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Inflammatory cytokine-associated depression

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Abstract

Inflammatory cytokines can sometimes trigger depression in humans, are often associated with depression, and can elicit some behaviors in animals that are homologous to major depression. Moreover, these cytokines can affect monoaminergic and glutamatergic systems, supporting an overlapping pathoetiology with major depression. This suggests that there could be a specific major depression subtype, inflammatory cytokine-associated depression (ICAD), which may require different therapeutic approaches. However, most people do not develop depression, even when exposed to sustained elevations in inflammatory cytokines. Thus several vulnerabilities and sources of resilience to inflammation-associated depression have been identified. These range from genetic differences in neurotrophic and serotonergic systems to sleep quality and omega-3 fatty acid levels. Replicating these sources of resilience as treatments could be one approach for preventing “ICAD”.

Keywords

Cytokine; mood; depression; vulnerability; interferon; interleukin

There are now multiple lines of evidence that inflammatory cytokines influence the brain, either directly and/or indirectly, resulting in increased risk for mood disorders. (i) Across multiple prospective studies, exogenous administration of cytokines to humans can trigger depression symptoms.¹⁻¹⁰ For example, there is a dose-response relationship between interferon-alpha (IFN- α) administration and depression,^{11, 12} with a gradual return to baseline mood after discontinuation.¹³⁻¹⁵ Similarly, endotoxin injections and vaccines can transiently increase inflammatory cytokines and worsen mood.¹⁶⁻¹⁸ (ii) In many illnesses and conditions, cytokine levels are cross-sectionally associated with depression risk.¹⁹⁻²¹ This includes coronary disease,²²⁻²⁶ cancer,²⁷⁻³² infectious illness,³³⁻³⁶ multiple sclerosis,³⁷ dermatitis,^{38, 39} lupus,^{40, 41} kidney disease,^{42, 43} chronic alcohol use,^{44, 45} pregnancy,^{46, 47} etc. Among each of these conditions, depressed patients tend to have higher levels of inflammatory cytokines. (iii) Across twenty-four studies of major depressive

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disorder (MDD) that purposefully excluded any medical co-morbidity, MDD was still associated with increased IL-6 and TNF- α .⁴⁸ **(iv)** In post-mortem studies, inflammation-related genes are differentially transcribed in the brains of depressed subjects.⁴⁹ **(v)** Genetic variability in various inflammatory system genes may be associated with risk for MDD.⁵⁰⁻⁵⁷ Genetic variability in the IFN- α gene is associated with changes in tryptophan metabolism.⁵⁸ **(vi)** Psychosocial stress, which can influence depression development, also has an effect on inflammatory cytokines.⁵⁹⁻⁶¹ Likewise, stress in humans can influence the transcription of genes that are regulated by inflammatory cytokines.⁶² Conversely, elevated IL-6 can normalize with successful antidepressant treatment.⁶³⁻⁶⁵ **(vii)** In animal models, inflammatory cytokines can influence behaviors that are homologous to depression,⁶⁶⁻⁸² including anhedonia and amotivation. In these same animal models, cytokines also affect central monoaminergic systems.⁸³⁻⁹⁰ Consistent with the case in humans, many behavioral effects take a couple weeks to develop.⁹¹ **(viii)** Various stress-induction paradigms result in behavioral changes along with activation of inflammatory cytokines^{92, 93} and subsequent suppression of neurogenesis and neuroplasticity.⁹⁴⁻⁹⁹ **(ix)** Inflammatory cytokines such as IFN- α can affect systems that are likely key in depressogenesis, including frontal lobe and anterior cingulate function,^{100, 101} dopaminergic activity,⁸⁷ serotonergic activity,¹⁰²⁻¹⁰⁵ glutamatergic activity,¹⁰⁶ and growth factors such as brain-derived neurotrophic factor (BDNF).^{107, 108}

There is therefore strong and broad support over the last several decades for the general hypothesis that inflammatory cytokines are key elements in the pathogenesis of MDD.^{86, 87, 109, 110} Because of the similarity between MDD and “acute illness” behaviors, some have hypothesized that there could be an evolutionarily adaptive reason for this relationship.^{7, 19, 21, 111-113, 101, 102} Recuperation from illness may benefit from decreased social behavior, altered motivation, and loss of libido.^{67, 76, 114-117} In addition, psychosocial behaviors such as tearfulness, dependency,^{118, 119} and somatization^{120-123, 123, 124} can elicit care from others when needed for recuperation.^{36, 125-129} Various primates,¹³⁰ dogs,^{131, 132} and cetaceans¹³³ naturally react to these care-eliciting behaviors¹³⁴ by adjusting travel pace, sharing food, or actively helping.^{116, 130, 135} Because of the likely importance of inflammatory cytokines in influencing these behaviors during acute illness, it is theoretically plausible that in people with MDD they similarly help trigger these same behaviors.

However, it would be difficult to conclude that all cases of MDD are associated with increased inflammation. First, not everyone with MDD has consistent evidence of increased inflammatory cytokine activity.¹³⁶⁻¹³⁹ In fact, most don't. Second, most people with increased inflammation do not develop MDD. In fact, only a minority do. Most people treated with IFN- α do not develop depression.¹⁴⁰ Third, not all species of animals develop depression-like behavioral responses to inflammation.¹⁴¹ Fourth, some treatments that target decrease inflammatory cytokine activity have not always been effective in treating MDD.¹⁴² These critiques of the inflammation-depression hypothesis suggest at least two areas of clinical research. **(I)** Could there, in fact, be a specific subtype of MDD that is uniquely associated with inflammatory cytokines (i.e., inflammatory cytokine-associated depression; ICAD)? Can this subtype be readily differentiated using biomarkers, does it have a different prognosis, and does it respond to treatments differently? **(II)** What are the sources of

resilience such that most people don't develop MDD despite elevated inflammatory cytokines? Can this resilience be replicated with therapy to prevent ICAD or other types of MDD? In addition to these two topics, further addressed below, it is feasible that associations between depression and inflammation could be the result of (a) depression causally influencing the immune system and (b) a third factor such as obesity or stress-induced glucocorticoid resistance that could influence both mood and inflammation. In fact, the likelihood of complicated bidirectional relationships is an important reason for the phrase "ICAD" rather than simply "inflammatory cytokine-induced depression."

(I) Is ICAD a distinct MDD subtype? Several studies have found no association between cytokine levels and depression,¹³⁶⁻¹³⁸ and some even report lower levels in depressed patients.¹⁴³ It is thus very plausible that there are some types of depression that are not related to cytokines. And although there can be some cytokine irregularities in dysthymia,¹⁴⁴⁻¹⁴⁶ there may be biological differences compared to more severe mood episodes.^{147, 148} There may also be differences that are associated with the amount of somatization reported.¹⁴⁹ The manifestation of depression may be a clue, as IL-6 is more likely to be elevated in patients with melancholic features (e.g., neurovegetative features such as insomnia, loss of appetite with weight loss, anhedonia, and loss of reactivity to pleasure) than in those with non-melancholic features.¹⁵⁰

A recent trial of the TNF- α moderating agent, infliximab (which is an antibody against TNF- α), did not alleviate MDD symptoms any better than placebo.¹⁴² However, post-hoc analyses indicated that a sub-group of patients benefitted from infliximab – those with pre-existing elevations in C-reactive protein (CRP), TNF- α levels, and TNF soluble receptor levels. Conversely, resistance to typical antidepressants has been associated with increased inflammatory activity.^{142, 151, 152} As one example, compared with early responders to duloxetine treatment, non-responders had elevated inflammatory cytokines.¹⁵³ Moreover, when there is no evidence of improvement in IL-6 levels, there was no antidepressant benefit.¹⁵⁴ Consistent with these clinical observations, in mice with genetically sustained elevations in central IL-6, the resulting depression-like behavioral phenotype does not reverse with SSRIs.¹⁵⁵ These various observations therefore do support the hypothesis that there could be an ICAD that is distinct from other MDD subtypes, and which improves more readily with anti-inflammatory treatment than with monoamine-based therapy.

Nonetheless, other than IL-6, cytokine changes during antidepressant therapy are not always well-replicated.¹⁵⁶ There is even some evidence that pre-existing elevation of IL-6 is associated with better antidepressant outcomes.^{128, 129} Further complicating the picture, noradrenergic agents such as tricyclic antidepressants and mirtazepine -- but not selectively serotonergic antidepressants - may influence TNF- α .^{157, 158, 159-162} Thus whether inflammatory cytokine levels can consistently be used to guide choice of antidepressant therapy remains unresolved.

ICAD, if it exists, may share similar pathoetiologies as other MDD types. Inflammatory cytokines can influence two canonical neuropharmacologic pathways: monoaminergic and glutamatergic. Both of these systems are often invoked in etiologies of MDD. For example, both IFN- α treatment and low-grade inflammation lead to decreased 5-HT availability (e.g.,

the amino acid precursor tryptophan is metabolized by increased levels of indoleamine-2,3-dioxygenase leading to less tryptophan available for 5-HT synthesis).^{163,164} There is an increase in neopterin levels during inflammation,¹⁶⁵ and tetrahydrobiopterin (BH4) is a critical co-factor for mono-amine synthesis, including 5-HT. Not only is there less 5-HT synthesized, but IL-6 may also increase 5-HT release and subsequent enzymatic metabolism to 5-hydroxyindoleacetic acid.^{166,167} TNF- α can similarly increase 5-HT metabolism centrally.^{168,169} As noted above, reuptake of serotonin back into the neuron by the synaptic transporter may be increased by I-L1 β ,¹⁷⁰ TNF- α ,¹⁷¹ and IFN- α ⁸³ -- likely by a mitogen-associated protein (MAP) kinase cascade leading to increased synthesis of the serotonin transporter.¹⁷² In addition to these effects on synthesis, release and metabolism of 5-HT, cytokines can also influence 5-HT1A¹⁰² and 5-HT2¹⁶⁰ receptor expression.

Similarly, there is also altered dopamine turnover but increased uptake in anhedonia associated with IFN- α therapy.¹⁷³ Functional brain imaging implicates basal ganglia regions for several IFN- α effects;¹⁷⁴ and cytokines are an important influence on the dopamine system.^{87, 175, 176} IL-1 β can acutely induce dopamine turnover in the hippocampus and hypothalamus.^{177,178} Dopamine levels are also lowered by IL-6, IL-2, and TNF- α .^{169,188, 179, 180} Dopamine metabolites are lower in the CSF of IFN- α treated monkeys; and lower levels correlate with reduced locomotion and increased huddling^{181, 182} -- similar to findings in humans.¹⁸² Dopamine synthesis may be decreased by inflammation-induced increases in oxidation and thus decreased availability of BH4 availability.¹⁶⁴ For example, increased CSF IL-6 is correlated with decreased BH4 during IFN- α therapy.¹⁷⁵ There could be increased dopamine transporter reuptake similarly to 5-HT,¹⁸³ and it is plausible that cytokines could affect vesicular transport resulting in less dopamine in individual vesicles.¹⁸⁴ Ultimately, decreased basal ganglia activity can be associated with inflammation.^{182, 185}

Cytokines also influence glutamate systems.¹⁸⁶ Both IL-18 and IL-1 β impair long term potentiation and NMDA-mediated transmission,^{187,188} likely through recruitment of the IL-1 receptor associated kinase (IRAK) and subsequent MAPK signaling. Increased indoleamine-2,3-dioxygenase (IDO) expression also shunts tryptophan to kynurenine and subsequent metabolites such as kynurenic acid (KA) and quinolinic acid (QA),^{186, 189} which both influence glutamate transmission¹⁹⁰⁻¹⁹³ and are both detectable in the CSF during IFN- α therapy.^{191, 194} Inflammatory cytokines and QA increase glutamate release and decrease astrocytic reuptake,^{195, 196} while KA may decrease glutamate reuptake.¹⁹⁰ The effects of QA might predispose to glutamate toxicity.¹⁹² Magnetic resonance spectroscopy further supports the possibility of altered cortical glutamate turnover in humans treated with IFN- α .^{106, 197} In addition, an adenosine deaminase (ADAR1) that edits mRNA (a potential antiviral effect of IFN- α) is induced by IFN- α and is capable of editing and functionally altering the AMPA glutamate receptor.¹⁹⁸

Thus a combination of both monoaminergic effects (including decreased synthesis and increased turnover) along with increased glutamatergic toxicity may be important elements in mediating the behavioral effects of inflammation in humans. The extent to which ICAD and other types of MDD share completely overlapping mechanisms, or just partially overlapping mechanisms, remains to be definitively determined. This will have clear

implications for targeting antidepressant treatments. Regardless, we are left with the difficult question of why most people do not develop depression, even when exposed to elevated inflammatory cytokine levels.

(II) What is the source of resilience to the behavioral effects of elevated cytokines?

Inflammatory cytokines can be elevated either because of exogenous administration (e.g., with IFN- α) or endogenously. One explanation for differences in endogenous levels is that chronic or severe trauma during childhood can increase the propensity for producing inflammatory markers such as IL-6 later in life.^{199, 200} This is likely to be, in part, because of long-lasting changes in glucocorticoid sensitivity.^{62, 201, 202} Also, repeated stressors can enhance IL-1 β production in the brain via elevated norepinephrine and the beta receptor.²⁰³ Fat cells (adipocytes) are another source of IL-6, and obesity is another potential influence on endogenous cytokine levels.²⁰⁴⁻²⁰⁷ Adipocytes also can release MCP-1, leading the macrophage infiltration and further inflammation.²⁰⁸ Moreover, fatty acids can activate toll-like receptors (TLRs), particularly TLR4 (which typically is activated by lipopolysaccharides from endotoxemia), and thereby lead to increased inflammatory cytokine production.²⁰⁶ Thus, obesity is a second important contributor. The immune system also releases cytokines in response to various danger-associated and microbe-associated molecular patterns (DAMPs and MAMPs), which include products of potential cellular damage like heat shock protein-72, ATP, uric acid, and lactic acid^{209, 210} and evidence of microbial infection such as endotoxin and double-stranded RNA.^{211, 212} DAMPs are detected by the pattern recognition receptor, NLRP3, which forms an inflammasome, resulting in the activation of caspase-1, which then cleaves immature IL-1 β and IL-18 into their mature releasable forms.^{213, 214} Thus, ongoing cellular damage in the brain or the periphery could be another source of increased inflammatory activity. Similarly, detection of microbes in the intestines can also lead to increased inflammatory cytokines.²¹⁵ Bacterial populations stimulate the inflammation system^{216, 217} along with subsequent influences on behavior.²¹⁸⁻²²⁰ Dietary-related deficiencies in omega-3 fatty acid can also result in increased inflammatory cytokine production²²¹⁻²²³ Of course, genetic variability in the inflammatory cytokine genes themselves can influence levels. There is an allele in the promoter region of the TNF- α gene (A-308G) that is associated with TNF- α levels (A allele has been associated with high levels),^{224, 225} as well as influential polymorphisms in the IL-6 gene (e.g., rs1800795, with CC possibly resulting in lower IL-6 production).^{226, 227} Finally, preliminary results in animal models suggest that CD4(+)CD25(+) T-regulatory cells are specifically involved as important influences on depressive behavior and related monoaminergic activity.²²⁸ Thus regulation of the types of peripheral white blood cells in the systemic circulation may be an important influence on depression vulnerability. Consequently, there are thus a number of influences on inflammatory cytokine activity apart from overt inflammation (with redness, swelling, and pain) – including stress, obesity, covert cellular damage, gut flora, diet, and genetics. However, even when inflammatory cytokines are elevated, only a few become depressed.

An important set of clues to explain resilience comes from people treated with IFN- α . First, there are likely to be differences in the serotonergic system that influence resilience to increased inflammatory activity. IFN- α increases expression of indoleamine-2,3-

dioxygenase (IDO), which catabolizes tryptophan to metabolites like kynurenine that have activity on glutamatergic receptors. Tryptophan is shunted down this pathway, thereby also decreasing serotonin.¹⁰⁵ A polymorphism in the IDO gene is associated with interferon-induced depression.²²⁹ Additionally, polymorphisms in the serotonin reuptake transporter^{227, 230} and in the 5-HT1A receptor²³¹ are also associated with increased depression risk. Interestingly, TNF- α increases serotonin transporter expression.²³² Consistent with this, preliminary observations using positron emission tomography to measure transporter binding in the limbic areas indicate that increases in the serotonin transporter during treatment are surprisingly strongly associated ($r=0.98$) with increases in Beck Depression Inventory scores.²³³ This observation that some people develop neither depression nor increases in serotonin transporters is similar to findings in rats where IL-1 β does not increase in serotonin transporter²³⁴ and IFN- α does not affect depression-like behavior.¹⁴¹ On the other hand, in mice, lipopolysaccharide-induced anhedonia requires the expression of the serotonin transporter.²³⁵ Consistently, lipopolysaccharide has more effects on both IDO and behavior in BALB/c mice than in C57 mice.²³⁶

Another key observation is that only a minority of people develop increased IL-6 during IFN- α therapy.²³⁷ In fact, in this minority, increased IL-6 was strongly predictive of depression and even occurred prior to depression symptoms.²³⁷ Mildly pre-existing elevations in IL-6 levels were a good predictor of vulnerability to both depression and subsequent further elevations in IL-6 levels, which is consistent with genetic findings.²²⁷ Likewise, following a stroke longitudinally, there is initially an increase in IL-6, which is followed by subsequent elevations in other cytokines.²³⁸ The mild early elevation of IL-6, possibly reflective of vulnerability, could be related to prior stress. Certainly, lipopolysaccharide-induced cytokine release is also enhanced by prior exposure to stress, as noted above.²³⁹ Additionally, an exaggerated glucocorticoid axis response to IFN- α predicts the subsequent develop of MDD during treatment.²⁴⁰ These findings could also be related to metabolic syndrome, where chronic unpredictable stress results in over-expression of suppressor of cytokine signaling 3 (SOCS3) in hypothalamic neurons resulting in insulin insensitivity.⁷⁴ Similarly, IL-6 is necessary in the hypothalamus for chronic stress effects on cortisol.²⁴¹ Regardless, the findings are congruent with a large literature that indicates glucocorticoid abnormalities in MDD, and specifically a resistance to feedback by cortisol on baseline inflammatory activity.^{242,243}

Of importance, none of these subjects (with serotonergic vulnerability genes, with elevated IL-6, or with abnormal stress responses) had depression when they started IFN- α therapy. Thus, these vulnerabilities were predispositions to susceptibility to the inflammatory cytokine – and not simply causes of MDD. This also appears to be the case for brain-derived neurotrophic factor (BDNF). Whether people develop depression or not, everyone treated with IFN- α has declining BDNF levels during treatment.¹⁰⁷ IFN- α can decrease cell proliferation in the hippocampus, which is plausibly mediated in part by effects on IL-1.²⁴⁴ Interestingly, decreases in BDNF from social isolation can be prevented by blocking IL-1 β signaling.²⁴⁵ However, having the Methionine (lower expressing) allele in the BDNF gene (compared to those with the Valine/Valine genotype) resulted in increased vulnerability to a set of depression symptoms during IFN- α treatment.¹⁰⁷ This indicates that inflammatory cytokine activity could interactively exacerbate pre-existing low expression of BDNF – as

opposed to simply adversely influencing neurogenesis to cause MDD. Once BDNF further decreases, then it is possible that this triggers the development of depression. IL-1 β , lipopolysaccharide, and parasitic infection all decrease BDNF signaling through related intracellular pathways,^{246,247,248} which may similarly exacerbate pre-existing vulnerabilities. Both mitogen associated protein kinase (MAPK) and NF κ B intracellular signaling pathways are influenced by BDNF and inflammatory cytokines,^{249,250,251,252} plausible loci for their shared and interacting effects.

Thus cytokines may be critical mediators between stress and its subsequent effects on neurotrophic signaling. As inflammatory cytokines lead to further reduced BDNF production and phosphorylation of its receptor, as well as reduce ERK and phospholipase C γ -1 signaling,²⁵³ depression may ensue. However, although monocyte-secreted cytokines decrease growth factors signaling in glial cells, BDNF is actually increased by TH2-related cytokines.²⁵⁴ Thus the relationship between inflammatory cytokines and BDNF is more complex than one of simple antagonism -- and is dependent upon cell type and anatomic region.

Two other important modulators of resilience to IFN- α are sleep^{255, 256} and omega-3 fatty acids (ω -3 FFA).²⁵⁷⁻²⁵⁹ Chronic sleep impairment can result in oxidative stress,²⁶⁰ decreased cell proliferation,^{261, 262} disrupted excitatory/inhibitory balance,^{263, 264} impaired hippocampal plasticity,²⁶⁵ altered cortical synaptic plasticity,²⁶⁶ abnormalities in the glucocorticoid system,^{267, 268} and associated changes in central serotonin turnover.^{269, 270} In turn, cytokines can regulate sleep.²⁷¹⁻²⁷⁷ Notably, IFN- α acutely decreases circadian genes such as CLOCK and BMAL1.²⁷⁸ However, it is also notable that poor sleep quality *precedes* both the depression induced by IFN- α as well the increases in IL-6.²⁵⁵

Supplementation with ω -3 FFA can reverse some of the inflammatory and behavioral effects of IL-1 in rodent models²⁷⁹ along with influencing depression-like behaviors.²⁸⁰ Cyclooxygenase (COX) and lipoxygenase (LOX) metabolites of ω -3 FFA (D- and E-series resolvins and protectins) have potent inflammation *resolving* properties, influencing both cytokine synthesis²⁸¹ and inflammation.²⁸²⁻²⁸⁷ As one example, 'neuroprotectin,' improves neuronal survival in Alzheimer disease models²⁸⁸ and may act at the formyl peptide receptor 2.²⁸⁹ Conversely, COX and LOX metabolites of ω -6 FFA such as arachidonic acid (e.g., prostaglandin E₂ and thromboxane) are often pro-inflammatory.^{282, 290, 291} Notably, ω -3 FFA supplementation could specifically be for ICAD, as it does not prevent post-partum depression²⁹² nor perinatal depression,²⁹³ nor vascular depression.²⁹⁴ Thus, both sleep and ω -3 FFA may be good clinical targets for preventing ICAD.

Conclusion

In summary, in addition to overt medical inflammation, a number of stimuli could contribute to increases in chronic inflammatory activity. This includes stress, obesity, covert cellular damage, gut flora, diet, and genetics. Behavioral vulnerability to the inflammatory cytokines produced could be exacerbated by decreased neurotrophic support, poor sleep quality, levels of inflammation-resolving fatty acids, and genetics -- particularly in serotonergic and inflammatory genes. The interaction between pre-existing vulnerabilities and inflammatory

stimuli is hypothesized to lead to changes in monoaminergic systems in the brain (partly through MAPK intracellular messaging pathways), influences on the glutamatergic system (partly through increases in IDO), as well as further worsening of both glucocorticoid systems and circadian regulation. These systems likely overlap with those involved in acute illness behavior and thus contribute to a complex set of symptoms known as MDD.

Of course, this set of hypotheses is unlikely to explain the development of all instances of MDD, but at least supports the possibility of a specific subtype, ICAD. But several basic questions remain to be resolved before ICAD could be considered a unique subtype of depression. (1) From an epidemiological perspective, how common is it? (2) Do people with ICAD have different rates of familial MDD? They appear to share some similar vulnerabilities (e.g., poor sleep and early history of stressful trauma) and would be predicted to co-occur in families. (3) Longitudinally, can non-inflammatory MDD evolve into ICAD or vice versa? Or is an episode of ICAD always distinct from other MDD types? For instance, once MDD develops, other events can plausibly prolong and perpetuate the mood episode (e.g., alcohol use, MDD-induced stressors such as divorce and job loss, poor sleep) after inflammation or grief has resolved. (4) Is there truly a different treatment response? To date, this possibility has only been hinted at by post-hoc analyses of efficacy studies. There are early hints that ICAD could respond differently to medications than other MDD types. The mechanistic pathways reviewed above highlight the possibility for a new generation of targeted treatments for MDD.^{7, 176} (5) Are there differences in fMRI and PET scans between patients with ICAD and other types of MDD? Or do they share overlapping effects on brain circuitry?

Identifying either specific vulnerabilities and/or inflammatory precipitants (e.g., using blood tests) could point to specific therapies. Although this speculative possibility is supported by an array of different types of evidence, there still remains a need for investigations into the actual clinical utility of the distinctness of ICAD.

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Highlights

- Stress, obesity, gut flora, diet, and genetics can increase inflammation.
- Vulnerability to inflammation can result from decreased neurotrophic support.
- Other vulnerabilities include sleep quality, fatty acids, and genetics.
- In vulnerable people, this leads to effects on monoamines and glutamatergic systems.
- This can potentially result in inflammatory-cytokine associated major depression.