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Inflammation and Depression: the Neuroimmune Connection

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Abstract

Purpose of Review: To update clinicians on the field of psychoneuroimmunology with respect to depression.

Recent Findings: A significant subset of patients with depression may have illness to which dysfunction of the immune system, typically viewed as inflammation, makes a significant contribution. Normal sickness behavior may sometimes manifest abnormally as mood episodes. Early evidence suggests that interventions that reduce inflammation may improve symptoms in these patients and that they may also respond differently to standard pharmacotherapy.

Summary: Treatment of patients with depression should consider inflammatory status, as part of medical and psychiatric health. Recommendations for healthy diet and exercise are important for all patients but may be more important for patients who have clinical evidence of inflammation. Methods of identifying patients in the inflammatory subgroup and treating them with therapy targeted specifically at the immune system are still experimental but likely to impact care for depression in the future.

Introduction: Why should psychiatrists care about the immune system?

Traditionally mental illnesses have been viewed as diseases exclusively of the brain. Syndromes were often tied, with only partial success, to specific anatomical regions (e.g. the amygdala was associated with anxiety). As neuroscience advances, this paradigm is being replaced with a more dynamic model of complex interactions among brain regions and between the brain and other systems of the body (1). One of the most fruitful of these paradigms is psychoneuroimmunology (PNI), which explores the surprisingly rich connections between the nervous and immune systems (2). Although the essential scientific principles of PNI are well established, many remain unaware of important advances that are poised to change the delivery of psychiatric care. In this review we will discuss the scientific basis of PNI, its relationship to mood and how it informs changing clinical practice.

While many mental disorders, including schizophrenia and autism, may have an immune component, depression is the disorder with the perhaps the largest body of evidence linking it to immunity. A good place to start exploring the PNI of mood is the observation that depression highly resembles being sick (3). Sickness has common elements that appear

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across species and infection type, including fatigue, loss of interest, changes in sleep, loss of appetite, psychomotor slowing, and impairments in cognition (4). This set of symptoms, dubbed ‘sickness behavior,’ would, in the absence of infection, be sufficient to diagnose depression. This resemblance is substantial enough that scientific curiosity about a possible relationship between the two follows naturally.

The fact that drugs that affect the immune system can induce pathological mood episodes is generally familiar to clinicians. Both steroids and antibiotics may cause mood episodes; in fact, the first antidepressant was an anti-tuberculosis drug whose mood action was a serendipitous side effect (5). Even stronger evidence comes from depression induced by interferon- α therapy, especially for hepatitis C virus (HCV) infection. Interferon therapy works by strengthening the immune response, and causes sickness behavior in almost all patients who receive it. Amazingly, close to half may go on to develop a full major depressive episode including symptoms such as worthlessness and suicidal ideation (6). Having a history of depression is a risk factor for interferon induced depression, and this appears to be biologically based (7, 8). Although it is not fully clear if interferon is associated with depression in patients not receiving interferon therapy, it is the best evidence we have that altering the immune system can cause depression.

Epidemiologists have noted the high rate of medical comorbidity in depressed patients for decades. Chronic disorders such as metabolic syndrome and cardiovascular disease carry an up to doubled risk of depression (9–11). Similarly, autoimmune disorders and severe infections increase future risk of depression by about 50% (12). Interestingly, depression is associated with varying increased risk of developing many of the same medical disorders, as well as cancer, over time (13, 14). Although the psychological toll of chronic medical illness may certainly contribute to the increased depression risk, there is evidence that immune activity has a specific additional effect. For example, Multiple Sclerosis (MS) and Amyotrophic Lateral Sclerosis (ALS) are both progressive neurodegenerative disorders with high morbidity and mortality. MS is an immune disorder associated with significantly increased inflammation, while ALS is not; until late in its course, ALS is associated with equivalent or better than normal inflammatory profiles (15–17). Depression prevalence in ALS is equivalent to other populations experiencing chronic stress, 10–20% (18, 19). The rate of depression in MS is much higher, at least 30% but perhaps as high as 50% (20). Although not definitive this pattern of higher prevalence of depression in inflammatory diseases is widespread and supports a specific role in inflammation in mood comorbidity.

Finally, even when examining medically healthy persons with depression, there is evidence of immune dysfunction. Markers of inflammation are elevated compared to non-depressed controls, a finding which has now been well replicated (21). Among the various markers, C-Reactive Protein (CRP), is perhaps the most studied. Easily obtainable as a marker of cardiovascular disease risk, CRP in most adults is less than 1mg/L, while levels above 5mg/L indicate high CVD risk, and levels above 10mg/L typically signal an active infection (22). Many patients with depression have CRP levels <1mg/L, but a larger fraction than in the general population have elevated levels. This suggests that “inflammatory depression” is a sub-type of illness. The increase in markers associated with fighting infection paradoxically does not protect patients with depression; they are at greater risk of minor

infections and may not respond successfully to vaccines (23). Depression is also associated with a significant longitudinal increase in risk for serious infection across body systems (24).

A Psychoneuroimmunology Primer

That it is important to understand the immune system in psychiatry does not make it easy; after the brain, it may be the next most complex organ of the body. It must be smart and nimble enough to ruthlessly attack a wide variety of pathogens while sparing friendly body cells as much as possible (25). An immune response at the site of infection or injury, where cells residing in the tissue detect pathogens or tissue damage (26). Next, they generate proinflammatory cytokines which attract and activate other immune cells from around the body; these include the Interferons, Interleukin-6 (IL-6), IL-1 β , and tumor necrosis factor- α (TNF- α). Some immune cells then travel to lymph nodes where they interact with the B and T cell ‘library’ of prior immune encounters (27). Immune cells attack and destroy pathogens before switching the immune response to a tissue repair phase called resolution. Resolution is an active process, with a different set of anti-inflammatory cytokines and other mediators (28).

Sickness is the normal behavioral component of the immune response. The brain monitors the body via the vagus nerve and appropriately adjusts behavior to maximize survival. Changes in dopamine transmission cause anhedonia and psychomotor slowing, and the hypothalamus controls fever and adjusts sleeping behavior (29, 30). Changes in frontal cortical regions are associated with changes in social behavior and cognition (31). While these changes in brain activity overlap with those seen in depression, sickness behavior is not *equivalent* to depression. Infections associated with sickness typically cause increases in cytokines of a few hundred-fold; depressed people have only 2–3x normal levels (21). Ultimately, sickness is adaptive, appearing and disappearing according to the internal and external environment of the person or animal (32). Depression by definition is not context appropriate or adaptive. It also features symptoms like worthlessness that are not part of sickness. Most investigators agree that a likely explanation is that some cases of depression are sickness behavior activated inappropriately, but we do not understand how or why this occurs. One theory is that gene variants supporting an immune system capable of surviving childhood infections are evolutionarily selected, and that these same alleles also increase the risk of depression later in life (33). Another common model attributes the inappropriate activation of sickness behavior to the failure of the immune system to “learn” accurately, so that in some cases of depression there is a false immune response, similar to autoimmunity. This may occur because modern humans are exposed to a very different pathogen environment than our ancestors (34).

Where Does Inflammation Come From?

The first step in using PNI in practice is to identify depressed patients in whom the immune system makes a clinically relevant contribution. Patients with a major chronic inflammatory illness which preceded depression represent the most obvious cases. However, most patients falling into the inflammatory depression subgroup probably suffer from subtler dysregulation of a neuroimmune-metabolic network. While this network is one of risk rather

than causality, in modern western societies, obesity may be the largest contributor to, and potential consequent of, network dysfunction.

Inflammation is commonly attributed to diet, often to specific foods, but it is not clear whether inflammation has an effect independent of weight. Consumption of a diet of processed carbohydrates and red meat high in saturated fatty acids (SFAs) is associated with obesity; conversely, a diet that is higher in fiber-rich vegetables is associated with normal body mass index (35). Similarly, a fair but less consistent body of evidence suggests that foods with higher glycemic index are also inflammatory. However, whether, after accounting for the differences in weight tied to these diets, there is any remaining inflammatory effect is unclear. Too few people maintain diets high in SFAs while maintaining low body weight for epidemiologic analysis. Generally, studies examining links between depression and diet have found the same pattern of associations that hold for inflammation, but are limited by not directly examining inflammation as a mediator (36). For example, an analysis of data from the Nurses' Health Study that computationally analyzed diet patterns found no association of diet with depression (37). However, when the same study was reanalyzed first for diet patterns predicting inflammation, that diet *did* predict depression, with a relative risk of ~1.3 for the highest inflammatory quintile (38). These results suggest that diet increases depression risk primarily through obesity and its associated chronic inflammation.

While the negative mental health effects of adverse experiences, especially in early life, are well known, there is less awareness of the strong evidence that trauma increases the risk of medical illness (39, 40). Early life trauma is associated with an increase in body weight and CRP in adulthood (41, 42), and this association likely holds for adult onset PTSD as well (43). Most likely this reflects the effects of cortisol resistance in survivors of childhood trauma, who also show behavior changes that impede maintenances of healthy weight such as insomnia (44). There is at least some evidence that unsurprisingly the effects of childhood and later-life trauma on inflammation are additive (45, 46).

Although it is premature to recommend routine monitoring of inflammation in all patients with depression, patients who have trauma histories and are overweight or obese are the best candidates, with the medically ill, for inclusion in this subgroup. Although research studies use CRP most commonly to subtype subjects there is insufficient evidence that this is superior in clinical practice compared to considering history alone.

Interventions for Inflammatory Depression

There are numerous treatment options available for patient with depression, but the current standard of care lacks personalization and relies heavily on trial and error, especially with medications. An inflammatory depression subgroup, therefore, presents an opportunity to improve treatment selection. There is growing evidence that inflammation is associated with poor response to treatment with selective serotonin reuptake inhibitors (47, 48) compared to drugs that modify other neurotransmitter systems, especially dopamine (49, 50). Another option is addressing inflammation directly via cytokine inhibitor therapy, which has been tested successfully in several autoimmune disease samples with depression symptoms as a primary or secondary outcome (51). To date, there has been only a single study in patients

with treatment resistant depression without medical comorbidity; it found TNF- α inhibitor treatment failed to beat placebo (52). There was some evidence that patients with CRP above 5mg/L benefited; however, the study was underpowered to stratify by inflammation, so replication is needed. Because cytokine inhibition therapy carries with it significant risk of immunosuppression, it is likely that this will be at best a high tier treatment reserved for very ill patients with verified inflammatory depression. More approachable off label medications are Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). Multiple studies, most testing augmentation treatment, have found that they are effective in reducing depression symptoms (53). Unfortunately, other studies have found no effect, and chronic NSAID use is not without risks (54). Today, while the benefits of off-label treatments may not outweigh the risks, clinicians can, in the absence of other clinical indicators, choose non-serotonin antidepressants over SSRIs in patients suspected to have “inflammatory depression” without undue risk.

Because it is a verified means of lowering inflammation, exercise should also be recommended (55). Exercise has been shown to be an effective treatment for depression, and there is some evidence that it may be especially useful in those in the inflammatory subgroup (56, 57). There is still debate about what types of exercise are most effective in reducing depression symptoms (58). Overall, any regimen a patient is willing to maintain should be considered valuable, regardless of whether it meets guidelines for type, amount or modality.

Diet recommendations should be informed by the evidence that maintaining a healthy weight is more important than diet composition per se (59). Certainly, recommendations targeting specific “super” foods as “fighting” inflammation are outside the realm of evidence-based medicine, but may be useful for some patients if they improve adherence to a healthy diet. As discussed above, diets including all macronutrient groups and emphasizing foods with unsaturated fats and fiber have the best evidence for supporting good mental health. Despite some promising work on supplements, especially omega-3 fatty acids, there is insufficient evidence to support recommendations for these routinely in the treatment of depression (60). Finally, because of high comorbidity, patients with depression who seek diet advice, or for whom weight loss is part of the recommended treatment should be screened and, if appropriate, treated for binge eating disorder (61).

Overall it is now clear that for at least some patients, depression involves abnormal immunity. While this model may not apply to all patients, treatments are already available that could improve the physical and mental health of a significant group if appropriately applied. Identifying the patients in the inflammatory subgroup is thus a major focus of translational research. This, and the development of new targeted treatments over the next few decades is poised to change psychiatric practice and result in better outcome for patients.

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