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HYPOTHESIS

The evolutionary significance of depression in Pathogen Host Defense (PATHOS-D)

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Given the manifold ways that depression impairs Darwinian fitness, the persistence in the human genome of risk alleles for the disorder remains a much debated mystery. Evolutionary theories that view depressive symptoms as adaptive fail to provide parsimonious explanations for why even mild depressive symptoms impair fitness-relevant social functioning, whereas theories that suggest that depression is maladaptive fail to account for the high prevalence of depression risk alleles in human populations. These limitations warrant novel explanations for the origin and persistence of depression risk alleles. Accordingly, studies on risk alleles for depression were identified using PubMed and Ovid MEDLINE to examine data supporting the hypothesis that risk alleles for depression originated and have been retained in the human genome because these alleles promote pathogen host defense, which includes an integrated suite of immunological and behavioral responses to infection. Depression risk alleles identified by both candidate gene and genome-wide association study (GWAS) methodologies were found to be regularly associated with immune responses to infection that were likely to enhance survival in the ancestral environment. Moreover, data support the role of specific depressive symptoms in pathogen host defense including hyperthermia, reduced bodily iron stores, conservation/withdrawal behavior, hypervigilance and anorexia. By shifting the adaptive context of depression risk alleles from relations with conspecifics to relations with the microbial world, the Pathogen Host Defense (PATHOS-D) hypothesis provides a novel explanation for how depression can be nonadaptive in the social realm, whereas its risk alleles are nonetheless represented at prevalence rates that bespeak an adaptive function.
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Introduction

Major depression is so detrimental to survival and reproduction that it is hard to understand why allelic variants that promote the disorder have not been culled from the human genome, why in fact—far from being culled—genes that promote depression are so common and numerous and appear to have actually increased in prevalence during recent human evolution.[1] To address this issue, we have developed a novel theoretical framework positing that risk alleles for depression originated and have been largely retained in the human genome because these alleles encode for an integrated suite of immunological and behavioral responses that promote host defense against pathogens. This enhanced pathogen defense is accomplished primarily via heightened innate immune system activation, which results in reduced death from infectious causes,[2–5] especially in infancy when selection pressure from infection is strongest,[6] and the adaptive immune system is not yet fully operational.[6–9] A vast literature has associated depressive symptoms and/or major depressive disorder (MDD) with increased innate immune inflammatory responses,[10] with meta-analyses reporting the most consistent findings for increased plasma concentrations of tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), C-reactive protein and haptoglobin.[11–13] Recent longitudinal studies extend these cross-sectional observations by reporting that increased inflammatory markers in nondepressed individuals predict the later development of depression.[14–16] Because infection has been the primary cause of early mortality and hence reproductive failure across human evolution,[9,17–21] it would be expected that if depressive symptoms were an integral part of a heightened immunological response, allelic variants that support this response would have undergone strong positive selection pressure and thus would be both numerous and prevalent, as they appear to be. However, because

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the survival benefits of inflammatory processes are tempered by their costs in terms of increased mortality from septic shock,[22,23] pathogen manipulation,[21,24] long-term tissue damage and chronic disease,[10] these alleles would not be predicted to go to fixation (that is, 100% prevalence) but would be expected to manifest an intermediate prevalence reflecting the benefit of enhanced host defense in any given environment minus attendant costs. Again, this is consistent with current findings in the genetics of depression.

It should be noted that this Pathogen Host Defense (*PAT*hos *HOS*t *D*efense = PATHOS-D) hypothesis is not the first theory to associate depression with protection from infection. Indeed, similar to PATHOS-D, at least one previous hypothesis has envisioned depression as a behavioral response that helps the immune system combat existing infections while avoiding additional pathogen exposure.[25] However, prior theoretical articulations have envisioned depressive symptoms as adaptive primarily because they compensate for various types of immune system vulnerabilities.[25] PATHOS-D suggests something qualitatively different and more far-reaching; specifically that depressive symptoms were integral components of immune-mediated host defense against pathogens in the ancestral environment. In this model, depressive symptoms are inextricably intertwined with—and generated by—physiological responses to infection that—on average—have been selected as a result of reducing infectious mortality across mammalian evolution (Figure 1). Thus, it is proposed that the alleles for depression, rather than having coevolved with immunological alleles that support pathogen defense, are in fact one in the same as those alleles, and therefore genes associated with depression would be predicted to be the same genes that are associated with successful host immune responses.

To fully elaborate this hypothesis, this article is structured to evaluate the foundations of the PATHOS-D theory (Table 1) by first examining the immune relevance of previously identified depression risk alleles, followed by an exploration of relationships among environmental risk factors for depression, inflammation and pathogen host defense. The role of depression-associated immune changes in promoting survival during infection is reviewed next, followed by an examination of the potential utility of depressive symptoms in host defense. We conclude with a consideration of the potential limitations of—and challenges to— the PATHOS-D theory.

Risk alleles for MDD and host defense

The failed promise of genome-wide association studies (GWASs) to unambiguously identify genetic risk variants for MDD has led increasingly to the suggestion that depression and other major psychiatric conditions arise not from common allelic variants with small effect sizes, but rather from an array of highly nonadaptive genetic variants too rare to be identified by GWASs that nonetheless have large effect sizes.[26,27] Confirmation of this would effectively preclude the possibility that depressive risk alleles conferred any selective advantage during human evolution.[28] However, an alternative possibility is that differences in common allelic variants between depressed and nondepressed individuals might be more apparent/consistent if the unit of analysis was extended from single genes to groupings of genes that form functional units. In the context of the PATHOS-D theory, this suggests that small allelic differences between depressed and nondepressed groups should not be randomly distributed across the genome, but rather should be largely localized to genes with host defense functions, and that the effect sizes for differences in individual host defense alleles should be additive (that is, positive *epistasis*), so that large effect size differences should emerge when functionally related host defense-enhancing alleles are evaluated as a unit. Support for this possibility comes from a recent network analysis of candidate genes for MDD. Although this analysis only interpreted findings in terms of potential central nervous system (CNS) effects,[29] from a PATHOS-D perspective, it is striking that pathways identified as central to the best-supported MDD gene networks all have well-documented inflammatory and/or anti-inflammatory effects.

To be fully consistent with the PATHOS-D theory, allelic risk variants should meet three criteria. They should (1) be located in genes with known immune effects; (2) increase signaling in inflammatory/host defense pathways; and (3) increase survival in the context of infection. Although a number of candidate gene studies have identified depression risk alleles that are associated with inflammatory processes,[30–34] to evaluate in the most conservative manner whether putative risk alleles meet the three criteria above, we have limited our examination to candidate genes confirmed either by GWASs or meta-analysis and to alleles identified in meta-analyses of GWAS data.

Candidate genes confirmed by GWASs

Currently, only two candidate single-nucleotide polymorphisms (SNPs; rs12520799 in *DCNP1* (*dendritic cell nuclear protein-1*) and rs16139 in *NPY* (*neuropeptide Y*)) and one candidate gene for MDD (*TNF-α*), smallest *P*-value for rs76917) have been confirmed by GWASs.[35] It is striking that each of these genes plays an important role in processes central to host defense, including proinflammatory cytokine signaling (*TNF*), antigen presentation (*DCNP1*) and T helper type 1 cell differentiation and function (*NPY*). Of these SNPs, functionality has only been established for rs16139 in *NPY*. Although NPY has numerous and contrasting effects on innate and adaptive immune functioning, its primary actions appear to be anti-inflammatory in both the brain and periphery.[36–38] Given this, the PATHOS-D theory predicts that MDD should be characterized by reduced NPY activity and that the depression risk T allele at rs16139 should be

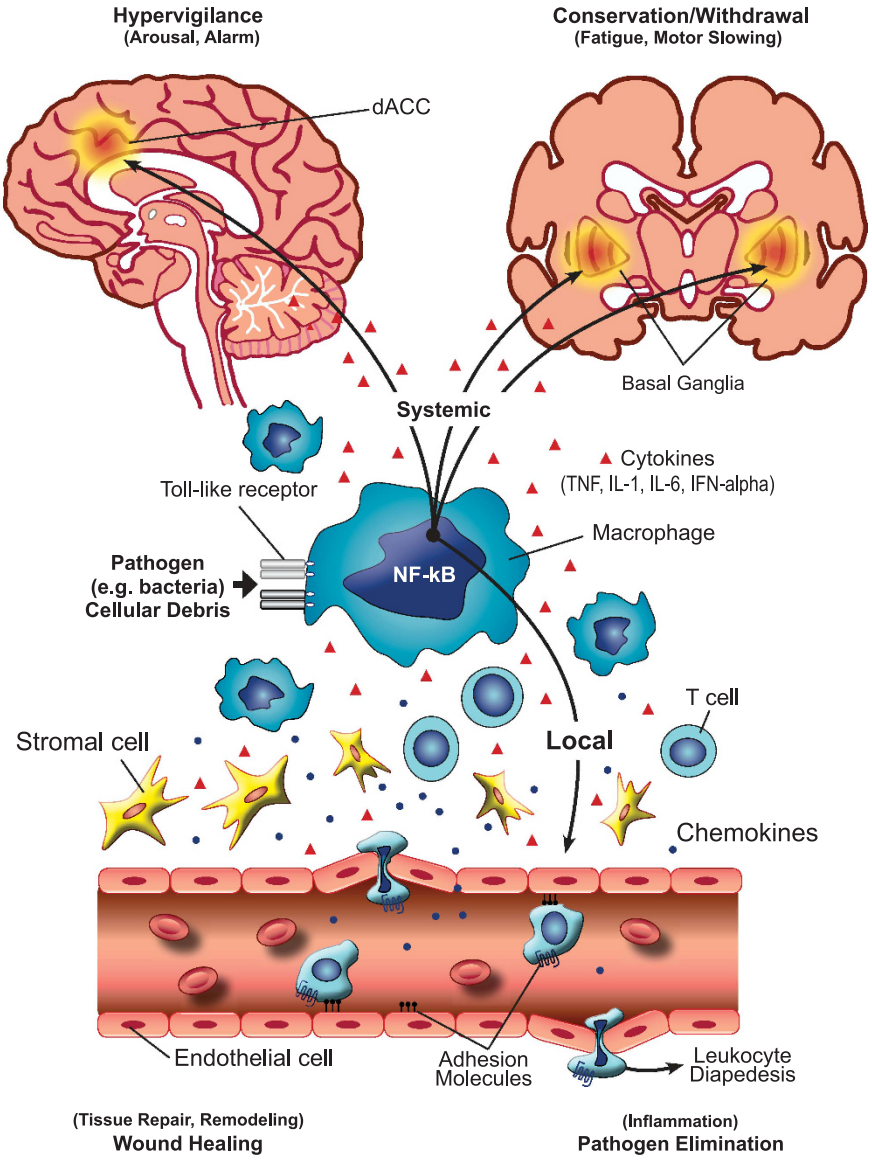

Figure 1 The integrated suite of immunological and behavioral responses to infection and wounding that comprise pathogen host defense. Upon encountering a pathogen or cellular debris from tissue damage or destruction, the body reacts with an orchestrated local and systemic response that recruits both immunological and nervous system elements. The response is initiated by interaction of pathogens and/or cellular debris with pattern recognition receptors such as Toll-like receptors on relevant immune cells including macrophages that in turn are linked to inflammatory signaling pathways such as nuclear factor-κB (NF-κB), a lynchpin transcription factor in the host defense cascade. Release of cytokines (including tumor necrosis factor-α (TNF-α), interleukin (IL)-1, IL-6 and interferon-α (IFN-α)) and chemokines as well as the induction of adhesion molecules attracts and activates cells such as T cells at the site of infection/wounding, leading to the cardinal signs of inflammation (redness, heat, swelling and pain) and ultimately promoting local pathogen elimination and wound healing. Cytokines and cells in the peripheral circulation mediate the systemic host response that engages neurocircuits in the brain that mediate hypervigilance (dorsal anterior cingulate cortex (dACC)) to avoid further wounding and pathogen exposure and conservation/withdrawal (basal ganglia), which promotes the shunting of energy resources to pathogen elimination and wound healing.

associated with reduced NPY production. Significant data support both predictions.[39–43]

Unlike *NPY*, the functionality of rs76917 in *TNF* is currently unknown. A clear prediction of PATHOS-D theory is that this SNP should be associated with increased TNF-α production, given that TNF-α is increased in MDD and appears to be especially relevant to enhanced survival from infection in the types of pathogen-dense environments that were normative during human evolution. A separate SNP (−308G/A) in the promoter region for *TNF* is worthy of comment in this regard. Although not found to be significant by GWASs,[35] several studies have associated the high-production A allele at −308 (ref. 44)

Table 1 Pathogen Host Defense (PATHOS-D) theory of depression: foundational hypotheses

(1) Depression should be associated with increased inflammation and inflammatory activation should induce depression.
(2) Allelic variants that increase the risk for major depressive disorder (MDD) should enhance host defense mechanisms in general and innate immune inflammatory responses in particular.
(3) Environmental risk factors for MDD should be associated with increased risk of infection and attendant inflammatory activation.
(4) On the whole, patterns of increased immune activity associated with MDD should have decreased mortality from infection in ancestral environments.
(5) Depressive symptoms should enhance survival in the context of acute infection and in situations in which risk of infection from wounding is high.

with depression and related states such as anger.[33,34,45] As predicted by PATHOS-D theory, the −308A allele has also been associated with reduced risk for infection with a number of pathogens, including *Mycobacterium tuberculosis*, parvovirus B19 and hepatitis B virus (HBV),[46–48] and with an increased likelihood of survival in critically ill hospitalized patients.[49] On a population level, Canadian First Peoples who are highly susceptible to tuberculosis have a markedly reduced prevalence of the A allele compared with Caucasians.[50]

DCNP1 was initially considered to be unique to dendritic cells,[51] although it has subsequently been identified in neurons.[52] The rs12520799 T allele, which is associated with MDD, codes for a truncated version of the protein. No data are available regarding the effect of this allele on either inflammatory signaling or infection outcomes, but given strong patterns of comorbidity between asthma/atopy and MDD, it is intriguing that the allele has been associated with increased levels of immunoglobulin E for common specific antigens in individuals with asthma.[53]

Candidate genes confirmed by meta-analysis

Although findings on candidate genes for depression have proven remarkably difficult to replicate,[35] a recent meta-analysis provides at least some additional support for several allelic variants being risk factors for MDD, including *GNB3* 825T, *MTHFR* 677T, *APOE* ε2, *SLC6A3* 40 bpVNTR 9/10 genotype and *SLC6A4* 44 bp ins/del short allele.[54] Although not traditionally considered as primarily immune related, each of these genes has well-documented immunological effects and hence meets the first of the three criteria for consistency with the PATHOS-D theory. In addition, each to a varying degree has some evidence consistent with either the second or third criterion.

GNB3 825T produces a shortened splice variant of the guanine nucleotide-binding protein subunit β-3 (GNB3) that has enhanced signal transduction properties.[55] Also, 825T has been reported to enhance *in vitro* cellular immune responses to recall antigens and IL-2 stimulation, to increase neutrophil chemotaxis in response to IL-8 and to increase both lymphocyte chemotaxis and the number of circulating CD4+ T cells.[55,56] These immune-enhancing effects come at the price of increased rates of microalbunemia, hypertension and cardiovascular disease in T allele carriers.[57,58] However, as predicted by the PATHOS-D theory, these effects also appear to translate into improved host defense, given associations between the T allele and reduced death from infection in infancy and evidence of positive selection for the T allele in geographical areas with high rates of infectious pathology.[59,60] Also consistent with enhanced host defense responses, the T allele is associated with improved antiviral responses following interferon-α (IFN-α) treatment for hepatitis C virus and highly active retroviral treatment for human immunodeficiency virus.[61–63] In addition, following HBV booster vaccination, the T allele increases *in vitro* lymphocyte proliferative responses to HBV surface antigen.[64]

The *MTHFR* 677T allele produces a version of the methylenetetrahydrofolate reductase (MTHFR) enzyme with reduced activity,[65] leading to elevations in plasma concentrations of homocysteine and other markers of inflammation.[66–72] Animal and human data suggest that this reduced MTHFR activity and concomitant increase in inflammatory tone may enhance host defense in at least some situations. For example, in a mouse model, MTHFR deficiency protects against cytomegalovirus infection,[65] and in pregnant females, increased MTHF is associated with the presence of a sexually transmitted disease and bacterial vaginosis.[73] Directly supporting a protective role for the T allele are data demonstrating that the allele protects against HBV infection in African populations.[72] Moreover, the hyperhomocysteinemia associated with reduced MTHFR activity has been posited as protective against malaria and has been suggested as a selection factor for the T allele in sub-Saharan Africa.[74] Interestingly, however, the prevalence of the T allele is actually far lower in sub-Saharan populations than in other ethnic/geographical groups despite these potential benefits, likely because homozygosity for the allele is lethal in situations of low folate availability such as pertain throughout much of the region.[72] On the other hand, given the array of disease states that has been associated with *MTHFR* 677T,[75–80] as well as reduced fertility,[81] its increased prevalence in environments of ready folate availability may reflect more substantial benefits for host defense than are currently recognized.

Apolipoprotein E (APOE), a glycoprotein central to lipid transport and metabolism, has been implicated as a risk and/or protective factor in a wide range of illnesses. The *APOE* gene has three primary alleles, termed ε2, ε3 and ε4, with ε3 being the most common worldwide, but with significant data suggesting that

ε4 is the ancestral human allele.[82–85] APOE affects immune functioning in complex and apparently contradictory ways, with both immune-enhancing and immune-suppressing effects reported. The depression-protective ε2 allele does not appear to be associated with reduced inflammation *per se*, as PATHOS-D theory would predict, but may meet the third criteria required by PATHOS-D by being a risk factor for diseases known to have exerted significant selection pressure on humans, including tuberculosis and malaria.[86] Conversely, the ε4 allele, which increases the risk for MDD when compared with ε2, is associated with increases in many measures of inflammation and related processes such as oxidative stress,[82–85] and has been reported to protect against the development of childhood diarrhea in high-pathogen environments.

Dopamine and serotonin are pivotal neurotransmitters in mood regulation, and yet like other factors linked to depression, these monoamines both affect, and are affected by, the immune system. The bulk of available evidence suggests that MDD is best characterized as a condition of low dopamine availability, at least in CNS regions linked to motivation and reward.[87–90] The possibility that reduced dopamine availability in MDD may serve host defense purposes is suggested by animal studies showing that hyperdopaminemia is associated with reductions in both innate and adaptive T helper 1-type cellular immunity, with resultant increased susceptibility to infection.[91,92] That dopamine transporter activity in particular may be important for host defense in humans is suggested by findings from two recent genome-wide linkage analyses of risk factors for tuberculosis in geographic areas in which the disease is endemic. Both studies localized a genetic protective factor to a locus of chromosome 15.[93,94] Fine mapping of this locus identified a SNP (rs250682) within the dopamine transporter gene (*SLC6A3)* as conferring the strongest protective effect.[93] The G allele of rs250682 was found to be associated with reduced skin reactions to the tuberculin test, which predicts reduced risk of later active disease in endemic areas.[93] However, no data were found indicating that rs250682 is in linkage disequilibrium with the *SLC6A3* 40 bpVNTR that has been associated with MDD. Nor do any data address whether the 9 repeat allele of the VNTR has immunological effects that would enhance host defense. Indeed, even the question of whether this putative depression risk allele is a gain-of-function or loss-of-function variant for the dopamine transporter remains to be definitively clarified.[95,96]

The *SLC6A4* 44 bp ins/del polymorphism (often referred to as 5HTTLPR) is by far the most extensively studied, and debated, genetic risk factor for MDD. Significant data suggest that the 'short' allele of this serotonin transporter polymorphism (which is less efficient in the reuptake of serotonin) increases the risk for developing depression in response to psychosocial adversity, both during development and in adulthood. Less well known, but consistent with PATHOS-D predictions, the short allele has also been shown to protect against sudden infant death syndrome, a condition often associated with unrecognized infectious morbidity.[97–100] Given the PATHOS-D prediction that stress should activate inflammation as a prepotent protection against the risk of wounding (see below), it is intriguing that the 5HTTLPR short allele is associated with an increase in the ratio of circulating proinflammatory to anti-inflammatory cytokines (for example, IL-6/IL-10) following a psychosocial stressor.[101] Further supporting a role for *SLC6A4* in host defense is the recent finding that the gene might account for 10% of the correlation between depressive symptoms and circulating levels of IL-6 in a group of medically healthy adults.[102] Finally, the prevalence of the short allele in cultures around the world is strongly correlated with historical burden of disease-causing pathogens in these cultures,[103] consistent with the possibility that the short allele has undergone positive selection as a result of enhancing host defense.[104]

Alleles identified by meta-analyses of GWAS data

Far less is known about the general functionality of alleles identified in GWASs, let alone which physiological effects may be relevant to MDD. Therefore, it should not be surprising that limited data are available regarding whether these potentially depressogenic SNPs affect immunity to enhance host defense. On the other hand, it is intriguing that associations with immune/inflammatory function or other aspects of host defense against pathogens have been demonstrated for 8 of the top 10 genes (or their very close homologs) identified in the largest GWAS meta-analysis of MDD conducted to date (Table 2).[105–140] Many other depression-relevant genes identified in earlier large GWASs (as well as meta-analyses of these studies), including *PBRM1*, *GNL3*, *ATP6V1B2*, *SP4*, *AK294384*, *LY86*, *KSP37*, *SMG7*, *NFKB1*, *LOC654346*, *LAMC2*, *ATG7*, *CUGBP1*, *NFE2L3*, *LOC647167*, *VCAN*, *NLGN1*, *BBOX1*, *ATF3*, *RORA*, *EIF3F*, *CDH13*, *ITGB1* and *GRM8*, have also been linked to immune system and/or host defense functions (see Supplementary Table S1 for additional information/relevant references).

An exception to the general lack of knowledge regarding GWAS-identified depression risk alleles is provided by the rs1006737 SNP in the *CACNA1C* gene, which codes for the α1 subunit of the L-type voltage-gated calcium channel (Cav1.2).[29] *CACNA1C* has been identified as a potential depression risk gene in several GWASs,[105,141,142] and convergent validity for its role in depression is provided by data demonstrating that carriers of the risk A allele have changes in brain function and morphology relevant to MDD.[143–145]

An examination of the immune effects of *CACNA1C* highlights both the promise and complexities of a PATHOS-D perspective. Calcium signaling pathways play central and essential roles in multiple aspects of

Table 2 Immune/host defense functions of single-nucleotide polymorphisms (SNPs) associated with major depression based on the largest meta-analysis of genome-wide association studies (GWASs) conducted to date for major depression (MDD)

Gene ID	*Gene name*	*SNP with minimum* P-*value*	*Immune/host defense function of gene*
SEL1L2	*Sel-1 suppressor of lin-12-like 2*	rs17226852	No specific immune or host defense functions identified for *SEL1L2*. However, the other member of the sel1 gene family, *SEL1L*, has been shown to be important for quality control of IgM,[100] and the infectious capacity of several viruses,[101] including human cytomegalovirus,[102] a microsatellite polymorphism of *SEL1L*, is associated with autoimmune thyroid diseases[103]
ADCY3	*Adenylate cyclase 3*	rs2384061	*ADCY3* is integral to a rapid, NF-κB-independent, signaling cascade initiated by microbial stimulation of TLR4.[104] *ADCY3* also regulates crosstalk between FP prostanoid and prostaglandin E2 receptors.[105] This crosstalk regulates expression of *SAT1* gene, which has been reported to be underexpressed in prefrontal cortex of suicide completers.[106]
UNC93A	*Unc-93 homolog A*	rs2076008	No specific immune or host defense functions identified for *UNC93A*, but a closely related homolog, UNC93B, plays a crucial role in antigen presentation and TLR functioning, and deficiency in its expression reduces TNF-α production and increases vulnerability to a number of infections.[107–109] Blockade of *UNC93B* may protect against autoimmunity.[110]
TEX10	*Testis expressed 10*	rs1930243	No specific immune or host defense functions identified.
TTLL2	*Tubulin tyrosine ligase-like family, member 2*		No specific immune or host defense functions identified for *TTLL2*; however, other TTLL family members have been shown to be essential for proper cilliary structure and function and with this ability to clear pathogens and other harmful substances from the airway.[111]
GAL	*Galanin*	rs2156464	Signaling through either type 1 or type 2 receptors, *GAL* has numerous anti-inflammatory effects;[112–115] Consistent with PATHOS-D, multiple lines of evidence indicate *GAL* signaling is reduced in MDD;[116–118] GMAP, which is produced by cleavage of the same precursor as galanin, has direct antifungal activity[119]
PDK4	*Pyruvate dehydrogenase kinase, isozyme 4*	rs11531570	*PDK4* gene expression is upregulated by IFN-α and by LPS and contributes to muscle glycogen breakdown and lactate accumulation;[120,121] conversely, *PDK4* is inhibited by TNF-α via p38 MAPK and NF-κB signaling, leading to increased glucose oxidation;[122] anti-inflammatory omega-3 fatty acids increase *PDK4* in immature dendritic cells via enhanced PPAR-γ signaling[123]
NPM1	*Nucleophosmin*	rs11134697	Functions as an endogenous 'alarmin' that activates proinflammatory cytokines;[124–126] identified as a host virulence factor in viral infection;[127,128] may aid in HIV and HSV1 virus dispersal within cells;[129,130] complexes with, and inhibits, PKR, which has important antiviral properties[131]
USP3	*Ubiquitin-specific peptidase 3*	rs7183892	Embedding of *USP* genes in the copy number variable β-defensin cluster on chromosome 8p23.1 suggests a close tie with innate immunity;[132] *USP3* is activated by IL-4 and IL-6 and has antiproliferative and apoptotic properties;[133] highly homologous *USP17* necessary for type I IFN production in response to virus infection;[134]
ASB4	*Ankyrin repeat and SOCS box-containing 4*	rs11531570	No specific immune or host defense functions identified.

Abbreviations: FP, prostaglandin F; GMAP, galanin message associated peptide; HSV1, herpes simplex virus type 1; IFN-α, interferon-α; IgM, immunoglobulin M; IL, interleukin; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MDD, major depressive disorder; NF-κB, nuclear factor-κβ; PATHOS-D, Pathogen Host Defense; PKR, protein kinase R; PPAR-γ, peroxisome proliferator-activated receptor-γ; TLR, Toll-like receptor; TNF-α, tumor necrosis factor-α.
Reference numbers in Table 2 correspond to reference numbers in paper bibliography.

immune function, and the Cav1.2 channel in particular contributes to the function of a variety of immune cell types, including dendritic cells, CD4+ and CD8+ T cells, mast cells and macrophages.[146–154] Consistent with an overall proinflammatory effect for Cav1.2, agents that block this calcium channel have been repeatedly observed to have anti-inflammatory properties.[155] Given these findings, the PATHOS-D theory predicts that the depressogenic A allele at rs1006737 should be a gain-of-function variant with an overall proinflammatory effect. In support of this, the A allele has been associated with reduced activation of the anti-inflammatory intracellular messenger Akt,[156] which is known from *in vitro* studies to downregulate TNF-α and inducible nitric oxide synthase production in response to challenge with bacterial endotoxin.[157] Moreover, if Cav1.2 activation promotes host defense via activation of inflammatory processes, one would predict that the A allele should be associated with increased CACNA1C protein production. Although this has yet to be confirmed, data from post-mortem brain tissue indicate that carriers of the A allele have increased *CACNA1C* mRNA production in the CNS.[144]

These data suggest that the A allele of *CACNA1C* meets the first two criteria for consistency with a PATHOS-D perspective (that is, located in a gene with known immune effects and associated with increased signaling in inflammatory/host defense pathways). The finding that Cav1.2 activation is necessary for T-cell defense against *Leishmania major* infection is consistent with the third criteria,[148] given that the A allele appears to be a gain-of-function variant. However, other lines of circumstantial evidence undermine any straightforward association between allelic variants that increase Cav1.2 function and enhanced host defense. In fact, the opposite appears to be the case, given that Timothy Syndrome, caused by a rare gain-of-function variant in *CACNA1C*,[158] is associated with a strikingly increased risk of infection.[154] Similarly, activation of Cav1.2 channels appears to actually impede host defense against *M. tuberculosis* by reducing the bactericidal activity of dendritic cell-activated T cells.[149] These results appear paradoxical given that calcium influx into immune cells is essential for eradication of *M. tuberculosis*, and significant data indicate that L-type voltage-gated channels play an important role in this regard.[150] However, conflicting data suggest that L-type calcium channels may actually downregulate overall calcium influx, given that blocking these channels increased calcium signaling and bactericidal activity in *M. tuberculosis*-infected macrophages.[149] These findings are consistent with the observation that bacterial endotoxin acutely downregulates L-type calcium channel mRNA, as would be expected if Cav1.2 has an anti-inflammatory function.[159]

These considerations introduce a critically important complication into our discussion of the immune effects of depressogenic gene variants. Up to this point we have proceeded as though pathogen host defense is a monolithic process, which is a simplification exposed by the bivalent effects of L-type intracellular calcium signaling on infectious outcomes. Because calcium signaling activates multiple facets of the immune system, it is not surprising that this signaling has been shown to contribute to the antipathogen capacities of a variety of cell types. For example, macrophages rely on L-type calcium channel activation in response to *Chlamydia pneumonia* lipopolysaccharide to kill the microorganism.[160] However, other microbes have evolved to manipulate this host defense system to their own benefit, such as *Legionella pneumophila*, which requires L-type calcium signaling to replicate within infected host cells.[161] These examples demonstrate that the same physiological process can enhance host defense to one pathogen, while simultaneously increasing vulnerability to another.

Infection, inflammation and environmental risk factors for MDD

If depressogenic alleles contribute to protection against pathogen invasion, the circumstances in which such invasion was likely or already a *fait accompli* should be especially potent activators of these genes, and hence especially likely to induce depression. Moreover, if these alleles heighten host defense in large part by increasing inflammation, inflammatory mediators released in response to environments rife with pathogen danger would be expected to induce depressive symptoms. These predictions are borne out by many studies demonstrating the depressogenic effects of inflammatory mediators,[10,162–173] as well as the remarkably diverse array of conditions that activate inflammatory processes and also increase the risk for depression.[174–221]

Psychosocial stress may be especially relevant in this regard. Stress is a universal and powerful risk for the development of depression both during development and adulthood.[222–225] This squares nicely with social theories of depression, and at first glance appears to challenge host defense perspectives. But if we consider that the vast majority of stressors in mammals over evolutionary time boiled down to risks inherent in hunting, being hunted or fighting conspecifics in dominance hierarchies for reproductive access/status, it is not surprising that these states are also circumstances in which the risk of pathogen invasion—and subsequent death from infection—was greatly increased as a result of traumatic opening of the protective skin barrier from wounding.[226] Such wounding is common in social species and was a significant source of morbidity and mortality among humans in the ancestral environment, and indeed well into the historical period.[227–229] Given this, it is not surprising that—to quote Firdaus Dhabhar—'stress perception by the brain may serve as an early warning signal to activate the immune system in

preparation for a markedly increased likelihood of subsequent infection'.[230] And although chronic stress is best known to suppress immune function,[231] the types of acute and/or psychosocial stressors most likely to be associated with immediate risk of wounding and hence infection activate both innate and adaptive immunity.[232–242] And while suppressing certain measures of adaptive immunity, chronic stress (whether experienced during childhood or as an adult) has been repeatedly associated with increased peripheral inflammatory biomarkers.[233,243–248]

From a PATHOS-D perspective, then, psychosocial stress may increase the risk for depression, at least in part, because it activates host defense mechanisms that reliably induce depressive symptoms. In ancestral environments, the association between stress perception and risk of subsequent wounding was reliable enough that evolution, operating by the so-called 'smoke detector' principle,[249] favored organisms that prepotently activated inflammatory systems in response to a wide array of environmental threats and challenges (including psychosocial stressors), even if this activation was often in vain. This perspective provides a parsimonious explanation for why psychosocial stressors reliably induce depression, even though depressive reactions to stressors often appear so patently maladaptive. Across evolutionary time, the benefit that depressive symptoms (and their underlying physiology) conferred in terms of host defense in situations of high infectious danger (including most psychosocial adversities) outweighed their cost in terms of any social impairment they incurred in these same contexts. A clear prediction of this hypothesis is that genes promoting inflammatory responses to psychosocial stress should decrease in prevalence over time in human societies in which the association between stressors and subsequent infection has been weakened by factors such as modern health practices. Consistent with this possibility, the prevalence of the short allele of the serotonin transporter gene, which has been associated with increased inflammatory responses to psychosocial stress, is lower in societies with reduced rates of historical infectious mortality.[104]

In addition to providing a novel explanation for why stress is a primary risk factor for developing depression, the PATHOS-D theory offers a unifying perspective on why many other facets of modern life are also depressogenic, a perspective not readily provided by theories focused more exclusively on the social realm. Indeed, if the adaptive value of depression is to be found primarily in its effects on social functioning, it is hard to understand why so many risks for depression, including obesity, sedentary lifestyle, dietary factors, diminished sleep and smoking, are at least partially nonsocial in nature. On the other hand, these conditions are all associated with increased inflammation (for reviews see refs. 207, and 250–252), suggesting that they may be depressogenic because they tap into pathways that initially evolved to fight infection.

Patterns of immune activation in MDD and protection from infectious mortality in ancestral environments

The hypothesis that patterns of immune activity associated with MDD should have decreased mortality from infection in ancestral environments appears to face a challenge from data indicating that depression worsens outcome in a number of infectious processes[253–260] and is associated with impairments in adaptive immune mechanisms important for protection against both viruses and bacteria.[13,261,262] To address this challenge, we have first to inquire whether innate immune inflammatory processes that are increased in MDD produce the patterns of infectious vulnerability and adaptive immune impairment that are apparent in depression. Surprisingly, the answer is yes.[263,264] Although essential for activating adaptive immunity in response to pathogen invasion, chronic inflammation can actually suppress T- and B-cell function through various mechanisms.[263–270] Consistent with this, rates of infection are often increased—not decreased—in autoimmune conditions characterized by chronic inflammation.[271] However, PATHOS-D theory requires only that across evolutionary time the survival benefits of enhanced inflammatory activity characteristic of depression outweighed any costs imposed by associated reductions in other aspects of immune functioning. Several lines of evidence support this possibility.

One such line of evidence comes from Ghana, a country in which some regions rely for drinking water on heavily contaminated rivers and other regions obtain clean water from boreholes. As would be expected, death rates from infection are higher in river-drinking regions than in areas where borehole-obtained water is available. Consistent with the prediction that increased inflammatory signaling is protective in the type of high-infection environments common during human evolution (and especially common since the origin of agriculture and the rise of cities),[272] a haplotype of the IL-10 gene associated with increased inflammation was found to be significantly more prevalent in populations that relied on river water than in populations that drank from boreholes—suggesting positive selection driven by enhanced pathogen protection.[2] Consistent with this possibility, during a 5-year follow-up period, the high-inflammation IL-10 haplotype was associated with increased survival in populations that drank from rivers, but reduced survival in individuals who drank from boreholes.[2] These results are consistent with the observation that cytokine-stimulated production of TNF-α declines with age in the Netherlands, a country with a low infectious burden, but does not decline with age in Ghana, a country with high rates of infection (that is, 85% of Ghanan study participants were infected with malaria),[273] again suggesting that increased proinflammatory cytokine production—as observed in MDD—promotes survival under conditions of high pathogen burden.[274]

Multiple facets of modernity have reconfigured our relationship with the microbial/parasitic world in ways that have reduced the benefits of inflammation and increased its costs.[274,275] Nonetheless, even in an environment so different from that in which humans evolved, multiple studies have identified associations between patterns of increased inflammation observed in MDD and improved outcome in the context of infection,[3–5,50,276–290] as shown in Table 3.

Survival-promoting elements of depressive/sickness symptoms in response to infection

Microbial activation of the mammalian inflammatory response produces a highly regulated suite of symptoms known as sickness behavior that bears a striking resemblance to behavioral changes induced by stress in laboratory animals, as well as to the symptoms of MDD in humans.[10,163–173] Many of these symptoms can be ameliorated by antidepressants in animal models,[291–295] further suggesting that cytokine-induced behavioral changes are either closely aligned with, or identical to, MDD in humans. Studies report that 20–70% of patients undergoing chronic immune activation as a result of treatment with the cytokine IFN-α meet symptom criteria for MDD, providing additional evidence in this regard.[164,296] Moreover, IFN-α-induced depression shares symptom homology with idiopathic MDD,[297] and responds to treatment with antidepressants.[164,298–301] In addition to a remarkable symptom overlap, sickness and depression during cytokine exposure also appear to be causally linked, given the strong association between sickness in the first week of treatment with IFN-α and the development of cognitive/emotional symptoms of depression over the ensuing 6 months of therapy.[302] Finally, peripheral inflammatory activation induces many—if not all—of the most replicated CNS and neuroendocrine abnormalities observed in MDD (Figure 1).[303–310]

The PATHOS-D theory asserts that depressogenic alleles are common not because depression is adaptive in managing social negotiations, but because these alleles promote symptoms and behaviors that decreased mortality from infectious causes across mammalian evolution. However, from an evolutionary perspective, there is no *a priori* reason why these antipathogen effects should overlap with the depressogenic effects of these risk alleles. That they do so is powerful evidence, we would suggest, for the primacy of immune defense in the pathogenesis of depression, regardless of the environmental adversity that initiates the disorder in individual cases. In keeping with this perspective is the possibility that some of the symptoms of depression promote survival in response to infection.

Fever and hypoferremia

Although once viewed as a maladaptive consequence of immune activation,[311] several decades of research have produced a consensus that sickness behavior is an adaptive central motivational state evolved to promote survival and necessitated to a large degree by the metabolic costs of mounting a fever.[163,169,311–314] Fever, in turn, has been shown to enhance resistance to both viral and bacterial pathogens, over and above other antipathogen effects of the inflammatory mechanisms by which fever is induced. In addition to retarding pathogen replication/spread,[315–318] febrile range temperatures have multiple stimulatory effects on the immune system relevant to host defense.[319–325]

Because these effects are enhanced in conditions of low iron availability, it should not be surprising that in addition to causing fever, inflammatory cytokines deplete bodily iron stores.[326] Nor should it be surprising that sickness is associated with hypoferremia,[327,328] which—after fever—is probably the feature of sickness that has been best established as of adaptive value.[329–331] For example, low bodily iron stores protect against infection in children in the developing world,[332] and multiple studies suggest that iron supplementation worsens an array of infection-related health outcomes and increases infectious mortality.[333–337]

If depressive symptoms aid in pathogen defense and if fever and hypoferremia are important in this regard, one would expect that MDD should be associated with elevated body temperature and reduced bodily iron stores, even in individuals with no evidence of an infectious process. In this regard, it is surprising, given the centrality of fever to the adaptive function of sickness behavior,[163,169,315] that so little attention has been paid to the fact that MDD appears to be reliably characterized by an elevation in body temperature into the range known to be maximally protective in the context of infection.[338–345] As with elevated body temperature, a number of studies have reported that depressive symptoms are associated with reductions in various measures of bodily iron stores.[346–350]

Because fever and hypoferremia are central to the adaptive purposes of sickness, their presence in depression is mandated from a PATHOS-D perspective, and their absence would strongly argue against the validity of this approach. On the other hand, their presence in depression is not parsimoniously explained by theories that focus on potential social benefits of depression. Similarly, if depression is simply a nonadaptive phenomenon, why would such ancient, highly conserved and highly complex physiological responses be a hallmark of the disorder?

Conservation-withdrawal

Proinflammatory cytokines induce a behavioral state of *conservation-withdrawal*,[351] characterized by depressed mood, anhedonia, psychomotor retardation, fatigue, social avoidance and anorexia.[163,252,352,353] This state is an integral component of depressive disorders and has been widely considered to develop in the context of infection and/or tissue injury as a means of marshalling limited metabolic resources for the expensive tasks of immune activation, fever generation and tissue repair.[311] In addition to energy

Table 3 Inflammation and infectious outcomes in industrialized societies

Biological factor	*Immune effect*	*Host defense findings*
Plasma concentration of interleukin (IL)-10; ratio of plasma IL-10 to tumor necrosis factor-α (TNF-α; IL-10/TNF-α)	IL-10 is a powerful anti-inflammatory cytokine that suppresses innate immunity and T helper type I (Th1) immune responses; TNF-α is an innate immune potent proinflammatory cytokine that produces sickness behavior and acutely plays important role in facilitating activation of the adaptive immune system.	In a large study of consecutive patients admitted to hospital with fever, elevations in plasma concentrations of the anti-inflammatory cytokine IL-10—as well as the ratio of IL-10/TNF-α—were associated with increased mortality;[3] Increased IL-10 production late in the disease course predicted reduced survival following infection with the pandemic A/H1N1/2009 influenza virus.[4]
Plasma concentration of C-reactive protein (CRP) via high-sensitivity assay	CRP is an acute-phase reactant primarily stimulated by IL-6 shown in multiple studies to predict the development of multiple illness associated with chronic inflammation	CRP has been associated with increased survival in children with meningococcal sepsis.[276]
Stimulated production of pro- and anti-inflammatory cytokines	*In vitro* measure of ability of immune cells to produce/release cytokines in response to an immune stimulus.	Families with a member who died from meningococcal disease were characterized by increased production of IL-10 and reduced production of TNF-α when compared with families with a member who had bacterial meningitis but survived.[5]
Th1 and Th2 cytokine concentrations in the supernatant of cultured peripheral blood mononuclear cells (PBMCs)	*In vitro* measure of ability of PBMCs to promote either Th1 or Th2 immunity	Reduced PBMC production of IFN-γ and IL-12 is associated with increased severity of respiratory syncytial virus symptoms in infants under 1 year of age.[277]
Increased activity alleles of the IL-10 gene (i.e., −1082G)	Associated with higher levels of IL-10	−1082G allele is associated with increased symptom severity and mortality in the context of community-acquired pneumonia,[278] −1082G allele is associated with reduced antibody responses to tetanus, influenza and hepatitis B virus (HBV) vaccines.[279–281]
Increased activity alleles of the interferon-γ (IFN-γ) gene (i.e., +874T)	The +874T allele increases Th1 immunity via increased IFN-γ production as a result of enhanced binding of nuclear factor-κβ (NF-κB)[283,284]	+874T allele has been associated with protection against Mediterranean Spotted fever.[282] Multiple studies and a large meta-analysis find that the +874T allele is associated with protection against the development of tuberculosis at the individual[285] and population levels.[50] In individuals with active tuberculosis, the T allele is associated with reduced severity and risk of disseminated disease.[286] +874T allele has been associated with reduced risk of leprosy,[287] severe acute respiratory syndrome (SARS),[288] and Chagas disease.[289]
Reduced activity alleles of the IFN-γ gene (i.e., +874A)	An allele at +874 is associated with reduced IFN-γ production and consequent reductions in Th1 activity	+874 A predisposes for hepatitis B and C persistence and negatively affects clinical course of these diseases.[290]

Reference numbers in Table 3 correspond to reference numbers in paper bibliography.

allocation, conservation-withdrawal symptoms may have also proved adaptive by reducing interpersonal contact and thereby limiting infectious exposure.[25] Because ancestral humans typically lived in small coalitional groups of genetically related individuals, the logic of *inclusive fitness* suggests that social withdrawal might have been adaptive for an individual's genes by reducing the risk of infection in kin, even if such withdrawal limited the provision of much needed care from others and thus reduced individual survival.[354,355] As would be predicted from this line of reasoning, acute exposure to an inflammatory mediator has been shown to induce feelings of social isolation/withdrawal in humans,[356] and increased neural sensitivity to social rejection (indexed by changes in activity in dorsal anterior cingulate and anterior insula cortices) is associated with increased inflammatory responses to psychosocial stress.[357] However, in addition to potential benefits related to kin selection, significant data demonstrate that viral infections promote aggressive immune responses to bacterial superinfections that can greatly increase mortality;[358–364] therefore, any decrement in survival from loss of social aid might have been more than offset by reduced risk of exposure to other pathogens while in a vulnerable state due to a pre-existing infection. Moreover, social withdrawal and reduced environmental exploration might also have promoted individual survival by limiting a sick person's contact with immunologically dissimilar out-group members who potentially harbored pathogens against which the sick person would have had reduced immunity compared with pathogens endemic in the home group.[354,365]

Hypervigilance

Although withdrawal-conservation-type behavior is prominent in MDD, depressed individuals also often manifest metabolically expensive symptoms more consistent with behavioral activation, including anxiety/agitation and insomnia.[366–370] By siphoning energy away from immune activity, these symptoms would be expected to impair host defense and hence to argue against a PATHOS-D perspective. However, sickness behavior—although of benefit for surviving infection—carries its own survival and reproduction costs as a result of increased risk for predation and reduced ability to care for one's young, as well as potential loss of status in a social species and/or loss of breeding territory.[371] Therefore, evolutionary logic dictates that inflammatory processes—especially when chronic—might promote hypervigilant behavior that, while shunting energy away from fighting infection, would nonetheless serve adaptive purposes by protecting against environmental dangers engendered by sickness. In fact, significant data demonstrate that chronic cytokine activation reliably produces hypervigilant behaviors/symptoms, including anxiety/agitation, insomnia and anger/irritability.[305,353,372] Neurobiological substrates for the mixture of withdrawal-conservation and behavioral activation/hypervigilance symptoms that is common to chronic inflammation/medical illness and MDD have been recently identified, including the effects of cytokines on both the basal ganglia (withdrawal-conservation) and the dorsal anterior cingulate cortex (hypervigilance) (Figure 1).[303,309,357,373–376]

Anorexia

As suggested above, anorexia may enhance survival during infection by redirecting energy away from food procurement to the metabolic demands of immune activation/fever, while also limiting the exposure to food-borne pathogens. But the metabolic requirements of fighting infection make the anorexic response a paradox in need of a more robust adaptive explanation. Although it remains unclear whether food restriction protects against the development of infection,[377] animal data indicate that force feeding rodents once they are infected increases mortality.[378] Similarly, the provision of total parenteral nutrition in animal models and to critically ill patients has been associated with increased risk for infection and subsequent mortality.[379–382] Interestingly, rats injected with lipopolysaccharide consume proportionately more carbohydrates—as do depressed individuals with hyperphagia[383]—even though more energy is available from ingesting lipids. This suggests that lipid consumption may be counterproductive during an infection. Several observations are consistent with this possibility. For example, preclinical data demonstrate that lipid consumption increases infectious mortality,[384] and a meta-analysis of total parenteral nutrition use found that infected patients provided lipids in their feedings had higher complication rates than those receiving total parenteral nutrition without lipids.[385] Finally, omega-3 fatty acids have been shown to activate peroxisome proliferator-activated receptor-γ signaling in dendritic cells, with a resultant downregulation of CD1a receptor expression.[129] These receptors play an essential role in activating T-cell responses to pathogens, as demonstrated by the ability of *Leishmania donovani* to survive in host cells by downregulating these receptors.[386] Moreover, CD1a expression in dendritic cells is also crucial for the presentation of *M. tuberculosis* antigens to cells of the adaptive immune system.[387]

Potential limitations of, and challenges to, PATHOS-D theory

In this article we have focused our analyses on allelic variants associated with phenotypic variability. Many genetic features contributing to MDD may have swept to fixation over evolutionary history and by becoming nonpolymorphic remain invisible to genetic association studies. It is possible that such sequences are preferentially associated with species-typical social, rather than immunological, factors. Were this to be the case, our analyses may have overestimated immune risk factors for depression at the cost of

universal depressogenic risk alleles maintained as a 'price of being human'.

It should also be noted that inflammatory biomarkers are not elevated in all individuals with MDD. Whether patients with increased inflammation represent a biologically and evolutionary distinct subset of MDD is an area of active research.[388] If this turns out to be the case, it may be that selection for enhanced host pathogen defense is relevant primarily to these individuals (and their allelic variants) and is thus only one adaptive factor driving the persistence of depressogenic alleles. Prior theorists have posited a variety of potentially fitness-enhancing psychosocial effects of low mood and/or depression not obviously related to host defense functions (that is, abandoning unattainable goals, yielding in dominance struggles and so on),[389–391] and it may be that these types of psychosocial benefits are promoted by allelic variants retained in the human genome independently of variants maintained as a result of conferring pathogen host defense benefits. If both immune and non-immune etiological pathways contribute to MDD, the next question is how they combine. One hypothesis consistent with the general absence of documented epistatic interactions among MDD risk alleles is that inflammation/immune alleles provide one hit and social/stress factors provide a second (biologically distinct) hit, which together sum to exceed an MDD symptom threshold. If distinct social and immune-related genetic risk factors were identified, statistical analysis of epistasis could help distinguish intrinsic interactions between pathways from a simple additive model.

On the other hand, findings from patients undergoing treatment with IFN-α suggest a more inclusive scenario for the role of pathogen defense in the evolution/persistence of depressogenic alleles. Specifically, although standardized dosages of IFN-α are employed, a wide range of behavioral responses are observed during treatment, from mild neurovegetative/sickness symptoms, such as fatigue, to completed suicide in response to catastrophic major depression. Individuals who develop significant depressive symptoms evince changes in CNS and neuroendocrine functioning that are also observed in idiopathic MDD,[305–310] but that are not observed to a significant degree in patients on IFN-α who do not develop depression. These findings raise the possibility that depression reflects a state of immune response element amplification, such that for any given amount of inflammatory input, depressed individuals react with enhanced downstream CNS/neuroendocrine activity. If so, depressogenic alleles that do not promote an increase in inflammatory biomarkers may nonetheless have undergone positive selection because they enhanced host pathogen defense via sensitization of downstream CNS/neuroendocrine pathways that themselves promote survival during infection. Some evidence for this hypothesis comes from the finding, noted above, that individuals who develop depression during IFN-α manifest enhanced sickness behavior at the start of treatment, which may aid in acutely clearing pathogens from the body during infection.[302] Moreover, a clear prediction of PATHOS-D theory is that changes in CNS/neuroendocrine function that typically accompany MDD should enhance survival in the context of acute infection. To date, few data support this possibility, although it is intriguing to note that glucocorticoid resistance, which is common in MDD[392] and is associated with the development of depressive symptoms during IFN-α treatment (Raison *et al.*, unpublished observations), has been associated with improved T-cell function in HIV infection,[393] and that enrichment paradigms known to enhance glucocorticoid sensitivity in animal models increase mortality in response to *Escherichia coli* infection.[394]

These two possibilities (that is, distinct additive social and immunological risks vs inflammatory mediation of social risk) might be genetically discriminated based on their contrasting implications for the functional relationship between social–environmental precipitants and immune-related genetic risks for MDD. In the former model, one would expect to find largely additive effects of social risk factors and immune-related genetic risk alleles, whereas the meditational model would suggest a product-term interaction (that is, a social stimulus shows larger depressogenic 'gain' in the context of a sensitizing genotype). This approach could be extended to use an instrumental variables analysis (for example, a Mendelian randomization study) to determine whether inflammatory signals function as mediators of, moderators of, or functionally independent additional additive influences with respect to, social precipitants of MDD.

Thus far, we have focused on the possibility that risk alleles promote depressive symptoms primarily as a result of increasing activity in inflammatory and/or immune-relevant downstream physiological pathways (that is, gene→immune effects→depression). However, many of the associations cited in this review could be equally well accounted for by the hypothesis that alleles directly influence CNS functioning to increase MDD risk, and that MDD subsequently affects immune function (that is, gene→depression→immune effects). This possibility is especially likely for genes such as *NPY*, which we have described in immune terms, but that also has well-documented effects on CNS functioning relevant to depression. In addition to downstream immune effects, such genes may also have enhanced host defense in ancestral environments by promoting behavioral patterns likely to reduce the risk of becoming infected, spreading infection to kin or of dying once an infection had commenced.[395,396] Just such effects have been proposed for the short allele of the serotonin transporter, which has been associated with collectivistic social behavior relevant to host defense.[104]

Immune changes associated with MDD are not only specific but also occur in other severe mental

disorders, including bipolar disorder and schizophrenia. Although the high prevalence of depression in these conditions is consistent with a PATHOS-D perspective, it is hard to imagine that other behavioral states associated with these diseases, including mania and psychosis, are adaptive for pathogen host defense. Indeed, the impaired decision-making characteristic of both states and the social isolation/reduced access to resources that is common in psychosis would be expected to increase vulnerability to pathogen exposure. Given overlapping genetic risk factors for these conditions and MDD, it is possible that they are best understood as purely maladaptive states supported at relatively low levels in the human population, at least in part, because their genetic antecedents enhanced host defense in carriers of immune-relevant risk alleles who responded to infectious challenges with enhanced immune activation and sickness behavior/depression without developing the full disease phenotype. Another possibility is that very severe disorders such as bipolar disorder and schizophrenia have been maintained in the human genome because immune benefits accrued to afflicted individuals that counteracted the fitness-reducing behavioral profiles (including increased risk of infection) associated with these diseases. This scenario would suggest that immune changes seen in schizophrenia and bipolar disorder should be more robust than those seen in depression, because they would have to be large enough to offset behavioral costs not present in depression. Although not entirely consistent,[397] some data support this possibility.[398–400]

Summary

By shifting the adaptive context of depressogenic alleles from any purported benefit of depressive symptoms on relations with conspecifics to the potential benefits of sickness behavior (and its attendant physiology) on relations with the microbial world, the PATHOS-D hypothesis provides a straightforward explanation for how depression can be nonadaptive in the social realm, whereas its risk alleles are nonetheless represented at prevalence rates suggesting an adaptive function. Across vertebrate evolution, innate immune inflammatory responses were essential for effective host defense against pathogens. In humans, these responses are especially relevant during the first several years of life when infectious mortality was highest and adaptive immunity was not yet fully functional. Given these considerations, it is not surprising that the immune system alterations most frequently observed in MDD are proinflammatory in nature, and that the best characterized MDD risk alleles appear to generally produce a proinflammatory phenotype. However, we should not infer from this that any given depressogenic allele will uniformly increase innate immune function or enhance host defense against all microbes. Rather, what PATHOS-D suggests is that depressogenic alleles—and the physiological processes they promote—can be understood as reflecting a summation of the most successful pathogen defense mechanisms against the wide array of pathogens encountered during human evolution, with all the imperfections and tradeoffs this has entailed. Moreover, knowing the effects of depressogenic alleles on outcomes following infection with specific pathogens may cast light on the relative importance of each pathogen for driving human evolution, because the high price imposed by depressogenic alleles mandates a compensatory high payoff in terms of pathogen defense. If confirmed in future studies, this perspective raises the intriguing possibility that gaining a better understanding of how genes promote MDD may significantly advance the field of immunology and that—conversely—a better understanding of the ongoing evolutionary 'arms race' between pathogens and their human hosts may suggest novel theoretical paradigms and treatment strategies for MDD.

Conflict of interest

The authors declare no conflict of interest. Charles L Raison serves as a consultant for Pamlab, Biolex Therapeutics and Bristol Myers Squibb. Andrew H Miller has served as a consultant for Abbott Laboratories, AstraZeneca, GlaxoSmithKline, Lundbeck Research USA, F. Hoffmann-La Roche, Schering-Plough Research Institute and Wyeth/Pfizer and has received research support from Centocor, GlaxoSmithKline and Schering-Plough Research Institute.

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Disclosure

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Mental Health, National Center for Complementary and Alternative Medicine or the National Institutes of Health.

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