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Higher Peripheral Inflammatory Signaling Associated with Lower Resting State Functional Brain Connectivity in Emotion Regulation and Central Executive Networks

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Abstract

Background—Research documents bidirectional pathways linking peripheral inflammation and neural circuitries subserving emotion processing and regulation. To extend this work, this paper presents results from two independent studies examining the relationship between inflammation and resting state functional connectivity (rsFC), as measured by fMRI.

Methods—Study 1 involved 90 rural African-American young adults, age 25 years (52% female), and Study 2 involved 82 urban African-American youth, ages 13–14 (66% female). Both studies measured circulating inflammatory biomarkers (CRP, IL6, IL10, TNFα), which were averaged to form a composite. Study 2 also enumerated classical monocytes, a key leukocyte sub-population involved in immune-to-brain signaling. All participants completed a resting state fMRI scan.

Results—Consistent with prediction, higher scores on the inflammatory composite were associated with lower rsFC within an emotion regulation network in Study 1, controlling for sex. Study 2 replicated Study 1, showing that higher scores on the inflammatory composite were associated with lower rsFC within the emotion regulation network, controlling for sex, age and pubertal status, and found a similar pattern for rsFC within a central executive network. Study 2 also found that higher numbers of classical monocytes were associated with lower rsFC within both the emotion regulation and central executive networks. There was no relationship between rsFC in the anterior salience or default mode networks with inflammation in either study.

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Conclusions—These findings document relationships between peripheral inflammation and rsFC within an emotion regulation and central executive network, and replicate these associations with the emotion regulation network across two independent samples.

Keywords

Inflammation; neuroscience; fMRI; resting state; mental health; physical health

Introduction

Growing evidence documents bidirectional signaling between the brain and immune system in the pathogenesis of emotional and physical health problems(1–4). For example, animal research implicates neuroimmune signaling in the acquisition and expression of behaviors related to anxiety(5,6) and antidepressants diminish stress-induced inflammation and corresponding anxiety and depressive behaviors(7–9). Neuroimmune signaling is amplified and dysregulated in animal models of multiple psychiatric disorders, ranging from depression and anxiety to schizophrenia and substance use(3,5,10–12).

Despite the strength of animal findings, there are only a handful of studies examining brain functioning and inflammatory signaling in humans. This research indicates that healthy adults subjected to immunologic challenges (with endotoxin, vaccines, or interferon-α) display disrupted neural activity in regions that subserve emotion processing and regulation, as well executive control(13–17). This work also suggests that heightened tonic inflammation is associated with alterations in brain functioning that have implications for health(18–22).

The present paper extends this work by examining the relationship between tonic inflammatory signaling and resting-state functional connectivity (rsFC) in large-scale brain networks, as measured by fMRI. We focus on tonic activity because chronic low-grade inflammation is implicated in a heterogeneous set of mental and physical illnesses(1–4,23–24). The foundation for rsFC analyses is the discovery that there is a functional architecture to the brain's activity when a person is not engaged in a task(25,26). This intrinsic activity is coordinated by a set of functional networks anchored to anatomically distributed nodes. This synchrony of functional activity during periods of rest is referred to as rsFC. An advantage of rsFC is that it allows researchers to examine large-scale brain networks that are not constrained by the parameters of a task(26). Recent work highlights the stability of these functional brain networks, suggesting we can use rsFC to measure s` traits within individuals(27). Individual differences in rsFC are apparent by late childhood(28).

We focus on four rsFC networks implicated in emotion processing, regulation, and other cognitive functions given their involvement in psychiatric illnesses(29). The first is the emotion regulation network (ERN), which supports the conscious, voluntary, and cognitive regulation of emotion(30)(31,32). The ERN is anchored in the inferior frontal gyrus, middle temporal gyrus, and precentral gyrus, and plays a key role in regulating limbic circuitry, including the amygdala (31). Complementing the ERN is the frontoparietal central executive network (CEN), which connects areas of the dorsolateral prefrontal cortex and posterior parietal cortex to support the cognitive regulation of emotion, behavior, and attention(26,33–

35). Young adults experiencing depression or anxiety display aberrant connectivity in both the ERN and CEN(29,31). The anterior salience network (aSN) is anchored in the anterior insula and dorsal anterior cingulate cortex and is important for monitoring the salience of external inputs and internal brain events(36). Finally, the default mode network (DMN) is anchored in the posterior cingulate cortex and medial prefrontal cortex and is implicated in self-related cognitive activity and mental simulation(37).

We present results from two distinct studies of African-American youth (12–14 years old) and young adults (25 years old). Compared with Whites, African-Americans have a similar (or lower) prevalence of most psychiatric disorders that involve inflammation(38,39). However, there are racial disparities in the course of many psychiatric disorders, with African-Americans experiencing more severe, disabling, and chronic manifestations(40–42). These disparities may stem from Black's higher exposure to inflammation-triggering stressors including childhood adversity, racial discrimination, and economic hardship(43–45). Also, the vast majority of human brain imaging research has been on Caucasians, with minimal attention given to racial/ethnic variation. Studying both youth and young adults allows us to assess neuroinflammatory signaling across a developmental period associated with neural maturation(46), increases in immune system competence(47), and elevated risk for psychiatric disorder onset(48).

Study 1 examined the relationship between rsFC and inflammatory biomarkers, as quantified by inflammatory cytokines and C-reactive protein (CRP), among rural African American young adults. Peripheral cytokines can access the brain through active transport or enter at circumventricular organs or leaky regions of the blood-brain barrier(2,49). Study 2 had two aims, the first of which was to replicate the analyses of Study 1 in an independent sample and determine whether they generalize to younger African American individuals living in an urban setting. Study 2 then enumerated leukocyte sub-populations to examine a novel immune-brain pathway recently identified in animal studies(5). Although inflammatory cytokines are a principal channel for immune-to-brain communication(10–12,54), recent preclinical studies reveal another mechanism for such crosstalk, which involves monocytes(5). This research shows that when mice are subjected to chronic social stress, a population of immature monocytes is mobilized from bone marrow into circulation(6,50). These cells traffic to the blood vessels supplying the brain, and acting in concert with resident microglia, increase neuroinflammatory signaling in stress-sensitive regions like the prefrontal cortex, amygdala, and hippocampus. (It is unclear whether these monocytes migrate into the brain parenchyma, or just signal microglia which are present there.) Regardless, this chain-of-events is critical to the emergence of anxiety: if immature monocytes are prevented from trafficking into the brain, stressed mice show minimal evidence of anxiety-like behavior(9). These immature monocytes are defined as Ly-6c^{high} in mice; their homologue in humans is the classical monocyte, defined as CD14++/CD16-. To date, no human studies have considered how these cells relate to brain function. Accordingly, we extended the animal research by examining, for the first time, the relationship between rsFC and tonic levels of classical monocytes in humans. To evaluate the specificity of any such association, we also enumerated other leukocyte sub-populations, and evaluated their association with rsFC.[1]

Our predictions varied across rsFC networks. We hypothesized that higher inflammatory signaling (i.e., inflammatory biomarkers and classical monocytes) would be associated with lower rsFC in both the ERN and CEN, because in both animal and human studies, systemic inflammation diminishes self-regulation and executive-control by modulating PFC structure, function, and development(11,15,16,51–53). By contrast, the aSN monitors the salience of stimuli and is implicated in threat processing(36). We hypothesized that more connectivity among aSN nodes constitutes a vulnerability for inflammation. We based this prediction on experimental studies showing that activation of threat circuitry primes immune cells to show larger cytokine responses to microbial stimuli(1,49), which, over time, should accumulate to produce systemic inflammation. The DMN is involved in self-referential cognition(37). It was not apparent how variations in such processes would relate to inflammation, and thus we made a null prediction for the DMN.

Study 1

Methods and Materials

Participants—A total of 119 right-handed rural African-Americans, age 25 years, were recruited from a larger longitudinal study(54). Participants grew up in rural Georgia in households characterized as working poor; primary caregivers worked an average of 39.4 hours per week, yet 46.3% of the sample lived below federal poverty standards. Participants were right handed and screened for MRI contraindications. Participants were free of any psychiatric medications for at least one month before participating. Subsequent analyses excluded 28 participants because of excessive movement (n=23) and other technical problems (n=6). Thus, the final analytic sample was 90 (52% female). Participants provided written informed consent.

Procedure—We assessed rsFC and inflammatory biomarkers on the same day using procedures outlined below.

MRI Acquisition: Imaging data were collected at the University of Georgia using a GE Signa HDx 3-Tesla scanner. Structural imaging consisted of a high-resolution T_1-weighted, fast spoiled gradient echo scan (TR=7.8ms, TE=3.1ms, flip angle=20°; FOV=25.6cm, matrix = 256×256, 160 contiguous 1mm axial slices, voxel size=1mm^3). Whole-brain functional images were acquired using T2* echoplanar imaging with a single-shot gradient echo pulse sequence (TR=2000ms; TE=25ms; flip angle, 90°; FOV=225×225mm; matrix=64×64; 38 contiguous 3.5mm axial slices; voxel size=3.5mm^3). The Study 1 resting state paradigm consisted of two 4-minute imaging runs of 120 brain volumes each.

MRI Image Processing: fMRI data preprocessing was conducted using Analysis of Functional Neuroimages software(55). Functional data were despiked, slice time shift corrected, and aligned to T_1 data before being registered into Montreal Neurological Institute standardized space. The first four volumes of each run were removed to allow the MR signal to reach steady state. Volumes with greater than 25% of voxels identified as

[1]Study 1 did not have the infrastructure to enumerate leukocyte sub-populations in order to assess the relationship between classical monocytes and rsFC.

outliers (AFNI based version of DVARS) or intervolume movement greater than 0.2mm along any axis were censored(56,57). Bandpass filtering was applied to remove low and high frequency noise (.01 to .08hz), and motion correction was accomplished by including the six standard (de-meaned) motion parameters and their temporal derivatives as regressors of no interest. Data were spatially smoothed using a 6mm full-width half-maximum Gaussian filter.

Resting State Functional Connectivity Analyses: For each region-of-interest (i.e., node) within a network, we placed a 5mm sphere around the coordinates of peak activation for each discrete cluster separately within the left and right hemisphere masks. Raw time series data for each voxel were de-meaned and converted to percent-signal-change scores to reduce variability between subjects. We calculated the region-of-interest (ROI) seed data as the average percent-signal-change for all voxels contained in a given region. rsFC was quantified using the correlation of the average time series in each ROI with the average time series in all other ROIs in the network using Pearson's *r*. Next, we converted *r* values to *Z*-scores using Fischer's *r* to *Z* transformation. Finally, we averaged the *Z*-scores of all possible connections to compute a total network value reflecting the connectivity of all possible nodes within the network. We a priori selected the ERN ROIs from an activation likelihood estimation meta-analysis(31), which identified an emotion regulation network across 23 studies/479 participants. We defined the CEN and aSN ROIs utilizing a publicly available atlas of resting state networks derived through an independent components analysis(58). DMN ROIs were defined based on a meta-analysis of default mode network connectivity(59). Table 1 presents the coordinates and labels for each ROI, and Figure 1 presents axial and sagittal views of the ROIs for each rsFC network.

Inflammation biomarkers: From antecubital blood, we quantified serum levels of CRP, interleukin-6, interleukin-10 and tumor necrosis factor-α (TNF-α).[2] CRP was measured by high-sensitivity immunoturbidimetric assay on a Roche/Hitachi cobas c502 analyzer (lower limit of detection, 0.2mg/L). The average intra- and inter-assay coefficients of variation were 2.5% and 5.6%. The cytokines were measured in duplicate by electrochemiluminescence on a SECTOR Imager 2400A (MesoScale Discovery) with a Human Pro-Inflammatory Ultra-Sensitive assay (MesoScale Discovery), following the manufacturer's instructions. The kit's lower limits of detection range from 0.19pg/mL (IL-6) to 0.57pg/mL (IL-10). Across runs, the intra-assay coefficients of variation for duplicate pairs were 4.01% (IL-6), 4.59% (IL-10), and 3.80% (TNF-α). Following previous work(60), we z-scored the values of each biomarker and then summed them to form a composite inflammatory biomarker score. A higher score on this composite reflects higher systemic inflammation.[3]

[2]Although IL-10 functionally is an anti-inflammatory cytokine, it is only expressed under conditions of inflammation. Thus, statistically, it behaves like the other inflammatory cytokines such that higher levels reflect more inflammatory activity.

[3]In Study 1, the mean and standard deviation for each biomarker in pg/ml were 3.07 and 4.38 for CRP, 2.02 and 2.12 for IL-6, 1.42 and 2.32 for IL-10, and 3.69 and 1.24 for TNF-α. The composite inflammatory biomarker score was significantly associated with each of the individual inflammatory biomarkers at $p < .001$ (IL-6, $r = .72$; IL-10, $r = .61$; TNFα, $r = .69$; CRP, $r = .69$).

Results

We regressed the composite inflammation score on to each of the rsFC networks in four separate hierarchical multiple regression analyses. We statistically controlled for sex in all models and we present the results of these adjusted analyses in Table 2.[4] In line with predictions, higher scores on the inflammatory biomarker composite were associated with lower rsFC in the ERN, ($B = -.21$, $t = -2.01$, $p = .05$; Figure 2A). There were no significant associations between the inflammation composite and the other rsFC networks, (p's>.15). (Supplemental Table S1 presents the relationships between rsFC in all networks and each separate inflammatory biomarker. Supplemental Figure S1 presents relationships between the inflammatory composite score and specific node-to-node associations within the ERN).

Study 2

Although inflammatory cytokines are a principal channel for immune-to-brain communication(10–12,61), recent preclinical studies reveal another mechanism for such crosstalk, which involves monocytes(5). This research shows that when mice are subjected to chronic social stress, a population of immature monocytes is mobilized into circulation(6,50). These cells traffic to the blood vessels supplying brain, and acting in concert with resident microglia, increase neuro-inflammatory signaling in stress-sensitive regions like the prefrontal cortex, amygdala, and hippocampus. (It is unclear whether these monocytes migrate into the brain parenchyma, or just signal microglia which are present there.) Regardless, this chain-of-events is critical to the emergence of anxiety: if immature monocytes are prevented from trafficking into the brain, stressed mice show minimal evidence of anxiety-like behavior(9). These immature monocytes are defined as Ly-6c^{high} in mice; their homologue in humans is the classical monocyte, defined as CD14++/CD16-.

We had three aims for Study 2. First, we sought to replicate the results of Study 1 in an independent sample, and determine if they generalize to younger African-Americans living in an urban setting. Second, we extended the animal research outlined above to humans, and assessed whether on a tonic basis, higher numbers of classical monocytes were associated with lower rsFC. Finally, to evaluate the specificity of any such association, we enumerated other leukocyte sub-populations, and evaluated their association with rsFC. Based on Study 1 and animal findings, we predicted that higher levels of inflammatory biomarkers and classical monocytes would relate to lower rsFC, but that other leukocyte populations would not.

Methods and Materials

Participants—Data were collected from 106 African-American youth from Chicago, Illinois. Participants were in eighth grade, English-speaking, and in good health, defined as being without a history of chronic medical or psychiatric illness, free of prescription medications during the past three months, and without acute infectious disease in the two weeks before participating. Participants were right handed and free of MRI

[4]We did not statistically control for age in Study 1 because all participants were approximately 25 years old (mean age = 24.92, SD = .57).

contraindications. Fourteen participants did not have rsFC data because they could be not be scheduled, or were too obese or too anxious to get into the scanner. Ten additional participants were excluded because of poor quality MRI data, leaving an analytic sample of 82. Youth in the analytic sample had a mean age of 13.9 (range 12–14) and 55 of them were female (67.1%). 24 of them were in early or middle stages of puberty (29.3%) and the others were late (42 or 51.2%) or post-pubertal (16 or 19.5%). In terms of socioeconomic conditions, 22% of youth resided in households whose income was below the federal poverty threshold (i.e., an income-to-poverty ratio ≤ .99). Another 35.4% had income-poverty ratios from 1.00–1.99, a category typically described as low income. Participants with complete and missing data were similar on age, gender, and pubertal stage (*p*'s ranging from .10 to .85).

Procedure—We assessed rsFC and inflammatory variables at two separate laboratory visits using procedures outlined below.

MRI Acquisition: Imaging data were collected at Northwestern University using a Siemens Prisma 3 Tesla scanner with a 64 phased-array head coil. Structural imaging consisted of a high-resolution navigated multiecho magnetization prepared rapid acquisition gradient echo (MEMPR) sequence (TR=2300ms, TE=1.86, 3.78, ms, flip angle=7°; FOV=256×256; matrix = 320×320, 208 slices, voxel size=0.8mm^3). Whole-brain functional images were acquired using T2* echoplanar imaging with a fast TR sequence (TR=555ms; TE=22ms; flip angle, 47°; FOV = 208×208mm; voxel size=2.0mm^3; multiband factor=8; partial Fourier Factor=6/8). The Study 2 resting state paradigm consisted of one 10-minute imaging run involving 1,110 brain volumes(62).

MRI Image Processing: Data were processed using Northwestern University Neuroimaging Data Archive (NUNDA)(63) in-house pipelines. We modified Study 2's processing pipeline to accommodate its multiband sequence and youth sample (see Supplemental Materials for details). Functional data were despiked and aligned to T1 data. Data were registered to Montreal Neurological Institute standardized space using a non-linear transformation(64). The first ten volumes were removed to allow the MR signal to reach steady state. Volumes with framewise displacement (FD) > 0.5mm or whole-brain changes in BOLD signal (DVARS) > 0.9% were regressed from the dataset(56), as were white matter and CSF. Participants needed to have 436 useable volumes (i.e., 4 minutes) to be included in analyses. Bandpass filtering was applied to remove low and high frequency noise (.01 to .08 hz). Data were spatially smoothed using a 6mm full-width half-maximum Gaussian filter.

Resting State Functional Connectivity Analyses: Network connectivity values were computed, and network ROIs were defined, using procedures identical to Study 1.

Inflammation Biomarkers and Leukocyte Phenotyping: Antecubital blood was collected between 8:00 and 10:00am, after an overnight fast, to minimize the influence of dietary intake and circadian variation. Serum levels of inflammatory biomarkers (CRP, IL-6, IL-10, TNF-α) were quantified using procedures and reagents that were identical to Study 1. The mean intra-assay coefficient of variation for duplicate pairs were 3.71% (IL-6), 3.42% (IL-10), and 3.57% (TNF-α).[5]

From the same blood draw, major leukocyte subsets (granulocytes, monocytes, lymphocytes) were enumerated with an automated hematology analyzer (AcT 5Diff, Beckman-Coulter). A standardized flow cytometry protocol was used to enumerate populations of classical and non-classical monocytes(65). Briefly, antecubital blood was drawn into Sodium-Heparin Vacutainers (Becton-Dickinson). After red blood cells had been removed (Pharm Lyse, Becton-Dickinson), the pelleted cells were washed, blocked with normal human serum, and stained with mouse, anti-human monoclonal antibodies against CD14(FITC), CD16(PE), HLA-DR (PerCPCy5.5), and CD45(APC), all purchased from Becton-Dickinson. Following a 20-minute incubation, the cells were washed and fixed (CytoFix/CytoPerm, Becton-Dickinson), and incubated for another 20 minutes. Data were acquired on a Guava 6HT2L (Millipore), with 30,000 events collected per specimen, and analyzed using FlowJo software. Following previous work(65), populations of classical (CD14++/CD16-) and non-classical (CD14+/CD16++) monocytes were defined by a sequential gating procedure.

Results

Using a series of hierarchical regression analyses, we regressed the inflammatory variables on to each of the rsFC networks. We statistically controlled for sex, age, and pubertal status in all models and present the results of these analyses in Table 3 Replicating the results of Study 1, higher scores on the inflammatory biomarker composite were associated with lower rsFC in the ERN, ($B = -.23$, $t = -2.07$, $p = .04$; Figure 2B). Higher scores on this composite also were associated with lower rsFC in the CEN, ($B = -.27$, $t = -2.42$, $p = .02$; Figure 2C). (Supplemental Table S2 presents the relationships between rsFC in all networks with each separate inflammatory biomarker).

Turning to cellular phenotyping data, our results paralleled findings from animal research on the role of classical monocytes in immune-brain communication. Specifically, higher counts of classical monocytes were associated with lower rsFC in both the ERN, ($B = -.25$, $t = -2.20$, $p = .03$; Figure 2D) and CEN, ($B = -.37$, $t = -3.38$, $p = .001$; Figure 2E). Also paralleling the preclinical literature, these associations were specific to the classical monocyte population – there were no significant associations between the ERN and CEN with any other leukocyte subpopulations considered (p's>.11). Finally, rsFC in the aSN and the DMN were not significantly related to any of the inflammatory variables (p's>.10). (Supplemental Figure S1 presents relationships between inflammatory variables and specific node-to-node associations within the ERN and CEN).

Discussion

This is the first investigation of the relationship between peripheral inflammatory signaling and functional connectivity of intrinsic brain networks in humans. Consistent with predictions, Study 1 found evidence that higher scores on an inflammatory biomarker composite (CRP, IL6, IL10, TNFα) were associated with lower rsFC within the ERN among rural African-American young adults. Study 2 replicated this finding in an independent

[5]In Study 2, the mean and standard deviation for each biomarker in pg/ml were 1.27 and 2.43 for CRP, 0.9 and 2.05 for IL-6, 2.71 and 8.43 for IL-10, and 2.43 and .048 for TNF-α. The composite inflammatory biomarker score was significantly associated with each of the individual inflammatory biomarkers at $p < .001$ (IL-6, $r = .64$; IL-10, $r = .59$; TNFα, $r = .44$; CRP, $r = .77$).

sample of African-American youth, and also found evidence that higher scores on the inflammatory biomarker composite were associated with lower rsFC in the CEN. Study 2 also found that higher counts of classical monocytes, a key leukocyte sub-population involved in immune-brain signaling, were associated with lower rsFC within both the ERN and CEN. These relationships were maintained after adjusting for sex, age, and pubertal status. There was no relationship between rsFC in the aSN or DMN with inflammatory signaling in either study.

The ERN and CEN support the cognitive regulation of emotion, attention, and behavior(26,31–33,35,58). The engagement of these regulatory processes has been associated with better mental and physical health(66–68). There is growing evidence, however, that chronic inflammation modulates the structure, function, and development of the prefrontal cortex (11,15,16,51–53). Here, and in our neuroimmune network model(1), we propose that by altering prefrontal processes, inflammation weakens the regulatory influence that the ERN and CEN have on limbic reactivity, thus heightening negative, and lowering positive affect. In line with this view is evidence that lower rsFC in the ERN and CEN are associated with dysphoria, depression, and anxiety(29,31). We next propose that reduced regulatory strength predisposes individuals to high-risk, proinflammatory behaviors like smoking, drug use, and high fat diets, in part, to self-medicate dysphoria. If the inflammation triggered by these behaviors spreads to the brain, it could establish a positive-feedback circuit, whereby reduced regulatory strength facilitates proinflammatory behaviors, which, in turn, further reduces prefrontal regulatory strength. When combined with evidence that inflammation elevates threat-, and reduces reward-related brain function(13–17), this positive-feedback circuit could overtime engender vulnerability for both emotional and physical health problems.

Study 2 extends animal research by examining the relationship between rsFC and tonic levels of classical monocytes. Although inflammatory cytokines are a principal channel for immune-to-brain signaling(10–12,61), recent work in rodents highlights classical monocytes as a key leukocyte sub-population in this crosstalk(5). To date, no studies have examined how these cells relate to human brain function. In line with prediction, higher counts of classical monocytes were associated with lower rsFC in both the ERN and CEN. Paralleling the animal literature, these associations were specific to the classical monocyte population, as there were no significant associations between other leukocyte subpopulations and rsFC in the ERN and CEN. Importantly, classical monocytes are mobilized into circulation when mice are subjected to chronic social stress, and amplify inflammatory signaling in brain regions involved in emotion processing and regulation(6,50). This chain-of-events appears to be critical to the emergence of anxiety, as stressed mice show minimal anxiety-like behavior if classical monocytes are prevented from trafficking into the brain(6,50). Taken together, this suggests that the trafficking of classical monocytes to the brain, and in particular to prefrontal regulatory systems, may be involved in the pathogenesis of anxiety and stress-related disorders in humans. Future research is needed to test this claim.

The present paper replicates the association between higher scores on the inflammatory biomarker composite and lower rsFC in the ERN across two independent samples of African-American youth (12–14 years old) and young adults (25 years old). This suggests

the linkage between inflammatory signaling and ERN activity is stable across development, and may reflect a preclinical biomarker for psychiatric symptoms which frequently emerge during adolescence(48). It is noteworthy that CEN activity was only associated with inflammatory signaling in Study 2. While the ERN and CEN share some common regulatory processes, there are distinctions across these networks. For example, while the CEN involves connections from the prefrontal cortex to posterior portions of the parietal cortex subserving higher-order attention, the ERN projects to the somatomotor area and precentral gyrus, which are implicated in behavior inhibition and motor control(31,69). One possibility is that ERN, as compared to CEN, regulatory processes are more reliably associated with inflammatory signaling across development (i.e., youth to young adulthood). A second possibility is that methodological differences account for the inconsistent results. Due to financial and feasibility constraints, Study 1 did not implement an overnight fast prior to blood draw, or restrict blood draws to a set time of day, both of which affect the reliability of inflammatory markers(70,71). Thus, further research is needed to better understand the reliability of CEN-inflammation associations across development.

Contrary to prediction, there was no relationship between inflammation and rsFC in the aSN. Task-based fMRI paradigms may be required to provoke the required variation in salience processing to assess its relationship with inflammatory signaling. Future research should test this possibility. We predicted the null association between inflammatory signaling and DMN activity because it was not apparent how variations in self-referential cognition might relate to inflammation. We analyzed DMN connectivity to assess for specificity between inflammatory signaling and other rsFC networks. Collectively, our findings suggest that inflammation most strongly relates to intrinsic brain networks implicated in emotion regulation and executive control. However, given that DMN abnormalities are common in neuropsychiatric disorders such as depression(29), future research should examine the relationship between DMN connectivity and inflammatory signaling in clinical samples.

The studies in this paper should be interpreted in the context of their limitations. First, the cross-sectional, observational nature of their designs preclude inferences about causality. A longitudinal study tracking rsFC and inflammatory signaling across development is needed. A study like this could test for the presence of the proposed positive-feedback circuit between inflammation and prefrontal regulatory strength, and answer mechanistic questions about how such a circuit might develop. Next, the present studies examined neuroimmune signaling in participants who, for the most part, were in good health. This is important for identifying neuroimmune profiles that predate illness onset and medication regimens. This restrictive eligibility criteria, however, precludes our ability to examine the relationship between neuroimmune signaling and emotional and physical health problems, which should be examined in future research. Finally, the present studies focused exclusively on African-American participants given blacks' higher exposure to inflammation-triggering stressors, including childhood adversity, racial discrimination, and economic hardship(43–45). Future research should examine whether our results extend to non-African-American participants.

Meanwhile, the present studies advance knowledge on neuroimmune signaling in humans. In particular, these studies report that higher inflammation, as measured at multiple levels of

analysis (inflammatory biomarkers, classical monocytes), is associated with lower functional connectivity in intrinsic brain networks implicated in emotion regulation and executive control. These findings have implications for understanding the pathogenesis of emotional and physical health problems, and the generation of neuroimmunological interventions for targeting these problems.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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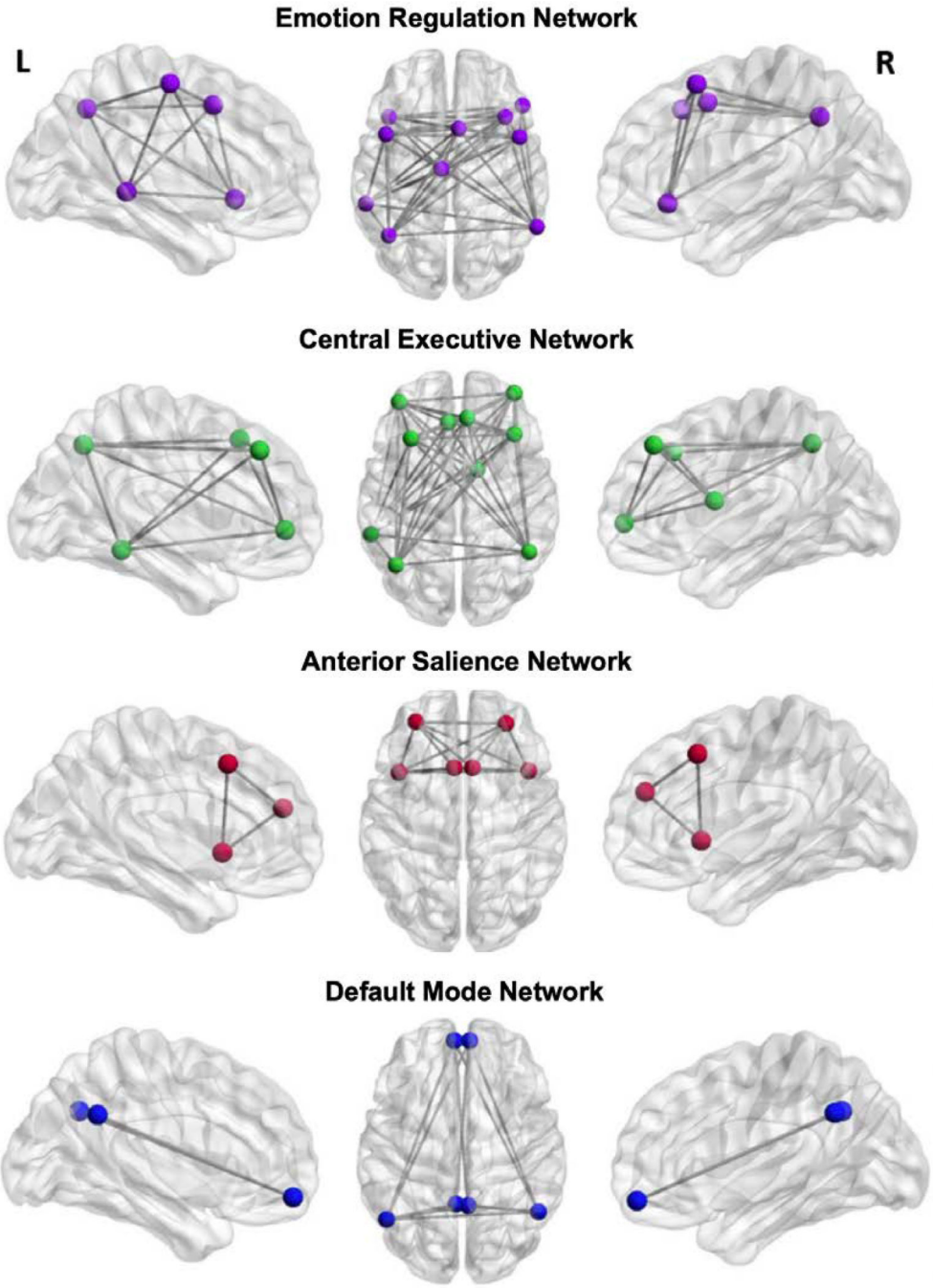

Figure 1.

Axial and both left and right hemisphere sagittal views of regions-of-interests (ROIs) for the resting state functional connectivity networks. For each region-of-interest (i.e., node) within a network, we placed a 5mm sphere around the coordinates of peak activation for each discrete cluster separately within the left and right hemisphere masks.

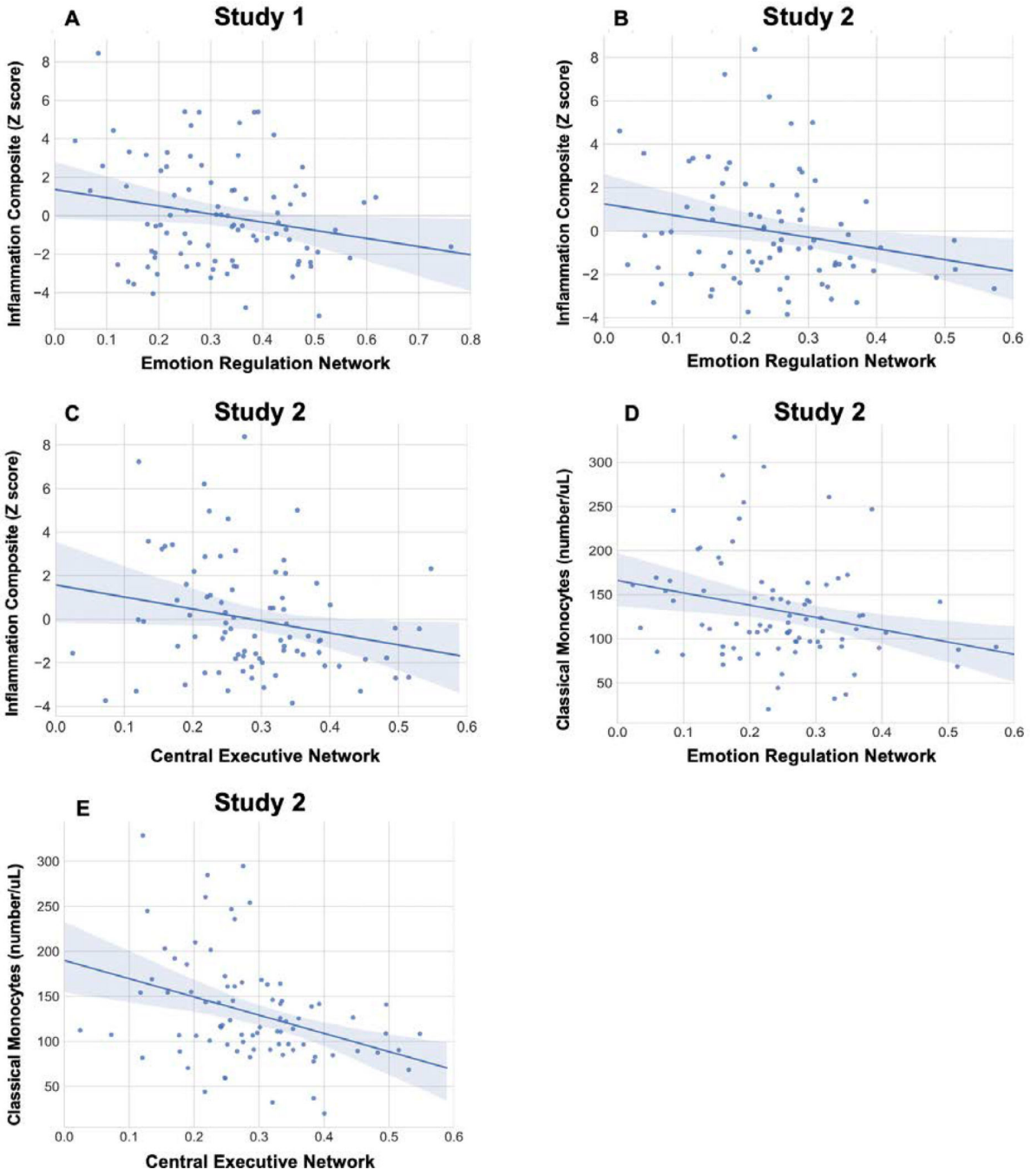

Figure 2.

Relationships between resting state functional connectivity (rsFC) in the emotion regulation and central executive networks with composite inflammation score (CRP, IL6, IL10, TNFα) and classical monocytes. Confidence intervals are 95%.

Table 1.

Regions-of-Interest for the Resting State Networks.

Network	MNI Coordinates (x, y, z)	Label
Emotion Regulation Network (ERN)	−06 14 58	L somatomotor area
	−42 22 −06	L inferior frontal gyrus
	−44 10 46	L precentral gyrus
	−58 −38 −02	L middle temporal gyrus
	−42 −60 44	L angular gyrus
	06 14 58	R somatomotor area
	50 30 −08	R inferior frontal gyrus
	48 08 48	R precentral gyrus
	38 22 44	R middle temporal gyrus
	60 −54 40	R angular gyrus
Central Executive Network (CEN)	−42 −63 46	L inferior parietal lobule
	−32 23 49	L middle frontal gyrus
	−40 48 −01	L middle frontal gyrus
	−59 −42 −12	L middle temporal gyrus
	−07 34 43	L medial frontal gyrus
	38 26 42	R middle frontal gyrus
	48 −54 47	R inferior parietal lobule
	38 54 01	R middle frontal gyrus
	13 02 14	R caudate
	06 37 46	R medial frontal gyrus
Anterior Salience Network (aSN)	−06 17 47	L dorsal anterior cingulate cortex
	−31 47 22	L middle frontal gyrus
	−42 14 −03	L anterior insula
	06 17 47	R dorsal anterior cingulate cortex
	28 46 26	R middle frontal gyrus
	−42 14 −03	R anterior insula
Default Mode Network (DMN)	−04 −52 32	L posterior cingulate cortex
	−05 55 −13	L ventromedial prefrontal cortex
	−49 −62 34	L temporoparietal junction
	04 −53 35	R posterior cingulate cortex
	05 55 −13	R ventromedial prefrontal cortex
	50 −57 36	R temporoparietal junction

Note: L = left. R = right. MNI = Montreal Neurological Institute standardized space. For each region-of-interest (i.e., node) within a network, we placed a 5mm sphere around the coordinates of peak activation for each discrete cluster separately within the left and right hemisphere masks.

Table 2.

Hierarchical multiple regression analyses of the relationship between resting state functional connectivity (rsFC) and the composite inflammation score (CRP, IL6, IL10, TNFα) controlling for sex in Study 1.

		Inflammation Composite	
	B	***t*- score**	**p**
Emotion Regulation Network (ERN)	−.21	−2.00	.05
Central Executive Network (CEN)	−.14	−1.3	.20
Anterior Salience Network (aSN)	−.15	−1.44	.15
Default Mode Network (DMN)	.07	.63	.53

Note: Separate regression analyses were conducted to examine the relationship between composite inflammation score and each of the resting state networks.

Table 3.

Hierarchical multiple regression analyses of the relationship between resting state functional connectivity (rsFC) and inflammatory variables controlling for sex, age and pubertal status in Study 2.

		Inflammation Composite			**Classical Monocytes**			**Non-Classical Monocytes**	
	B	***t*-score**	**p**	**B**	***t*-score**	**p**	**B**	***t*-score**	**p**
ERN	−.23	−2.07	.04	−.25	−2.20	.03	−.16	−1.40	.17
CEN	−.27	−2.42	.02	−.37	−3.38	.001	−.19	−1.68	.10
aSN	.09	.72	.48	−.17	−1.56	.12	−.02	−.15	.88
DMN	−.09	−.74	.46	−.18	−1.62	.11	−.05	−.47	.64
		Lymphocytes			**Total White Blood Cells**				
	B	***t*−score**	**p**	**B**	***t*−score**	**p**			
ERN	−.04	−.39	.70	.03	.22	.82			
CEN	−.09	−.86	.39	−.08	−.70	.49			
aSN	−.10	−.90	.37	−.08	−.75	.46			
DMN	−.02	−.19	.85	.02	.14	.89			

Note: Separate regression analyses were conducted to examine the relationship between inflammatory variables and each of the resting state networks. ERN = emotion regulation network; CEN = central executive network; aSN = anterior salience network; DMN = default mode network.