

PERSPECTIVE

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Reconceptualizing major depressive disorder as an infectious disease

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Abstract

In this article, I argue for a reconceptualization of major depressive disorder (major depression) as an infectious disease. I suggest that major depression may result from a parasitic, bacterial, or viral infection and present examples that illustrate possible pathways by which these microorganisms could contribute to the etiology of major depression. I also argue that the reconceptualization of the human body as an ecosystem for these microorganisms and the human genome as a host for non-human exogenous sequences may greatly amplify the opportunity to discover genetic links to the illness. Deliberately speculative, this article is intended to stimulate novel research approaches and expand the circle of researchers taking aim at this vexing illness.

Keywords: Genomics, Virus, Bacterial, Parasite, Depression

Background

Despite decades of substantial research efforts, major depressive disorder (MDD) remains among the most common mental disorders, with a 16.6% lifetime prevalence rate [1]. Pharmacological treatment approaches have not changed during this period, targeting primarily receptor-ligand interactions [2]. These types of antidepressants may bring relief to patients with severe symptoms but are not clinically more effective than placebos in mild to moderate cases [3]. Indeed, recurrence rates of 50% for first-episode patients and of 80% for second-episode patients [4] suggest that the core of the illness goes untreated.

Given this track record, I argue that it is time for an entirely different approach. Instead of conceptualizing MDD as an emotional disorder, I suggest to reconceptualize it as some form of an infectious disease. I propose that future research should conduct a concerted search for parasites, bacteria, or viruses that may play a causal role in the etiology of MDD. I present three arguments why this may be a fruitful endeavor. I have outlined the idea in much greater detail elsewhere [5], but will highlight some key points here.

Main text

My first argument is that patients with MDD exhibit sickness behavior. Patients experience loss of energy; they commonly have difficulty getting out of bed and lose interest in the world around them. Although our Western conceptualization puts affective symptoms front-and-center, non-Western patients who meet DSM criteria for major depression report primarily somatic symptoms [6-11], reflecting in part cultural differences in the stigmatization of mental illness.

Yet, studies of inflammatory biomarkers in major depression strongly suggest an illness-related origin. For example, a meta-analysis of 24 studies confirmed prior reports of elevated TNF α and IL-6 in patients with major depression [12]. A second meta-analysis of 29 studies further extended the list of significantly elevated inflammatory markers to also include the soluble interleukin-2 receptor [13].

Several postmortem studies report the presence of inflammatory markers in the brains of depressed or mood-disordered patients. For example, compared to controls, female suicide victims showed elevated levels of IL-4 and male suicide victims showed elevated levels of IL-13 in Brodmann Area (BA) 11 [14], a brain region previously associated with suicidal ideation [15,16]. Compared to age-matched controls, patients diagnosed with major depression showed elevated levels of transmembrane TNF α (tmTNF α) in BA46 [17], a region associated with emotion

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regulation [18-20]. Patients with major depression, relative to controls, showed differential expression of a large set of both anti- and pro-inflammatory markers (including IL1 α , 2, 3, 5, 8, 9, 10, 12A, 13, 15, 18, and IFN γ) in BA10 [21], a region associated with reward processing [22].

These inflammatory markers may represent activation of the immune system in response to some kind of pathogen, which could be a parasite, bacterium, or virus, and which could play a causal role in the etiology of depression. There is currently no direct evidence that major depression is caused by such microorganisms, but nature has offered some examples to illustrate that such a process is conceivable.

Thus, my second argument is that nature has already provided examples by which parasites, bacteria, or viruses can affect emotional behavior. The best-known example of a parasite that affects emotional behavior and that is relevant to human health is *Toxoplasma gondii*. *T. gondii* lives in the feline intestinal tract, where it lays its eggs, which are dispersed into the environment upon excretion. When a rat comes in contact with these eggs and becomes infected, it becomes attracted to the scent of cat urine [23,24]. This manipulation of the rat's behavior involves the deposit of parasitic cysts across the rodent brain including the amygdala [25]. The mechanism for loss of fear to the scent of cat urine appears to involve a reduction in circulating corticosterone and dendritic retraction in the basolateral amygdala [26]. The mechanism for the rat's attraction to the odor may involve activation of sexual arousal pathways [27].

The specificity of the behavioral change in the rat's behavior appears to reflect functional changes that are limited to catecholaminergic neurons [28]. Infected animals have elevated levels of dopamine [29], but *T. gondii* can only synthesize tyrosine hydroxylase (which converts tyrosine to L-DOPA), and would therefore need to rely on catecholaminergic neurons to provide the needed DOPA decarboxylase to convert the L-DOPA to dopamine.

Human exposure to *T. gondii* is pervasive, with one-third of the world's population [30] and one-fifth of the U.S. population [31] believed to be infected. Infection is associated with elevated inflammatory cytokines IL-6, IL-12, TNF, and IFN- γ [32,33], similarly as observed in depressed patients. A study of 20 European countries reported a positive correlation between *T. gondii* prevalence rates and national suicide rates [34]. Among patients with diagnosed major depression or bipolar disorder, those with a history of suicide attempt had higher *T. gondii* antibody titers [35]. Yet, large-scale studies of major depression and *T. gondii* or systematic searches to discover other potential parasitic infections have not yet been conducted.

Bacteria could be another causal factor for major depression. Studies of bacterial colonies residing in the gastrointestinal tract have begun to examine links to

emotional behavior. In the first study of this kind, germ-free (GF), specific pathogen-free (SPF), and gnotobiotic mice were compared in their response to restraint stress [36]. GF mice exhibited higher levels of plasma ACTH and corticosterone and had lower levels of brain-derived neurotrophic factor in the cortex and hippocampus, compared to SPF mice. The elevated stress response of GF mice was normalized with administration of the bacterium *Bifidobacterium infantis*. Another rodent study showed that administration of *B. infantis* in rats reduced the levels of IFN- γ , TNF- α , and IL-6 following mitogen stimulation and altered tryptophan, 5-HIAA, and DOPAC levels in the frontal cortex and amygdala [37]. Administration of the *Lactobacillus rhamnosus* strain in mice was shown to alter GABAergic expression in the brain: elevating GABA_{B1b} mRNA in the cingulate and prelimbic cortices, while reducing it in hippocampus and amygdala, among other regions [38].

The 'leaky gut' hypothesis proposes a mechanism by which gastrointestinal bacteria may contribute to major depression [39,40]. According to this hypothesis, cytokines or other stressors may render the intestinal tract permeable to lipopolysaccharides (LPS) from gram-negative bacteria to activate the immune system. Indeed, the model is supported by data showing elevated serum concentrations of IgM and IgA against LPS of the gram-negative enterobacteria in depressed patients [39,40]. These studies were conducted with relatively small numbers of patients and suggested that this mechanism may apply to some subgroups of patients but not others. It would be useful to expand the search using large patient cohorts and a wide range of different antibodies. Future work should then examine potential neural mechanisms.

Viruses represent the third pathogenic route in the etiology of major depression. A meta-analysis of 28 studies explicitly examined the link between infectious agents and depression [41]. Among viruses that had significant associations with the illness were the Borna disease virus (BDV), herpes simplex virus-1, varicella zoster virus, and Epstein-Barr virus. Among these, BDV has been studied most extensively and was 3.25 times more likely to be found in depressed patients than in normal controls [41]. One postmortem study reported BDV infection in 2 out of 30 depressed patients in the frontal and temporal cortex, olfactory bulb, and hippocampus [42], although a larger study failed to detect any infection [43]. A small open-label study of BDV-infected depressed patients reported a reduction in both depressive symptoms and BDV infection upon treatment with the antiviral drug amantadine [44].

The mechanism between BDV infection and depression could involve glutaminergic transmission, because amantadine is an antagonist of the N-methyl-D-aspartate (NMDA) receptor, one of the receptors targeted by

glutamate. The related NMDA antagonist memantine has been evaluated in a randomized, double-blind study of patients diagnosed with bipolar depression, where it was applied to augment treatment with the presynaptic glutamate release inhibitor lamotrigine, and found to accelerate treatment response [45]. Another NMDA receptor antagonist, ketamine, also has antidepressant effects [46], which appear to be mediated by changes in mTOR signaling [47]. However, the literature on BDV infection and depression remains controversial, with several studies failing to replicate any association between the two [48-51].

My third argument is that reconceptualizing major depression as being causally linked to parasites, bacteria, or viruses is useful when thinking about the genetics of this illness. Evidence from twin studies notwithstanding, the search for specific genes linked to major depression has come up empty [52,53]. Perhaps, we have been looking at the wrong organism. Genetic studies to date have focused the search on human genes within our genome. Yet, 8% of the human genome is based on exogenous sequences from retroviruses [54]. These retroviral insertions may sometimes benefit the human host and therefore be protected from mutational degeneration [55]. Indeed, the BDV discussed earlier inserted some of its sequences into vertebrate genomes approximately 40 million years ago [56], and presence of these sequences correlates with disease resistance to BDV. Parasites could also add exogenous sequences to the human genome through the process of horizontal gene transfer [57]. It is possible that polymorphisms within such exogenous sequences, or interactions between these exogenous sequences and other variables such as human gene polymorphisms or stressful life experiences, could render some individuals vulnerable to major depression.

Furthermore, if we view the human body as an ecosystem that is a host to numerous microorganisms which may be passed across generations, the opportunity for genetic discoveries is vastly amplified. For example, an estimated thousand species of bacteria reside in the human gastrointestinal tract [58], and these could be passed during birth or through common environmental exposure between parents and offspring [59]. Humans also carry vast numbers of viruses, which can be unknown and go undetected until subjected to a concerted search using new approaches such as deep sequencing [60].

Conclusions

In light of the above considerations, an important point of reflection concerns the relation between the immune response and MDD and the specificity of any putative mechanism. The literature implicating the immune system in MDD [61] can be read as suggesting that the immune response itself is the causal mechanism in depression.

Indeed, conditions such as hypoxia known to produce sterile inflammation ([62], i.e., activation of the immune system sans a pathogen) may increase the risk of depression [61] in conditions such as obstructive sleep apnea [63] or chronic obstructive pulmonary disease [64]. Yet, most cases of MDD are not attributable to sterile inflammation. Thus, I suggest that some unknown pathogen(s) could play a causal role, and that the immune response is secondary to the infection; interventions that only target the immune response may bring symptom relief but would not address the root cause of the illness.

If a pathogen played a causal role in MDD, the next question would concern the specificity of the mechanism. One perspective would favor a very general, non-specific mechanism. For example, chronic fatigue syndrome (CFS)—which is characterized by sickness behavior that may include depressive symptoms—has been hypothesized to be caused by vagus nerve infection, regardless of the type of pathogen [65]. My view is that, for MDD, the type of pathogen may matter a great deal, and that it plays a very specific causal role: the examples I presented above suggest plausible mechanisms by which pathogens may alter neurotransmission. However, there may not be a single pathogen that causes all cases of MDD. Instead, there may be a class of pathogens, similar to those discussed above, which share common modes of action. This class of pathogens would specifically target the nervous system in a manner that causally contributes to MDD. I use the term ‘contribute’ to indicate that these pathogens may act in concert with other variables. For example, an individual may carry a latent infection and be asymptomatic for depressive symptoms. This individual would be characterized by susceptibility to MDD which may only emerge after the pathogen was activated by other factors such as stressful life events; this activation could then also trigger a concomitant immune response. It is possible that such a pathogen-driven mechanism is not limited to MDD but may contribute to other psychopathologies. For example, posttraumatic stress disorder could be one such extension of the same mechanism: not every individual develops the disorder in response to a traumatic experience (suggesting individual differences in susceptibility), and the illness is accompanied by immune system activation [66,67].

In closing, I think it would be worthwhile to conduct large-scale studies of carefully characterized depressed patients and healthy controls, using gold-standard clinical and infectious disease-related study protocols, as have already been developed for bacteria [68,69] and viruses [70-76]. Such efforts, if successful, would represent the ‘end of the beginning’, as any such discovery would represent the first step toward developing a vaccination for major depression.

Abbreviations

BA: Brodmann Area; BDV: Borna disease virus; GABA: gamma-aminobutyric acid; IFN- γ : interferon gamma; IgA: immunoglobulin A; IgM: immunoglobulin M; IL: interleukin; L-DOPA: L-3,4-dihydroxyphenylalanine; LPS: lipopolysaccharides; MDD: major depressive disorder; NMDA: N-methyl-D-aspartate; TNF α : tumor necrosis factor alpha; tmTNF α : transmembrane tumor necrosis factor alpha.

Competing interests

The author declares that he has no competing interests.

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