Biological Psychiatry: Celebrating 50 Years

Commentary

Disentangling the Effects of Peripheral Inflammatory Markers on Brain Functional Connectivity

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Discovery of the role of inflammatory processes in mental health and ill health, particularly mood disorders, represents a major advance in understanding in psychiatry and with it the opportunity to develop/repurpose immunotherapies for real patient benefit (1). In the context of acute inflammation, proinflammatory mediators (e.g., cytokines) rapidly activate parallel neural and humoral immune–brain communicatory pathways to perturb local (e.g., neurotransmitter) as well as distributed networks of neural activity to impair mood, motivation, and cognition (2). Recent studies are beginning to suggest that similar mechanisms may also be at play in the context of chronic low-level inflammation (3). In rodents, chronic stress leads to the migration of immature monocytes into corticolimbic brain regions implicated in the regulation of mood and behavior. These cells appear to be necessary for the emergence of anxiety-like behaviors (4). However, no study to date has investigated how these cells relate to brain function in humans. In this issue of *Biological Psychiatry*, Nusslock *et al.* (5) address these issues in two well-powered studies that combine molecular (and in the second study, cellular) inflammatory markers with resting-state functional magnetic resonance imaging.

This study has several important strengths and implications. First, by repeating their analyses in two independent cohorts, Nusslock *et al.* (5) demonstrate that a composite index of inflammation (combining C-reactive protein, interleukin-6 [IL-6], IL-10, and tumor necrosis factor alpha) negatively scales with functional connectivity within the emotional regulation network across both cohorts—i.e., individuals with a higher inflammatory index showed weaker function connectivity within this network. In the second cohort (performed with a more advanced multiband functional magnetic resonance imaging sequence), this inflammatory index also scaled negatively with functional connectivity within the central executive network, a network that is implicated in the cognitive regulation of emotion, behavior, and thought. Interestingly, the design of their second study allowed them to also investigate associations with circulating immune cells and test the specific hypothesis that higher levels of circulating classical ($CD14^{++}$/$CD16^{-}$) monocytes, which are homologous to immature (Ly6c) monocytes linked to stress-induced anxiety in mice, would be associated with lower functional connectivity within brain networks linked to emotional regulation. Their data support this hypothesis, with classical monocytes negatively scaling with functional connectivity within both the emotion-regulation network and the central executive network in keeping with rodent data regarding monocyte trafficking to the brain. Importantly, this relationship was not observed for any of the other tested leukocyte subsets.

Another important feature of Nusslock *et al.*'s (5) study was that it was performed in two cohorts that differed across a range of socioeconomic, age, sex, and environmental factors, supporting the ecological validity and generalizability of their findings. In the first study, participants were 25-year-old African Americans living in rural Georgia in households that were defined as "working poor." Of 90 participants, 52% were female and 46% lived below the federal poverty line. The second study included 82 African American youths (67% female) living in Chicago, Illinois, who were a mean of 13.9 years of age. In this cohort, all reported good health (no history of chronic medical or psychiatric illness and free of prescription medications for 3 months) and 22% lived in households below the federal poverty level. Furthermore, identification of a consistent relationship between an index of peripheral inflammation and functional connectivity within an emotional control network despite marked differences in age suggests that this linkage is relatively stable across development. Previous epidemiological studies have linked raised inflammatory markers (IL-6) in early life (at 9 years of age) to an increased risk or later depression (and psychotic experiences) at 18 years of age (6). Though not tested here, it would be intriguing to know whether changes in functional connectivity mediate this association or if they reflect a preclinical vulnerability marker for the later emergence of psychiatric symptoms.

Nusslock *et al.*'s (5) finding of an association between circulating classical monocytes and decreased functional connectivity within emotion regulation networks in the second ostensibly healthy adolescent cohort has potentially important implications. It raises questions about how broadly monocyte trafficking to the brain influences human brain function in apparent health and the importance of this mechanism in psychiatric disorders, particularly posttraumatic stress, depression, and anxiety. The concept that immune cell trafficking to the central nervous system can influence normal brain function and neuronal connectivity is not without precedent. For example, preclinical studies have suggested that meningeal resident T-lymphocytes are necessary to support neuronal connectivity and social behavior (7). Further, as mentioned earlier, the preclinical literature implicates monocyte trafficking to the brain in the development of stress-induced anxiety (4). However, to date the preclinical literature implicating monocyte trafficking to the brain in stress-induced

SEE CORRESPONDING ARTICLE ON PAGE 153

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anxiety is largely restricted to models that include repeat exposure to severe social stress (using the repeated social defeat model), a model that is associated with marked increases in sympathetic outflow that acts on the bone marrow and spleen to bias myeloid precursor cells (particularly monocytes) toward a glucocorticoid-resistant and primed lineage. Furthermore, even in this context, signaling from the central nervous system must occur for monocytes to traffic to the central nervous system (4). Nusslock *et al.*'s (5) important findings suggest a potentially broader relationship between monocyte trafficking and brain function in humans. This finding will undoubtedly stimulate future studies aiming to clarify the range, magnitude, and duration of stressors that activate this pathway.

Two further (negative) findings from Nusslock *et al.*'s (5) study deserve further consideration and interpretation within the broader inflammation imaging literature. The first is their prediction of a positive association between peripheral inflammation and functional connectivity within the anterior salience network, which included nodes within the bilateral anterior insula, dorsal anterior cingulate cortex, and middle frontal gyri. Interestingly, though this prediction was not supported in either of their study cohorts, activation of the insula and anterior cingulate cortex (which form the primary anchors for the salience network) is a common feature of studies using robust and even relatively mild acute inflammatory challenges (2). In this context they have been interpreted as representing activation of neurally mediated immune–brain communicatory pathways that project to the posterior insula with forward projections to the anterior insula, providing a consciously accessible representation of inflammation frequently experienced as fatigue (2). Though the basis for this discrepancy remains incompletely understood (perhaps owing to an absence of interoceptive surprise in the context of chronic low-level inflammation), it has also been observed in a meta-analysis by Kraynak *et al.* (8) comparing studies using acute inflammatory challenges versus observational inflammatory studies. This meta-analysis also highlighted activations within regions encompassing the broader salience network, including the amygdala, striatum (particularly ventral regions), substantia nigra, hypothalamus, dorsomedial thalamus, and dorsal anterior cingulate cortex, as well as some regions such as the subgenual cingulate and hippocampus/parahippocampus that fall within the default mode network or limbic network, that appear relatively commonly activated across both acute challenge and observational inflammatory studies (2,8). Furthermore, some of these structures appear to play relatively specific roles in discrete aspects of inflammation-associated behavioral change. For example, actions on the ventral striatum have been linked to impaired reward sensitivity, and actions on the anterior insula have been linked to heightened sensitivity to punishment and the subjective experience of fatigue (2).

In their currently study, Nusslock *et al.* (5) adopted a hypothesis-driven approach and consequently constrained their analysis to a restricted group of networks that are principally associated with emotion regulation. This powerful and commonly adopted approach has been associated with several other notable successes within the field. One example is the demonstration that in major depressive disorder, circulating C-reactive protein negatively scales with functional connectivity of the ventral striatum and the medial prefrontal reward processing areas, and that this scaling of ventral striatal to medial prefrontal functional connectivity mediates the relationship between C-reactive protein and experienced anhedonia (3). However, the restriction of analyses to preselected functional networks as opposed to adoption of an unconstrained data-driven approach (9) risks providing an incomplete snapshot of how inflammatory mediators modulate whole brain connectivity and can introduce heterogeneity (through variation in network selection and definition) that likely contributes to some of the inconsistencies in the published literature. For example, though Nusslock *et al.* (5) did not identify an association between peripheral inflammation and default mode network connectivity in either of their cohorts, another recent study in 98 middle-aged adults reported that IL-6 positively scaled with the functional connectivity of the subgenual cingulate component of the default mode network and negatively scaled with the dorsal medial prefrontal cortex component at robust statistically corrected thresholds—though Marsland *et al.* (10) did not investigate the relationship of IL-6 with any other functional brain networks.

As the field matures and larger data sets become available, it will be important to comprehensively characterize how broadly peripheral inflammatory markers influence brain functional connectivity networks and to disentangle which discrete inflammatory mediators mediate these effects (e.g., cytokines and/or cellular processes, such as classical monocytes). Disrupted functional brain connectivity is commonly reported across a range of psychiatric disorders, many of which are also linked to elevated levels of inflammatory markers. Clarification of the role of immune mediators in this process will not only aid understanding of the pathogenesis of these disorders but also may help in the development of novel immunotherapies.

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