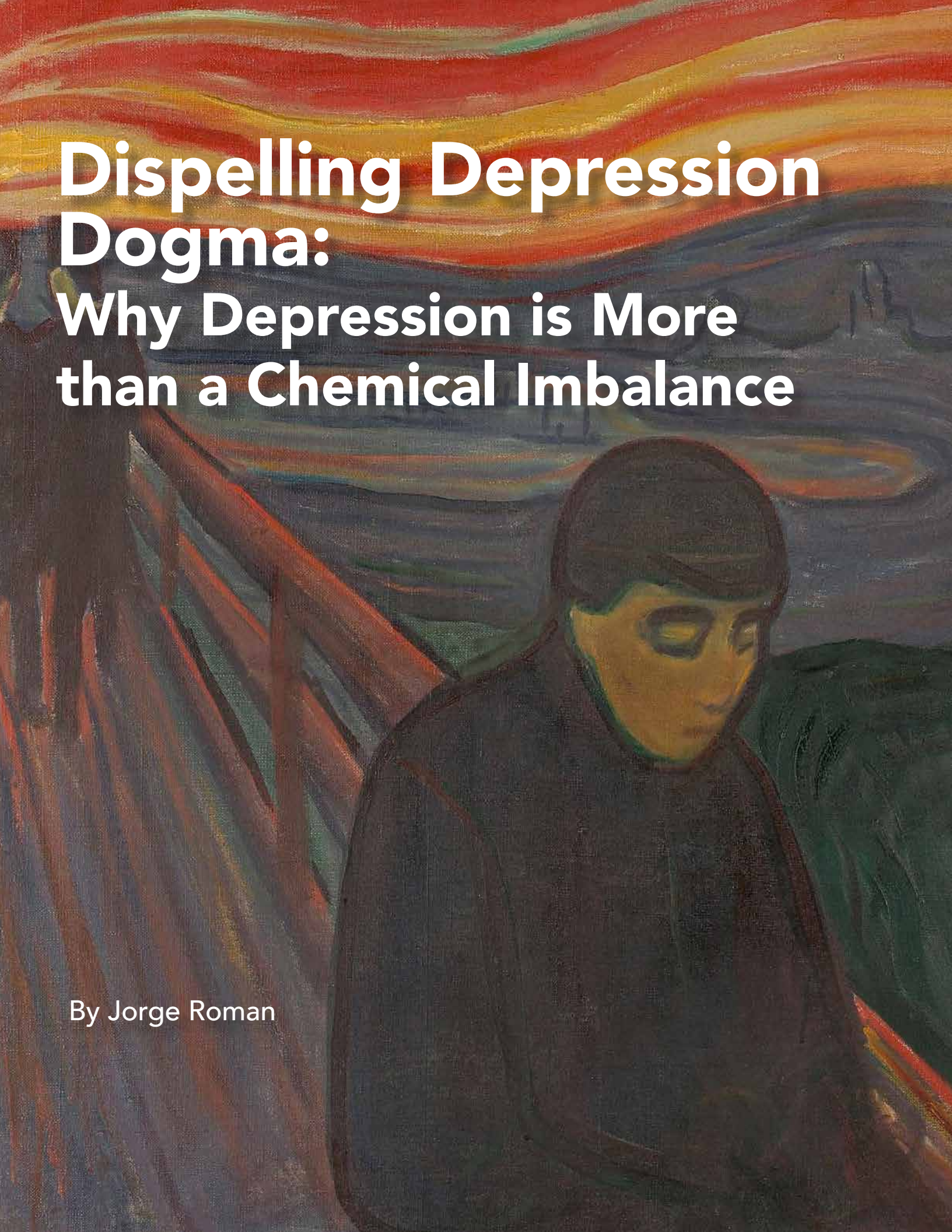


Dispelling Depression Dogma:
Why Depression is More than a Chemical Imbalance

By Jorge Roman

You have been tossing and turning all night, unable to sleep. In the early morning, you're finally able to beckon your body into REM sleep, only to be rudely interrupted by a blaring alarm clock. Frustrated, you give the snooze button a swift slap. Needless to say, you are absolutely exhausted. Thus, it took every bit of willpower to get out of bed and get dressed. As you imagine how your day might go, you immediately cringe at the thought of social interaction. You make breakfast and are severely disappointed to find the eggs taste like flavorless jello and the toast like bland cardboard. What was happening? Unfortunately, you have just come down with the flu.

Except for the loss of smell and taste, the rest of these symptoms might be reminiscent of another condition. Social withdrawal, fatigue, and lack of motivation for daily activities closely resemble the symptoms of individuals with depression. Admittedly, it seems crazy to compare the simple flu to the devastating condition of Major Depressive Disorder (MDD), one of the most debilitating conditions affecting almost 200 million adults worldwide, many of which are severely physically and emotionally impaired as a result [1].

Despite the apparently wild connection, scientists have discovered that there are indeed shocking similarities underlying the shared symptoms between infectious diseases and depression. In other words, these simple flu-like symptoms, known as "sickness behavior", have revealed that the immune system is intimately linked to the brain, and is implicated in Major Depressive Disorder [2].

At this point, you may be thinking to yourself: "Hold on a second, I thought we had depression figured out. It's caused by a chemical imbalance, right?". Indeed, a survey showed that the majority of the public believes depression to be caused by an imbalance of brain chemicals, despite scant evidence in support of the theory [3],[4]. Furthermore, most of the pharmaceutical treatments for depression were developed according to this chemical imbalance theory. So, how is it that the majority of the public perception of and medical treatments for depression are largely based on a theory with little scientific backing?

"Isolation & Depression" by David S Serano.. Liscensed under CC-BY-SA 4.0.

All You Need Is...Serotonin?

You have likely heard that depression is caused by a deficiency in serotonin, often colloquially referred to as one of the "happy chemicals". In the scientific literature, this notion is known as the monoamine theory of depression, which has been the prevailing scientific dogma since the 1960s [4]. One of the first pieces of evidence in support for the theory came from the discovery that the tuberculosis drug iproniazid was allegedly found to improve depression symptoms as a side effect [5]. This unintentional antidepressant effect was attributed to the fact that iproniazid decreased the degradation of serotonin, leading to its increased concentration in the brain. Conversely, the blood pressure medication reserpine was found to decrease serotonin levels in the brain. This depletion of serotonin led to sedation, impaired movement, and disrupted cognitive function, which the researchers claimed resembled the symptoms of depression [5].

Thus, the monoamine theory of depression was born, and pharmaceutical companies rushed in to take full advantage. In this paradigm, the development of Selective Serotonin Reuptake Inhibitors (SSRIs) wasthe obvious

solution. The idea was that SSRIs would increase the amount of available serotonin in the brain by preventing serotonin from being cleared from neurons. The result, in theory, would be a nearly immediate increase in serotonin and an improvement in depression symptoms. Depression cured!

Not so fast. Unfortunately, the true effects of SSRIs in the real world paint a much different picture. The degree to which they work in different contexts, as well as the actual mechanism behind their effects are debated. For adolescents with depression, for example, research shows that almost half show no meaningful improvement in depression symptoms after SSRI treatment, and many will take weeks, if not months to see improvements in mood [6]. Of course, this means that the majority of adolescents with depression who take SSRIs will still have an improvement in symptoms.

So, SSRIs do still provide a benefit in some instances. Unfortunately, another problem exists. Research has shown that the results of studies funded by or tied to pharmaceutical companies are significantly biased in favor of the drug—in this case SSRIs [7]. In the sciences, there is a type of study known as a meta-analysis, basically a study of many studies. This type of research helps to provide an overview of a field or subfield as a whole, rather than relying on a single study. With respect to SSRIs, meta-analyses help to compile data from dozens, if not hundreds, of studies on SSRIs to determine their benefits, risks, and proper dosage. The problem is that many of the meta-analyses— which are meant to objectively evaluate the effectiveness of antidepressants — are written by the very own pharmaceutical companies which profit from the drugs [7]. This bias has led to understating the potential adverse side effects and exaggerating the benefits of SSRIs [8].

Let's take one step back. If the rationale for using SSRIs is still as airtight as it seemed to be in the 60s, there must be recent convincing evidence that depression is tied to a deficiency of serotonin, right? Dr. Joanna Moncrieff, a practicing British Psychiatrist and academic researcher, was the lead author of a meta-analysis which analyzed hundreds of studies attempting to answer this exact question [4]. Strikingly, Moncrieff and colleagues not only found no evidence that depression is caused by a deficiency in serotonin, but also not even a correlation between serotonin levels and depression [4]. Although SSRIs were intended to solve the apparent problem of a serotonin deficiency, they may actually be working to relieve depression symptoms by another unintended mechanism: decreasing inflammation. Although not conclusive, animal and human studies have both shown that treatment with SSRIs may decrease inflammation [2].

This shocking finding has prompted researchers to ask: if not serotonin, then what truly underlies Major Depressive Disorder?

Move Over Serotonin: How the Immune System has Rightfully Stolen the Spotlight

Beginning in the 1970s, one scientific discovery hinted at a potential link between the brain and the immune system [2]. Similar to the classical conditioning experiment with Pavlov's dog, Drs. Ader and Cohen, a psychiatrist and an immunologist, respectively, found that they could condition mice to avoid a sugary liquid if it was paired with a drug which caused the mice to get sick. Naturally, the mice learned to avoid the sweet liquid altogether, associating it with the negative effects from the drug. Simple stuff, but here's where it gets interesting. After this association was made, the researchers gave the mice only the sweet solution against their will. The result? The mice actually got sick because they learned that the sugary liquid couldn't be trusted! In other words, they learned to associate the delicious, sugary liquid with sickness, even after the drug was no longer paired with it. This sort of learning is a process that occurs in the brain, and thus, this seemingly simple study showed that a connection between the brain and the immune system must exist. Now the question was: what is the connection?

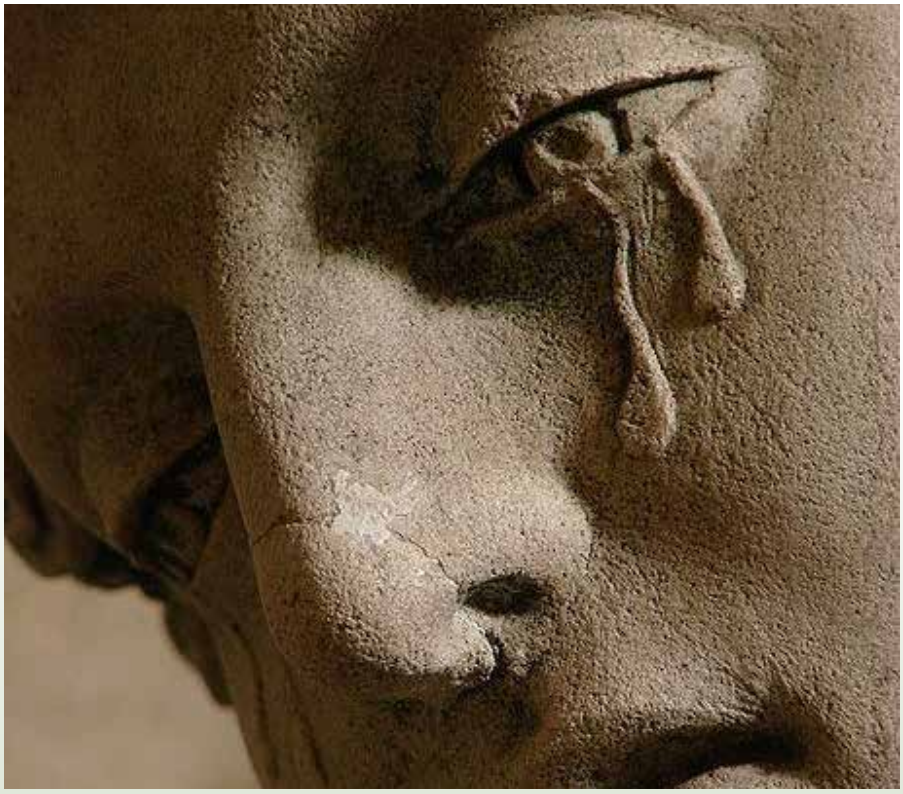
In the 80s, we began to inch closer to finding this connection. Remember the "sickness behavior" described earlier? Dr. Benjamin Hart was among the first to coin this phrase, comparing the collection of flu-like symptoms to the symptoms of depression [9]. In order to make the leap from sickness to depression, however, there needed to be direct evidence of what the connection was between the immune system and the brain. As with any new hypothesis, people were highly skeptical. Despite Ader and Cohen's studies, the idea that there was a link between the immune system and the brain was somewhat controversial. In 1989, however, a critical review paper was published which made the controversial argument that the missing link between the

immune system and the brain was a cytokine, a protein made by immune cells [10]. It is the cytokines which are responsible for "sickness behavior". This makes sense from an evolutionary perspective.When you come down with the flu, it becomes increasingly important not to expend unnecessary energy so that you can get over it and get on with your life. Furthermore, it is wise for the body to decrease motivation for social interaction so as not to infect other unsuspecting humans. It is the cytokines which accomplish these important, but uncomfortable, symptoms by communicating with the brain.

Towards the end of the 20th century, one promising study showed that treating mice with cytokines leads to "sickness behavior"[11]. Years later, this hypothesis continued to be supported by studies on cancer and hepatitis C patients receiving IFN-α, a cytokine which was used to treat both of these conditions. They found that the patients receiving this cytokine treatment were significantly more likely to develop depressive-like symptoms as a side effect of the treatment [10]. Recently, it has become increasingly clear that cytokines are involved in Major Depressive Disorder. Studies have shown that patients diagnosed with MDD have higher levels of inflammatory cytokines, such as IL-6 and TNFα, in their bloodstream compared to healthy individuals [12].

To understand how this newfound link between depression and the immune system can be used to develop innovative treatments for MDD, we must first get a clearer understanding of how the immune system works.

The Immune System: The Body's Trusty Alarm System



"Mary Magdalene Crying Statue" by Vassil. Liscensed under CC BY 3.0.

The brilliant scientists of the late 20th century not only began to cast doubt on the serotonin theory of depression, but also laid the foundation for a new understanding of depression: the immune-inflammation hypothesis. Inflammation is a huge buzzword nowadays, but for now it can be thought of as an alarm signal, a process which aggravates the body's immune system. This is important to understand because the immune system is a critical detector and communicator of inflammation. In other words, it is the immune system which sounds the alarm, telling the rest of the body there is a problem. More specifically, cytokines, (proteins made by immune cells), sound the alarm, communicating with the brain and body that there is a problem that needs to be addressed. If cytokines are the alarm signals, what serves as the homebase for the respondents?

Immune cells serve as the home base, responding to the alarms and producing cytokines in response. We have many different types of immune cells in the body, but two of the most important are blood-borne immune cells and microglia, the immune cells of the brain. For now, we will focus on the blood-borne immune cells. In a healthy human, these immune cells are happy to just exist, traversing our circulatory highways with ease. However, they are subject to a plethora of challenges — inflammatory factors from our environment, such as viruses or bacteria. In response to these external insults, immune cells can become "activated". In other words, these blood-borne immune cells sense a fire and panic, producing cytokines which travel through the bloodstream to signal: there's a fire!

Eventually, the signal reaches our precious blood-brain-barrier, an important line of defense

preventing many toxins in our blood from entering the brain. Cytokines, however, sneak right through the barrier, affecting brain areas which control our behavior, as well as the immune cells of our brain, the microglia. Like the immune cells of the blood, the microglia also become activated, in this case as a result of the cytokines.

In postmortem studies on humans, the brains of patients previously diagnosed with depression who committed suicide had significantly greater levels of activated microglia than the brains of healthy individuals [13] . Other studies have explored the microglia of living individuals by using a PET scan, a type of imaging which allows scientists to determine how an organ or organ system works. Although not a perfect method of measuring the state of microglia, it is one of the best ways scientists can get a look into the brains of humans without having to wait until death or unethically opening up a living human's skull. They found that more microglia were activated in patients who have experienced a Major Depressive episode [14]. But what's the deal with these activated microglia—why are they causing all sorts of problems?

Activated microglia are meant to clean up the brain. However, during this process, they unintentionally ravage the brain. In some cases these activated microglia can cause the death of neurons in certain brain areas [15]. The hippocampus is of particular interest because it has been shown to be smaller in patients with Major Depressive Disorder [16]. Unsurprisingly, a smaller hippocampus is associated with impaired memory and learning, which is very common in patients with depression [16]. Furthermore, the more times a patient recovers from and relapses back into depression, the more the hippocampus shrinks, making it critical to develop treatments to stop this deteriorating hippocampus [17].

Let's return our attention to sickness behavior. When you come down with the flu, sickness behavior is adaptive, a beneficial response that allows you to get over the sickness, decrease the spread of infection, and get back to your normal self. Depression, on the other hand, seems to be a chronic version of this sickness behavior. In the case of the flu, a virus is the cause of the inflammatory immune response, eventually leading to sickness behavior. But what could be chronically aggravating the immune system and causing inflammation in the case of depression?

Where is the Inflammation Coming From?

There are many different sources of inflammation, four of which are shown in the above figure. Studies have shown that adults with a history of early life stress, especially childhood maltreatment, have higher levels of activated blood-borne immune cells [18]. The risk of depression is higher in individuals with a history of childhood adversity, or trauma [19]. In animal studies, mice are often subjected to chronic stress because it results in depressive-like behaviors: mice stop grooming themselves, eating food, and interacting with their fellow mice. How? One theory suggests we should look no further than the microglia. Chronic stress increases the activation of microglia, leading to damage to the hippocampus [15]. However, even acute social stress may aggravate our immune cells [20]. A 2003 study employed the Trier Social Stress Test, a test which requires the participant to give an interview-style presenta-

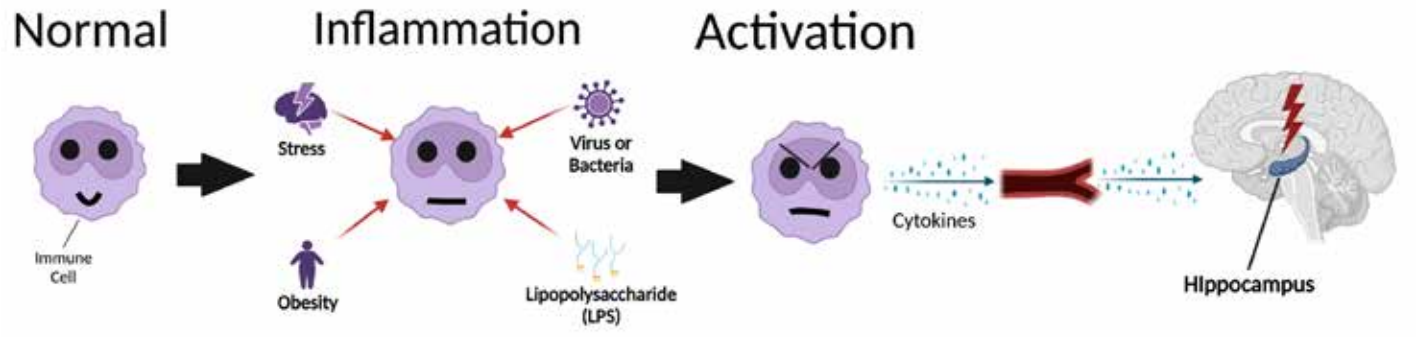


Figure 1. *How circulating immune cells become activated to produce cytokines and brain inflammation. Adapted from: Beurel, Toups, and Nemeroff 2020; Bierhaus et al., 2003; Capuron, Lasselin, and Castanon 2016. Created with BioRender.com*

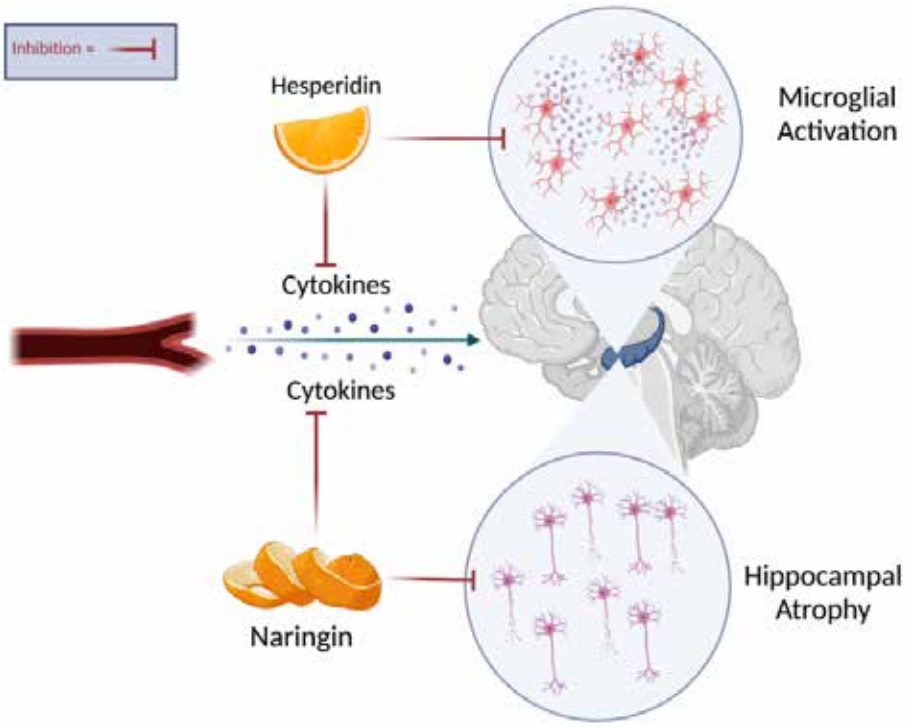


***Figure 2**. How naringin and hesperidin affect microglial activation, cytokines, and hippocampal atrophy (Blunt arrows indicate inhibition). Adapted from: Xie et al., 2020; Gao et al., 2022. Created with BioRender.com*

tion, as well as solve on-the-spot arithmetic in front of several researchers who stare blankly at the participant, providing no encouragement whatsoever. In effect, the test is designed to evoke social stress. The researchers found that this social stress was enough to activate immune cells, increasing the production of inflammatory cytokines [20].

Obesity is another source of inflammation which may contribute to depression. Indeed, 30% of obese individuals are diagnosed with depression [21], which begs the question: how? Although there are many factors, one answer comes from the effects of obesity on the immune system. Obese individuals have higher immune cell activation compared to normal weight individuals [21]. Indeed, fat cells themselves actually produce inflammatory cytokines [21]. This again results in the long inflammatory cascade shown in Figure 1, eventually ending in brain inflammation and increasing the risk of depression.

Finally, a substance known as lipopolysaccharide (LPS) is another source of inflammation [22]. LPS is found on the surface of some bacteria found in our vast gut microbiome. LPS is normally innocuous, as it sits in our gut minding its own business. The problem occurs when LPS deviously sneaks through our gut lining, shimmying its way into our bloodstream. Our trusty immune cells sound the alarms, producing cytokines which eventually make their way into the brain. Indeed, studies have repeatedly shown that giving rodents or humans LPS increases cytokines, such as IL-6 and TNFα, and leads to depression symptoms [2]. Strikingly, treating humans with LPS leads to increased feelings of social disconnection, one of the common symptoms in people experiencing Major Depressive Disorder [2]. But if LPS plays a critical role, or any role whatsoever, in Major Depressive Disorder, surely we should expect to find higher levels of LPS in the blood of MDD patients compared to healthy individuals. As expected, higher LPS has been found in the bloodstream of depressed patients compared to healthy people [23].

Overwhelming? Probably. Hopeless? Not at all. Scientists are currently exploring many innovative ways to calm our immune systems and decrease inflammation in hope of improving quality of life for those living with depression.

Putting Out the Fire… with Orange Juice?

So, inflammation is increasingly being recognized as one the driving forces of the debilitating condition of depression. It follows that this newfound knowledge should be exploited to create new treatments. This is the tricky part, however, because inflammation is incredibly broad. What exact mechanism in the painfully long cascade of inflammatory events should be targeted? Body fat? Microglia? The cytokines themselves?

One unexpected answer comes from the humble breakfast beverage, orange juice. Orange juice consumption is associated with lower inflammatory markers as well as lower risk of depression in some groups [24] , [25]. One study focused on the effects of OJ on the inflammatory response induced by LPS, the sneaky substance found in our gut. Typically, after a high fat, high carbohydrate meal typical of a standard Amer-

ican diet, LPS creeps into our blood, sounding the immune cell fire alarm and causing inflammation. However, in the group given a glass of OJ during the meal, LPS no longer made its way into the bloodstream, in a sense stopping the inflammation at the source [25]. More compelling evidence for OJ's anti-inflammatory and antidepressant role comes from a clinical trial which recruited individuals with depression. The researchers split the participants into two groups: one group of OJ drinkers and another group drinking an orange-flavored drink matched for calories and carbohydrates. The groups were given their assigned drink for a total of 8 weeks, once before breakfast and again before dinner. The results were shocking: the OJ drinkers had significantly decreased depression severity [26]. So, what is it about this golden, pulpy drink which could be responsible for these beneficial health effects?

When we think of orange juice, most people think of vitamin C. While likely an important contributor to the health benefits of OJ, it is far from the only one. Compounds found in plants known as flavonoids have recently garnered attention for their anti-inflammatory, antioxidant, and antidepressant properties [24]. In fact, higher consumption of flavonoids are linked to a decreased risk of depression, with orange juice being a major source of flavonoids [24].

Naringin, a flavonoid found mainly in orange peels, oranges, and grapefruit juice, targets inflammation at multiple steps of the inflammatory cascade. In mice treated with LPS, naringin decreases cytokine levels in the blood, preventing downstream brain inflammation [27]. Naringin also has direct protective effects on the brain. It has been shown to improve memory and anxiety, decrease depressive-like behaviors, and promote the growth of new neurons in the hippocampus of mice (Figure 2) [27],[28].

Another flavonoid of interest found mainly in orange juice is hesperidin. Remember microglia, the immune cells of the brain? Well, these immune cells can exist either in a harmless state or in an aggravated (activated) state, where they produce pro-inflammatory cytokines which can damage brain regions associated with depression. Hesperidin has been found to calm down these microglia and alleviate the brain damage they cause in mice [29]. In humans supplementing with hesperidin, there is a decrease in their levels of the pro-inflammatory cytokines IL-6 and TNFα [25]. Of course, getting into the brains of humans is practically, and ethically, difficult, but these initial results are exciting nonetheless.

Looking Ahead

The initial findings of citrus flavonoids, and orange juice itself, suggest that they may have significant, positive impacts on the immune system, inflammatory markers, and depression. Given the limited amount of flavonoids one can consume from OJ, flavonoid supplements may strengthen the antidepressant and anti-inflammatory effect of OJ. Although human studies looking at flavonoid supplementation are still in the early stages, results from animal studies are very promising.

Mental disorders like depression and anxiety weigh heavily on individuals, their families, and the economy at large, with over 193 million people worldwide suffering from depression [1]. The financial, social, and psychological burden of these conditions have been exacerbated by the COVID-19 pandemic as a result of social distancing, decreased in-person care, unemployment, long term effects from the virus itself, and the fear surrounding the pandemic [1]. In fact, an additional 53.2 million cases of depression were diagnosed during the COVID-19 pandemic [1]. Despite treatments such as cognitive behavioral therapy and SSRIs, there has not been a decrease in the prevalence of MDD since the 1990s [1].

If we are truly to make a significant change in the lives of people living with depression, it is imperative to do away with the old chemical imbalance paradigm which is based, at least in part, on pharmaceutical zealotry and bias, rather than on rigorous science. Now, a new key player in depression should be acknowledged: the immune system.

References

1.Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic. Lancet Lond Engl. 2021;398(10312):1700-1712. doi:10.1016/S0140-6736(21)02143-7

2.Beurel E, Toups M, Nemeroff CB. The Bidirectional Relationship of Depression and Inflammation: Double Trouble. Neuron. 2020;107(2):234-256. doi:10.1016/j.neuron.2020.06.002

3. Pescosolido BA, Martin JK, Long JS, Medina TR, Phelan JC, Link BG. "A disease like any other"? A decade of change in public reactions to schizophrenia, depression, and alcohol dependence. Am J Psychiatry. 2010;167(11):1321-1330. doi:10.1176/appi.ajp.2010.09121743

4. Moncrieff J, Cooper RE, Stockmann T, Amendola S, Hengartner MP, Horowitz MA. The serotonin theory of depression: a systematic umbrella review of the evidence. Mol Psychiatry. Published online July 20, 2022. doi:10.1038/s41380-022-01661-0

5. Hirschfeld RM. History and evolution of the monoamine hypothesis of depression. J Clin Psychiatry. 2000;61 Suppl 6:4-6.

6. Brent D, Emslie G, Clarke G, et al. Switching to Another SSRI or to Venlafaxine With or Without Cognitive Behavioral Therapy for Adolescents With SSRI-Resistant Depression. JAMA J Am Med Assoc. 2008;299(8):901-913. doi:10.1001/jama.299.8.901

7.Ebrahim S, Bance S, Athale A, Malachowski C, Ioannidis JPA. Meta-analyses with industry involvement are massively published and report no caveats for antidepressants. J Clin Epidemiol. 2016;70:155-163. doi:10.1016/j.jclinepi.2015.08.021

8.Jakobsen JC, Gluud C, Kirsch I. Should antidepressants be used for major depressive disorder? BMJ Evid-Based Med. 2020;25(4):130. doi:10.1136/bmjebm-2019-111238

9.Hart BL. Biological basis of the behavior of sick animals. Neurosci Biobehav Rev. 1988;12(2):123-137. doi:10.1016/s0149-7634(88)80004-6

10.Dantzer R, Kelley KW. Twenty Years of Research on Cytokine-Induced Sickness Behavior. Brain Behav Immun. 2007;21(2):153-160. doi:10.1016/j.bbi.2006.09.006

11.Yirmiya R, Weidenfeld J, Pollak Y, et al. Cytokines, "depression due to a general medical condition," and antidepressant drugs. Adv Exp Med Biol. 1999;461:283-316. doi:10.1007/978-0-585-37970-8_16

12.Osimo EF, Pillinger T, Rodriguez IM, Khandaker GM, Pariante CM, Howes OD. Inflammatory markers in depression: A meta-analysis of mean differences and variability in 5,166 patients and 5,083 controls. Brain Behav Immun. 2020;87:901-909. doi:10.1016/j.bbi.2020.02.010

13.Steiner J, Bielau H, Brisch R, et al. Immunological aspects in the neurobiology of suicide: Elevated microglial density in schizophrenia and depression is associated with suicide. J Psychiatr Res. 2008;42(2):151-157. doi:10.1016/j.jpsychires.2006.10.013

14. Setiawan E, Wilson AA, Mizrahi R, et al. Role of translocator protein density, a marker of neuroinflammation, in the brain during major depressive episodes. JAMA Psychiatry. 2015;72(3):268-275. doi:10.1001/jamapsychiatry.2014.2427

15. Fan Y, Bi Y, Chen H. Salidroside Improves Chronic Stress Induced Depressive Symptoms Through Microglial Activation Suppression. Front Pharmacol. 2021;12:635762. doi:10.3389/fphar.2021.635762

16.MacQueen G, Frodl T. The hippocampus in major depression: evidence for the convergence of the bench and bedside in psychiatric research? Mol Psychiatry. 2011;16(3):252-264. doi:10.1038/mp.2010.80

17. Roddy DW, Farrell C, Doolin K, et al. The Hippocampus in Depression: More Than the Sum of Its Parts? Advanced Hippocampal Substructure Segmentation in Depression. Biol Psychiatry. 2019;85(6):487-497. doi:10.1016/j.biopsych.2018.08.021

18. do Prado CH, Grassi-Oliveira R, Daruy-Filho L, Wieck A, Bauer ME. Evidence for Immune Activation and Resistance to Glucocorticoids Following Childhood Maltreatment in Adolescents Without Psychopathology. Neuropsychopharmacology. 2017;42(11):2272-2282. doi:10.1038/npp.2017.137

19. X X, X W. Childhood adversity and major depression in later life: A competing-risks regression analysis. Int J Geriatr Psychiatry. 2021;36(1). doi:10.1002/gps.5417

20. Bierhaus A, Wolf J, Andrassy M, et al. A mechanism converting psychosocial stress into mononuclear cell activation. Proc Natl Acad Sci U S A. 2003;100(4):1920-1925. doi:10.1073/pnas.0438019100

21.Capuron L, Lasselin J, Castanon N. Role of Adiposity-Driven Inflammation in Depressive Morbidity. Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol. 2017;42(1):115-128. doi:10.1038/npp.2016.123

22. Berk M, Williams LJ, Jacka FN, et al. So depression is an inflammatory disease, but where does the inflammation come from? BMC Med. 2013;11:200. doi:10.1186/1741-7015-11-200

23. Maes M, Kubera M, Leunis JC. The gut-brain barrier in major depression: intestinal mucosal dysfunction with an increased translocation of LPS from gram negative enterobacteria (leaky gut) plays a role in the inflammatory pathophysiology of depression. Neuro Endocrinol Lett. 2008;29(1):117-124.

24. Chang SC, Cassidy A, Willett WC, Rimm EB, O'Reilly EJ, Okereke OI. Dietary flavonoid intake and risk of incident depression in midlife and older women. Am J Clin Nutr. 2016;104(3):704-714. doi:10.3945/ajcn.115.124545

25. Coelho RCLA, Hermsdorff HHM, Bressan J. Anti-inflammatory properties of orange juice: possible favorable molecular and metabolic effects. Plant Foods Hum Nutr Dordr Neth. 2013;68(1):1-10. doi:10.1007/s11130-013-0343-3

26. Park M, Choi J, Lee HJ. Flavonoid-Rich Orange Juice Intake and Altered Gut Microbiome in Young Adults with Depressive Symptom: A Randomized Controlled Study. Nutrients. 2020;12(6):E1815. doi:10.3390/nu12061815

27. Ben-Azu B, Nwoke EE, Aderibigbe AO, et al. Possible neuroprotective mechanisms of action involved in the neurobehavioral property of naringin in mice. Biomed Pharmacother Biomedecine Pharmacother. 2019;109:536-546. doi:10.1016/j.biopha.2018.10.055

28. Gao C, Wu M, Du Q, Deng J, Shen J. Naringin Mediates Adult Hippocampal Neurogenesis for Antidepression via Activating CREB Signaling. Front Cell Dev Biol. 2022;10:731831. doi:10.3389/fcell.2022.731831

29. Xie L, Gu Z, Liu H, et al. The Anti-Depressive Effects of Hesperidin and the Relative Mechanisms Based on the NLRP3 Inflammatory Signaling Pathway. Front Pharmacol. 2020;11. Accessed September 21, 2022. https://www.frontiersin.org/articles/10.3389/fphar.2020.01251