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Adding to the neuroimmune network model: A commentary on Nusslock et al. (2024)

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Over the last several decades, research has ushered in a wave of evidence linking psychological states with peripheral markers of stress and inflammation. Long gone are the days in which some may have thought of the brain as an isolated organ. Acknowledgement of such links between brain and body are perhaps most prominent in stress and stress-related disorders. In response to chronic stress, for instance, people often display increased inflammation. In addition, people may also develop psychiatric symptoms including depression following chronic stress. Work by many groups, including the authors of the target article (Nusslock, Alloy, Brody, & Miller, 2024), have demonstrated links between peripheral markers of inflammation and symptoms of depression. This correlative evidence has led researchers to begin to test the hypothesis that inflammation is a cause of depression as well as conversely the hypothesis that depression is a cause of inflammation, with some emerging evidence supporting such linkages.

Notably, this article adds to the existing literature in two important ways. First, the authors suggest specific neural circuits that may cause heightened inflammation. One principal circuit highlighted by the authors includes the amygdala and prefrontal cortex (PFC) and is hypothesized to be involved in threat detection. Here, heightened threat sensitivity resulting from early life stress is suggested to cause increases in inflammatory signaling. Moreover, the authors also suggest that reward circuits, including the striatum and PFC, may be targets of increased inflammation. That is, Nusslock and colleagues suggest that alterations in reward sensitivity, which has commonly been observed in people with depression, may be a consequence of increased inflammation. A second way this article notably adds to the existing literature is by adding a developmental lens to their neuroimmune model, incorporating knowledge of the timing of maturation of specific neural circuits to inform when and how increased peripheral inflammation may occur.

With these features as a backdrop, in this commentary I will attempt to add context onto these two notable threads to suggest areas where future research may focus.

Neural circuits

First, while the amygdala is an essential node in a network involved in threat detection, it is likely that the neural pathways involved in promoting inflammation extend well beyond interactions between the medial PFC and amygdala. For instance, while the amygdala is clearly central for detecting salience and necessary for Pavlovian threat learning, recent analyses from the large UK Biobank suggest that depression is not directly associated with abnormalities in amygdala activity – at least to fear faces (Tamm et al., 2022), and if it is, the percent of variance accounted for is vanishingly small (Grogans, Fox, & Shackman, 2022). This begs the question of what causal role the amygdala may have in the development of internalizing symptoms? Given a long and well-validated line of research demonstrating that the amygdala appears to be necessary for threat learning (LeDoux, 2012), it may be useful to reconsider the amygdala's neuroimmune role as not being one of broad threat *sensitivity*, but more narrowly one of threat *learning*. This reinterpretation fits existing data in at least two ways. First, conceptualizing the amygdala as playing a role in threat learning fits with well-validated learned helplessness models of depression, wherein individuals who encounter repeated stressful experiences 'give up', ultimately forming extremely pessimistic expectations for the future. Second, the amygdala plays a key role in forming these threat associations that are hypothesized to produce learned helplessness. Thus, individuals are 'learning' from chronic and uncontrollable stressors that lead to depression and the 'sickness syndrome' that the authors so nicely review. This perspective also suggests that regions beyond those reviewed by the authors may be critical to linking depression and inflammatory signaling.

In that vein, perhaps one of the best replicated findings of neural abnormalities in depression is that of reduced hippocampal size (Miller & Hen, 2014). Human and nonhuman work has repeatedly found that hippocampal dendrites retract, partly as a result of hypercortisolemia due to chronic stress, in individuals with depression. These morphological changes lead to reduced hippocampal neurogenesis and smaller hippocampi. It is interesting then, that people with depression tend to have poorer memory than people without depression and this may be due in part to changes in hippocampal volume.

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Moreover, there is some evidence that successful depression treatment leads to normalization of the hippocampus, providing suggestive evidence for causal links between the hippocampus and depression. Interestingly, the hippocampus also appears to regulate, and be regulated by, peripheral inflammation. That is, alterations to the hippocampus, as a result of chronic stress and/or threat learning can lead to changes in peripheral inflammation (Wu & Zhang, 2023). Taken together, this work suggests an important role for the hippocampus in addition to amygdala and PFC in modulating the immune system following stressful life events.

Evidence for what is called hippocampal replay further implicates the hippocampus as an area ripe for investigation in research on depression. After learning about appetitive or aversive outcomes, during periods of quiescence, patterns of hippocampal activity tend to be 'replayed' (Foster, 2017). It is thought that hippocampal replay facilitates consolidation of experiences into long-term memory. Interestingly, when encountering rewarding or aversive contexts and the choice-sets that have been encountered before, the hippocampus performs forward replay – a process thought to be a form of prospection. During forward replay, previous hippocampal patterns are replayed and predict the choices the organism will make.

Moreover, certain cognitive habits, including a tendency towards ruminative and repetitive negative thinking, prospectively predict the development of depression. These cognitive habits are likely to be mediated by cortical-thalamo-striatal-cortico loops that may be initiated by hippocampal replay (Heller & Bagot, 2020). These hippocampal patterns initiate and gate cortical activity and may be a key mechanism by which repetitive negative thinking, such as worry and rumination is initiated. Critically, once instantiated, these ruminative-like brain states are cyclical, habitual, and difficult to break. As a result, to the degree that certain cognitive styles promote risk for depression and the accompanying inflammatory signaling, it may be that the instantiation of these neural loops – driven by hippocampal patterns – is critical for outcomes the Nusslock and colleagues described.

Mechanisms of learning in development

Decades ago, Underwood suggested that the study of individual differences is essential for theory testing (Underwood, 1975). Applying this same perspective will be critical to test the validity and generalizability of the updated neuroimmune network model presented here by Nusslock and colleagues. By adding a neurodevelopmental lens to the neuroimmune model, the authors invite researchers to begin to formally ask *who* goes on to develop heightened inflammation following stressful life events (and critically who does not), and as a result, *what* are the neural and computational mechanisms determining outcomes of heightened inflammation and psychiatric symptoms for some, but not others. It is well-documented, for instance, that while many people experience trauma, approximately only 30% of those individuals go on to develop PTSD (Ressler et al., 2022). Similarly, why might some people experiencing stressful life events go on to develop depression and inflammatory changes, but others not?

One way to begin to address this question is to view the study of development and developmental psychopathology as inherently one of learning. That is, such a developmental perspective requires researchers to build models of what information people extract (either explicitly or implicitly) from their environment and how this impacts the expectations they have about the future. Such a 'predictive processing' framework is inspired by reinforcement learning, which attempts to understand how people (and machines) make choices and form future expectations based on experience.

I would argue it will be key to integrate into this developmentally informed neuroimmune network model a computational assessment of who is learning what about their environment. In reinforcement learning, part of this model can be operationalized as the learning rate – how much one updates their future expectations given past surprises (i.e. prediction errors). It has been suggested that one's predisposition for internalizing disorders comes in part from their individual learning rate, and particularly their learning rate for negative prediction errors (such as getting a poorer grade on an exam than a person predicted they would). That is, people who tend to update their expectations more extremely following negative prediction errors (e.g. developing the belief that they will fail every test after being unpleasantly surprised by a poor grade on one exam) are at heightened risk for internalizing symptoms. For example, and as noted above, not everyone experiencing trauma goes on to develop PTSD – that is, some people experiencing a trauma will update their worldview more extremely following trauma (leading one to withdraw from the world and view it as threatening), whereas others will not adjust their worldview as much. Individual differences in the degree to which someone updates expectations in the face of unwelcome surprises (like a traumatic experience) may be stable and trait-like and may be a computational mechanism by which early life stress, in some people, leads to the pathways described by Nusslock and colleagues.

For instance, using longitudinal designs to determine the drivers of internalizing disorder development, we have begun to test whether such learning phenotypes predict the development of psychopathology. Starting from the hypothesis that individuals at-risk for internalizing disorders (i.e. heightened neuroticism) asymmetrically update

their expectations in response to positive or negative feedback, we have been able to test, using naturalistic and highly personally relevant outcomes whether this is the case. Taking advantage of such events, we have found that individuals at-risk for depression and anxiety are less accurate in their expectations (Villano et al., 2023) and that this inaccuracy is due to a tendency to make pessimistic updates after negative prediction errors and even when receiving small positive prediction errors. Critically, longitudinal work in these same subjects suggests that those at-risk people whose expectations were most inaccurate – who's learning rates were most misaligned with reality – were those reporting the highest levels of anxiety symptoms 2 years later.

The developmental neuroimmune network model adds a very important perspective to the pathophysiology of depression. Without question, plasticity in neural circuits, resulting from life experiences can promote inflammation and, as argued by the authors, also be impacted by inflammation. This cycle can cause some of the cardinal symptoms of depression. A better understanding of the circuits involved in this process is essential to improve treatment. Moreover, it is likely that the neural mechanisms involved in such changes to the immune system are myriad, and that a formal computational framework for understanding who is at-risk and why will be very helpful to guide model building in the coming years.

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