Advancing an Inflammatory Subtype of Major Depression

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Chronic inflammation plays a prominent role in multiple medical disorders, including psychiatric diseases such as major depression. Exposure to inflammatory stimuli leads to changes in neurotransmitter systems and neurocircuits in the brain that are associated with depressive symptoms. Blockade of inflammatory cytokines can reduce depressive symptoms in medically ill and medically healthy individuals with depression. Increased levels of biomarkers of inflammation are associated with an overrepresentation of neurovegetative symptoms, including anhedonia, fatigue, and psychomotor slowing, and can predict response to antidepressant treatments. Importantly, however, increased inflammatory biomarkers occur in only a subgroup of individuals with depression. Thus, there appears to be a subset of patients with depression with a unique symptom presentation and treatment response whose disease is primarily driven by inflammation. Further identifying and characterizing this inflammatory subtype of depression can foster the development of treatments targeting the immune system and its effects on the brain. Moreover, by using this mechanism-based approach to parsing the heterogeneity of depression, we can refine our diagnostic nosology and model a strategy for precision medicine and targeted therapeutics in psychiatry.

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Depression is a common and devastating disorder, being a leading cause of disability as well as death by suicide (1). A hallmark of depression is its heterogeneity, making a one-size-fits-all approach to its treatment often ineffective (2). A better understanding of the mechanisms of depression can lead to personalization of its treatment and ultimately improved outcomes. One mechanism that contributes to depression is inflammation (3). Inflammation has effects on neurotransmitter systems and neurocircuits in the brain leading to alterations in behaviors related to neurovegetative function and threat sensitivity. Moreover, a significant percentage of patients with depression exhibit increased levels of inflammatory biomarkers, which in turn can predict response to antidepressant treatments, including conventional antidepressant therapies, such as serotonin reuptake inhibitors, as well as ketamine and ECT and treatments targeting the immune system. These data suggest that there is an inflammatory subtype of depression with a unique symptom presentation and response to treatment. Further instantiating this depressive subtype can improve our diagnostic nosology while unraveling pathophysiologic mechanisms and leading to targeted treatments, thereby supporting precision psychiatry (Figure 1).

MAKING THE CASE

Inflammation Occurs in a Subgroup of Patients With Depression

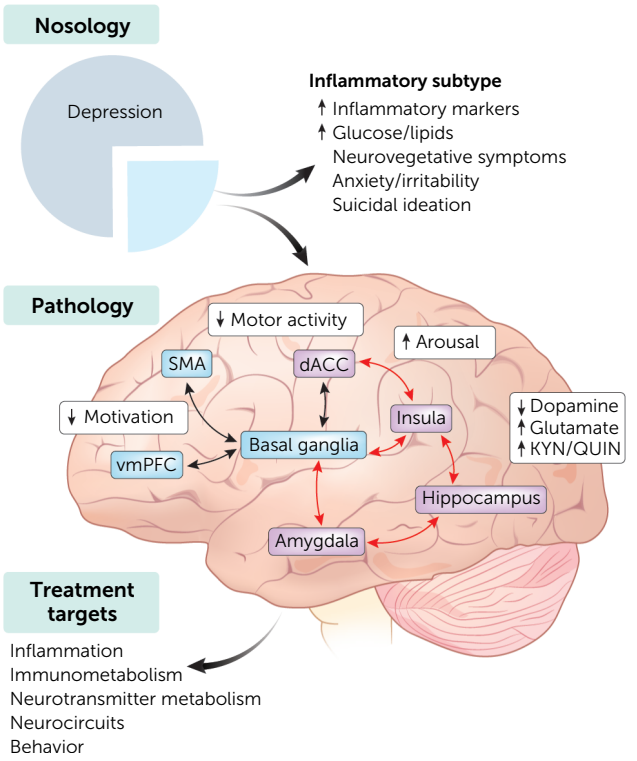
Multiple meta-analyses have substantiated reliable increases in mean peripheral blood concentrations of inflammatory biomarkers, including tumor necrosis factor (TNF), interleukin-1 beta (IL-1β), IL-6, and the acute-phase reactant C-reactive protein (CRP), in patients with depression compared with control subjects (3–6). These findings are robust, with increases in peripheral blood CRP, for example, being apparent in large population samples, even after adjusting for relevant covariates such as age, sex, race, body mass index, and smoking status (7). Evidence of increased inflammation is also found in postmortem brain samples of patients with depression, including increased levels of inflammatory signaling molecules in brain parenchyma (8) and the presence of macrophages and activated microglia (9) (the immune cells of the brain), as well as increased levels of inflammatory biomarkers in CSF (10). In addition, increased inflammatory mediators such as TNF, IL-1β, and signal transducer and activator of transcription-3 (STAT3; a pivotal IL-6 signaling molecule) are primary upstream regulators of molecular signatures of depression in multiomics analyses of tissues and cells from the brain and periphery of subjects with depression (11). Nevertheless, not all patients with depression exhibit increased biomarkers of inflammation.

Based on a meta-analysis of 30 studies, only about 25% of patients with depression exhibit evidence of chronic low-grade inflammation as indexed by a peripheral blood CRP level >3 mg/L (12). A CRP level >3 mg/L is one of several cut points used to identify elevated inflammatory risk for inflammation-related disorders such as cardiovascular disease, with CRP levels <1 mg/L representing low risk, CRP levels of 1–3 mg/L moderate risk, and CRP levels >3 mg/L

high risk (13). Thus, while mean differences in inflammatory biomarkers exist between samples of patients with depression and control samples, the effect is accounted for by a subgroup of individuals with depression. Of note, chronic inflammation has been characterized in multiple other psychiatric disorders, including anxiety disorders, posttraumatic stress disorder, and schizophrenia, thereby potentially representing a transdiagnostic pathophysiology. However, depression has been the most studied to date and therefore has received the most attention.

Although early theories regarding the immunology of inflammation in depression emphasized the primacy of myeloid cell populations, as outlined in the "macrophage theory of depression" (14), more recent work has indicated that inflammation in depression may be more complex, potentially involving multiple immune cell subsets. For example, in one large study using an unsupervised analysis that obviated binarizing patients into low- or high-inflammation groups, patients with depression who had increased levels of peripheral blood biomarkers of inflammation, including CRP and IL-6, segregated into two populations, one characterized by a predominance of cells of myeloid lineage (neutrophils and monocytes/macrophages) and the other by a predominance of lymphoid cells (T and B lymphocytes) (15, 16). These findings are consistent with data suggesting that highly inflammatory T helper 17 cells as well as B cell production of brain-reactive antibodies may contribute to depressive-like behavior in laboratory animals and humans (17, 18). Moreover, these findings suggest either that there are distinct immune pathways to inflammation in depression or that there are stages of immunopathology that evolve over time, progressing from early innate immune responses of a myeloid nature to subsequent engagement of more adaptive immune responses characterized by T and B lymphocytes (16). Of note, the latter has been observed in other inflammation-related disorders, such as diabetes (16).

FIGURE 1. The inflammatory subtype of major depression[a]



[a] Understanding the mechanisms of psychiatric disorders can allow us to revise our nosology and reduce heterogeneity. Identifying an inflammatory subtype of major depression based on biomarkers and symptoms will further refine the pathology and elucidate treatment targets. Tailoring treatment to pathology and patient preference will personalize care and promote precision medicine. dACC=dorsal anterior cingulate cortex; KYN=kynurenine; QUIN=quinolinic acid; SMA=supplementary motor area; vmPFC=ventromedial prefrontal cortex.

Inflammation Is Associated With Specific Symptoms

Increases in inflammatory biomarkers, including CRP and IL-6, in patients with depression have been associated with a cluster of neurovegetative symptoms, including anhedonia, lack of motivation, fatigue, and psychomotor slowing, as well as disruptions in sleep and appetite (19–21). Neurovegetative symptoms in the context of inflammatory exposures such as infectious diseases were initially described as "sickness behavior" (22, 23). Sickness behavior refers to a coordinated set of behavioral responses believed to subserve evolutionary imperatives of conserving resources for the substantial energy demands of an activated immune response and its containment of pathogens as well as wound healing (24, 25). Inflammation is also associated with symptoms related to threat sensitivity, including anxiety, irritability, and symptoms of arousal, such as in PTSD (21, 26, 27). These symptoms align with the adaptive nature of hypervigilance against subsequent attacks in a sick or wounded animal and are considered a requisite component of a survival response (24, 25). Suicidal ideation has also been linked to increased inflammation, as evidenced by peripheral and central inflammatory biomarkers, including measures of the translocator protein (TSPO) using positron emission tomography (PET) (28, 29). TSPO binding in the brain is a putative marker of activated microglia, although its expression on multiple other cell types in the brain has limited interpretation of imaging results (30).

The relationship between inflammatory markers and specific symptoms also appears to include systemic and cellular markers of metabolic function. Indeed, patients with depression who have increased inflammation plus anhedonia (vs. those with increased inflammation without anhedonia) exhibit activation of gene expression pathways in peripheral blood immune cells related to a shift in cellular metabolism from the energy-efficient oxidative phosphorylation to the more energy-expedient (and costly) glycolysis (31). This shift in cellular metabolism, which involves signaling pathways including mammalian target of rapamycin (mTOR), 5′ AMP-activated protein kinase (AMPK), phosphoinositide 3 kinase (PI3K), and protein kinase B (akt), is a critical component of immune cell activation, allowing for rapid proliferation and release of inflammatory mediators

(32). Transcriptomic signatures of psychomotor slowing in patients with depression also reveal an overrepresentation of glycolysis-related genes (33). Of note, these metabolic pathways have become novel targets for inhibiting inflammatory responses in a variety of autoimmune and inflammatory disorders (34). Interestingly, systemic measures of immunometabolism, including lipids and measures of glucose metabolism, have also been associated with neurovegetative symptoms, including anhedonia, fatigue, hypersomnia, and hyperphagia (19, 20, 35, 36). Indeed, the concept of immunometabolic depression, which integrates dysregulation of both immune and metabolic systems, is gaining increasing traction and may reflect the full complement of pathology represented in the inflammatory subtype of depression (19, 36).

Inflammation Is Associated With Treatment Response

Increased levels of baseline peripheral blood inflammatory and metabolic biomarkers predict a poor response to conventional antidepressant medications, especially selective serotonin reuptake inhibitors (SSRIs), in ambulatory patients with depression and females (37–39). Of the largest studies to date, two included over 100 patients, and each showed a preferential response to a catecholaminergic agent (nortriptyline or bupropion) compared to the SSRI escitalopram in patients with depression who had increased inflammation as indexed by a CRP level >1 mg/L (an indicator of at least moderate inflammatory risk) (40, 41). In addition, peripheral blood expression of relevant inflammatory genes, including mRNA levels of TNF, IL-1β, and macrophage inhibitory factor, predict a poor response to conventional antidepressant treatment, along with polymorphisms in several immune genes, including IL-1β and STAT3, as well as genes that support T cells (42–44). Patients with depression and a history of nonresponse to antidepressant treatment also exhibit increased levels of peripheral blood inflammatory biomarkers, including TNF, IL-6, and CRP (45, 46). Moreover, increased inflammation is associated with a poor response to psychotherapy (47).

Interestingly, increased inflammation, including increased peripheral blood IL-6 level, has been shown to predict a positive response to both ketamine and ECT (48–50). Several studies also indicate that increased concentrations of inflammatory markers, including CRP, and the expression of inflammatory genes as well as markers of immunometabolic function (e.g., lipid and glucose metabolism) predict a positive response to treatments that target inflammation and its effects on the brain, including anti-inflammatory drugs such as the TNF antagonist infliximab and minocycline as well as the dopamine precursor levodopa (see below) (51–58). Taken together, these data suggest that inflammatory biomarkers and the inflammatory subtype of depression may have clinical utility in predicting response to available antidepressant treatments and may ultimately help guide therapy with novel treatment strategies targeting immune and metabolic pathways in depression.

IDENTIFYING TREATMENT TARGETS

Mechanisms by Which Inflammation Affects the Brain and Behavior

Cause and effect. It has been suggested that the presence of increased immune biomarkers in certain patients with depression may reflect an epiphenomenon of behavioral and lifestyle factors associated with depression that are also known to increase inflammation, including psychological stress, sedentary behavior, poor diet, obesity, sleep disruption, and the use of alcohol and tobacco. Relevant in this regard, multiple longitudinal studies have demonstrated that elevated CRP levels predict future depressive symptoms, whereas prospective associations of depression with CRP are less robust (59). Although these data support the notion that inflammation can cause subsequent depressive symptoms, more definitive data come from the administration of inflammatory stimuli to otherwise nondepressed individuals. For example, treatment with the inflammatory type I interferon IFNα for infectious diseases or cancer is associated with the development of significant depressive symptoms in 30%–50% of patients, depending on the dose, with 45% of patients meeting symptom criteria for major depression following high-dose IFNα treatment for malignant melanoma (60, 61). Neurovegetative symptoms, including anhedonia, fatigue, and psychomotor retardation, tend to predominate early during IFNα therapy and predict later cognitive symptoms (60, 62). Similar depressive symptoms, including anhedonia and motivational deficits, as well as psychomotor slowing have been observed following laboratory exposures to inflammatory stimuli, including endotoxin and vaccination with typhoid or influenza (63–66). Reversal of depressive symptoms has also been demonstrated following administration of drugs that block inflammatory cytokines (i.e., anticytokine antibodies) in patients with autoimmune and inflammatory disorders as well as in otherwise healthy patients with depression who had increased levels of inflammatory biomarkers (e.g., CRP) (57, 67–69). Taken together, these data provide robust evidence of a cause-and-effect relationship between inflammation and depression.

Neurotransmitters and neurocircuits. Much attention has been paid to the neurotransmitter systems and neurocircuits that are affected by inflammation and mediate its effects on the brain and behavior (Figure 1). Early studies focused on patients administered IFNα as well as endotoxin and typhoid vaccination. Using functional MRI (fMRI) and PET, these investigations revealed that subcortical brain regions including the basal ganglia were primary targets of inflammatory stimuli (36, 70). A consistent finding across stimuli and across laboratories is that inflammation has reproducible effects on reward processing, including reduced activation of the ventral striatum during reward anticipation, which in turn is associated with reduced motivation (66, 71, 72). Of note, data suggest that these effects may be

more prominent in females (73). Alteration in neural activity of the substantia nigra in association with psychomotor slowing and increased IL-6 levels has also been described, as has decreased connectivity between subgenual anterior cingulate cortex (ACC) and nucleus accumbens in association with depressed mood following typhoid vaccination (63, 64). Studies in patients with depression have confirmed these effects of inflammation on corticostriatal networks. Indeed, increased peripheral blood CRP level was found to correlate with decreased resting-state functional connectivity between ventral striatum and ventromedial prefrontal cortex, which in turn correlated with increased anhedonia (74). Increased CRP level and increased peripheral blood immune cell reactivity in patients with depression have also been associated with decreased ventral striatal responses to reward anticipation (75, 76). Of note, inflammation-related disruption of corticostriatal pathways in patients with depression correlates with psychomotor slowing as well as with gene and protein markers of immunometabolic dysfunction (74, 77). Consistent with the effects of inflammation on corticostriatal pathways and symptoms of anhedonia, treatment trials of anticytokine therapies in patients with depression have shown preferential improvement in symptoms of anhedonia as compared to overall depressive symptom severity (57, 68, 69). Moreover, a recent study focusing on inflammation's effects on motivational anhedonia showed that compared to placebo, a single dose of the TNF antagonist infliximab significantly increased objective measures of effort-based motivation in patients with depression who had a CRP level >3mg/L in association with changes in a network of brain regions, including the ventral striatum (78). Interestingly, data from laboratory animals indicate that inflammatory cytokines, including IL-6, may have direct access to ventral striatal brain regions, including the nucleus accumbens, during stress (79). These effects, which are associated with stress-induced depressive-like behavior in these animals, are believed to be related to breaches in the blood-brain barrier due to decreases in Claudin-6, which plays an important role in blood-brain barrier integrity (79). Decreases in Claudin-6 expression have also been found in the nucleus accumbens in postmortem brain samples of patients with depression (79).

In terms of neurotransmitter systems, both dopamine and glutamate have been implicated in the effects of inflammation on subcortical brain regions (3, 36). Early studies in both laboratory animals and humans revealed decreased dopamine availability and release in the striatum following exposure to inflammatory stimuli, including IFNα and IL-6. For example, using in vivo microdialysis, nonhuman primates administered IFNα exhibited decreased dopamine both at rest and after stimulation with potassium or amphetamine, an effect that could be reversed by administration of the dopamine precursor levodopa via reverse microdialysis (80, 81). Decreased dopamine release was in turn associated with decreased effort-based motivation in these animals (80). Similar results were found in rodents administered IL-6 intraperitoneally (82). Further confirming the central role played by dopamine in inflammation's effects on the brain and behavior is a study demonstrating that administration of levodopa to patients with depression reverses decreased functional connectivity in corticostriatal reward circuitry in individuals with high but not low inflammation as indexed by CRP (54). Moreover, repeated administration of levodopa across a range of doses to patients with depression who have increased inflammation (CRP levels >2 mg/L) was found not only to increase functional connectivity in reward circuitry but also to increase effort-based motivation and reduce symptoms of anhedonia and overall depression severity (53). These preliminary data provide compelling support for a unique treatment response profile to a dopaminergic agent in patients with the inflammatory subtype of depression.

Alterations in glutamate metabolism in the basal ganglia also occur in the context of inflammatory exposure (83). Increased basal ganglia glutamate measured by MR spectroscopy is seen following 4 weeks of IFNα administration as well as in patients with depression who have increased CRP levels (84, 85). Increased basal ganglia glutamate in both IFNα-treated and depressed patients is in turn associated with symptoms of anhedonia and decreased psychomotor speed (84, 85). Patients with depression who have increased levels of CRP and basal ganglia glutamate also exhibit multiple brain regions of decreased regional homogeneity, a measure of local coherence of neuronal activity (86). Decreased regional homogeneity is associated with decreased functional connectivity in corticostriatal reward circuitry and anhedonia. Glutamate alterations in the context of inflammation are believed to be related to the direct effects of inflammatory cytokines, including TNF and IL-1β, on the function of astrocytes that play a pivotal role in controlling extracellular glutamate concentrations, which can be excitotoxic (83). Inflammatory cytokines are known to decrease the expression of excitatory amino acid transporter 2, limiting the reuptake of glutamate from the synapse (87, 88). Excess glutamate can spill out of the synapse and bind to extrasynaptic *N*-methyl-D-aspartate (NMDA) receptors, which can decrease neuronal growth factors such as brain derived neurotrophic factor while activating adjacent neurons, leading to chaotic, incoherent, and imprecise local neuronal signaling (87, 88).

Increased inflammatory cytokines can also activate indoleamine 2,3-dioxygenase, leading to production of kynurenine (KYN) and its metabolites (89). KYN is taken up into the brain by the large neutral amino acid transporter and is converted into quinolinic acid (QUIN) by activated microglia and macrophages. Indeed, in patients with depression, plasma inflammatory mediators, including TNF, are strongly associated with KYN and its metabolites in the periphery, which are in turn strongly associated with KYN metabolites, including QUIN, in the brain (90). QUIN can directly activate extrasynaptic NMDA receptors while also stimulating glutamate release and blocking glutamate

reuptake by astrocytes (89). In patients with major depression, increased plasma QUIN levels have been associated with increased basal ganglia glutamate and, together with cerebrospinal QUIN, are associated with anhedonia and decreased functional connectivity in corticostriatal networks (91). Of note, another metabolite of KYN, kynurenic acid (KYNA), is an NMDA antagonist that is believed to have neuroprotective effects in the brain (89). Decreased plasma KYNA levels are associated with increased basal ganglia glutamate levels (91), and a decreased blood KYNA/QUIN ratio is correlated with increased anhedonia (92). Taken together, these data suggest a convergence of inflammatory pathways to pathology in depression involving KYN and its metabolites and glutamate, which characterize the inflammatory subtype of depression.

In addition to effects on subcortical neural networks involved in mood regulation, inflammation also engages cortical circuits involved in anxiety, arousal, and alarm as measured using fMRI (24). For example, administration of IFNα was found to increase activation of the dorsal ACC in association with increased sensitivity to task-related errors (93). Moreover, increased peripheral blood concentrations of the soluble receptor for TNF (sTNFR2) in response to a psychosocial laboratory stressor were associated with increased activity of the dorsal ACC and insula during a social rejection task (94). Administration of IFNα as well as endotoxin has been associated with increased activation of the amygdala in response to sad faces (95, 96), whereas administration of the TNF antagonist infliximab reduced amygdala reactivity during sad face exposure (96). Finally, in a sample of highly stressed inner-city study participants, plasma CRP level was associated with decreased functional connectivity between the amygdala and the ventromedial prefrontal cortex, which in turn was associated with anxiety symptoms (97). These data suggest that inflammation impacts multiple cortical and subcortical brain regions and circuits, leading to a host of symptoms that may align more closely with an inflammatory subtype of depression as opposed to the currently conceived and overinclusive nosology reflected in what is now diagnosed as major depression.

CLINICAL TRIALS

Lessons Learned

Given the detailed understanding of the pathways from the immune system to the brain and ultimately behavior, there is an unprecedented opportunity for the development of treatments for the inflammatory subtype of depression (Figure 1). Unfortunately, results from clinical trials using anti-inflammatory drugs to treat otherwise healthy individuals with depression have been underwhelming and inconsistent (98), with two of the largest clinical trials to date showing no effect of either celecoxib or minocycline, two of the most commonly used anti-inflammatory agents to treat depression (99, 100). Not surprisingly, most clinical trials have used outdated clinical trial designs that have taken a "one-size-fits-all" approach with heterogeneous populations of patients with depression and nonspecific outcome variables, such depressive symptom severity as represented, for example, by the Hamilton Depression Rating Scale (HAM-D) (101, 102). Moreover, whether the treatment has hit the target (e.g., reduced inflammatory biomarkers in the brain or periphery) has rarely been assessed. Of note, when inflammatory biomarkers such as CRP or IL-6 have been used to stratify samples of patients with depression, as noted above, treatment effects have been observed for infliximab, minocycline, and levodopa, and especially for symptoms related to anhedonia (52, 54, 57, 68). Albeit in studies with relatively small sample sizes, these data reinforce the notion that mechanism-based clinical trials will require more tailored designs that are aligned with the populations and outcomes of interest as well as the target of treatment.

Designs for the Future

Several components are inherent to mechanism-based clinical trials for the inflammatory subtype of depression: enrichment, outcome alignment, and target engagement.

Enrichment. Strategies for enrichment may include the use of biomarkers for immune and/or metabolic pathways that characterize the inflammatory subtype of depression. Based on guidelines provided by the U.S. Food and Drug Administration (FDA) (103), these biomarkers should be developed within a context of use where a "predictive" biomarker can be used to enrich for a subgroup of patients with depression (i.e., inflammatory subtype) who are more likely to respond to a particular therapeutic agent (e.g., anti-inflammatory drug). Biomarkers must go through a rigorous process of validation, including the establishment of reliable measurement parameters and a qualification process that links the biomarker with biological mechanisms and clinical endpoints. It should be noted that for FDA approval, a drug tied to a biomarker should be effective in patients with the biomarker and not in those without. Establishing such efficacy in a match/mismatch design can add considerable complexity and cost to the drug development process. There are several candidate biomarkers that have received attention for the inflammatory subtype of depression, including notably CRP. CRP is measured under standardized conditions throughout the United States and has been linked to multiple aspects of the impact of inflammation on the brain and behavior in depression, as noted above. Moreover, peripheral blood CRP concentrations are associated with other inflammatory biomarkers, in both peripheral blood and CSF (104). Thus, CRP may be a good starting point to enrich for patients with the inflammatory subtype of depression. Of note, establishing a diagnostic subgroup within major depression (e.g., by using an inflammatory specifier) could potentially obviate the need for enrichment and allow drug development efforts to specially focus on an inflammatory subtype (105).

Outcome alignment. As with biomarkers, the FDA has a formal regulatory process for establishing clinical outcome assessments that are well-defined, validated, and reliable assessments of patients' symptoms, overall mental state, or function (106). It should be noted that according to the FDA, the qualification pathway for a novel clinical outcome assessment "is a multi-year process that requires a high degree of commitment" (106). Nevertheless, given that inflammation has rather specific effects on neurotransmitters and neurocircuits in the brain, it is unlikely that the currently FDA-accepted, nonspecific measures of depressive symptom severity as reflected by scales such as the HAM-D will be sufficient for novel drug development for the inflammatory subtype (101). Indeed, there are no currently FDA-approved measures for neurovegetative symptoms or anhedonia. Thus, the development of novel clinical outcome assessments that align with the effects of inflammation on the brain is imperative (101).

Target engagement. Although not part of the regulatory process, a major advantage of developing therapeutics for a mechanism-based nosology is that it can be readily determined early in the drug development process whether a treatment is "hitting the target." In the case of the inflammatory subtype, virtually all of the treatment targets can be measured as proximal endpoints, thus obviating the reliance on behavioral outcomes in the early phases of drug development. Such proximal endpoints can be highly specific with limited variance, therefore requiring a much smaller sample size for proof of concept. A recent example was the use of functional connectivity within reward circuitry as a proximal endpoint to assess the efficacy of levodopa in patients with high versus low inflammation (53). Demonstration of improved connectivity following a single dose of levodopa in patients with depression and high inflammation led to a follow-up clinical trial indicating sustained improvement in effort-based motivation, anhedonia, and HAM-D scores following repeated administration of levodopa to patients with high inflammation (53).

CONCLUSIONS

A tremendous amount of progress has been made in detailing the pathways leading from an activated immune response to changes in behavior that can contribute to diseases such as major depression. Recognition that this is but one mechanism leading to pathology allows a modernization of our current nosology of depression and ushers in the exciting new era of precision medicine. Nevertheless, in order for the field to embrace these opportunities, all stakeholders will need to fully commit to accelerating the incorporation of biomarkers and novel clinical outcome assessments into our clinical trial designs. Such a commitment will lead us into the next generation of targeted therapeutics.

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