macrophages (Wohleb et al., 2015). For example, despite IL-6 recognised anti-inflammatory properties (Scheller et al., 2011), its pro-inflammatory properties act as a contributing factor to MDD-related stress sensitivity (Hodes et al. 2016). Under normal physiological conditions, IL-6 activates HPA axis, elevating levels of cortisol towards anti-inflammatory responses (Fisman & Tenenbaum, 2010). Because during chronic stress, ventral noradrenergic bundle pathway signalling is increased (Seki et al., 2018), the pro-inflammation causes elevated inflammatory expression in the PVN (Martín-Cordero et al., 2011). This response activates ACTH production to upregulation of cortisol, deepening the immune insult (Beurel et al., 2020). This understanding is consistent with the findings of increased IL-6 levels in incidences of daily life-stresses correlating with compromised immune system functioning (Mikulska et al., 2021). As significant biomarkers for inflammation-associated MDD, elevated levels of C-reactive proteins leading to hypersecretion of CRH and cortisol, resulting in immune downregulation (McFarland et al., 2019). Stress-maintained hypercortisolaemia exhausts organism's capacity to innate self-defence (Seal & Turner, 2021), leading to conditions of blood coagulation, thrombosis and cardiovascular complications (Luan & Yao, 2018).

In MDD, catabolism of tryptophan is accelerated *via* decreased intestinal peptide production thereby reducing serotonin synthesis (Dantzer et al., 2008). The downregulation of dietary tryptophan led to decreased levels of serotonin (Dantzer, 2004),

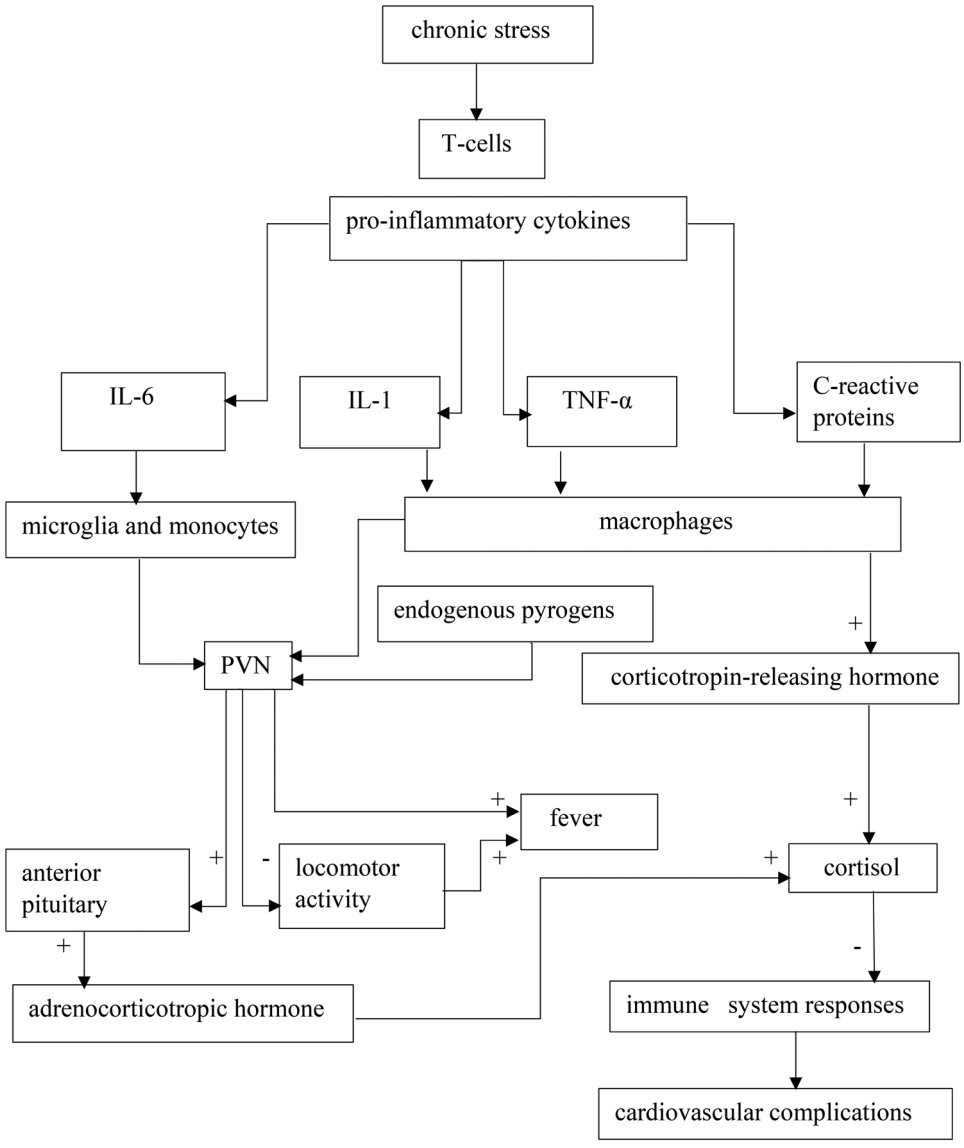

Figure 5. Inflammation-mediated MDD and sickness behaviour responses (+ = hyperfunction; – = hypofunction; IL-1β (interleukin-1β), IL-6 (interleukin-6), TNF-α (tumour necrosis factor-α), PVN (paraventricular nucleus) of hypothalamus.

resulting in an overactive HPA axis, raising glucocorticoid receptor resistance, both downregulating CRH and elevating the levels of cortisol (Keller et al., 2017). Pro-inflammatory cytokines increase the activity and expression of monoamine transporters while reducing concentration of monoamine precursors (Rogers et al., 2013) and particularly, serotonin (Audet & Anisman, 2013). Since a major part of serotonin is produced in the digestive system, its unstable levels lead to disbalances in the gut microbiota, reducing the beneficial microflora along with impairing further synthesis and neurogenesis (Mikulska et al., 2021). Reduced serotonin mediation between the CNS and peripheral immune function, resulting in storing chronic stress in the body, leading to depressed mood (Drevets et al., 2008) as well as producing social withdrawal behaviours (Robson et al., 2017), as shown on Figure 5.

Gene-environment interactions in Gene x environment

Genetic contribution to MDD pathology has a number of pathways furthered by the interaction of the chronic maladaptive functions across HPA axis, neurotransmission and immune factors. For example, serotonin transporter 5-HTT has been researched for its relationship to the polymorphic variation *serotonin-transporter-linked promoter region* (5-HTTLPR) that further transcribes into short (s) and long (l) alleles (Li et al., 2014). There is evidence that 5-HTTLPR-s is more susceptible to MDD pathogenesis (Yokoyama et al., 2015), internalising the stress experiences and leaving those unprocessed (Conway et al., 2014), resulting in somatic MDD symptomatology (Lotrich et al., 2013). Related to this is one influential pathway of 5-HTTLPR is the *default mode network* (DMN) closely linked to adverse childhood occurrences (Showraki, 2019). DMN is a body of neuronal network that addresses self-referential attitudes and is normally active during rest (Raichle et al., 2001). In depression, DMN expands across both mPFC to reflect low self-esteem (Li et al., 2014), and the ACC to initiate rumination or a negative self-talk (Chou et al., 2023). DMN is also active across amygdala, in relation to perceived threat and emotionally unprocessed memories (Fisher & Hariri, 2013). Since mPFC have demonstrated to be highly sensitive to reduction of serotonin (Pereyra et al., 2021), 5-HTTLPR-s variation pathway can effect activation of DMN in mediating impulsive and disruptive behaviours (Cha et al., 2018).

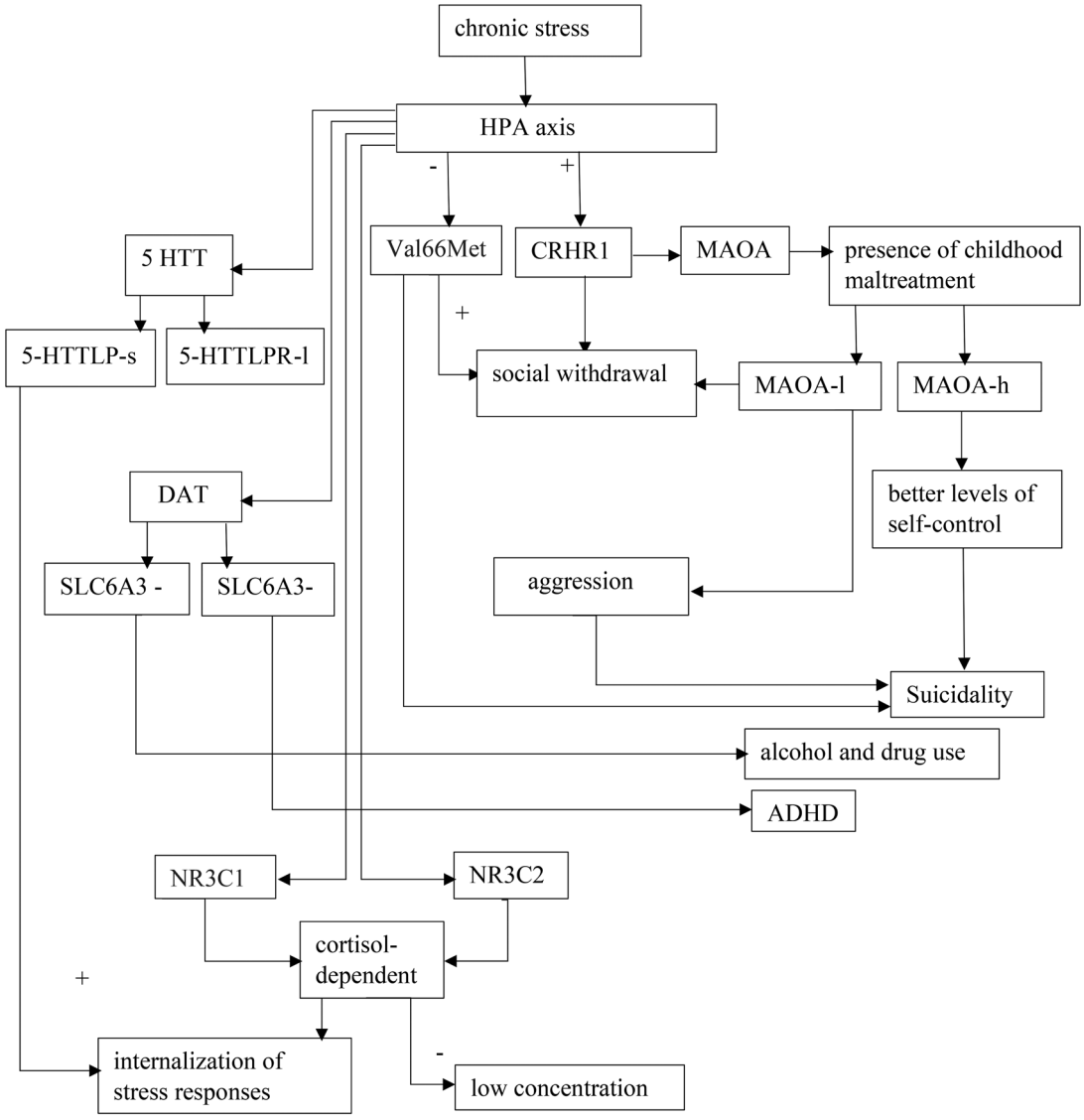

Figure 6. Genetic MDD implication (+ = hyperfunction; – = hypofunction; 5-HTT (serotonin transporter), 5-HTTLPR (serotonin-transporter-linked promoter region), 5-HTTLPR-s (short allele serotonin-transporter-linked promoter region), 5-HTTLPR-l long allele serotonin-transporter-linked promoter region, DAT dopamine transporter gene, SLC6A3 (solute carrier family six member three), SLC6A3-s (solute carrier family six member three, short allele), SLC6A3-l (solute carrier family six member three long allele), Val66Met (valine change to methionine at position sixty six of the BDNF protein), CRHR1 (Corticotropin-releasing hormone receptor 1), MAOA (gene monoamine oxidase A), MAOA-s (gene monoamine oxidase A-short allele, MAOA-l (gene monoamine oxidase A-long allele).

It has been shown that it is the dopamine transporter gene (DAT) and not the brain metabolic function that controls the levels of dopamine at the synapse, in the dorsal striatum and NAc (Cass et al., 1993). In the PFC, noradrenaline transporter gene is in higher concentrations than DAT, making dopamine uptake dependent on the concentrations of noradrenaline (Morón et al., 2002), establishing direct connections with the uprise of depressed mood and cognitive pathology (Drevets et al., 2008). While DAT is implicated in regulation of social stress and emotional vulnerability (Davis et al., 2017), DAT variant *solute carrier family six member three* (SLC6A3) has been researched for its neuropsychiatric expression (López León et al., 2005). Downregulated SLC6A3 synaptic re-uptake predicted increased risk to psychotic symptomatology and was found to be amongst the candidate gene risk factors for severe depression with suicidal ideation (Rafikova et al., 2021). SLC6A3 is of *high activity variants* (SLC6A3-h) in alcohol and other drug use and of *low activity variants* (SLC6A3-l) exhibited across attention deficiency and hyperactivity disorders (ADHD) (Reith et al., 2022). Research shows that SLC6A3 overall expression increased with high stress levels and high fat foods intake (Ong & Muhlhausler, 2011) while it was decreased by an establishment of a neuroprotective environment inclusive of compliance with intake of prescribed medicinal substances (Amato et al., 2020).

Emerging findings link the glucocorticoid receptors *nuclear receptor subfamily 3, group C, member 1* (NR3C1) and *nuclear receptor subfamily 3, group C, member 2* (NR3C2) from the HPA axis to the gene expressions that moderate the effect of traumatic stress on depression (Vinkers et al., 2015) (see Figure 6). Risk factors such as self-perceived stress, absence of leisure activities and tobacco use were found to significantly dysregulate NR3C1 transcription (Borçoi et al., 2020). NR3C1 variation predicted reduction in PFC-related cognition, capacity to attention and task-execution while reduction in NR3C2 predicted hippocampal reduction with difficulties in retrieval of long-term memories (Keller et al., 2017). NR3C2 transcription was found to be repressed after a stressful exposure however with adjacent antidepressant use (Galbally et al., 2020). Conclusively, both NR3C1 and NR3C2 expressions are

a result of dysregulations inteconnected with maladaptive stress responses.

BDNF reduction has been linked to depressed mood (Cowen & Browning, 2015) due to a decrease in the growth and plasticity of serotonin neurons (Koponen et al., 2005). BDNF has been a significant part of MDD neurotrophin hypothesis found to contribute to psychiatric expression and suicide symptomatology (Dwivedi, 2009). Chronic stress downregulates BDNF in hippocampus and PFC (Pittenger & Duman, 2008), particularly during late life stresses (Brown et al., 2014), causing social withdrawal (Duman, 2009). Perpetuation of chronic stress factors in late life amplifies and complicates the reduced BDNF expression, leading to the expression of a valine change to methionine at position sixty six of the BDNF protein (Val66Met) gene polymorphism (Egan et al., 2003). With personality trait neuroticism, prevalent in depression (Hettema et al., 2006; Terracciano et al., 2010) and the BDNF Val66Met links to anticipatory anxiety (Zou et al., 2019), overlooking this factor across geriatric populations, can have fatal consequences.

Corticotropin-releasing hormone receptor 1 (CRHR1) plays a key role across an overactivated HPA axis, in relation to chronic stress as well as in the downregulation of mental health status after adverse life occurrences, leading to symptoms of fatigue and other somatic symptomatology (Vetkas et al., 2020). Additionally, CRHR1 is recognised to increase risk of depressive disorders, anxiety and childhood trauma (Rogers et al., 2013), that have contributed to chronic stress later in life (Showraki, 2019). CRHR1 variants were found to take important part in gene x environment interaction with aggression, hostility and impulsiveness (Ben-Efraim et al., 2011), resulting in MDD suicidality symptomatology (Wasserman et al., 2008) (see Figure 6).

Gene monoamine oxidase A (MAOA) was significantly linked to depression pairing with psychiatric malfunctioning and leading to anti-social conduct and other complex behaviours (Naoi et al., 2018). For example, MAOA implication in MDD expresses a low and a high genetic activity (Cicchetti et al., 2007; Smeijers et al., 2020), with the low activity form (MAOA-l) expressing increased levels of aggression and with the high activity form (MAOA-h) showing capacity to a better self-control (McDermott et al. 2009). The complexity of their biological interactions indicates MAOA-l connection to somatic and other MDD symptomatology, originally linked to childhood maltreatment (Sohrabi, 2015), while MAOA-h was related to MDD suicidal symptomatology (Du et al., 2002) (see Figure 6). There is a growing body of research that link of MAOA to 5-HTT where gene x environment interaction moderate coping strategies in high-risk behaviours following traumatic life experiences such as sexual abuse (Cicchetti & Rogosch, 2014).

Limitations and recommendations to clinical practice

Commencing with an initial reactivity to stress and dysfunctional neurotransmitter systems, MDD current view involves its rapid development into an endogenous condition combining complex emotional, neurophysiological and gene x environmental disturbances. MDD pathogenesis is exacerbated by chronic stress, expressing overactivity and underactivity of selected biomarkers that lead to a number of systemic complications triggering various comorbidities. Chronic stress overstimulates hypothalamic structures, resulting in decreased neurotransmission on the dPVA pathway, causing disturbance in sleeping patterns (Charles et al., 2020). Treatment pathways to balancing hyperactive HPA axis and the noradrenaline production are difficult to allocate perhaps because noradrenaline is involved across all MDD circuitry, as a primary stress response agent. Some suggestions include practicing various relaxation techniques (Robson et al., 2017), mindfulness meditation and yoga (Krishnakumar et al., 2015) while others suggest that cognitive-behavioural psychotherapeutic interventions explicitly balance out noradrenaline overproduction (Goldapple et al., 2004). Serotonin downregulation across VTA leads to reduced hippocampal responses resulting in thoughts, considerably examining negative emotional consequences (Cowen & Browning, 2015). While As a key modulator of the peripheral nervous system, the reduced singalling of serotonin neurotransmission affects the signalling of the vagal nerve across brain gut axis, mediating inflammatory immune responses (Borovikova et al., 2000). Practice based evidence shows that normalised signalling of serotonin is achieved by incoporating psychodynamic therapy approaches (Karlsson et al., 2010) and cognitive-behavioural approaches (Amsterdam et al., 2013). Amongst the current emerging serotonin-focused treatments are targeted nutritional medicine interventions (Mikulska et al., 2021) with increased growing in popularity of the complementary and alternative therapies (Rao et al., 2008). While little is known about the afferent circuits that carry dysfunctional transmission in dopamine regulation to anhedonia (Belujon & Grace, 2017), the evidence-based practices support exposure therapy *via* error-based learning, challenges to unhealthy beliefs and dysfunctional emotional and behavioural patterns by prioritising construction of safe memories (Papalini et al., 2020). Research into the brain areas involved with anhedonic experiences may recommend these as helpful in improvement of dopaminergic neuronal plasticity (Madadi Asl et al., 2019).

The increase of inflammatory biomarkers considers the involvement of a hyperactive immune system within MDD, bearing notable similarities with systemic inflammations such as cardiovascular disease, diabetes, and cancer (Leonard, 2014; McFarland et al., 2019) and their pathological expression overlaps with MDD somatic symptomatology (Caruso et al., 2020; McFarland et al., 2019). Research however cautions that the pathogenesis of MDD inflammatory processes largely depends on the levels of severity, and more studies are needed to confirm the direct and not inverse correlation between the two (Sharpley, 2017). However, recognition of *sickness behaviour*' signs and symptoms can be addressed by early psychotherapy interventions (Cuijpers et al., 2019) as a potential to recovery, particularly focusing on previously unaccounted for motivation to cope better (Hart, 1988).

An overactive HPA axis links MDD gene x environment interaction with childhood maltreatment (Showraki, 2019), confirming that higher maladaptive stress responses were directly related to depressive symptomatology and moderated the results of interpersonal childhood traumatic experiences (Starr & Huang, 2019). This fact can be useful in support to use of interpersonal psychotherapy, found particularly helpful with PFC disturbances towards improvement of social deficiencies symptomatology (Brody et al., 2001). Although MDD pathogenesis features prominently altered genetic mark ups (Uher, 2008), Shadrina et al. (2018) noted that attempting epigenetic and environmental changes in attempt to modify genetic functions without changing their coding sequence, altering MDD pathways working towards reversing its pathogenesis.

It is difficult to predict a clinical intervention based on a psychological or a biological dysfunction *separately* as MDD's dynamics present a bi-directional relationship. As both MDD and depressive disorders epidemiology continue to grow, they call for constant professional development towards an improved neurobiological understanding. Continued investigation into the pathways to MDD expression can deepen the understanding of the presenting symptoms and lead to better approach to individual's

care-seeking behaviours to recovery such as psychotherapy, improved nutritional behaviours, sleep hygiene and better lifestyle choices.

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