tion can be readily identified by inflammatory biomarkers, including CRP, we are uniquely poised to target inflammation-relevant symptom clusters, notably anhedonia and possibly anxiety, across psychiatric disorders. Such strategies represent an important step toward precision medicine in psychiatry.

Nevertheless, there are limitations. If the expectation is to treat disorders as they are defined by current nomenclature, therapies targeting inflammation and its effects on the brain may fall short. For example, a recent study found that an anti-cytokine therapy to block inflammation improved symptoms of anhedonia but did not separate from placebo on overall depression scores[9]. These results suggest that, in order to fully leverage current knowledge, clinical trials and clinical practice should take into consideration both the level of inflammation and relevant symptom profiles, treating the behavioral consequences of inflammation and not the disorder; whether it is anhedonia in PTSD, symptoms of amotivation in schizophrenia, or anxiety in depression.

While at first glance this approach may run counter to current clinical practice that focuses on diagnostic entities, recognizing that different symptom profiles within diagnoses may be driven by distinct pathophysiologic processes such as inflammation can be liberating. In addition, it may encourage the field to move away from the notion of one size fits all, to a multimodal approach that addresses the many contributing factors that drive the disorders we treat.

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DOI:10.1002/wps.20723

Inflammation affects social experience: implications for mental health

Deemed as one of the breakthrough findings of the last two decades, inflammation – the immune system's first line of defense against foreign agents – can play a role in negative mental health states such as depression. For instance, depressed individuals have higher levels of circulating pro-inflammatory markers, and experimentally increasing inflammation in healthy subjects can induce depressed mood[1].

Part of the reason why inflammation can elicit depressive symptoms is that inflammatory processes can signal the brain to initiate "sickness behavior", an adaptive response to illness which includes symptoms such as loss of appetite, fatigue and social withdrawal, bearing a striking resemblance to the hallmark features of depression.

But, is inflammatory-induced depression simply a function of the lethargy that accompanies sickness, or does inflammation actually play a distinct and larger role in the psychological and socioemotional changes that often accompany depression? Mounting evidence shows that inflammation plays a role not only in sickness behavior, but also in enhancing feelings of social disconnection and in altering sensitivity to the social world. Investigating how inflammation affects social experience may be key to better understanding the many psychiatric disorders that involve altered social sensitivity.

To explore the causal effect of inflammation on social experience, researchers have used an inflammatory challenge paradigm, in which participants are randomly assigned to receive an injection of endotoxin, a bacterial agent that triggers a time-limited inflammatory response, or a placebo injection.

In the first study to examine the socioemotional consequences of this inflammatory challenge in humans, participants exposed to endotoxin not only showed depressed mood, but also an increase in feelings of social disconnection. Moreover, enhanced feelings of social disconnection mediated the relationship between inflammation and depressed mood[1]. A subsequent study with a larger sample replicated this basic finding, and also found that inflammatory-induced feelings of social disconnection were enhanced in female participants[2].

These findings demonstrate that inflammation is a powerful organizer of social experience. But why would this be? Though it may seem surprising that the activity of the immune system could affect social experience, this unlikely pairing may provide a survival advantage. Being in a "sick" state puts an organism in a uniquely vulnerable position, and thus sensitivity to the social world may be modulated in order to help survive this vulnerable situation. Thus, for humans as well as other social species, heightened inflammation may lead to: a) a greater sensitivity to threatening social experiences in order to avoid threats to well-being during times of illness, and b) a greater sensitivity to and approach towards loved ones who could provide support and care during these times[3]. Research provides support for both of these hypothesized outcomes.

In line with the idea that inflammation increases sensitivity to negative social experience, participants who showed larger increases in inflammation in response to endotoxin also showed greater pain-related neural activity in response to social rejection[4]. Similarly, participants exposed to endotoxin (vs. placebo) showed greater pain- and threat-related neural activity in response to negative social feedback[5]. This increased sensitivity to

negative experiences appears to be specific to the social domain: participants exposed to endotoxin showed enhanced neural activity in response to threatening stimuli that were social in nature (e.g., angry faces), but not to threatening stimuli that were non-social (e.g., snakes)[6].

Inflammation also increases sensitivity to positive social stimuli. Participants exposed to endotoxin reported having a greater desire to be with their loved ones, and showed enhanced reward-related neural activity to viewing images of their loved ones[7]. Similarly, participants exposed to endotoxin showed greater reward-related neural activity in response to receiving positive feedback from others[5]. These results support the idea that, during states of sickness, it may be adaptive to show increased reward- and approach-related responding to loved ones or to friendly others who could provide help and support. This inflammation-enhanced sensitivity to positive stimuli also seems specific to the social domain, as inflammation actually reduces reward-related neural responding to positive stimuli that are non-social, such as money[8].

Interestingly, the relationship between heightened inflammation and increased sensitivity to social stimuli is reminiscent of what is observed in loneliness, another emerging mental health issue. Lonely individuals show elevated inflammation, an increased sensitivity to negative social experiences, and, just like participants exposed to endotoxin, greater reward-related neural activity in response to viewing images of close others[9].

Thus, loneliness and states of heightened inflammation share the same characteristic pattern of heightened sensitivity to the social world. Building on these overlaps, we are currently examining whether experiences of loneliness and the corresponding enhanced social sensitivity can be reduced through an over-the-counter non-steroidal anti-inflammatory drug.

Altogether, these findings advocate for a stronger consideration of the role of inflammation in psychiatric disorders that involve altered social sensitivity. For instance, while not all forms of depression are inflammatory in nature, it is possible that inflammatory-related depression could be distinguished from non-inflammatory depression by a characteristic increase in reward-related neural activity to close others. Distinguishing between these forms of depression might help to better inform treatment strategies (e.g., anti-inflammatory drugs vs. cognitive-behavioral therapy).

Moreover, these findings also suggest a stronger consideration of the mental health consequences of inflammatory diseases. Those who have chronic inflammatory disorders may be at a greater risk for enhanced social sensitivities, which may put them at a higher risk for loneliness and depression, and may increase the strain placed on their social relationships.

Appreciating the intimate links between the immune system and social behavior may provide a new perspective from which to understand and treat mental health issues.

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DOI:10.1002/wps.20724

The synaptic pruning hypothesis of schizophrenia: promises and challenges

Schizophrenia is widely considered a neurodevelopmental disorder, as suggested by its typical onset in adolescence and young adulthood, neurocognitive and social impairments preceding onset, and neuropathologic alterations of aberrant cellular organization, decreased neuronal volume, and dendritic spine loss.

Recent genome-wide association studies in large samples have revealed 108 genetic loci significantly associated with the risk of the disorder. The strongest risk was repeatedly identified in the major histocompatibility complex, a region rich with immune system genes and complex linkage disequilibrium patterns. Later studies determined that part of the variance for risk arises from the complement component 4 (C4) gene[1].

The complement system is involved in both immunological and regenerative processes, which include dampening inflammatory activation, angiogenesis, apoptotic cell removal, wound healing, and stem cell mobilization. In the central nervous system, complement factors play a role in synaptic pruning that may involve phagocytosis of redundant (or ineffective) synapses as well as enhanced pro-inflammatory cytokine secretion by glial cells inducing neuronal damage and death[2].

Exposure to maternal complement protein during pregnancy may be a risk factor for the development of schizophrenia in offspring[3]. Sellgren et al[4] used a reprogrammed in vitro model of microglia-mediated synapse engulfment and demonstrated increased synapse elimination in schizophrenia patient-derived neural cultures and isolated synaptosomes. Some of this effect was accounted for by carriers of schizophrenia risk-associated variants within the C4 locus.

All of these observations fit nicely into an early model original-