FROM INEQUALITY TO INFLAMMATION: EXPLORING INTERNAL AND EXTERNAL CONTRIBUTIONS TO AFFECTIVE PROCESSING

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ABSTRACT

Gabriella M. Alvarez: From inequality to inflammation: Exploring internal and external contributions to affective processing
(Under the direction of Keely Muscatell)

From influencing our social interactions to molding our physical and mental health, how our brain processes affective stimuli plays a crucial role in healthy human functioning. Utilizing results from 3 unique studies, the current dissertation aims to contribute empirical support for newer theoretical assertions that affective processing is significantly influenced by prior as well as internal physiological information to support allostasis. In Chapter 2, I explore how one's contextual history may differentially shape how the brain processes affective information by examining the link between socioeconomic position and efficiency within the allostatic interoceptive network. In Chapter 3, I explore inflammation as one source of physiological information that can influence affective processing. In Chapter 4, I examine how shifting inflammation may alter affective processing via changes in motivated behavior. This dissertation closes with a synthesis of the studies discussed and a discussion of 3 future studies that aim to respond to the remaining outstanding questions.

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CHAPTER 1: OVERALL INTRODUCTION

Affective processing plays a crucial role in shaping diverse aspects of the human experience. From influencing our social interactions to molding our physical and mental health, how our brain processes affective stimuli plays a crucial role in healthy human functioning. Understanding how the brain attends to affective, or negative, positive, and/or arousing, stimuli provides insight into the neural mechanisms that govern our emotional experiences and how they relate to various aspects of our lives, such as decision-making, cognitive function, and social behavior.

Given affective processing's broad relevance, neuroscientists have been pursuing empirical and theoretical questions regarding the neurobiological underpinnings of affective processing. Recently, a consistent idea recapitulated by numerous researchers is that the brain functions in a predictive manner (Rao & Ballard, 1999; Friston et al., 2006; Bar, 2009; Friston, 2010; Barrett & Simmons, 2015). Rather than viewing the brain as reactive to stimuli, these newer frameworks propose that the brain is predictive in nature, updating based not only on new inputs but also prior information and internal physiological signals. This paradigm shift is especially influential for understanding affective processing, as it further clarifies how the brain processes affective stimuli (Barrett, 2017). This provides a useful framework for examining how the brain anticipates and generates affective responses, how prior experiences shape affective processing, and how internal physiological signals influence the interpretation and valuation of affective stimuli. Building upon this perspective of the brain as predictive, the current

dissertation aims to contribute empirical support for newer theoretical assertions that affective processing is significantly influenced by prior as well as internal physiological information.

Allostasis: A neurobiological framework for understanding affective processing

As the central organ enervated by all other body systems, the brain is thought to manage the metabolic needs of the organism in a process called allostasis (Sterling & Eyer, 1988). Allostasis is defined as the dynamic process through which the brain predicts and coordinates physiological changes (such as metabolic, autonomic, neuroendocrine, and immune responses) to adapt to current and future environmental challenges, ultimately supporting the organism's survival, growth, reproduction, and movement (Sterling, 2004; McEwen & Stellar, 1993; Picard et al., 2018). Through the process of allostasis, the brain is continuously monitoring and integrating information from the external environment and the internal body, as well as adjusting its responses to maintain stability. While several theories about the role of the brain in allostasis have emerged, specifics regarding the regions and set of networks that may underlie this fundamental process remain underspecified. Recent work by Kleckner et al., (2017) has proposed the existence of a large-scale brain system, or the allostatic interoceptive network (AIN), that primarily predicts and regulates physiological systems in the body. The AIN is composed of the salience and default mode intrinsic networks and a set of subcortical regions (i.e., central nucleus of the amygdala and regions within the ventral and dorsal striatum) and has been shown to subserve visceromotor regulation and interoceptive ability (Kleckner et al. 2017). Future work is needed to further examine the function of AIN to shed light on how the brain may guide representations of affective cues and regulate the physiological states of the body.

Affective processing has a significant role in allostasis, as affect is considered to originate from and contribute to the brain's predictions regarding physiological regulation (Barrett, 2017).

This is partly because all behaviors, including affective and cognitive functions, require metabolic energy in addition to our baseline energy expenditure (Magistretti & Allaman, 2015). Moreover, certain behaviors and affective situations entail higher metabolic costs compared to others, such as a tense social confrontation versus a relaxed moment on the couch. Perceiving a threatening affective situation can therefore trigger physiological responses that increase the mobilization of metabolic resources to support the cognitive resources to cope (Picard et al., 2018). Meanwhile, positive affective experiences like relaxing on the couch with a close other can serve to enhance immune function (Muscatell & Inakagi, 2021) further supporting allostatic processes. In sum, affective processing emerges as a crucial component of allostasis, contributing to the brain's predictions and regulation of physiological responses.

The necessity of prior experiences for the predictive brain

One of the primary ingredients used for predictive processes in the brain includes an individual's experiential history. In the service of maintaining allostasis, the brain heavily relies on prior experiences to make predictions that help to minimize the potential cost of surprise (Friston et al., 2006; Friston et al., 2010). Much of the early work providing convincing evidence of this idea centers around the study of vision (e.g., Summerfield et al., 2009; Alink et al., 2010; Enns & Lleras, 2008), where the brain has been found to capture and store statistical regularities in sensory-motor patterns to form stored representations (Bar, 2003). As Bar (2009) originally argued, the brain uses these stored representations to identify analogies or associations with the incoming stimuli to answer the question "what is this like?" These stored representations are then instantaneously used by the brain to predict the incoming visual inputs within the context of the environment.

Similar predictive processes have been extended beyond vision to affective processing (Barrett & Bar, 2009; MacCormack & Lindquist, 2019; Fugate, MacDonald, & O'Hare, 2019; Siegel, Wormwood, Quigley, & Barrett, 2018). These studies suggest that affective processing is uniquely integral to the predictive function of the brain as it helps to guide perception and behavior by reducing ambiguity to make good sense of the current environment (Siegel et al., 2018; Wormwood, 2018; Barrett & Bar, 2009). This argument is supported by several studies demonstrating the "affective misattribution effect" whereby participants tend to differentially identify the same neutral face as more happy or angry depending on the (positive or negative) affective information presented before the face (Weisner & Brosch, 2012). Overall, the integration of prior knowledge is a critical process that underlies the brain's predictive function, enabling individuals to navigate a constantly changing environment.

Notably, the prior information that the brain references in the process of prediction may extend much further than those that can be probed in an experimental session. For example, several studies have explored the role of early adversity on the neurobiological mechanisms underlying affective processing. Across human and rodent models, exposure to threatening physical abuse profoundly influences the ways individuals perceive and interpret affective stimuli and has been found to produce hypersensitivity to negative and threatening stimuli (Petchel & Pizzagalli, 2010). However, childhood adversity is not the only type of life experience that may significantly alter affective processing and influence the nature of the information that individual brains receive.

Socioeconomic position is another life experience that can also potentially influence affective processing (Muscatell, 2018). Indeed, exposure to resource scare environments (Oshri et al., 2019) and differences in social norms and expectations (Kraus et al., 2012) can all

influence the type of experiences an individual has and the resulting predictions that that brain may make. This is especially true for individuals in a lower socioeconomic position who comparatively lack access to resources (e.g., quality health care and education, food, financial opportunities). Prior work has found that this environmental context produces greater exposure to unpredictable and negative affective experiences (Grzywacz et al., 2004; Steptoe et al., 2003) resulting in a state of chronic stress (Baum et al., 2003). These chronic negative affective experiences, arising from the individual's lower socioeconomic context, may indeed alter how the brain makes predictions in its environment and regulate metabolic resources to optimize stability in this context (McEwen & Gianaros, 2011). In this example, the brain may begin to favor predictions that increase sensitivity to ambiguous and threatening information to best meet the demands of the environment. Despite the profound relevance socioeconomic position might have on shaping one's psychosocial experiences, there are very few studies examining the role that socioeconomic position may have on general affective processing. Thus, to fill this gap, the first study in the dissertation attempts to address this by exploring how one's socioeconomic position may influence the function of the allostatic interoceptive network (AIN) when processing affective information.

To explore the association between one's experiential history and affective processing, I examined the link between socioeconomic position and neural responses to positive and negative affective stimuli in study 1. Although associations between socioeconomic position and affective processing have been examined before, prior studies in this area have focused on reporting associations for negative social stimuli and has relied on region-of-interest (ROI) analyses focused on the amygdala and mPFC (Gianaros et al., 2008; Muscatell et al., 2012; Kim et al., 2017; Swartz et al., 2017; Gonzalez et al., 2015; Javanbakht et al., 2015; Muscatell et al., 2016).

Moving beyond ROI analyses is important given increasing acknowledgement that brain regions do not act in isolation. Rather, brain regions function together as coordinated components of broadly distributed networks that underlie complex psychological functions (McMenamin et al., 2014; Pessoa & McMenamin, 2017; Bassett & Sporns, 2017). In this study, we aimed to expand work in this area to include positive affective stimuli and conducted a network-based analysis.

The necessity of internal physiological signals for the predictive brain

The second ingredient useful for predictive processes in the brain includes the integration of internal physiological information from the body (Barrett, 2017). Afferent signals from the body to the brain help to provide information about the metabolic state of different physiological systems in the body (Critchley, 2004). These physiological signals from the body are used by the brain to generate predictions and update the brain's internal model of its metabolic needs (Barrett, 2017; Craig, 2015) because they provide valuable information about an individual's available metabolic resources. Importantly, afferent signaling from the body serves as a mechanism by which physiological changes can influence psychological states, ultimately guiding behavior (e.g., conserve energy, seek out new resources; MacCormack & Muscatell, 2019). For example, recent work found that the physiological state of hunger was associated with intensified affective processing. Specifically, those who reported greater levels of hunger were more likely to perceive and experience ambiguous situations as negative (MacCormack & Lindquist, 2019). These findings suggest that metabolic signals from the body can influence the nature and intensity of affective experiences.

The immune system is one such physiological system that influences affect. The immune system has humoral, cellular, and neural pathways to directly innervate the central nervous system (reviewed in Capuron & Miller, 2011). As an adaptive defense mechanism, the

inflammatory response is activated when harmful pathogens are present, helping the body heal (Furman et al., 2019; Franceschi & Campisi, 2014). This process is driven by proteins called pro-inflammatory cytokines that send signals to the brain to trigger an inflammatory response. While it is commonly known that local inflammatory responses occur when the body is injured or infected, inflammation can also exist in a more systemic way that often goes unnoticed (Danzter et al., 2008). Even in the absence of physical injury or infection, inflammation can still occur in response to psychological experiences and psychosocial stressors (Dickerson et al., 2009; Irwin & Cole, 2011).

Although shifts in the activation of the immune system are not always perceptible, there is some evidence that inflammation plays a vital role in altering affective processing. One of the most well-studied examples of this involves the psychosocial changes that occur in response to inflammation called "sickness behaviors" (Hart, 1988). Sickness behaviors, such as fatigue, anhedonia, and social withdrawal, are important for shifting an organisms' priorities to facilitate recovery and restoration (Aubert, 1999). These sickness behaviors are not simply a consequence of a degraded state but also serve to encourage the individual to prioritize metabolic resources for supporting the immune system rather than other physiological processes (Hennessy et al., 2014).

In light of these known effects, there remain outstanding questions regarding the link between inflammation and more general affective processing. For instance, prior studies in this area have primarily utilized acute inflammatory manipulations (Eisenberger et al., 2010; Eisenberger et al., 2009; Harrison et al., 2009); as such, we have limited knowledge about the association between chronic, low-grade inflammation and affective processing. While acute manipulation produces a robust pro-inflammatory response comparable to levels during illness,

lower-level fluctuations in pro-inflammatory signaling is more common and perhaps more influential in shaping day-to-day changes in affective processing. Additionally, prior studies in this area have focused on examining responses to negative affective stimuli (e.g., Inagaki et al., 2012; Kullmann et al., 2013; Muscatell et al., 2016) and monetary reward tasks (e.g., Capuron et al., 2012; Eisenberger, Berkman, et al., 2010), which has left gaps in knowledge regarding the association between inflammation and neural responses to positive, non-monetary affective stimuli. Therefore, in study 2 of this dissertation, I examined the association between low-grade inflammation and neural activity to a variety of positive and negative scenes.

In study 2 of this dissertation, I explored links between levels of systemic inflammation and neural activity to both negative and positive stimuli among a community sample of older adults. Although associations between inflammation and affective processing have been examined before, prior studies in this area focused on one valence category (i.e., negative or positive; Inagaki et al., 2012) and following acute changes in inflammation at much higher levels (Capuron et al., 2012). Here, I aimed to examine whether prior associations between inflammation and neural activity to affective stimuli persisted at lower, every-day levels of inflammation and in response to a larger variety of stimuli (i.e., beyond negative faces and monetary gains). Overall, analyses from this study suggested that systemic levels of inflammation may be most relevant for understanding affective reactivity to positive affective stimuli.

Consequences of affective processing for behavior

The process of allostasis does not solely serve to influence perception and physiological processes at a subconscious level. Critically, action serves an important role. Satisfying hunger or thirst, for instance, necessitates the individual's active engagement with the external world

(Pezzulo et al., 2015). While at a basic level, human actions support allostasis by obtaining resources to meet metabolic needs, humans are capable of performing a wide array of more complex behaviors. These complex behaviors, or motivated behavior, are often in the pursuit of goals to not only support primary survival goals but also secondary goals like social connection and personal aspirations. Affective processing plays an important role in guiding motivated behavior by influencing the salience and motivational value assigned to different stimuli (Berridge, 2004). Therefore, affective processing can drive the selection of behaviors to meet physiological and psychological needs. Motivated behavior and allostasis are intricately linked via affective processing (Touroutoglou et al., 2019) as the brain continuously monitors and adjusts allostatic responses while simultaneously facilitating metabolic and cognitive resources to achieve goal-directed behavior.

The relationship between motivated behavior and allostasis is evident in the context of the immune system, particularly in response to inflammation-induced metabolic changes. Inflammatory signaling molecules play a crucial role in conveying information related to changes in immunometabolism (Treadway et al., 2019), which have a direct impact on available energy resources in the body. This occurs because inflammation requires a significant amount of metabolic resources. In cases of infections or injuries accompanied by inflammation, the immune system's energy expenditure can surge up to 60%, making it the primary consumer of energy (Straub, 2017). This metabolic shift is aimed at mobilizing glucose urgently, fueling a robust protective response against perceived threats, which results in a redirection of resources from growth, reproduction, and related behaviors (Wang et al., 2019). Similarly, chronic low-grade inflammation observed in conditions such as stress or metabolic disorders can further elevate daily energy expenditure by approximately 30% (Straub, 2017). Given the metabolic expense

supporting inflammation, afferent signals notifying the brain of these shifts can serve to alter affective processes and alter the salience and motivational value of different stimuli to support allostasis. Indeed, studies have found that inflammation may alter the brain's estimation of reward value and guide the allocation of effort and energy expenditure via changes in the mesolimbic dopaminergic system (Lasselin et al., 2017; Treadway et al., 2019).

Although recent years have seen a rise in the number of studies exploring the link between inflammation and motivated behavior, there exist three significant gaps in the literature. First, much of the research exploring the relationship between inflammation and motivated behavior has been conducted in preclinical rodent studies (for review see Vichaya & Dantzer, 2018). While preclinical studies provide more causal insights than are ethically possible to assess in humans (Heim & Nemeroff, 2001), there are limitations in generalizability and validity with such models. Thus, translating these findings to human samples is crucial to fully understand the impact of inflammation on motivated behavior in humans. Second, the limited work exploring links between inflammation and motivated behavior in humans, have largely focused on clinical samples of individuals experiencing depression (for review see Stanton, 2019). However, the association between inflammation and motivated behavior is not limited to individuals with depression (Boyle et al., 2019; Kuhlman et al., 2018) and is more generally associated with shifts in basic cognitive and neurobiological processes regardless of diagnoses. Finally, the experimental work that has been conducted in non-clinical samples have primarily relied on monetary-based reward tasks (Capuron et al., 2012; Eisenberger et al., 2010). Monetary rewards do not represent the full breadth of positive motivational stimuli and work examining links to other rewarding stimuli (e.g., primary rewards, social rewards) is needed to further explore the internal and external validity of the association. Therefore, an important expansion to this area is

to explore links between inflammation and behavioral changes in response to other types of non-monetary rewards. In study 3 of the dissertation, I set out to fill some of these gaps by experimentally probing the relationship between motivated behavior and inflammation.

In the final study of the dissertation, I shifted metabolic states in the body by inducing low-grade levels of inflammation by administering the influenza vaccine to participants to see how this affected their behavior on a reward task. Notably, the study was conducted with a non-clinical sample of humans who also engaged with positive, non-monetary stimuli to explored effects beyond monetary rewards. Additionally, this study allowed me to explore whether the association between inflammation and neural function was specific to affective processing or also implicated in other neurocognitive processes like response inhibition, one facet of cognitive function. Fifty-five young adult participants were administered the influenza vaccine to elicit a low-grade inflammatory response. The morning before and approximately 24 h after the vaccine, participants provided a blood sample to measure interleukin-6 (IL-6) and completed a rewarded go/no-go task to measure response inhibition. The results obtained here may have implications for understanding the mechanisms linking inflammation to affective and cognitive behaviors.

The current studies

The current dissertation aims to contribute empirical support for newer theoretical assertions that affective processing is significantly influenced by prior as well as internal physiological information to support allostasis. The first study (chapter 2) explores how one's contextual history may differentially shape how the brain processes affective information by examining the link between socioeconomic position and the efficiency within the allostatic interoceptive network. In study 2 (chapter 3), I explore inflammation as one source of physiological information that can influence affective processing. Then, in study 3 (chapter 4), I

examine how shifting inflammation may alter affective processing via changes in motivated behavior. By investigating how affective processing integrates prior external information (study 1) and internal physiological information (studies 2 & 3), the current set of studies seeks to enhance our understanding of the constituent elements the brain may utilize to generate affective experiences and guide behavior.

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CHAPTER 2: LOWER SOCIOECONOMIC POSITION IS ASSOCIATED WITH GREATER ACTIVITY IN AND INTEGRATION WITHIN AN ALLOSTATIC-INTEROCEPTIVE BRAIN NETWORK IN RESPONSE TO AFFECTIVE STIMULI[1]

Introduction

One's socioeconomic position (SEP) (i.e., income, educational achievement) can profoundly shape an individual's life (Krieger et al., 1997; Krieger et al., 2005). Specifically, SEP has been consistently tied to physical and mental health such that individuals with lower SEP have higher rates of cardiovascular disease (Kaplan & Keil, 1993; Galobardes et al., 2006) and depression (Lund et al., 2010), worse cancer prognosis (Zheng et al., 2021), and have shorter lifespans (Seeman et al., 2004). Given these well-established links between SEP and important life outcomes, recent work has begun to investigate the association between SEP and neural functioning to understand how SEP "gets under the skull" to influence health and well-being (Farah, 2017; Hackman et al., 2010; McEwen & Gianaros, 2010; Muscatell, 2018; Yaple & Yu, 2020). To date, most of this work has been conducted in children and young adults, and has primarily focused on examining associations between SEP and activity in a limited set of regions (i.e., amygdala, medial prefrontal cortex). As such, important questions remain about the association between SEP and neural functioning during later periods of development, such as midlife when diverging health trajectories due to SEP begin to emerge. Further, our understanding of how SEP is related to activity and connectivity within larger neural systems

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(i.e., beyond individual regions) engaged during affective processing is limited. The present study addresses these critical gaps in our current knowledge by examining associations between SEP and network-wide activity and connectivity while processing affective information among a sample of mid- to late-life adults.

There are good theoretical reasons to expect that SEP might shape neural responses to affective information. Namely, individuals with lower SEP report greater exposure to daily stressors (Almeida et al., 2005; Grzywacz & Almeida, 2008; Grzywacz et al., 2004; Surachman et al., 2019) and unpredictable threats (Cundiff et al., 2020). This is often accompanied by a lack of resources to cope with the greater stress/threat that they experience (Gallo et al., 2005; Gallo et al., 2009; Taylor & Seeman, 1999). These negative affective experiences are theorized to generate a perception of generalized unsafety for those with lower SEP, ultimately promoting a chronically hyperactive stress response (Brosschot et al., 2016, 2018). Thus, heightened exposure to negative affective experiences among individuals with lower SEP likely alters how the brain responds to affective information.

Indeed, prior literature provides some evidence that SEP is related to neural responses to affective cues. Specifically, several studies have reported an inverse relationship between SEP and neural responses to negative social cues, such that children and young adults with lower SEP demonstrate heightened activity in regions associated with affective processing, including the amygdala (Gianaros et al., 2008; Muscatell et al., 2012; Javanbakht et al., 2015; Kim et al., 2017; Swartz et al., 2017) and medial prefrontal cortex (mPFC; Muscatell et al., 2012, Gonzalez et al., 2015; Javanbakht et al., 2015; Muscatell et al., 2016), compared to those with higher SEP. While this literature provides foundational evidence relating SEP to neural responses to affective information, it is not without limitations. Most of this work has examined neural responses to

facial expressions of negative emotion (e.g., fear, anger), which, while important, do not represent the full breadth of stimuli and experiences that can elicit affective responses. Further, many studies in this area have relied on region-of-interest (ROI) analyses primarily focused on the amygdala and mPFC, thus limiting our understanding of associations between SEP and neural functioning beyond these two regions. Thirdly, this prior work has almost exclusively focused on children and young adults, leaving important questions about the association between SEP and neural functioning during later periods of development unanswered. Given these methodological limitations within the prior literature, the present study focused on exploring associations between SEP and network-wide neural responses to negative and positive affective scenes in midlife and older adults.

In addition to the literature on SEP and neural responses to negative affective stimuli, there is some limited evidence regarding the association between SEP and neural responses to positive affective stimuli. Reactivity to positive stimuli is important to study, as evidence suggests that positive affect is associated with lower morbidity and increased longevity among elderly adults (Cohen & Pressman, 2006) and lower mortality risk among individuals reporting higher levels of stress (Okely et al., 2017). However, few studies have explored associations between SEP and neural activity to positive affective stimuli despite the relevance of positive affect for health. Among the prior studies that have investigated this, two found a positive association between SEP and neural responses to positive stimuli, such individuals with lower SEP showed blunted activity in the amygdala and insula to happy infant faces (Kim et al., 2017) and blunted activity in several subcortical regions (e.g., caudate, hippocampus) to positive scenes (Silverman et al., 2009). Thus, some initial work suggests that individuals with lower SEP may

show diminished activity in regions that encode the salience and value of stimuli in response to positive affective cues like happy babies and pleasant scenes.

Other work on the association between SEP and neural responses to positive affective stimuli has utilized reward processing paradigms, such as the Monetary Incentive Delay (MID) task, wherein participants can earn a monetary reward for responding quickly to stimuli. Research in this area has produced mixed results, such that both positive and negative associations between SEP and neural responses to rewarding stimuli have been reported. For example, one study found that lower SEP is associated with *blunted* activity in a variety of regions, including the mPFC, during monetary reward processing (Gianaros et al., 2011), while two other studies found that lower SEP is associated with *heightened* mPFC activity during monetary reward processing (Gonzalez et al., 2016; Romens et al., 2015). Thus, while the evidence is equivocal regarding the directionality of the relationship between mPFC activity and SEP during the processing of monetary rewards, findings generally suggest that SEP does indeed modulate neural activity to positive and rewarding stimuli. Additional research is needed, however, to help clarify the discrepancies in directionality that have been observed in this area.

Finally, there is currently a paucity of knowledge regarding associations between SEP and neural network configuration during affective processing. This work is needed given growing consensus that brain regions do not act independently and instead communicate via large-scale networks to produce cognitive and affective states (McMenamin et al., 2014; Pessoa & McMenamin, 2017; Bassett & Sporns, 2017). As such, it is critical to examine if there are SEP-related differences in task-based network configuration during affective processing. Thus, another aim of the current study was to provide initial evidence linking SEP to network connectivity while processing positive and negative stimuli.

Two brain networks whose properties may be particularly likely to be modulated by SEP are the "allostatic-interoceptive network" [AIN; (Kleckner et al., 2017; Wei et al., 2020; Kraft & Kraft, 2021; MacCormack & Muscatell, 2019)] and the "executive control network" [ECN; (Rosen et al., 2018; Yaple & Yu, 2020; Rakesh et al., 2021)]. The AIN is composed of the salience and default mode intrinsic networks and a set of subcortical regions (i.e., central nucleus of the amygdala and regions within the ventral and dorsal striatum, such as the periaqueductal gray, parabrachial nucleus, and nucleus of the solitary tract) and has been shown to subserve energy metabolism and visceromotor regulation (Kleckner et al., 2017). The AIN is theorized to jointly observe and anticipate sensations from within the body (i.e., interoception) and the external environment, and manage energy balance across peripheral systems in the body (i.e., allostasis) to prepare to mount the resources needed for a given situation. Connectivity within this network guides perception and action by forming representations of affective cues and regulating physiological states of the body (Craig, 2009; Khalsa et al., 2009; Kleckner et al., 2017). Specifically, the AIN has been linked to responding to threats, HPA axis activity, and sympathetic nervous system mobilization (Gianaros et al., 2008; Xia et al., 2017; Kleckner et al., 2017). Thus, differences in AIN configuration may be a mechanism linking SEP to enhanced reactivity across physiological systems, ultimately leading to poorer health outcomes. Additionally, connectivity of the executive control network (ECN), which interfaces with the AIN (Kleckner et al., 2017) and has been linked to SEP in prior work using resting-state fMRI (Nusslock et al., 2019; Miller et al., 2018), may also be modulated by SEP in response to affective stimuli. Given the potential relevance of these networks to affective processing, the current analyses examined whether SEP was associated with topological properties of the AIN

and AIN+ECN in response to affective stimuli, to establish links between SEP and differences in network configuration.

To address the association between SEP and network configuration of the AIN and ECN, we used graph theory. This technique is a powerful tool for identifying how network organization changes across conditions or individuals (e.g., Park & Friston, 2013; Cohen & D'Esposito, 2016; Shine & Poldrack, 2018). The ability to derive metrics of integration (i.e., the tendency for regions to become highly interconnected) and hubness (i.e., the tendency for a region to be central to information processing) within a network are major advantages to this computational approach, given that integration and hubness have been shown to predict important outcomes (e.g., Sanz-Arigita et al., 2010; Krukow et al., 2019). In the current study, we selected three well-validated metrics commonly used to assess different aspects of network integration. Specifically, we calculated global efficiency to assess network integration in the form of efficient information transfer across the entire graph, participation coefficient to assess across-network connectivity, and betweenness centrality to assess the importance of specific nodes in driving efficient communication within a network. Given past research showing that the amygdala and mPFC are particularly relevant regions for processing affective stimuli and are likely modulated by SEP, we also assessed whether SEP modulated the centrality of these regions while an individual was viewing affective images. Additionally, we explored the betweenness centrality of the insula given its role in dynamically switching between different networks (Sridharan, Levitin, & Menon, 2008).

In sum, while some research suggests that SEP is associated with differential neural activity and connectivity in response to affective stimuli, numerous gaps in our knowledge remain. The current study sought to provide additional insight into the relationship between SEP

and neural functioning by: 1) examining neural responses to both negative and positive affective images, extending prior work that has largely focused on negative facial expressions and monetary reward; 2) exploring associations between SEP and neural activity across the entire brain, thus moving beyond ROI approaches; 3) determining if associations between SEP and the topology of the AIN and ECN brain networks exist, to establish relationships between SEP and neural network configuration in response to affective stimuli; and 4) including a sample of mid- and late-life adults, given that most work in this area to-date has been conducted in youth. To accomplish these objectives, we analyzed differences in neural activity and connectivity to affective images as a function of SEP in a sample of 122 mid- to late-life adults.

Methods

Participants

Data for this paper were drawn from the Midlife in the United States (MIDUS) study, a national study examining the biopsychosocial factors influencing health across the lifespan. For the current study, participants were enrolled in the overall MIDUS Refresher Neuroscience Project that began in 2013. Most participants were recruited via random digit dialing throughout the United States, and, to oversample Black Americans, a subset of participants were recruited via door-to-door solicitation in Milwaukee, WI. Participants were eligible if they lived in the Midwest and able to travel to complete an MRI scan, met MRI inclusion criteria (e.g., no metal implants, no claustrophobia), were right-handed, and had no prior history of a neurological disorder. While 127 individuals enrolled in the fMRI data collection portion of the study, four were excluded for missing fMRI data and one for excessive motion (see fMRI preprocessing for more details). Thus, the final sample included in the current analyses were 122 participants who

were on average 47 years old (SD= 11.82; range = 26 – 72), female (N=67; 55%), and White (N=78, 64%); see Table 1 for complete demographic information.

Table 2.1: *Demographic summary of the study sample (N=122)*

Variable	Count (N)	Percentage (%)
Female (N, %)	67	54.92
Ethnicity: Latin American origin/descent	1	0.82
Race: Asian/Asian American (n, %)	1	0.82
Race: Black (n, %)	36	29.51
Race: Native American or Aleutian Islander (n, %)	1	0.82
Race: White (n, %)	78	63.93
Highest education: No school/some grade school (n, %)	0	0.00
Highest education: Middle school (n, %)	0	0.00
Highest education: Some high school (n, %)	8	6.56
Highest education: GED (n, %)	2	1.64
Highest education: High school (n, %)	17	13.93
Highest education: Some college, no degree (n, %)	19	15.57
Highest education: 3 or more yrs. of college, no degree (n, %)	5	4.10
Highest education: Associates Degree (n, %)	17	13.93
Highest education: Bachelor's degree (n, %)	29	23.77
Highest education: Some Graduate school, no degree (n, %)	3	2.46
Highest education: Master's Degree (n, %)	15	12.30
Highest education: PhD or Professional Degree (n, %)	7	5.74

Procedures

All participants in the study completed an initial interview, a battery of self-report questionnaires, and then a cognitive interview via phone. Once those interviews were completed, participants were eligible to participate in other projects—including the Neuroscience substudy. Participants reported on their education, household income, and other demographic information during the initial eligibility interviews. After meeting eligibility for the Neuroscience substudy, participants were scheduled for an MRI Project visit.

Socioeconomic Position Measure

During the telephone interviews, participants reported their highest level of educational attainment to date. Participants selected from twelve response categories ranging from "no school/some grade school" (category 1) to "PhD, MD, JD, or other professional degree" (category 12). Household income was computed using participant responses to several financial questions. Participants reported on the 12-month income earned by themselves, their spouse/partners, and other adults in their household. Participants also reported income from household social security, government assistance, and any other sources of income. Responses on these items were summed to create a household income variable that represented an estimate of total dollars earned within the participant's household in the past year. For the current analysis, the measures of educational attainment and household income were standardized and combined to form a composite index of SEP (Kraus et al., 2009; Muscatell et al., 2012). Overall, the median education level was category 8, or graduation from a 2-year college, vocational school, or associate degree, and the median household income was $71,500 per year (*M*=$81,171, SD=$59,266). There was substantial variability across the sample for both

education (range = some high school – the attainment of a PhD or other professional degree) and income (range = $0-287,000). Given established associations between neural function and age (MacCormack et al., 2020), as well as statistically significant differences in SEP among males and females [$t(120)= -2.259$, $p=0.026$] and racial groups in our sample [$F(4,117)=6.747$, $p<0.001$], we included age, sex, and race/ethnicity as covariates in all models. This allowed us to improve our ability to assess unique associations between SEP and neural activity and connectivity.

Affective Reactivity Task

During MRI scanning, participants completed a task that involved viewing 30 positive, 30 negative, and 30 neutral images selected from the International Affective Picture System (IAPS; Lang et al., 2008) over the course of three runs (data from which are also published in Grupe et al., 2018). The IAPS images used in the task were matched across valence for luminosity, complexity, and degree of social content. On average, the arousal ratings for the negative ($M= 5.46$, $SD=0.66$) and positive images ($M=5.47$, $SD=0.53$) were greater than those for the neutral images ($M=3.16$, $SD=0.42$).

At the start of each trial in the task, participants saw a fixation cross appear for 1 second, following which an IAPS image was presented for 4 seconds in a pseudorandomized order. No more than two images from the same valence category were presented sequentially. Following each picture was a 2-second inter-stimulus interval in which participants viewed a black screen, and then a neutral face appeared for 0.5 seconds. Using a button box, participants were tasked with indicating whether the person depicted identified as male or female. Following the face presentation, each trial ended with a jittered inter-trial interval between 3.5 and 27.5 seconds ($M=7.5$ seconds) in which participants viewed a black screen. Because the current project

focused on examining neural responses to affective images, the face stimuli were coded as regressors of non-interest. Analyses focus on the 4-second period during which an IAPS image was presented.

MRI acquisition

Neuroimaging data for the current study was acquired using a 3 Tesla scanner (MR750 GE Healthcare, Waukesha, WI) and an 8-channel head coil. First, a T1-weighted anatomical image was collected using a three-dimensional magnetization-prepared rapid gradient-echo sequence (TR=8.2 ms, TE=3.2 ms, flip angle=12 º, field of view=256 mm, acquisition matrix=256 x 256, 160 axial slices, inversion time=450 ms). Next, the blood oxygen level-dependent (BOLD) signal was measured using echo planar imaging (EPI) during the fMRI task. The task consisted of three runs lasting 7 minutes, 42 seconds each for a total of 23.1 minutes of BOLD data. Each EPI scan acquired 40 interleaved sagittal slices that used the following parameters: TR=2,000 ms, TE=20 ms, flip angle=60º, field of view=220 mm, acquisition matrix=96x64, 3 mm slice thickness with 1 mm gap, 231 volumes, and ASSET (Array coil Spatial Sensitivity Encoding) parallel imaging with an acceleration factor of 2.

fMRI preprocessing

Whole-brain neuroimaging data were preprocessed and analyzed utilizing FSL version 6.0.0 (Jenkinson et al., 2012). The analysis pipeline first utilized the fsl_motion_outliers program to identify excessive motion. Task runs with framewise displacement exceeding 0.9 mm for greater than 25% of the volumes were excluded from analysis (N=2; Siegel et al., 2014). For all other runs, single-point outliers were included in each person-level general linear model (GLM). Following outlier detection, preprocessing included motion correction with MCFLIRT, removal

of non-brain voxels with BET, normalization with FLIRT, removal of low-frequency drifts by applying a high-pass filter (100Hz), and spatial smoothing with a Gaussian kernel of 5-mm full width at half maximum.

Analysis Overview

We implemented several computational techniques to examine the association between SEP and neural activity and network configuration while processing affective images. First, we conducted whole-brain regression analyses to explore associations between SEP and neural responses while viewing affective images. Following preregistration for our graph theoretic network analyses (see details here: https://osf.io/5zkxp/), we assessed whether SEP was related to differences in global efficiency (i.e., network integration) within the allostatic-interoceptive network (AIN), as well as a network that combined regions of the AIN and the executive control network (ECN) together into one graph, during affective processing. Next, we examined whether SEP was related to differences in participation coefficient (i.e., between-network integration) between the AIN and ECN during affective processing. Then, we assessed whether SEP was associated with differences in amygdala, mPFC, and insula centrality within the AIN, AIN+ECN, and within the entire brain. Finally, we conducted exploratory (i.e., non-preregistered) analyses to examine whether SEP was related to differences in (1) global efficiency within the ECN, (2) global efficiency across the whole-brain, and (3) participation coefficient across the whole-brain. More details about each specific analysis approach are provided below.

Whole-brain regression analyses

Following preprocessing, a GLM was conducted for each participant and for each run. The individual-level GLMs included regressors that modelled each of the three trial types of interest (i.e., positive, negative, neutral images), and the stimuli of non-interest (i.e., face presentation). The GLMs also modelled motion artifacts (i.e., outliers), as well as each individual's six motion parameters and their derivatives. Higher-level analyses were conducted using FSL FLAME to combine BOLD activation across runs. Then, individual estimates of BOLD activity were included in the group-level random effects models.

Two whole brain regression analyses examined associations between the SEP composite score and neural activity to negative (versus neutral) images, as well as positive (versus neutral) images, while controlling for age, sex, and race/ethnicity. Cluster-level correction ($z>2.3$, $p<0.001$) was applied to identify regions that differentially activated to affective stimuli as a function of SEP. In conjunction with FSL FLAME 1 (Woolrich et al., 2004), the correction parameters used in this study have been found to effectively decrease type II errors (Eklund, Nichols, & Knutsson, 2016).

Betaseries Regressions for Connectivity Analyses & Graph Construction

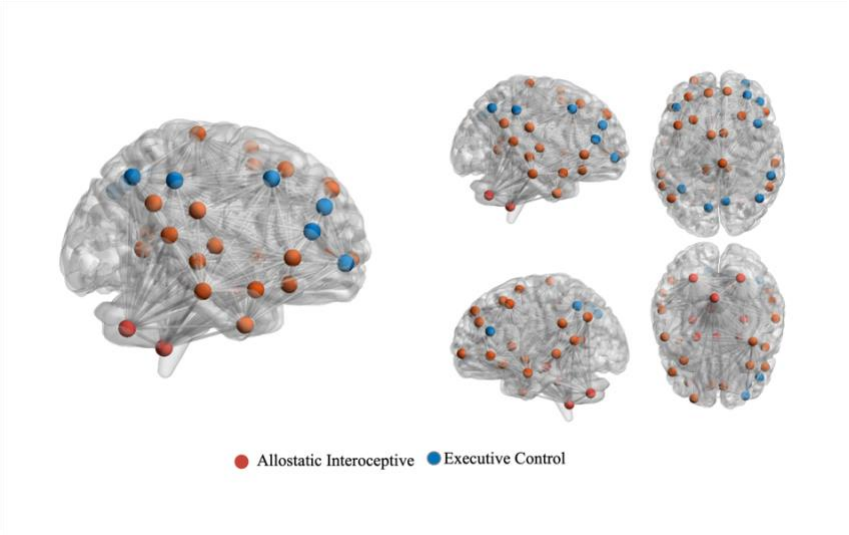
Similar post-processing steps outlined above for the whole-brain activity analyses were implemented for the betaseries regressions to measure connectivity. Additionally, aCompCor (Muschelli et al., 2014) was utilized to derive time series data from white matter and cerebrospinal fluid (CSF). The individual-level GLMs for betaseries regressions included regressors that modeled each of the three trial types of interest (i.e., positive, negative, and neutral images) and one trial type of non-interest (i.e., face presentation). The GLMs also

modeled each individual's six motion parameters and their temporal derivatives, outlier scans (i.e., framewise displacement above 0.9mm or global BOLD signal changes above 5 SD), and time series from white matter and CSF components (i.e., five potential noise components for white matter and CSF; Chai et al., 2012) as additional regressors of non-interest. To examine network topology during negative, positive, and neutral image viewing, betaseries connectivity matrices were extracted from the CONN functional connectivity toolbox (Whitfield-Gabrieli & Nieto-Castanon, 2012). Connectivity matrices were weighted, undirected, and unthresholded. The matrices were then r-to-z transformed and utilized to generate network metrics via the Brain Connectivity Toolbox (www.brain-connectivity-toolbox.net; Rubinov & Sporns, 2010). All network metrics were computed using positive and negative connections. Our analyses focused on four distinct matrices, including an AIN-only graph, an ECN-only graph, an AIN+ECN graph, and a whole-brain graph to derive unique values of integration (i.e., global efficiency) among each set of ROIs. First, an AIN-only graph was constructed by combining 55 cortical, subcortical, and brainstem ROIs as in Kleckner et al., (2017; see Allostatic-Interoceptive Network Connectivity Matrix for greater detail regarding construction of the AIN). Second, an ECN-only graph included the 12 cortical ROIs from the executive control network in the Yeo/Schaefer 7 networks 100 parcellation (Schaefer et al., 2018). Third, the AIN+ECN network graph combined the 55 ROIs of the AIN and the 12 ROIs of ECN. In total, the AIN+ECN graph included 67 ROIs (see Figure 1 for visualization of the network graph). Fourth, a whole-brain graph was constructed by adding all additional cortical ROIs from the Yeo & Schaefer 7 networks 100 parcellation (Schaefer et al., 2018) to the AIN+ECN graph for a total of 119 ROIs.

Allostatic-Interoceptive Network Connectivity Matrix. Regions of interest comprising the AIN were selected a-priori based on past theoretical work outlining the regions that make up

this network (Kleckner et al., 2017, Barett & Simmons, 2015). Because most common parcellations do not encompass subcortical and brainstem regions that are critical to the AIN, we supplemented the existing parcellations by importing masks for the missing ROIs. See Appendix A for the full list and source of regions in the AIN. We combined ROIs from several sources to create the entire hypothesized AIN, which includes the default mode and salience networks, subcortical regions, and several "connector" regions (i.e., regions that are functionally connected to both the default mode and salience networks). Specifically, the ROI masks used to construct the AIN were drawn from all 12 ROIs in the salience/ventral attention network and 24 ROIs in the default mode network from the Yeo/Schaefer 7 networks 100 parcellation (Schaefer et al., 2018); the thalamus, amygdala, and hippocampus from the Melbourne Subcortex atlas (Tian et al., 2020); the periaqueductal gray (PAG) and parabrachial nucleus (PBN) from the Harvard Ascending Arousal Network atlas (Edlow et al., 2012); one ROI of the entire cerebellum from the MNI structural atlas (Collins et al., 1995); the ventral striatum from the Oxford-Imanova Striatal atlas (Tziortzi et al., 2011, 2014); the hypothalamus from the California Institute of Technology subcortical atlas (Pauli, Nili, & Tyszka, 2018); and the nucleus of the solitary tract (NTS) from a 7T *in vivo* parcellation mask (Priovoulos et al., 2019). Together, the AIN graph included 55 ROIs, or nodes.

Figure 2.1. **Visualization of regions of interest, or nodes, that make up the allostatic-interoceptive network** (AIN; pictured in red) and executive control network (ECN; pictured in below). Spheres depict the general location of each ROI mask used in analyses.



Network Topology Metrics to Assess Network Configuration

To assess associations between SEP and network topology during affective image processing, we computed three primary graph metrics of interest: global efficiency, participation coefficient, and betweenness centrality. Global efficiency is a summary measure of integration amongst all nodes within a network. It is a measure of the average inverse distance (e.g., shortest paths) between all nodes in a given graph (Latora & Marchiori, 2001). A graph with high global efficiency is characterized by short path lengths between nodes that support parallel or distributed processing within a system. Participation coefficient and betweenness centrality are node-level metrics that quantify how individual regions are interconnected and influence information transfer across networks of interest. Participation coefficient measures the diversity of between-network connections and quantifies the level of cross-network communication (Guimerà & Nunes Amaral, 2005). A high participation coefficient suggests that a node facilitates inter-network communication. When averaged across nodes within a network, a higher

network participation coefficient signifies greater integration between networks defined in a graph. Betweenness centrality calculates the shortest paths between all pairs of regions in a graph (Brandes, 2001). High betweenness centrality indicates nodes that participate in the largest number of shortest paths. Thus, nodes with high betweenness centrality are characterized as central hubs that influence the flow of information within and between networks. The process for deriving each metric with the current data are discussed below.

Network Integration. Network integration was measured by computing global efficiency separately for the AIN, ECN, AIN+ECN, and whole brain graphs. Participation coefficient was computed between the AIN and ECN to assess how widespread and varied the connections were across our primary networks of interest. Each node was assigned to one of two networks, the AIN (55 ROIs) or the ECN (12 ROIs). Because the participation coefficient measures the strength of a node's connections across networks, each node had a single value denoting integration with the network it was not assigned to. Thus, as a measure of cross-network integration between the AIN and ECN, participation coefficient values for each node were averaged together to provide a measure of average network participation coefficient for the combined AIN+ECN graph. An exploratory analysis also computed participation coefficient for the whole-brain graph across 6 distinct modules (i.e., AIN, ECN, Dorsal Attention, Visual, Somatosensory Motor, and Limbic networks). Measures of global efficiency and participation coefficient were computed on graphs for each of the three affective conditions separately (i.e., positive, negative, neutral).

Nodal Centrality. We calculated betweenness centrality on graphs for each affective condition for the amygdala, mPFC, and insula a) within the AIN graph, b) within the AIN+ECN graph, and c) across the entire brain. When there was more than one ROI for a specific structure

(e.g., bilateral amygdala, multiple sub-ROIs for mPFC), the values for each ROI were averaged together to form a single metric for that region.

Quality Control

Once network metrics were derived for a condition (i.e., positive, negative, and neutral) for each participant, the values were averaged across conditions in order to assess the correlation between connectivity values and mean motion. Importantly, there were no differences in framewise displacement across conditions (M_{neu}= 0.217, M_{neg}=0.221, M_{pos}=0.215; $F(2, 121)$ = 1.066, p=0.346). Condition-specific values were entered into repeated measures ANCOVA models (rm-ANCOVA) to assess the effect of SEP (between-subjects) and condition (within subjects) on each network property, while controlling for age, sex, racial/ethnic identity. Additionally, mean head motion across conditions (framewise displacement; M=0.218) was added into rm-ANCOVAs for the metrics that were significantly associated with motion (i.e., participation coefficient: $r(122) = 0.528$, $p<.001$; betweenness centrality: $r(122) = -0.353$, $p<.001$). To control for the false discovery rate (FDR) due to multiple comparisons testing, the Benjamini-Hochberg procedure was applied (Benjamini & Hochberg, 1995) when comparing results with the same graph metric of interest. Finally, although we outlined a data-driven approach to identify top nodes for exploratory centrality analyses in our preregistration, further reading revealed that this approach was not warranted. To avoid the possibility of spurious results and issues related to circularity (Kriegeskorte et al., 2009), we omit those analyses here.

Results

Association Between SEP and Neural Activity to Negative Images

To examine the relationship between SEP and neural activity to negative images, we ran regression analyses to identify clusters of activity that were significantly associated with the composite measure of SEP while participants viewed negative (vs. neutral) images, controlling for age, sex, and race/ethnicity. This analysis showed a negative association between SEP and activation in three clusters (see Table 2 for full details). Specifically, lower levels of SEP were associated with greater activity in clusters encompassing voxels in the lateral occipital cortex, as well as clusters within midline cortical structures of the AIN (e.g., anterior-, dorsal- and ventral-mPFC, posterior parietal cortex), subcortical structures within the AIN (e.g., thalamus, anterior insula, hippocampus, amygdala, anterior midcingulate cortex) and lateral PFC regions within the ECN (e.g., inferior frontal gyrus [IFG], parietal cortex, middle temporal gyrus); see Figure 2 for visualization. There were no significant clusters of activity positively associated with SEP.

***Figure* 2.2.** Depiction of voxels showing a significant negative association between SEP and neural activity during negative (versus neutral) image viewing, while controlling for age, sex, and racial/ethnic identity (z>2.3, p<0.001).

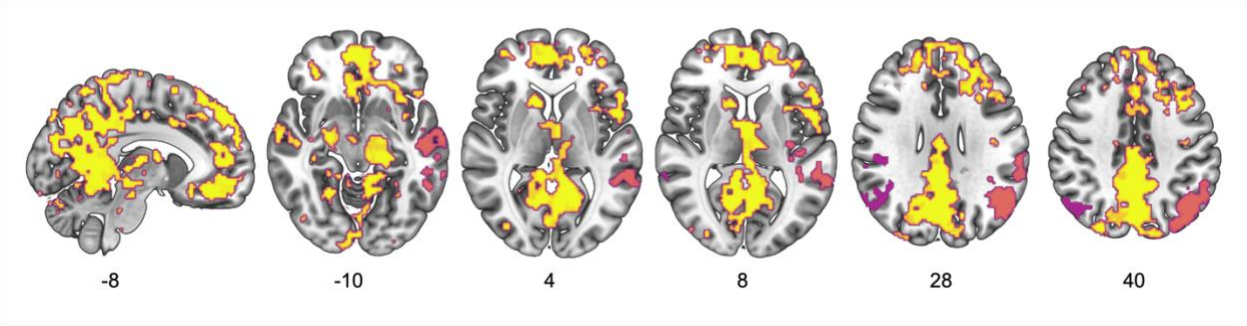


Table 2.2: *Clusters significantly negatively associated with socioeconomic position during negative (versus neutral) image viewing*

Negative vs Neutral (z>2.3, p<0.001)							
Cluster Index	Regions	Hemisphere	Z-max MNI Coordinates			Z-Max	size (k)
			x	y	z		
1	lateral occipital cortex, angular gyrus	R	40	-66	56	4.14	1221
2	lateral occipital cortex, angular gyrus; mid-posterior insula; STS; middle temporal gyrus; angular gyrus	L	-38	-64	38	5.76	3845
3	MPFC (AMPFC, DMPFC, VMPFC); posterior parietal cortex; IFG; thalamus; anterior insula; cerebellum; hippocampus; amygdala; caudate; anterior midcingulate; nucleus accumbens; SMA	L/R	-14	26	54	5.53	29076

Note. STS = superior temporal sulcus; AMPFC= anterior medial prefrontal cortex; DMPFC= dorsomedial prefrontal cortex; VMPFC=ventromedial prefrontal cortex; SMA=supplementary motor area; IFG=inferior frontal gyrus. Analyses controlled for age, sex, and racial/ethnic identity.

Association Between SEP and Neural Activity to Positive Images

To examine the relationship between SEP and neural activity to positive images, we ran regression analyses to identify clusters that were significantly associated with the composite measure of SEP while participants viewed positive (vs. neutral) images, controlling for age, sex, and race/ethnicity. This analysis showed a negative association between SEP and activation in three clusters (see Table 3 for full details). Lower levels of SEP were associated with greater activity in clusters encompassing voxels in posterior regions of the AIN (e.g., precuneus, angular gyrus, posterior cingulate cortex), lateral regions within the ECN (e.g., midfrontal gyrus, IFG), and corticostriatal reward-related regions (e.g., caudate, nucleus accumbens, ventral-mPFC); see Figure 3 for visualization. There were no significant clusters of activity positively associated with SEP.

Figure 2.3. Depiction of voxels showing a significant negative association between socioeconomic position (SEP) and neural activity during positive (versus neutral) image viewing, while controlling for age, sex, and racial/ethnic identity (z>2.3, p<0.001).

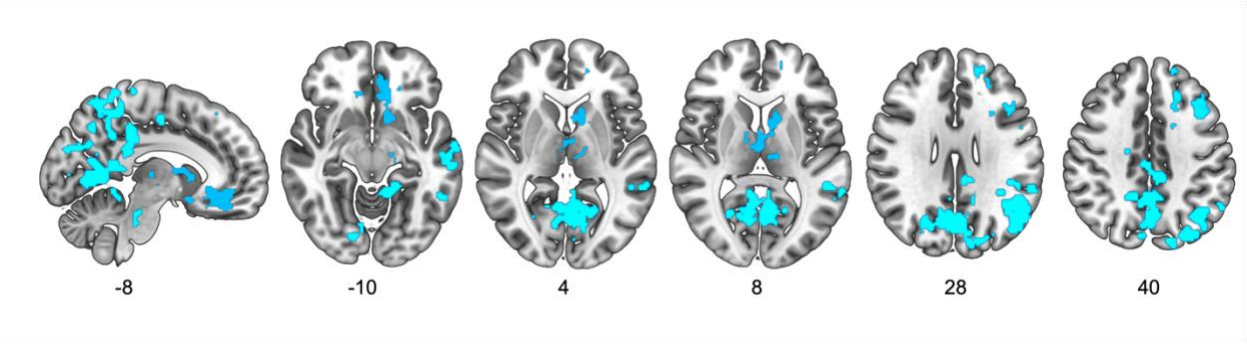


Table 2.3: *Clusters significantly negatively associated with socioeconomic position during positive (versus neutral) image viewing*

Positive vs Neutral (z>2.3, p<0.001)							
Cluster Index	Regions	Hemisphere	Z-max MNI Coordinates			Z-Max	size (k)
			x	y	z		
1	thalamus, caudate, nucleus accumbens, VMPFC	L	-12	12	-10	4.08	1192
2	middle frontal gyrus, SMA, IFG	L	-26	26	52	4.27	1255
3	precuneus, posterior cingulate gyrus, lateral occipital ortex, angular gyrus, middle temporal gyrus	L/R	-36	-64	38	4.34	7942

Note. VMPFC=ventromedial prefrontal cortex; SMA=supplementary motor area; IFG=inferior frontal gyrus. Analyses controlled for age, sex, and racial/ethnic identity.

Association between SEP and Global Efficiency of the AIN, ECN, and AIN+ECN

Next, we assessed whether SEP was related to global efficiency of the AIN, a measure of network integration, during affective processing. A rm-ANCOVA found a main effect of SEP on AIN global efficiency during the task, $F(1, 117) = 7.387$, $p=0.008$. Specifically, as SEP decreased, integration of the AIN increased; see Figure 4A for a scatterplot of the association. There was no significant main effect of image valence on AIN global efficiency (i.e., no significant differences in AIN global efficiency across affective image types), nor was there a significant interaction between SEP and image valence in predicting AIN global efficiency (see Table 4 for full reporting of results).

We also assessed if SEP was related to global efficiency of the combined AIN and ECN graph during affective processing. A rm-ANCOVA found a main effect of SEP for AIN+ECN global efficiency during the task, $F(1, 117) = 6.332$, $p=0.013$. Specifically, as SEP decreased, integration across the entire graph consisting of both the AIN and ECN networks increased (i.e., similar to the result above showing greater integration of the AIN with lower SEP; see Figure 4B for scatterplot of the association). There was no significant main effect of image valence on AIN+ECN global efficiency, nor was there a significant interaction between SEP and valence in predicting AIN+ECN global efficiency (see Table 4 for full reporting of values).

Exploratory analyses also assessed whether SEP was related to global efficiency of the ECN alone during affective processing. A rm-ANCOVA found that there was no significant main effect of SEP or valence on ECN global efficiency, nor was there a significant interaction between SEP and valence in predicting ECN global efficiency (see Table 4 for full reporting of values).

Table 2.4: *ANCOVA table reporting differences in global efficiency and participation coefficient by SEP and valence.*

Predictors	*Sum of Squares*	*df*	*Mean Square*	*F*	*p*	*Partial* η^2
AIN Global Efficiency						
Valence	0	2	0	0.137	0.872	0.001
Valence x SEP	0.002	2	0.001	0.752	0.418	0.006
SEP*	**0.047**	**1**	**0.047**	7.387	**0.008**	**0.059**
Age	0.002	1	0.002	0.256	0.614	0.002
Sex	0.021	1	0.021	3.257	0.074	0.027
Race	0.00003	1	0.00003	0.004	0.947	0
ECN Global Efficiency						
Valence	233.691	2	116.845	0.43	0.651	0.004
Valence x SEP	375.376	2	187.688	0.691	0.492	0.006
SEP	218.102	1	218.102	0.86	0.356	0.007
Age	57.85	1	57.85	0.228	0.634	0.002
Sex	264.667	1	264.667	1.044	0.309	0.009
Race	1.521	1	1.521	0.006	0.938	0
AIN+ECN Global Efficiency						
Valence	0.00004	2	0.00002	0.031	0.969	0
Valence x SEP	0.002	2	0.001	1.775	0.172	0.015
SEP*	**0.022**	**1**	**0.022**	**6.332**	**0.013**	**0.051**
Age	0.008	1	0.008	2.192	0.141	0.018
Sex	0.012	1	0.012	3.557	0.062	0.03
Race	0	1	0	0.102	0.75	0.001
AIN+ECN Participation Coefficient						
Valence	0.00005	2	0.00005	0.181	0.834	0.002
Valence x SEP	0	2	0.00007	0.481	0.619	0.004
SEP	0.003	1	0.003	2.591	0.11	0.022
Age*	**0.007**	**1**	**0.007**	**6.378**	**0.013**	**0.052**
Sex*	**0.008**	**1**	**0.008**	**6.378**	**0.008**	**0.59**
Race	0.00007	1	0.00007	0.063	0.803	0.001
Motion*	**0.033**	**1**	**0.033**	**31.442**	**0**	**0.213**

Note. Bolded predictors denote that the effect is significant at $p_{\text{uncorrected}}<0.05$. Asterisk* denotes that the effect is significant at $p_{\text{FDR}}<0.05$.

Association between SEP and Participation Coefficient of the AIN+ECN

Next, a rm-ANCOVA was performed to assess the association between SEP and between-network connectivity, or the participation coefficient, of the AIN and ECN. This analysis showed there was no main effect of SEP for the participation coefficient of the AIN and ECN during the task. There was no significant main effect of image valence on participation coefficient, nor was there a significant interaction between SEP and valence in predicting AIN+ECN participation coefficient (see Table 4 for full reporting of values).

Association between SEP and Betweenness Centrality of the Amygdala, mPFC, and Insula

Next, to assess if SEP was related to differences in nodal centrality during affective processing, we calculated betweenness centrality for several regions defined *a priori*. Measures of betweenness centrality for the amygdala, mPFC, and insula within the AIN, AIN+ECN, and whole brain connectivity matrices during each condition were extracted. A rm-ANCOVA analyses showed no statistically significant associations between SEP and centrality of these regions within any of the three graphs (see Table 5 for full reporting of values).

Table 2.5. *ANCOVA table reporting associations between SEP and amygdala, medial prefrontal cortex (MPFC), and insula betweenness centrality within AIN, AIN+ECN, and whole brain graphs. Note.* Bolded predictors denote that the effect is significant at $p_{uncorrected}<0.05$. Asterisk* denotes that the effect is significant at $p_{FDR}<0.05$.

ROIs	AIN Betweenness Centrality							AIN+ECN Betweenness Centrality							Whole Brain Betweenness Centrality						
	Predictors	*Sum of Squares*	*df*	*Mean Square*	*F*	*p*	*partial* η^2	*Predictors*	*Sum of Squares*	*df*	*Mean Square*	*F*	*p*	*partial* η^2	*Predictors*	*Sum of Squares*	*df*	*Mean Square*	*F*	*p*	*partial* η^2
Amygdala	Valence	200.22	2.00	100.11	0.42	0.66	0.00	Valence	2717.04	2.00	1358.52	2.54	0.08	0.02	**Valence***	**20876.41**	**2.00**	**20876.41**	**8.98**	**0.00**	**0.07**
	Valence x SEP	741.73	2.00	370.86	1.57	0.21	0.01	Valence x SEP	704.11	2.00	352.05	0.66	0.52	0.01	Valence x SEP	962.93	2.00	481.47	0.41	0.66	0.00
	Age	3863.78	1.00	3863.78	3.58	0.06	0.03	**Age***	**7840.00**	**1.00**	7840.00	**7.77**	**0.01**	**0.06**	**Age**	**16126.45**	**1.00**	**16126.45**	**5.70**	**0.02**	**0.05**
	Sex	1327.64	1.00	1327.64	1.23	0.27	0.01	Sex	2440.85	1.00	2440.85	2.42	0.12	0.02	Sex	7864.71	1.00	7864.71	2.78	0.10	0.02
	Race	112.27	1.00	112.27	0.10	0.75	0.00	Race	448.55	1.00	448.55	0.44	0.51	0.00	Race	0.09	1.00	0.09	0.00	1.00	0.00
	SEP	2775.28	1.00	2775.28	2.57	0.11	0.02	SEP	2134.99	1.00	2134.99	2.12	0.15	0.02	SEP	146.00	1.00	146.00	0.05	0.82	0.00
	Motion	1296.38	1.00	1296.38	1.20	0.28	0.01	Motion	847.76	1.00	847.76	0.84	0.36	0.01	Motion	1254.35	1.00	1254.35	0.44	0.51	0.00
MPFC	Valence	795.66	2.00	397.83	0.99	0.37	0.01	Valence	2073.59	2.00	2073.59	0.98	0.38	0.01	Valence	2177.84	2.00	1088.92	0.52	0.59	0.00
	Valence x SEP	1396.16	2.00	698.08	1.74	0.18	0.02	Valence x SEP	2899.91	2.00	2899.91	1.38	0.25	0.01	Valence x SEP	7210.16	2.00	3605.08	1.73	0.18	0.02
	Age	723.94	1.00	723.94	0.54	0.46	0.01	**Age**	**9030.94**	**1.00**	9030.94	**5.19**	**0.03**	**0.04**	**Age**	**16569.19**	**1.00**	**16569.19**	**4.50**	**0.04**	**0.04**
	Sex	4.59	1.00	4.59	0.00	0.95	0.00	Sex	303.62	1.00	303.62	0.18	0.68	0.00	Sex	2343.59	1.00	2343.59	0.64	0.43	0.01
	Race	1800.53	1.00	1800.53	1.34	0.25	0.01	Race	1383.20	1.00	1383.20	0.80	0.37	0.01	Race	150.85	1.00	150.85	0.04	0.84	0.00
	SEP	**7108.02**	**1.00**	**7108.02**	**5.30**	**0.02**	**0.04**	**SEP**	**7524.99**	**1.00**	**7524.99**	**4.33**	**0.04**	**0.04**	SEP	10156.41	1.00	10156.41	2.76	0.10	0.02
	Motion*	**22397.19**	**1.00**	**22397.19**	**16.68**	**0.00**	**0.13**	**Motion***	**16147.59**	**1.00**	**16147.59**	**9.29**	**0.00**	**0.07**	**Motion**	**22348.14**	**1.00**	**22348.14**	**6.07**	**0.015***	**0.05**
Insula	Valence	1467.97	2.00	733.99	3.00	0.05	0.03	Valence	952.09	2.00	952.09	0.94	0.39	0.01	Valence	916.60	2.00	458.30	0.29	0.75	0.00
	Valence x SEP	0.53	2.00	0.26	0.00	1.00	0.00	Valence x SEP	353.15	2.00	353.15	0.35	0.71	0.00	Valence x SEP	1655.84	2.00	827.92	0.53	0.59	0.01
	Age	203.27	1.00	203.27	0.24	0.63	0.00	Age	32.81	1.00	32.81	0.03	0.86	0.00	Age	680.30	1.00	680.30	0.19	0.66	0.00
	Sex	2396.84	1.00	2396.84	2.78	0.10	0.02	Sex	2443.19	1.00	2443.19	2.27	0.14	0.02	Sex	9472.02	1.00	9472.02	2.69	0.10	0.02
	Race	60.04	1.00	60.04	0.07	0.79	0.00	Race	213.94	1.00	213.94	0.20	0.66	0.00	Race	303.52	1.00	303.52	0.09	0.77	0.00
	SEP	**3372.24**	**1.00**	**3372.24**	**3.91**	**0.05**	**0.03**	SEP	2418.11	1.00	2418.11	2.24	0.14	0.02	SEP	6887.22	1.00	6887.22	1.96	0.16	0.02
	Motion	159.92	1.00	159.92	0.19	0.67	0.00	Motion	118.60	1.00	118.60	0.11	0.74	0.00	Motion	5709.05	1.00	5709.05	1.62	0.21	0.01

Association between SEP and Network Integration across the Whole Brain

Finally, we conducted exploratory rm-ANCOVA analyses to examine whether there were associations between SEP and network integration across the whole brain during affective processing. This analysis showed a significant SEP by valence interaction, $F(2, 117) = 3.429$, $p=0.034$, such that as SEP decreased, global efficiency across the whole-brain graph increased in response to the positive, but not negative or neutral, image conditions. There were no significant main effects of SEP or valence on whole brain global efficiency (see Table 6 for full reporting of values).

To assess whether SEP was related to participation coefficient (i.e., between-network integration) across the whole-brain during affective processing, a rm-ANCOVA was conducted. There was a significant SEP by valence interaction, $F(2, 117) = 3.142$, $p=0.045$, such that as SEP decreased, the participation coefficient across the whole-brain graph increased in response to the neutral, but not positive or negative, images. There were no significant main effects of SEP or valence on whole brain participation coefficient (see Table 6 for full reporting of values)."

Table 2.6

ANCOVA table reporting differences in global efficiency and participation coefficient by SEP and valence for the whole brain graph

Predictors	***Sum of Squares***	***df***	***Mean Square***	***F***	***p***	***partial***
Whole Brain Global Efficiency						
Valence	3.13E-05	2	1.56E-05	0.205	0.814	0.002
Valence x SEP*	**0.001**	**2**	**0**	**3.745**	**0.025**	**0.031**
SEP	0.002	1	0.002	3.036	0.084	0.026
Age	0.001	1	0.001	1.544	0.217	0.013
Sex	0.002	1	0.002	2.966	0.088	0.025
Race	0	1	0	0.4	0.528	0.003
Whole Brain Participation Coefficient						
Valence*	**0.001**	**1**	**0.001**	**4.424**	**0.038**	**0.037**
Valence x SEP*	**0.001**	**1**	**0.001**	**4.869**	**0.029**	**0.04**
SEP	0.001	1	0.001	1.082	0.3	0.009
Age	0.001	1	0.001	1.217	0.272	0.01
Sex	0.001	1	0.001	2.157	0.145	0.018
Race*	**0.003**	**1**	**0.003**	**4.577**	**0.035**	**0.038**
Motion*	**0.002**	**1**	**0.002**	**35.626**	**0**	**0.235**

Note. Bolded predictors denote that the effect is significant at $p_{\text{uncorrected}}<0.05$. Asterisk* denotes that the effect is significant at $p_{\text{FDR}}<0.05$.

Discussion

The current study examined whether SEP was related to differences in neural activity and brain network connectivity during affective processing in a sample of mid- to late-life adults. There are three key findings from the present research. First, we found that lower SEP was related to greater neural activity to negative (vs. neutral) images in regions within the allostatic-interoceptive network (AIN; e.g., mPFC, precuneus, posterior cingulate cortex, anterior insula, anterior cingulate cortex, amygdala, hippocampus), as well as regions within the executive control network (ECN; e.g., IFG), among other regions. Second, we found that lower SEP was related to greater neural activity to positive (vs. neutral) images in corticostriatal regions such as the caudate, nucleus accumbens and ventral-mPFC, as well as posterior regions in the AIN (e.g., precuneus, posterior cingulate) and regions within the ECN (e.g., IFG, middle frontal gyrus). Finally, we showed that SEP is related to neural network topology during affective processing; specifically, that individuals with lower SEP showed greater global efficiency (i.e., stronger network integration) of the AIN and AIN+ECN across all affective conditions. The results of the present study add to the growing literature showing that SEP modulates neural responses to affective information in regions implicated in integrating information from the external and internal environment to regulate the energy and resources needed to respond appropriately. These findings also shed light on a possible neural pathway by which SEP may influence mental and physical health.

First, we found that lower SEP was associated with greater activity in medial and lateral PFC, parietal lobe, and limbic regions in response to viewing negative (vs. neutral) images. These findings are consistent with past research showing that lower SEP is associated with greater amygdala and mPFC activity during the processing of negative facial expressions and

other types of negative social feedback (Gianaros et al., 2008; Muscatell et al., 2012; Javanbakht et al., 2015; Gonzalez et al., 2015; Muscatell et al., 2016; Kim et al., 2017; Swartz et al., 2017), and extend this prior literature to show that SEP is additionally related to activity in other regions that have been linked to social-affective processing (e.g., anterior insula, posterior and anterior cingulate, IFG). The combination of cortical and subcortical regions seen here and in prior work converge to suggest that SEP is related to neural activity in regions within the AIN, a network thought to integrate information from the environment together with physiological signals within an individual to prepare and mount resources to respond to a situation (Craig, 2009; Khalsa et al., 2009; Kleckner et al., 2017). The increased activity within the AIN in response to negative affective stimuli may reflect an increased tendency for individuals with lower SES to make predictions that negative information is highly salient, and that there is greater need to mount physiological responses to meet the demands of the salient negative situation. Over time, this enhanced activation can disrupt physiological systems (i.e., allostatic load) and lead to poorer health (McEwen & Gianaros, 2010).

Second, we found that lower SEP was associated with greater activity in regions within the middle frontal gyrus, cingulate cortex, and caudate in response to positive (vs. neutral) images. These findings are consistent with a recent meta-analysis which found that across a variety of tasks (e.g., executive function, reward, social, affective), lower SEP was associated with increased activity in reward-related regions (e.g. caudate; Yaple & Yu, 2020). Given that regions within the caudate nucleus are linked to associative learning (Delgado et al., 2004) and shifts in behavior to maximize potential gains (Haruno et al., 2004), this enhanced activity to positive stimuli among individuals with lower-SES may suggest greater attention and preparation for gain. Life history theory contends that individuals may become more vigilant and prepared to

secure potential gains in environments with fewer resources and greater uncertainty (Gonzalez et al., 2016; Ellis et al., 2009). Together, these results suggest that individuals with lower SES are sensitive to positive stimuli and the enhanced activity in the AIN may reflect an increased tendency to prepare to mount the resources needed to secure a potential gain. Generally, the association between SEP and representations of positive stimuli observed in the current study, coupled with the findings for the negative images, converge to suggest that individuals with lower SEP may be more "neurally sensitive" to affective cues specifically in regions that support shifting behavior to manage metabolic resources.

Third, we found that lower SEP was related to higher global efficiency of the AIN, and the AIN together with the ECN. These results are the first demonstration that SEP is associated with network configuration while processing affective images and suggest that individuals with lower SEP show stronger integration among networks associated with affective responding and cognitive control. In other words, among individuals with lower SEP, affective information is more efficiently transferred among regions within the AIN and between the AIN and ECN (Achard & Bullmore, 2007; Berroir et al., 2016; Laughlin & Sejnowski, 2003). This is interesting given that greater global efficiency may confer some potential advantages in cognitive function (Li et al., 2009; Kesler et al., 2018), suggesting that lower SEP may shape the efficiency of brain networks that specifically help identify salient information in the environemt and respond accordingly. However, enhanced efficiency among AIN and ECN nodes may be useful for individuals lower in SEP, who may experience greater chronic unpredictable threats (Baum et al., 1999; Crielaard et al., 2021). Greater efficiency between these two networks may be adaptive in helping individuals lower in SEP to quickly detect salient information in the environment and make decisions about how to regulate responses to such information. In the

longer term, however, this enhanced efficiency between AIN and ECN may come with costs. Global workspace theory argues that the neural architecture underlying effortful processing engaged during complex cognitive tasks is characterized by more integrated processing (i.e., increased global efficiency) over longer connections, which takes energy to maintain (Dehaene, Kerszberg, & Changeux, 1998; Kitzbichler et al., 2011). As such, it is possible that the global workspace is activated or enhanced when individuals attend and respond to salient (i.e., novel, unpredicted, emotional) stimuli. Therefore, prolonged increases in global network efficiency may be associated with higher metabolic cost (Bullmore & Sporns, 2012), which is detrimental in the long term and could be deleterious to overall health and mental functioning (Colich et al., 2020). Future longitudinal work is needed to examine if SEP-related modulation of global efficiency is related to the emergence of SEP-based health inequities over time.

These findings of greater global efficiency of the AIN and the AIN together with ECN parallel a recent theory of generalized unsafety that is posited as one pathway by which lower-SEP may be linked to poorer health outcomes (Brosschot et al., 2016; Brosschot, Verkuil, & Thayer, 2017; Brosschot et al., 2018). The generalized unsafety theory argues that constant activation due to a sense of uncertainty and preparation for threat among those lower in SEP may be physiologically costly. Indeed, prior work shows that individuals demonstrate greater global efficiency in highly attentive and vigilant states (Yang et al., 2019). Thus, increased integration within the AIN, which also underlies physiological activation, may be a pivotal process for maintaining and regulating the consequences of generalized unsafety. This interpretation is speculative at this stage and future research is needed to examine if greater integration of the AIN is a mechanism linking lower SEP to greater physiological activation, and perhaps poorer health.

Finally, exploratory analyses across the whole brain revealed intriguing associations between SEP and network topology during affective processing. We found that there was a negative association between SEP and global efficiency across the whole-brain graph specifically during the positive condition, perhaps suggesting that positive affective states depend on increases in global efficiency of the entire brain among individuals with lower SEP. A similar SEP by valence interaction was found for whole-brain participation coefficient. Specifically, individuals with lower SEP demonstrated an increased participation coefficient while viewing neutral images. These analyses were exploratory and will need to be replicated.

There were also several null findings in the present study worth noting, particularly with regard to the network metrics. First, we did not find an interaction of SEP and image valence for measures of network integration or hub centrality. In other words, while SEP was related to AIN and AIN+ECN integration broadly across all trial types in the task, the association between SEP and network integration did not vary as a function of affective image condition. A possible reason for this lack of SEP by image valence interaction might be because static measures of network organization such as those studied here are more strongly linked to individual traits, such as SEP, than dynamic changes across task conditions, such as differences in valence (Eichenbaum et al., 2021; Liégeois et al., 2019). Second, we found that there were no differences in global efficiency within the ECN-only graph as a function of SEP. Because regions within the ECN are hypothesized to underlie cognitive regulation processes and the task used here did not explicitly instruct individuals to regulate their emotions, this null result is not entirely surprising. Third, there was also no main effect of valence on metrics of participation coefficient and betweenness centrality. These results are consistent with recent work showing that networks critical for processing emotional content are not differentially responsive to valence (Lindquist et

al., 2016; Lindquist et al., 2012). That is, networks such as the AIN are valence-*general* (Barrett & Simmons, 2015; Satpute & Lindquist, 2019). More research is needed to fully understand the extent to which neural systems such as the AIN dynamically configure in response to different stimuli and task demands.

Several limitations need to be considered. First, we measured SEP by creating a composite score of education and income, and there are several other ways to conceptualize SEP given that it is a multifaceted construct (Braveman et al., 2005). Results may be different if other measures of SEP are examined (e.g., occupational prestige, change in socioeconomic mobility from childhood). Second, the cross-sectional design precludes drawing any causal conclusions regarding neural alterations due to SEP. Future longitudinal work that examines the influence of SEP on brain activation and network dynamics in response to affective stimuli over time is needed to gain clarity on the directionality of effects. Additionally, although we controlled for effects of age, sex, and racial/ethnic identity, these covariates are factors that are importantly associated with SEP (e.g., Backholer et al., 2017; Poulton et al., 2002; Williams et al., 2010). While limitations in sample size precluded our ability to meaningfully examine intersections between SEP and these other demographic factors, future work with larger sample sizes and greater variability in demographic characteristics ought to explore the effects of intersectionality of SEP and age, sex, and racial/ethnic identity on neural functioning. Third, although the network metrics we selected are commonly used to measure integration and centrality in the literature, future work can explore links between SEP and network configuration utilizing other metrics to assess reproducibility and compare results across metric selection. Finally, it is important to note that node selection is an ongoing limitation in network neuroscience such that network metrics

may vary depending on the parcellation or specific nodes selected (see Stanley et al., 2013 or Hallquist & Hillary, 2019 for discussion).

Overall, our data suggests that SEP is associated with hyperactivity in and integration among regions comprising an allostatic-interoceptive brain system while processing affective information. This study establishes for the very first time that broader features of an individual's context, like SEP, may influence the activity and topology of an allostatic-interoceptive system. These findings suggest that lower SEP is associated enhanced neural sensitivity to affective cues, and that this heightened activity and connectivity in response to such cues may be metabolically costly to maintain. This generalized hypervigilance and metabolically expensive integration of the AIN and ECN during responses to affective information may be one pathway linking SEP, affective processing, and detrimental health outcomes.

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CHAPTER 3: SYSTEMIC INFLAMMATION IS ASSOCIATED WITH DIFFERENTIAL NEURAL REACTIVITY AND CONNECTIVITY TO AFFECTIVE IMAGES[2]

Introduction

Systemic inflammation, a component of the innate immune system, is increasingly appreciated for its role in the pathophysiology of chronic disease and psychopathology (Bennett, Reeves, Billman, & Sturmberg, 2018; Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008; Liu, Wang, & Jiang, 2017). The inflammatory response is primarily an adaptive defense mechanism that activates to harmful pathogens and promotes healing; however, chronic and uncontrolled inflammation can have negative consequences for physical and mental health (Franceschi & Campisi, 2014; Furman et al., 2019; Gabay, 2006). Interestingly, a growing literature in psychoneuroimmunology shows that, in addition to its role in both acute infection and chronic disease, systemic inflammation both affects and is affected by psychological experiences (Dickerson, Gable, Irwin, Aziz, & Kemeny, 2009; Irwin & Cole, 2011). The purpose of the present study was to investigate the association between systemic, low-grade inflammation, and one such psychological experience, affective reactivity. Specifically, we examined the relationship between markers of inflammation and neural responses to positive and negative images, compared to neutral images, to further our nascent understanding of the bi-directional links between the innate immune system and brain function.

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What do we currently know about links between affective reactivity and inflammation? Most prior work in this area has focused on the links between negative affect, both chronic (e.g., depression) and acute (e.g., in response to a psychological stressor), and inflammation. Meta-analytic evidence suggests that elevated depressive symptoms are associated with higher levels of systemic inflammation (Howren, Lamkin, & Suls, 2009) and that acute stressors elicit increases in markers of systemic inflammation (Marsland, Walsh, Lockwood, & John-Henderson, 2017). A handful of functional MRI (fMRI) studies have investigated the neural correlates of negative affect-inducing experiences and inflammation, showing that both social evaluation (Muscatell et al., 2016) and grief elicitation among recently-bereaved individuals (O'Connor, Irwin, & Wellisch, 2009) are associated with greater activation in the medial prefrontal cortex, amygdala, and anterior cingulate cortex, and with greater levels of inflammation.

Some work has also investigated the "bottom-up," afferent influence of inflammation on negative affective processes. This area of work demonstrates that experimentally-induced increases in markers of inflammation (via inflammatory challenge studies utilizing lipopolysaccharide or typhoid vaccination) are associated with higher depressive symptoms and greater feelings of social disconnection (Eisenberger, Inagaki, Mashal, & Irwin, 2010; Eisenberger, Inagaki, Rameson, Mashal, & Irwin, 2009; Harrison et al., 2009). Complementary neuroimaging work has investigated the influence of peripheral inflammation on neural reactivity to negative affect-related stimuli, such as threatening faces (Inagaki, Muscatell, Irwin, Cole, & Eisenberger, 2012), negative social feedback (Muscatell et al., 2016), social exclusion (Eisenberger, Inagaki, Rameson, Mashal, & Irwin, 2009), and threatening images (Kullmann et al., 2013). Together, these studies show that higher levels of inflammation are associated with

increased activity in limbic (e.g., amygdala, hippocampus) and cortical (e.g., medial prefrontal cortex, cingulate cortex) regions in response to negative stimuli. Thus, a growing literature shows that systemic inflammation both affects and is affected by negative emotional experiences and stimuli, via alterations in subcortical (i.e., amygdala) and cortical (i.e., ACC, insula, dmPFC) neural activity.

Fewer studies have explored the bidirectional links between positive affect and levels of inflammation, especially as they relate to neural functioning. This paucity of work is surprising considering that several studies have found that both dispositional positive affect (Hartanto, Lee, & Yong, 2019; Marsland, Cohen, Rabin, & Manuck, 2006; Stellar et al., 2015) and momentary positive affective states (Steptoe, Wardle, & Marmot, 2005) are associated with lower levels of inflammation. To date, no known neuroimaging studies have examined the efferent pathway, or how the induction of a positive affective experience influences levels of inflammation. Correlational studies show that activity in the medial prefrontal cortex in response to positive stimuli (e.g., favorite actor; positive autobiographical memories) is related to better innate immune system functioning (i.e., natural killer cell count; Matsunaga et al., 2008) and lower inflammation (i.e., interferon-γ; Matsunaga et al., 2013), respectively, suggesting that greater neural responses to positive stimuli might be related to lower levels of systemic inflammation. A more substantial literature has examined how manipulating inflammation results in changes in neural responses to positive affective stimuli. Most of the work examining this afferent pathway has focused on documenting inflammation-related changes in neural reactivity to monetary reward tasks. These studies generally find that inflammation causes a decrease in neural activity in reward-related regions (i.e., ventral striatum) in response to monetary gain (Capuron et al., 2012; Eisenberger, Berkman, et al., 2010; Moieni et al., 2019, c.f. Inagaki et al., 2015; Muscatell

et al., 2016). Together, these studies suggest that higher levels of inflammation might be associated with decreased activity in regions within the basal ganglia in response to positive stimuli. Generally, a growing literature demonstrates that systemic inflammation can both affect and be affected by positive experiences and stimuli, via alterations in subcortical (i.e., ventral striatum) and cortical (i.e., medial prefrontal cortex) neural activity, although less work has been conducted in this area.

Interestingly, there is substantial overlap in the brain regions that are implicated in inflammatory processes reviewed above and in regions that show significant activation to positive and negative stimuli. For example, recent meta-analytic work has revealed that activity in several corticolimbic regions [e.g., dorsal medial prefrontal cortex (dmPFC), amygdala, hippocampus, striatum, insula] is consistently associated with levels of peripheral inflammation (Kraynak, Marsland, Wager, & Gianaros, 2018). In another meta-analysis that examined the brain basis of affective processing (Lindquist, Satpute, Wager, Weber, & Barrett, 2016), similar limbic (e.g., amygdala, insula, striatum) and cortical regions (e.g., dmPFC and dACC) were also implicated in the processing of positive and negative information. Findings from these two meta-analyses converge to suggest that corticolimbic regions are involved in both affective and inflammatory processes. Thus, these corticolimbic regions may be important in facilitating cross-talk between the brain and the innate immune system in response to affective information.

Although prior research has identified associations between peripheral inflammation and corticolimbic activity in response to affective experiences, numerous gaps in our knowledge still exist. For example, most prior studies have utilized acute inflammatory challenge manipulations to study links between inflammation and neural activity; as such, we have limited knowledge about the association between chronic, low-grade inflammation and corticolimbic activity to

affective stimuli. Further, most prior studies focus on monetary rewards as a proxy for positive experiences and angry/fearful faces for negative stimuli, leaving gaps in our knowledge of the associations between inflammation and neural responses to other types of affective stimuli (e.g., positive and negative scenes). Finally, although several psychoneuroimmunological studies have examined the associations between inflammation and functional connectivity while individuals are at rest (J C Felger et al., 2016; Kraynak, Marsland, Hanson, & Gianaros, 2019; Lekander et al., 2016; Marsland, Kuan, et al., 2017; Mehta et al., 2018; Nusslock et al., 2019), few known studies have examined how markers of systemic inflammation might relate to functional connectivity while participants are engaged in a dynamic affective reactivity task. In several studies, task-based connectivity has been shown to outperform resting-state models for detecting relationships between neural activity and individuals differences in behavior (Greene et al. 2018; Jiang et al. 2020), suggesting that investigations of associations between inflammation and task-based connectivity are warranted. Thus, the present study was designed to fill these gaps in our knowledge by exploring associations between low-grade peripheral inflammation and neural reactivity and connectivity in response to viewing affective images.

To accomplish this, we examined associations between markers of systemic inflammation and neural reactivity/connectivity to affective images in a sample of 66 adults from the Midlife in the United States (MIDUS) study. Specifically, we examined the relationship between levels of interleukin-6 (IL-6) and C-reactive protein (CRP) and corticolimbic responsivity and connectivity to positive and negative images. IL-6 and CRP are two commonly-measured markers of inflammation in psychoneuroimmunology research. IL-6 is an inflammatory cytokine that is released into circulation in response to both physical and psychological threats to help facilitate communication among immune cells, among other

functions. IL-6 also stimulates the production of CRP, an acute-phase protein produced by the liver that plays several roles during an inflammatory response. Elevated levels of IL-6 and CRP in the absence of acute infection are often conceptualized as representing chronic, low-grade inflammation (O'Connor et al., 2009).

Methods

Participants

Data for this project were drawn from the Midlife in the United States (MIDUS) study, a national longitudinal study that examines biopsychosocial factors influencing health across later life. A subset of individuals from the MIDUS cohort completed the Neuroscience Project, beginning in 2007. Participants were eligible for this sub-study if they completed the Biomarker Project 4 visit, met MRI inclusion criteria (e.g., no metal implants, no claustrophobia, not currently pregnant), and had no prior history of a neurological disorder. Of the 72 total individuals enrolled in the Neuroscience Project, for the present paper, we excluded six: two for excessive head motion, one due to incomplete fMRI data, and four due to levels of CRP greater than 10 mg/L which likely indicates a current or recent infection (Jaye & Waites, 1997). The 66 participants included in analyses had a mean age of 54.98 years (SD= 10.76; range=35-76) and consisted of 44 women (66.67%). See Table 3.1 for additional demographic information. Participants in the fMRI subsample were of similar age and exhibited comparable values of CRP and IL-6 to those in the larger MIDUS study, such that there were no significant differences between the samples for these characteristics (p's> 0.42).

Table 3.1 Demographic and biomarker summary of the study sample

Variable	Count (N)	Percentage (%)
Sex (female, %)	44	66.7
Race/Ethnicity		
Black	19	28.8
Native American or Aleutian Islander	1	3
White	45	68.2
Other	1	3
Educational Attainment		
Less than high school	27	40.9
High school	21	31.8
Bachelor's degree	8	12.1
Master's degree	10	15.2

Variable	Mean (SD)	Range
Age	54.98 (10.76)	35 - 76
BMI	29.52 (5.67)	19.51 - 46.78
IL-6 (pg/mL)	2.21	0.16 - 18.40
IL-6 (natural log)	0.74	-1.83 - 2.91
CRP (ug/mL)	2.88	0.16 - 7.62
CRP (natural log)	0.38	-1.83 - 2.03

Procedures and Materials

Overview. Participants in this study first completed the Biomarker Project 4 visit. The visit was an overnight session in which participants completed questionnaires and provided urine, blood, and saliva samples to assess biological indicators of physiological functioning and health status, including markers of inflammation. Following the biomarker collection, participants then completed an fMRI scan.

IL-6 and CRP. After overnight fasting, participants provided blood samples later assayed for levels of IL-6 and CRP. Assays were conducted using commercially-available kits according to manufacturer instructions. Both CRP and IL-6 assays showed acceptable inter-assay CVs (2.1-12.3%). More details are provided in Supplemental Materials. Both IL-6 and CRP values were natural log-transformed to adjust for the positive skew in the data. Finally, given the significant correlation between IL-6 and CRP in the present sample ($r=0.63$, $p<0.001$) and the known physiological association (i.e., IL-6 can stimulate the production of CRP), the natural log values of IL-6 and CRP were standardized and averaged to create a composite inflammation score to assess the combined associations between these inflammatory markers and neural activity. See Supplementary Materials for exploratory analyses separated by inflammatory markers.

fMRI task. For the fMRI task (data from which are also published in Heller et al., 2013; van Reekum et al., 2018), participants viewed 60 positive, 60 negative, and 60 neutral pseudo-randomized images selected from the International Affective Picture System (IAPS; Lang et al., 2008) for five runs (see Supplementary Materials for list of IAPS images used). The stimuli were matched across valence categories for complexity, social content, arousal, and luminosity. Each trial progressed as follows: a fixation crosshair was displayed for 1 second, followed by an IAPS image presented for 4 seconds, and then a blank screen intertrial interval (ITI) was displayed (M

length = 8.89 sec, range = 5.5-17.6 sec). Participants were instructed to indicate on a button box the valence (i.e., positive, negative, or neutral) of the image presented. After 40 out of 60 trials in each valence category, a neutral male face was presented for 0.5 seconds after the IAPS image was displayed. Because the current project focused on examining neural responses to the affective images, the face stimuli were coded as regressors of no-interest in analyses. Across runs, the order the valence of the images presented was consistent across participants, though the specific stimuli presented within each valence category were randomized across participants.

fMRI data collection. Neuroimaging data for the current study were collected on a GE SIGNA 3.0 Tesla high-speed MRI scanner with a standard clinical whole-head transmit-receive quadrature head coil. The blood oxygen level-dependent (BOLD) signal was acquired using a T2*-weighted gradient-echo echo-planar imaging (EPI) pulse sequence across five runs of approximately 8 minutes each. Each EPI acquired 30 sagittal slices that used the following parameters: TR=2,000 ms, TE=30 ms, flip angle=60º, field of view=240 mm, acquisition matrix=64x64, 4 mm slice thickness with 1 mm gap. A T1-weighted anatomical image was also collected using a T1-weighted inversion recovery fast gradient echo with the following parameters: acquisition matrix= 256 x 256, a field of view= 240 mm, with 124 x 1.1 mm axial slices.

Data Analysis

fMRI preprocessing and analysis. Neuroimaging data were preprocessed utilizing an in-house pipeline. The *fsl_motion_outliers* program (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012) was used to identify artifacts and excessive motion. Motion spikes were included in each person-level general linear model (GLM) to control for motion exceeding 2mm. Further, runs with 2mm of framewise displacement for greater than 20% of volumes acquired were

excluded (N= 10; 0.03% of total runs). Next, a four-dimensional registration algorithm utilizing NiPy to conduct spatio-temporal transformations that simultaneously motion and slice-time corrected (Roche, 2011) was implemented. In two steps, this algorithm aligned all five functional images to a mean image computed after initial realignment. FSL's FLIRT algorithm coregistered T2*-weighted images to the T1-weighted images, which were then anatomically coregistered to each individual's high-resolution structural image. Images were nonlinearly registered to the Montreal Neurologic Institute's (MNI) standard space utilizing the Advanced Normalization Tools (ANTs) software (Avants et al., 2011). Finally, spatial smoothing was applied with a Gaussian kernel of 5-mm full width at half maximum.

fMRI data were analyzed using FSL's FEAT (FMRI Expert Analysis Tool) Version 6.00. A general linear model (GLM) was constructed for each run per individual. The GLMs included regressors modeling the positive, negative, and neutral events, as well as the nuisance regressors of motion (i.e., each individual's six motion parameters and their first derivatives, and single-point motion outliers) and the face events. For each run, a high-pass filter (100Hz) was applied to remove low-frequency drifts. Higher-level analyses were conducted utilizing FLAME stage 1 (Woolrich, Behrens, Beckmann, Jenkinson, & Smith, 2004), a fixed-effects GLM approach, to combine BOLD activation and differences in variance across runs. The two contrasts of interests were negative images versus neutral images and positive images versus neutral images. The whole-brain main effects for both contrasts (cluster-based threshold at $z > 2.3$, $p < .05$) are reported in the Results section.

Regions-of-Interest Construction. A mask was constructed by combining meta-analytic maps of neural activation related to affective processing (Lindquist et al. 2016) and peripheral inflammation (Kraynak et al., 2018). The binary maps derived from the meta-analyses were

multiplied using *fslmaths* to create a mask that encompassed overlapping voxels from both of the meta-analyses. The regression analyses conducted in this study were restricted to the a-priori limited search space represented by the combined meta-analytic mask by specifying this as the pre-threshold mask in FEAT. Thus, regression analyses searched for significant clusters of activity within the search space that were associated with systemic inflammation, while controlling for covariates (see below for additional details).

Next, this combined meta-analytic mask was used to guide the selection of ROIs for the functional connectivity analysis. Corticolimbic regions present in the mask included the amygdala, insula, hippocampus, thalamus, striatum, pallidum, and mPFC. The amygdala, insula, hippocampus, pallidum, and thalamus ROIs for connectivity analyses were derived from the Harvard-Oxford Subcortical Structural atlas (Desikan et al., 2006). The striatum mask was generated using the Oxford-Imanova Striatal Structural atlas (Tziortzi et al., 2014). The mPFC mask was generated using the Sallet Dorsal Frontal connectivity-parcellation atlas (Sallet et al., 2013). ROI clusters 3 and 4, which consisted of Brodmann Areas 9 and 10 (Lieberman, Straccia, Meyer, Du, & Tan, 2019), were combined to create an mPFC mask.

Regression Analyses Associating Levels of Inflammation with Neural Activity. Two general linear models were employed to assess the relationship between inflammation (composite of CRP and IL-6) and activity in clusters encompassed within the combined meta-analytic mask when participants viewed positive (versus neutral) and negative (versus neutral) images. Consistent with prior work in this area (O'Connor et al., 2009), group-level regression models controlled for age and gender. Considering adipose tissue's role in systemic inflammation (Mohamed-Ali et al., 1997), body mass index (computed via measures of height and weight) was also included as a covariate. The higher-level models conducted for these analyses utilized

cluster-based thresholding at $z > 2.3$, $p < .05$. In conjunction with FSL FLAME 1, the correction parameters used in this study have been found to effectively decrease type II errors (Eklund, Nichols, & Knutsson, 2016).

Functional Connectivity Analyses. Finally, functional connectivity analyses were conducted utilizing the Functional Connectivity Toolbox (CONN-Toolbox v.18.b; Whitfield-Gabrieli and Nieto-Castanon, 2012). The CONN toolbox was used to perform ROI-to-ROI regression analyses to examine associations between inflammation and corticolimbic ROI connectivity during the two contrasts of interest. Trial onsets and durations were imported into the toolbox to implement the generalized Psychophysiological Interaction procedure (gPPI; McLaren, Ries, Xu, & Johnson, 2012). Following the standard CONN denoising pipeline, a simultaneous linear regression and temporal band-pass filtering procedure was conducted to remove the influence of non-neural variability in the data (Hallquist, Hwang, & Luna, 2013). The pipeline implemented an anatomical component-based noise correction process (aCompCor) to remove the first five principal noise components from white matter and cerebrospinal fluid. Twelve motion parameters, outlier scans, constant linear session effects, and constant task-related effects were also included as regressors. Finally, temporal frequencies above 0.09 Hz and below 0.008 Hz were removed to minimize further the influence of physiological and motion sources of noise.

While controlling for age, gender, and BMI, two separate models examined the association between inflammation and functional connectivity between all possible combinations of the seven ROIs while participants viewed negative (versus neutral images) and positive (versus neutral images). An analysis-wise false discovery rate (FDR) at $p < 0.05$ was implemented to correct for multiple comparisons.

Results

Negative vs. Neutral Images

Overall Neural Reactivity. Results from the whole-brain analysis for the negative versus neutral contrast identified three significant clusters ($z > 2.3$, $p < .05$). Two clusters extended from the lateral occipital cortex, through the middle temporal gyrus to the inferior temporal gyrus within both hemispheres ($z = 5.98$, $k = 2794$, $p = 0.0001$; $z = 6.65$, $k = 2615$, $p = 0.0002$). The final cluster extended from the left and right amygdala through to the right thalamus ($z = 4.87$, $k = 2728$, $p = 0.0001$). See Supplemental Table S1 for full details.

Inflammation and Neural Reactivity. To examine the relationship between inflammation and neural reactivity to negative images, we ran regression analyses looking for clusters of activity within our search space mask to negative (vs. neutral) images that were significantly associated with the composite measure of inflammation, controlling for age, gender, and BMI. Contrary to hypotheses, we found no significant associations between levels of inflammation and activity in any clusters within the mask when participants viewed negative (vs. neutral) images.

Inflammation and Functional Connectivity. Next, we conducted an ROI-to-ROI regression analysis to examine the relationship between inflammation and connectivity between the corticolimbic regions of interest in response to negative images. While controlling for age, gender, and BMI, inflammation was not significantly associated with connectivity between any of the ROIs (p-FDR>0.05).

Positive vs. Neutral Images

Overall Neural Reactivity. Results from the whole-brain analysis for the positive versus neutral contrast identified three significant clusters. One large cluster encompassed regions in the occipital cortex extending into the putamen, hippocampus, and amygdala ($z = 7.49$, $k = 13{,}949$, p

< 0.001). Another cluster was found in the vmPFC (z = 5.37, k = 1726, p = 0.0019). A final cluster extended from the cingulate gyrus through to the precuneus (z = 4.13, k = 1180, p = 0.016). See Supplemental Table S2 for full details.

Inflammation and Neural Reactivity. Next, we ran regression analyses looking for clusters of activity within our search space mask to positive (vs. neutral) images that were significantly associated with the composite measure of inflammation, controlling for age, gender, and BMI. There was a negative association between inflammation and activation in one cluster, such that higher levels of inflammation were associated with lower levels of activity in a cluster encompassing voxels in the anterior insula, amygdala, hippocampus, and temporal pole (peak coordinate: x= 30, y= -10, z=; z = 3.74, k = 515, p = 0.0134; see Figure 3.1). See Table 3.2 for more information regarding the regions encompassing the cluster.

Figure 3.1. The rendered image on the left depicts the cluster of voxels that showed a significant negative association between inflammation and neural activation to positive (versus neutral) images while controlling for age, gender, and BMI. The image on the right illustrates a scatterplot of the negative association between composite inflammation and activation in that cluster to the positive (versus neutral) images.

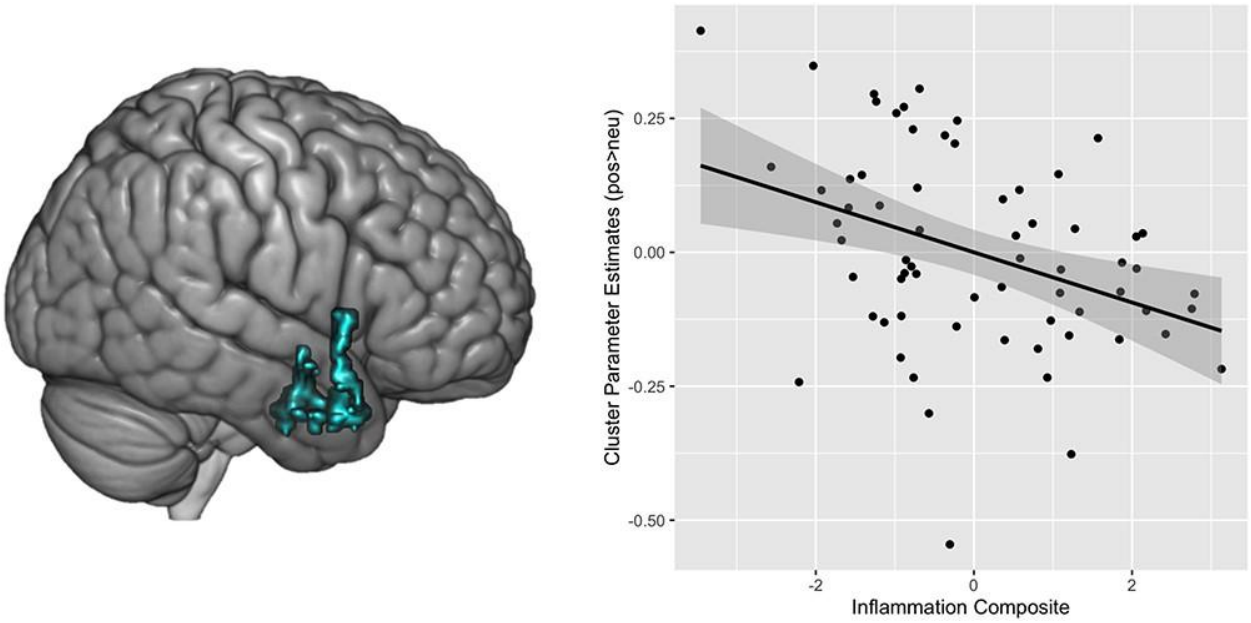


Table 3.2

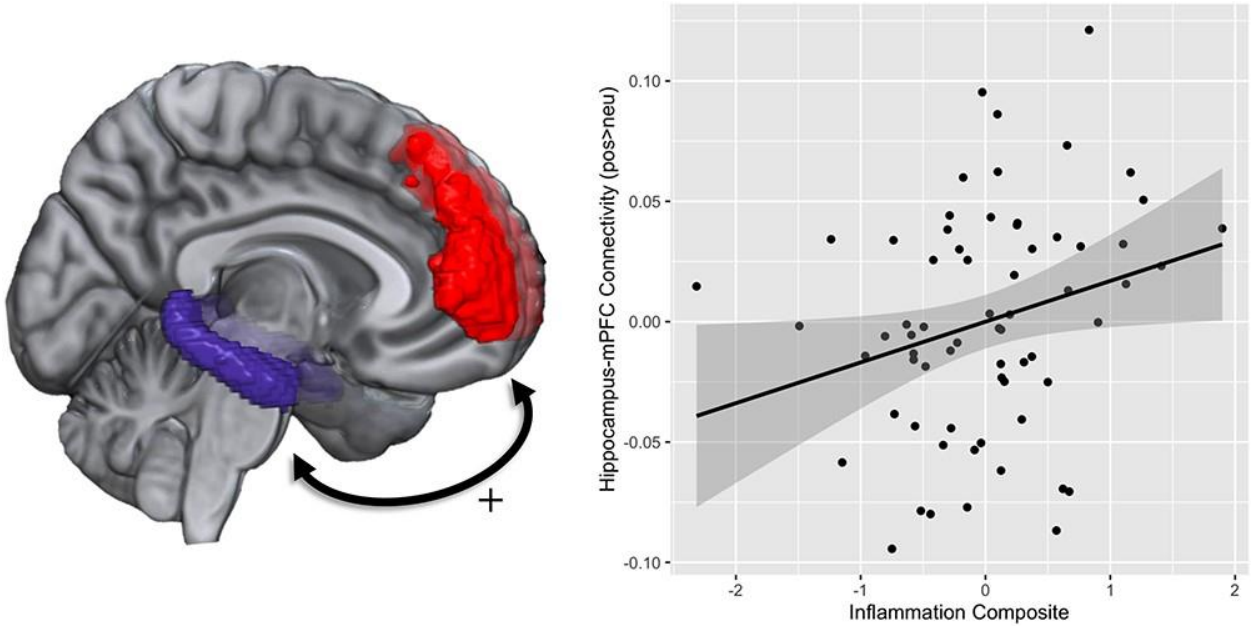
Local Maxima within Significant Cluster Negatively Associated with Inflammation during Positive > Neutral Images

Region	x (mm)	y (mm)	z (mm)	Z statistic
Parahippocampal gyrus	30	-10	-32	3.74
Insular cortex	44	14	0	3.6
Inferior temporal gyrus	44	2	-32	3.51
Temporal pole	34	12	-32	3.29
Right amygdala	26	-3	-23	2.83

Inflammation and Functional Connectivity. Next, we conducted an ROI-to-ROI regression analysis to examine the relationship between inflammation and connectivity between

the corticolimbic regions of interest in response to positive images. While controlling for age, gender, and BMI, the composite inflammation score was positively associated with bilateral hippocampus-mPFC connectivity (t(61)=3.68, p-FDR=0.028; see Figure 3.2).

Figure 3.2. The scatterplot illustrates the positive association between inflammation and hippocampus-mPFC connectivity while viewing positive (versus neutral) images.



Discussion

Results from the present study suggest that levels of peripheral inflammation are associated with differences in neural reactivity and connectivity while processing positive affective information among mid- to late-life adults. First, higher levels of peripheral inflammation were associated with lower activation in the amygdala, hippocampus, anterior insula, and temporal pole in response to positive images (vs. neutral). There were no associations between markers of inflammation and neural reactivity to negative images (vs. neutral). Second, the present study also found that greater inflammation was associated with stronger connectivity between the hippocampus and medial prefrontal cortex in response to positive images (vs. neutral). Together, these results add to a growing literature in health neuroscience documenting associations between peripheral inflammation and neural responses to social and affective information. The present results extend past findings by looking at an older sample of individuals and novel affective reactivity paradigm while also exploring the associations between inflammation and task-based functional connectivity.

Our first set of findings showing that greater inflammation is associated with lower neural activity in the amygdala, hippocampus, insula, and temporal pole activity in response to positive stimuli is consistent with a growing literature documenting associations between inflammation and blunted neural reactivity to positive stimuli (Capuron et al., 2012; Eisenberger, Berkman, et al., 2010; Moieni et al., 2019). Lower reactivity to positive images in canonical regions implicated in the detection of and attention to salient stimuli suggests that less sensitivity to positive stimuli may be linked to higher low-grade inflammation. One possible psychological interpretation of these findings is that inflammation may blunt neural sensitivity to positive experiences, which may generally reduce one's interest in positive information and motivation to

engage with positive stimuli (Eisenberger et al., 2017), perhaps in an effort to conserve metabolic resources. Although we do not see inflammation-related differences in activity in the regions implicated in processing reward (e.g., basal ganglia) that other studies have found (Capuron et al., 2012; Eisenberger et al., 2010; Felger & Miller, 2012), our findings are consistent with the general idea that inflammation is related to lower levels of neural activation to positive stimuli. Further, the present findings extend previous literature in this area, which has focused almost exclusively on neural responses to monetary reward tasks (c.f., Inagaki et al., 2015; Muscatell et al., 2016), to document that inflammation is also associated with lower levels of activity in temporal-lobe regions in response to a wider variety of positive stimuli (i.e., pictures of positive scenes). Thus, the present results are consistent with prior research showing that inflammation is associated with reduced neural responsivity to positive stimuli.

Surprisingly, we did not find an association between levels of peripheral inflammation and corticolimbic activation to negative images. This lack of association is inconsistent with prior research indicating that reactivity to negative stimuli is positively associated with inflammation (e.g., Gianaros et al., 2014; Inagaki, Muscatell, Irwin, Cole, & Eisenberger, 2012; Muscatell, Eisenberger, Dutcher, Cole, & Bower, 2016). Though null findings should be interpreted with caution, differences between the current study and past work in this area provide potential explanations for this lack of association. For example, others have found that neural activity to negative stimuli varies as a function of participant age (Mather, 2012), and the present study utilized a mid- to later-later life sample, whereas most other work on associations between inflammation and neural responses to negative stimuli have utilized younger samples (Gianaros et al., 2014; Swartz, Prather, & Hariri, 2017). Thus, age differences in participants may partially explain the divergence between the present findings and past work in this area. Additionally,

others have found that inflammation differentially influences neural activation to social versus non-social stimuli (Inagaki, Muscatell, Irwin, Cole, & Eisenberger, 2012) and most of the work in this area examines neural responses to negative social stimuli (e.g., threatening faces, negative social feedback; Inagaki, Muscatell, Irwin, Cole, & Eisenberger, 2012; Muscatell et al., 2016; c.f. Gianaros et al., 2014). To conserve power, neural activity to social and non-social images were collapsed in this study, which may also explain the lack of expected associations. Additional work is needed to examine whether there is indeed no association between low-grade inflammation and neural reactivity to negative information broadly, or if specific characteristics of the present sample or task contribute to the lack of association observed in the current analysis.

In response to the positive stimuli, inflammation was positively associated with connectivity between the hippocampus and the medial prefrontal cortex. These findings are consistent with past literature showing that inflammation is associated with differential corticolimbic connectivity (Felger et al., 2016; Kraynak, Marsland, Hanson, & Gianaros, 2019; Kraynak et al., 2018), although the specific pattern of positive associations between inflammation and hippocampal-cortical connectivity conflicts with findings from several resting-state studies. Specifically, among healthy volunteers, markers of inflammation have been shown to be negatively associated with connectivity among corticolimbic regions (Kraynak et al., 2019) and regions in the emotion regulation, central executive, and default mode networks (Dev et al., 2017; Marsland, Kuan, et al., 2017; Nusslock et al., 2019). Thus, there may be differential associations between inflammation and corticolimbic connectivity depending upon if the connectivity is measured at rest, or in response to a task.

Not only does the current study suggest the need for studies exploring task-based functional connectivity and inflammation, but it also expands our understanding of the neuro-immune influences on affective reactivity. Results from the current study support the preclinical and clinical studies that implicate the hippocampus as a critical node in neuroinflammatory processes (Colasanti et al. 2016; Williamson and Bilbo 2013). Inflammation has been shown to alter hippocampal neurogenesis (Giannakopoulou et al. 2013), and synaptic plasticity (Nisticò et al. 2013), which may extend to the inflammation-related differences in hippocampal activity and connectivity observed in the current study. Additionally, prior work suggests that hippocampus-mPFC connectivity is critical for cognitive and emotion regulation as well as spatial and emotional memory processes (Jin & Maren, 2015). Further, inflammation has also been implicated in emotion and cognition-related impairment (Appleton, Buka, Loucks, Gilman, & Kubzansky, 2013; Patki, Solanki, Atrooz, Allam, & Salim, 2013). Though speculative, these results suggest the possibility of a neuro-immune pathway whereby affective and memory-related disruptions relate to inflammatory processes via differences in hippocampal-medial prefrontal connectivity. Although this study provides initial evidence regarding task-based corticolimbic connectivity and inflammation, future studies should explore the links between task-based neural connectivity, inflammation, and the behavioral sequelae to expand our understanding of the neuro-immune influences on social and affective processes.

Multiple bidirectional physiological pathways provide plausible mechanisms for the observed links between systemic inflammation and neural activity/connectivity (Irwin & Cole, 2011). First, neural activity can alter peripheral inflammation via "top-down," efferent pathways. Corticolimbic activity in response to negative stimuli can elicit the activation of the sympathetic nervous system and release of catecholamines, which can then lead to greater inflammation

(Sternberg 2006; Nusslock & Miller, 2016). Likewise, more positive affect has been linked with increases in cardiac vagal tone (Kok et al. 2013), and the vagus nerve can dampen pro-inflammatory responses (Pavlov and Tracey 2012; Metz and Tracey 2005). Second, peripheral inflammation can alter neurotransmitter, neuron, and cerebral microvasculature functioning via a "bottom-up," afferent pathway. Cytokines such as IL-6 can reach the central nervous system through active transport, binding to receptors on peripheral nerves (e.g., the vagus nerve), and by crossing the blood-brain barrier in areas of increased permeability (Dantzer, Konsman, Bluthé, & Kelley, 2000; Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008). As such, systemic inflammation may affect corticolimbic function by entering the central nervous system to alter neurotransmitter (e.g. dopamine) and neuron functioning (Capuron et al., 2012; Jennifer C Felger & Treadway, 2017; Menard et al., 2017). Considering the multiple differing routes by which inflammation and neural activity relate, the precise mechanism linking inflammation and neural responses in this study is unknown. Future work is needed to gain clarity on the specific pathways linking inflammation and neural reactivity to affective information.

The present findings should be interpreted in the context of the study's limitations. First and foremost, the current study was cross-sectional, which precludes concluding the direction of the association between neural responses and peripheral inflammation. Second, as with many fMRI studies, our project has a relatively small sample size (N=66), and thus future work with larger samples is needed to replicate the findings observed here. Finally, only two markers of systemic inflammation (i.e., CRP and IL-6) were explored in this analysis. Other studies that explore how neural activation varies as a function of a diverse set or pattern of inflammatory markers would be an important contribution to future literature.

In sum, the present project utilized publicly-available data from the MIDUS study to bring together methods from psychoneuroimmunology and affective neuroscience to explore a question at the core of health neuroscience research (Erickson, Creswell, Verstynen, & Gianaros, 2014): How are physiological processes implicated in disease development associated with neural functioning? The results are consistent with theorizing on the neuro-immune network (Nusslock & Miller, 2016), suggesting that inflammation in the periphery is associated with neural activity in and connectivity between regions that are critical for supporting successful social behavior and emotional functioning. More broadly, the present findings highlight the utility of health neuroscience approaches to map the connections between the brain and the body, showing that physiological processes such as inflammation are related to how our brains respond to affective information. As such, physiologic functioning may represent an often-overlooked contributor to and consequence of social and affective processes that social cognitive and affective neuroscience should work to incorporate into future empirical work and theoretical models of functioning within the social brain.

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CHAPTER 4: INCREASES IN IL-6 IN RESPONSE TO THE INFLUENZA VACCINE PREDICTS DECREMENTS IN RESPONSE INHIBITION

Introduction

Both clinical and pre-clinical studies have demonstrated that sustained low-grade inflammation is associated with cognitive impairments (Lai et al., 2017; Su et al., 2019). Other studies report that chronic inflammation may even expedite age-related neurodegenerative diseases (Gorelick, 2010; Bettcher & Kramer, 2014; Beydoun et al., 2018) with increased levels of peripheral markers of inflammation accounting for a 45% increased risk for all-cause dementia (Koyama et al., 2012). While the association between inflammation and cognition has received much attention in cross-sectional studies, fewer studies have experimentally explored how acute increases in inflammation are related to cognitive function in humans. Of the few experimental studies exploring these associations, there are mixed findings regarding whether acute inflammation impairs (Capuron et al., 2001; Meyers & Abbruzzese, 1992) or *improves* (Cohen et al, 2003; Grigoleit et al., 2011) performance on cognitive tasks. Thus, more mechanistic work is needed to fully delineate the effects of acute increases in inflammation on cognitive function.

One potential reason for the mixed findings in experimental studies exploring links between acute inflammation and cognitive function may be due to a lack of precision in the measures of cognitive function within this literature. Within this area, neuropsychological batteries are the most frequently used measures of cognitive function (Fard et al., 2022). While informative, these tests are designed to identify significant pathology in cognition more broadly

(e.g., following stroke) and are less effective at detecting more subtle or specific changes in cognitive functioning of the sort that are likely to accompany short-term increases in inflammation. The trail making test is one example of a common neuropsychological test administered to assess several cognitive abilities (Salthouse, 2012). In this test, individuals are tasked with connecting a series of numbers that are presented in a randomized order. Performance on the task, indicated by completion speed and accuracy, are used to assess several cognitive processes including an individual's ability to sustain attention, alter psychomotor speed, plan and execute tasks, and demonstrate cognitive flexibility. While neuropsychological tests may aide in more general clinical assessment, there is a need for more granular studies that aim to explore links between acute inflammation and specific subcomponents of cognitive function.

One of the most important facets of cognitive function is executive functioning, or the ability to plan, adapt, maintain, and manipulate information (Gilbert & Burgess, 2008). A core sub-component of executive functioning is response inhibition. Like the ability to stop at traffic lights, response inhibition is important for completing everyday tasks as it suppresses prepotent but unwanted actions that may interfere with higher-order cognitive or motor goals. Furthermore, response inhibition is important for attentional control, as inhibiting responses to distracting stimuli is also important for completing cognitive and motor goals. Given how central the ability to discern and inhibit unnecessary responses is to daily function, response inhibition is considered a fundamental component of executive function (Barkley, 1997). Moreover, deficits in response inhibition are implicated in several neuropsychiatric disorders (Mostofsky & Simmonds, 2008), such as attention-deficit hyperactivity disorder (ADHD) and dementia (Migliaccio et al., 2020), and importantly, effective response inhibition facilitates self-regulatory

health behaviors (Papies et al., 2008; Nederkoorn et al., 2010). As a core sub-component of executive function that has important implications for effective functioning in daily life, response inhibition is thus a critical cognitive process to examine when exploring the links between inflammation and executive function. However, to our knowledge no known studies have examined link between inflammation and response inhibition[3].

Another factor that influences response inhibition and is affected by inflammatory processes is sensitivity to rewards (Herrera et al., 2019). Prior work has demonstrated that reward modulates responses on inhibition tasks (Chiew et al., 2016; Geier & Luna, 2012; Wang et al., 2018) and a recent meta-analysis clarified that the prospect for rewards significantly improve inhibition (Burton et al., 2021). Although there was an overall positive association between reward and response inhibition, other studies found that characteristics of the reward may differentially alter the link between reward and performance on response inhibition tasks. For example, other studies reported that the performance on response inhibition tasks are worse when the magnitude of the reward is greater (Freeman et al., 2014; Freeman & Aron, 2016). At higher magnitudes, rewards may intensify difficulty in inhibiting the prepotent response, suggesting a conflict between a natural tendency to approach rewards and the task demands of withholding such approach responses.

Interestingly, inflammation also alters sensitivity to rewards. Inflammation is generally associated with reductions in the sensitivity to rewards (Frenois et al., 2007; Shen et al., 1999; Eisenberger et al., 2010), although recent findings suggest some nuance depending on if the reward is non-social (e.g., winning money) or social (e.g., receiving positive feedback). For

[3] While participants in Brydon et al. (2008) and Handke et al. (2021) completed response inhibition task, Stroop and GNG respectively, authors did not measure response inhibition as they reported associations with reaction time (vs performance and accuracy) speaking to psychomotor function and not executive functioning specifically.

example, inflammation may enhance reward-related neural sensitivity to positive *social* cues (Inagaki et al., 2015; Muscatell et al., 2016) even while decreasing reward-related neural sensitivity to monetary rewards (Eisenberger et al., 2010). Thus, the presence of rewards and the type of reward may interact with levels of inflammation to modulate performance on response inhibition tasks, though this is yet to be explored empirically.

Not only might inflammation influence sensitivity to rewards differentially based on the type of reward to be earned for good task performance, but also based on the magnitude of reward at stake. Indeed, pre-clinical work has found that inflammation alters motivated behavior depending on the potential magnitude of the gain (Vichaya et al., 2014). Following an endotoxin challenge, rodents chose to expend effort to obtain food rewards only when it was highly advantageous. This was demonstrated by an overall reduction in energy expenditure among those exposed to an inflammatory challenge, but an increase in effort for more calorie-rich rewards. These findings suggest that inflammation may also alter the perceived value of an incentive to shift behavior. Along with the variable impact of reward magnitude on response inhibition tasks, these findings suggest that reward magnitude may be an especially relevant factor when exploring the association between inflammation and performance on response inhibition tasks.

Given these nuances in links between cognitive function and inflammation and rewards, the current study aimed to explore whether inflammation alters the impact of reward on response inhibition as a function of reward type and magnitude. To examine this, participants were exposed to a mild inflammatory challenge (i.e., receipt of influenza vaccine) and completed a rewarded go/no-go (GNG) before and after the vaccine. Participants provided blood samples to measure IL6 before and after being administered the influenza vaccine. For this study, participants also completed a modified GNG with four reward types: high social, low social, high

money, and low money outcomes. Participants also provided blood samples to measure change in proinflammatory levels (interluekin-6; IL-6) before and after the influenza vaccine was administered. Overall, we assessed whether an inflammatory challenge and/or reward type modulated performance on a response inhibition task. Specifically, we examined whether greater inflammatory reactivity would be associated with impaired response inhibition and whether the magnitude or sociality of the reward would moderate that association.

Methods

Participants

Fifty-five undergraduate students (37 biologically female; M_{age}=20.06 years, SD_{age}=1.34) at a southeastern university participated in the study from January to April 2022. Participants primarily identified as biologically female (N=37) and White American (43%). Thirty percent identified as Asian American, 9% as Latinx or Latin American, 2% as Black American, and 16% identified as multiracial. Participants were recruited via postings to class listservs and on social media, in which they were first directed to an online eligibility questionnaire. Inclusion criteria were similar to prior studies using the influenza vaccine paradigm (Jolink et al., 2022; Boyle et al., 2019; Kuhlman et al., 2018). Participants were eligible for the study if they were between 18 and 25 years of age and had a non-familial close other in their lives whom they saw every day. Participants were excluded if they (a) had already received the annual influenza vaccine or had had influenza that season, (b) used tobacco products, (c) used mood or immune-altering medications (e.g., anti-depressants, antihistamines), (d) had a current psychiatric diagnosis or reported history of depression or anxiety, (e) had any major medical condition (e.g., diabetes, asthma), (f) had had Guillain-Barre Syndrome (GBS), (g) were allergic to the influenza vaccine or ingredients present in the vaccine (e.g., eggs), or (h) had a current illness. Because the study

was conducted during the COVID-19 pandemic, participants were also screened for self-reported exposure to COVID-19 or any current respiratory symptoms.

Experimental Design

Data were collected as part of a larger study examining the relationship between inflammatory reactivity to the influenza vaccine and social and affective processes. Eligible participants consented via Zoom and were scheduled for two in-lab study sessions, one before and one after receiving the annual influenza vaccine. Given evidence that IL-6 levels peak approximately 24 hours after influenza vaccination (Radin et a., 2021), the post-vaccine session was scheduled to take place approximately 24 hours after the pre-vaccine session. Before the pre-vaccine session, participants provided photos of one close other who they identified as a consistent support figure for them (see photo details below). Both sessions were similar in that participants completed several computer tasks and surveys and provided a blood sample to be assayed for levels of inflammation. The distinguishing feature between sessions was that at the end of the pre-vaccine session, participants received the 2022 influenza vaccine. The vaccine was a 0.5 mL single-dose of GSK's Flulaval Quadrivalent and included the following virus strains: A/California/07/2009 (H1N1), A/Texas/50/2012 (H3N2), B/Massachusetts/02/2012 (Yamagata lineage), B/Brisbane/60/2008 (Victoria lineage).

Measures

Close and Stranger other photos. To participate in the study, participants were asked to choose and provide four photos of a close other who "is not a family member and you see almost every day (close friend, roommate or romantic partner); this is someone in your life you can go to for help or for comfort." They were told that they would be asked questions about this person throughout the study. Because participants could select their choice of a support figure, the

selections spanned various relationship types, with the majority choosing a close friend or romantic partner. A binary relationship type variable was included as a covariate on non-interest in analyses to explore whether inflammation covaried with accuracy on the task regardless of relationship type. Prior to participant arrival, a stranger other photo was selected by the researcher that matched the close other's gender and ethnicity. This photo was selected to be used as the low-magnitude social incentive. One of the close-other photos was used as an incentive in the response inhibition task.

Inflammation. We examined inflammatory reactivity by comparing levels of interleukin-6 (IL-6) in dried blood spots before and after the vaccine. In previous studies examining within-subject variations in inflammation in response to the influenza vaccine, IL-6 exhibits consistent increases after the vaccination (Jolink et al., 2022; Christian et al., 2013; Segerstrom et al., 2012; Tsai et al., 2005; Boyle et al., 2019; Kuhlman et al., 2018; 2020; Radin et al., 2021). At both blood draws, approximately 20uL of blood was collected by finger prick using Neoteryx's Mitra Clamshell devices (https://www.neoteryx.com/mitra-clamshell-blood-collection-device?hsLang=en). Samples were dried overnight and stored in a -80 freezer until study completion. Assays were conducted in triplicate using a high-sensitivity ELLA immunoassay platform to assess IL-6 levels. All samples were detectable, ranging from 0.56–2.37 pg/mL pre-vaccine and 0.59–2.4 pg/mL post-vaccine. Inter-assay CVs were < 12%. Three IL-6 values were more than 3 SDs above the mean; those values were winsorized and retained in the data for analyses. All IL-6 values were log-transformed to adjust for the positive skew in the data.

Go/No-Go Task. We used the Go/No-Go task (GNG) to measure response inhibition. This task has typically been used to measure inhibitory behavior in ADHD (Bezdjian et al., 2009) and health behaviors like smoking, dieting (Meule et al., 2014), and substance use

(Kaufman et al., 2003). This task has also been modified to explore the interaction between incentives and inhibitory behavior (e.g., Lydon et al., 2015). In this GNG task, participants were instructed to press the 'J' key, using their dominant hand, as fast as possible when a blue circle appeared on the screen ("go" trials). However, they had to inhibit the pre-potent "go" response and NOT press the key when an orange circle appeared on the screen ("no-go" trials). Each participant completed 288 trials per session, of which 83.33% (N=240) were go trials and 16.67% (N=48) were no-go trials for each session. To promote sustained attention throughout the task, trial length varied between 250-500ms by 50ms intervals.

At the start of each block of the task (which was randomized across participants and sessions), participants were informed whether accurate performance on that block would earn them money (i.e., monetary reward condition) or time viewing an image of a person (i.e., social reward condition). The magnitude of reward to be earned was also varied across blocks. For the monetary reward blocks, participants could either win $0.08 (high-monetary block) or $0.01 (low-monetary block) for correctly pressing for go cues or $0.25 (high-monetary block) or $0.03 (low-monetary block) for correctly withholding a response for no-go cues. In the social reward blocks, participants could either win time viewing a picture of their smiling close other (high-social block) or a smiling stranger (low-social block), depending on their accuracy. The smiling stranger pictures were matched on gender and ethnic presentation to the close other photos the participants provided. At the end of each block, participants received either a message with the total money they earned for that block or had the chance to view the picture of the close other or stranger. There were 36 trials per block, and each of the four block types (i.e., high monetary, low monetary, high social, low social) was administered twice.

Data Analysis

All analyses were conducted using mixed effects logistic regression models using the *glmer* package in R. This approach allowed us to avoid aggregation and to model individual trial performance nested within the same participant. First, we evaluated task data to explore whether the reward manipulations were successful and differentially related to performance on the task. We explored whether there were significant differences in performance on the GNG task as a function of reward sociality (i.e., monetary or social), reward magnitude (i.e., high or low), and trial type (i.e., go or no-go trials). Additionally, we computed dprime (d') based on signal detection theory to assess overall discriminability success between go and no-go stimulus in the task using the *psycho* package in R. Furthermore, we also explored differences in reaction time and reaction time variability among successful go trials.

For the first model, accuracy on each trial from both the pre- and the post-vaccine sessions was treated as the criterion variable, and participant ID as the random intercept. This model explored whether there were significant differences in commission errors (incorrectly responding to the no-go cue) or omission errors (failure to respond to the go cues) by reward sociality, reward magnitude, as well as the 2-way (i.e., trial type by reward sociality; trial type by reward magnitude) and 3-way (i.e., trial type by reward sociality by reward magnitude) interactions between these factors. For d', reaction time, and reaction time variability, a similar model was conducted; however, the trial type factor was omitted. Thus, the overall models included the main effects of reward sociality and reward magnitude, as well as the 2-way interaction (i.e., sociality by magnitude).

Next, we examined whether IL-6 reactivity to the vaccine, which we computed as the difference between post-vaccine IL-6 and pre-vaccine IL-6, was significantly associated with

accuracy on the GNG task. Given that our primary interest was the association between IL-6 reactivity and accuracy, we tested two- and three-way interactions between IL-6 reactivity and reward sociality and/or reward magnitude. Specifically, we explored the main effect of IL-6 reactivity on accuracy, as well as the 2-way interactions between IL-6 reactivity and the main task factors including trial type, reward sociality, and reward magnitude. As a final contrast, we also explored the interaction between IL-6 reactivity, reward sociality and reward magnitude. A similar analysis was conducted for the d', reaction time, and reaction time variability task outcomes. We again explored the main effect of IL-6 reactivity on the additional task outcomes, as well as the 2-way interaction between IL-6 reactivity and the main task factors including reward sociality and reward magnitude. The interactions between IL-6 reactivity, reward sociality and reward magnitude were also explored on the remaining task outcomes. Significant interactions were probed using the *interactions* package in R (Long, 2019).

Model covariates. Because pre-vaccine IL-6 levels and IL-6 reactivity were significantly negatively correlated ($r = -0.66$, $p<.001$) and following recommended best practices when using change scores in analyses (Llabre et al., 1991; O'Connell et al., 2017), we controlled for pre-vaccine IL-6 levels in reactivity models. This control allowed us to isolate associations with change in IL-6 to the vaccine. To explore whether IL-6 reactivity was uniquely related to task performance after the vaccine, baseline accuracy during the pre-vaccine session was included as a predictor of non-interest in our reactivity model to account for individual level differences in response inhibition ability. We also accounted for close-other relationship type in our analyses by including relationship type (close friend N = 41 or romantic partner N = 14) as an additional covariate. Finally, body mass index (BMI) and assigned sex at birth (ASAB) were added to both models as level 2 covariates (O'Connor et al., 2009).

Results

Effects of Reward Type and Magnitude on Overall Go/No-Go Task Performance

Accuracy. We first examined overall accuracy on the GNG task across both sessions. Participants accurately responded correctly on 70.95% of trials (SD=0.08) pre-vaccine and 74.04% of trials post-vaccine (SD = .07) on the trials (see table 1 for overall task performance).

Table 4.1. Overall Performance Outcomes for GNG Task

Metric	Overall	Pre-vaccine	Post-vaccine
Accuracy	0.81	0.79	0.82
Commission error rate	0.69	0.70	0.67
Omission error rate	0.19	0.21	0.18
dprime	0.39	0.30	0.48
Go Reaction Time	256.26	262.89	249.64
Go Reaction Time Variability	62.39	58.50	66.29

Replicating the standard go/no-go effect, analyses revealed a main effect of trial type (see table 4.1 for full details) such that participants had lower accuracy on the no-go trials versus the go trials. There were no significant main effects of reward type or magnitude on accuracy (i.e., see Table 4.2 for details). However, there was a sociality-by-trial type interaction, whereby there were significant differences in performance on no-go trials by the sociality of the outcome. Participants produced fewer errors of commission (i.e., were more likely to NOT press the button on no-go trials) when the reward to be earned was social versus monetary. There was also a marginal interaction between reward magnitude and trial type, such that participants completed fewer errors of commission (i.e., were more accurate on no-go trials) during low versus high gain

conditions. However, there was no sociality-by-magnitude effect on accuracy. Finally, there was not a 3-way interaction between sociality (i.e., social vs. monetary), magnitude (i.e., high vs. low), and trial type (i.e., go vs. no-go trials).

Table 4.2. Task Effects of Reward Type and Magnitude on GNG Accuracy				
	Estimate	Std. Error	z value	Pr(>|z|)
(Intercept)**	1.41	0.48	2.91	0.00
ASAB	0.17	0.12	1.40	0.16
BMI	-0.02	0.02	-1.01	0.31
Session**	0.19	0.03	6.62	3.49E-11
Relationship type	0.06	0.14	0.46	0.65
Sociality	0.02	0.05	0.41	0.68
Magnitude	-0.05	0.05	-1.05	0.29
Trial type**	-2.53	0.07	-35.07	1.94E-269
Sociality by Magnitude	-0.03	0.06	-0.50	0.62
Sociality by Trial type**	0.22	0.10	2.16	0.03
Magnitude by Trial type	0.19	0.10	1.87	0.06
Sociality by Magnitude by Trial type	0.07	0.14	0.49	0.62

**Denotes significant at p<0.05; ASAB=assigned sex at birth; BMI=body mass index

Dprime. We examined overall dprime on the GNG task across both sessions. Participants demonstrated an average dprime of 0.30 pre-vaccine and 0.48 post-vaccine on the trials (see table 4.1 for overall task performance). There was a significant main effects of reward type (b= 0.15, SE=0.07, p=0.03), whereby dprime was greater during social versus non-social trials. There was no main effect of magnitude on dprime (p=0.75). Furthermore, the 2-way interaction between sociality and magnitude on dprime was also not significant (p=0.70).

Reaction Time. We examined reaction time difference on the correct go trials across both sessions of the task. Participants demonstrated an average reaction time of 262.89 ms pre-vaccine and 249.64 ms post-vaccine on the trials (see table 4.1 for overall task performance).

There was a significant main effects of reward type (b= -4.84, SE=1.17 , p<0.001) on reaction time, whereby participants were faster to respond on social versus non-social go trials across both sessions. There was also significant main effects of reward magnitude (b= -2.53, SE=1.18 , p=0.03) on reaction time, whereby participants were faster to respond on low versus high reward go trials across both sessions. Finally, the 2-way interaction between sociality and magnitude on reaction time was also not significant for go trials across both sessions (p=0.19).

Reaction Time variability. Finally, we examined differences in reaction time variability on the correct go trials across both sessions of the task. Participants demonstrated an average reaction time variability of 58.5 ms pre-vaccine and 66.29 ms post-vaccine on the trials (see table 1 for overall task performance). There was a significant main effects of reward type (b= 3.13, SE=0.23, p<0.001) on reaction time variability, whereby participants were more variable in their responses on social versus non-social go trials across both sessions. There was also significant main effects of reward magnitude (b= 2.24, SE=0.23 , p<0.001) on reaction time variability, whereby participants were more variable in their responses on low versus high reward go trials across both sessions. Finally, the 2-way interaction between sociality and magnitude on reaction time was also not significant for go trials across both sessions (p=0.21).

Effects of Inflammatory Reactivity on Go/No-Go Accuracy

Accuracy. Next, we conducted a mixed effects logistic regression model to examine whether IL-6 reactivity to the influenza vaccine (i.e., change in IL6 pre- to post-vaccine) predicted accuracy on the GNG task. There was no main effect of IL-6 reactivity on overall task accuracy (p>0.05; see Table 4.3). However, there was a significant trial type by IL-6 reactivity interaction on GNG task accuracy. Specifically, greater IL-6 reactivity to the vaccine was associated with poorer performance on the NG trials. In other words, participants who

experienced larger increases in IL-6 made more commission errors during the NG trials (i.e., they were less likely to inhibit the button press on NG trials see Figure 4.1). There were no other significant 2- or 3- way interactions between IL-6 reactivity and incentive type or magnitude (see Table 3 for full details).

Table 4.3. IL-6 Reactivity and Accuracy on Rewarded GNG

	Estimate	Std. Error	z value	Pr(>|z|)
(Intercept)**	-1.15	0.42	-2.72	0.01
IL6_change	0.62	0.42	1.48	0.14
ASAB	0.00	0.08	0.05	0.96
BMI	-0.01	0.01	-1.22	0.22
Relationship type	-0.04	0.09	-0.42	0.67
Session 1 accuracy**	**3.58**	**0.44**	**8.14**	**3.87E-16**
Session 1 IL6	-0.17	0.37	-0.45	0.65
IL6_change by Sociality	-0.05	0.40	-0.13	0.90
IL6_change by Trial type**	**-5.16**	**0.66**	**-7.84**	**4.34E-15**
IL6_change by Magnitude	0.09	0.40	0.22	0.83
IL6_change by Sociality by Magnitude	-0.37	0.56	-0.66	0.51
IL6_change by Sociality by Trial type	0.59	0.92	0.64	0.52
IL6_change by Magnitude by Trial type	-0.14	0.93	-0.15	0.88

**Denotes significant at p<0.05; ASAB=assigned sex at birth; BMI=body mass index

Figure 4.1. Plot of interaction between IL-6 reactivity and trial type accuracy

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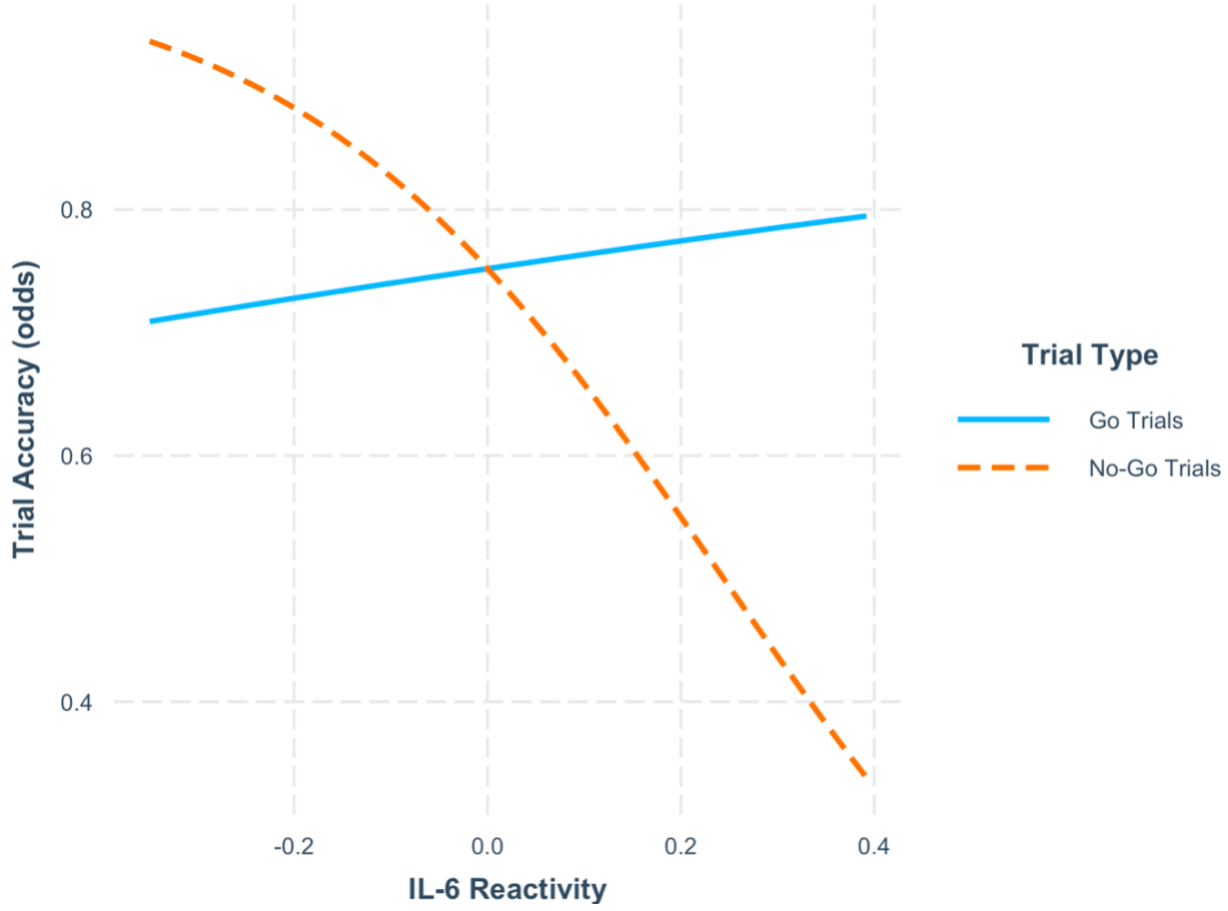


Dprime. Next, we conducted a mixed effects regression model to examine whether IL-6 reactivity to the influenza vaccine (i.e., change in IL6 pre- to post-vaccine) predicted dprime on the GNG task following the vaccine. There was no main effect of IL-6 reactivity on dprime ($p=0.39$). Moreover, there were no other significant 2- or 3- way interactions between IL-6 reactivity and incentive type or magnitude ($ps>0.05$) on dprime.

Reaction time. Again, we conducted a mixed effects regression model to examine whether IL-6 reactivity to the influenza vaccine (i.e., change in IL6 pre- to post-vaccine) predicted reaction time on the GNG task following the vaccine. There was no main effect of IL-6

reactivity on reaction time (p=0.84). Moreover, there were no other significant 2- or 3- way interactions between IL-6 reactivity and incentive type or magnitude (ps>0.05) on reaction time.

Reaction time variability. Finally, we conducted a mixed effects logistic regression model to examine whether IL-6 reactivity to the influenza vaccine (i.e., change in IL6 pre- to post-vaccine) predicted reaction time variability on the GNG task following the vaccine. There was no main effect of IL-6 reactivity on overall reaction time variability (p>0.05; see Table 4.4).

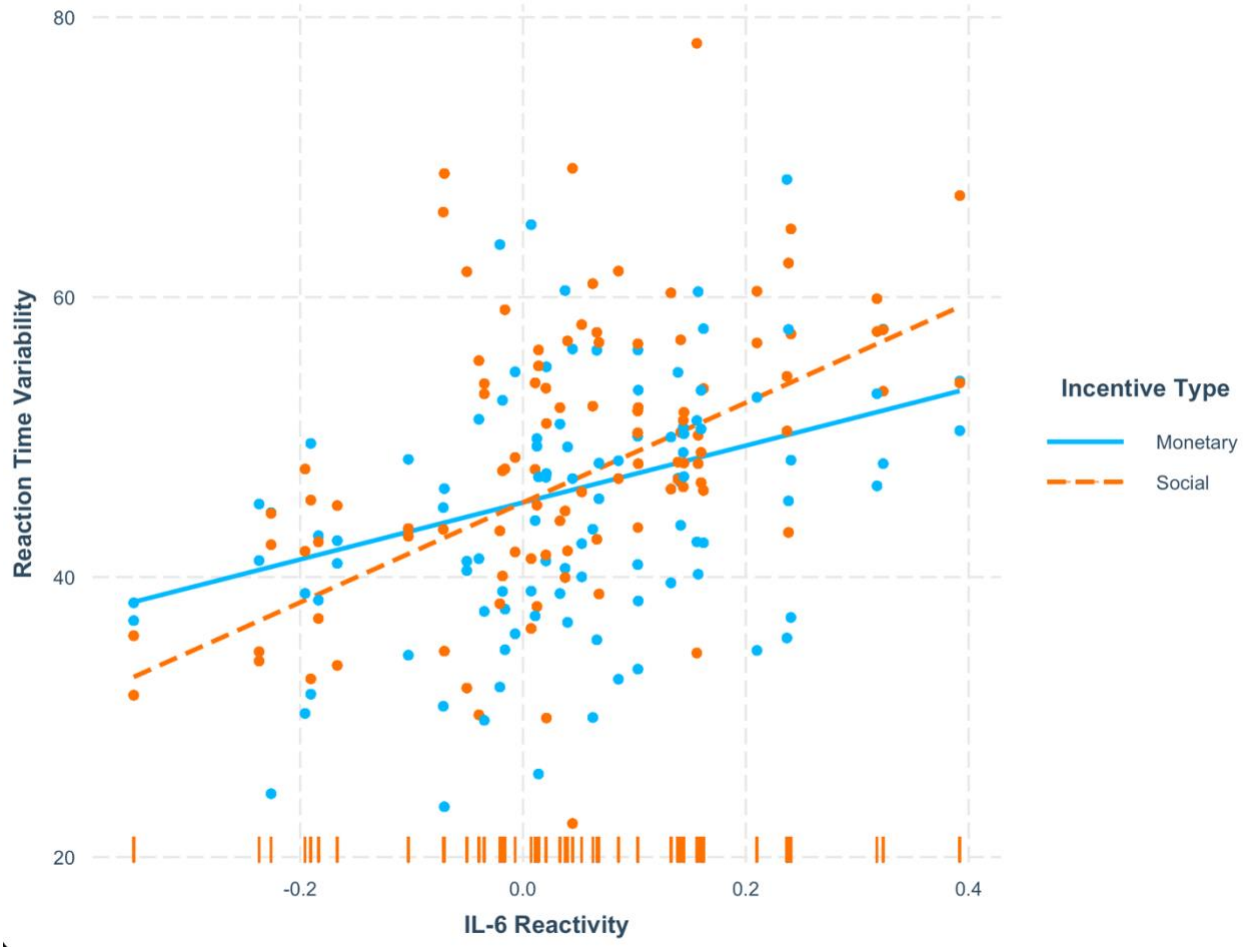
Table 4.4. IL-6 Reactivity and Reaction Time Variability

	Estimate	Std. Error	df	t value	Pr(>|t|)
(Intercept)	9.87	17.69	44.00	0.56	0.58
IL-6 change	20.33	15.41	44.30	1.32	0.19
ASAB	10.05	12.33	44.00	0.82	0.42
BMI	-0.63	0.49	44.00	-1.29	0.20
Session 1 IL-6	10.07	16.03	44.00	0.63	0.53
Session 1 Reaction Time Variability**	**0.92**	**0.11**	**43.99**	**8.22**	**0.00**
IL-6 change by Sociality**	**15.34**	**1.50**	**10031.05**	**10.21**	**0.00**
IL-6 change by Magnitude**	**4.22**	**1.49**	**10031.02**	**2.83**	**0.00**
IL-6 change by Sociality by Magnitude**	**-17.51**	**2.12**	**10031.07**	**-8.25**	**0.00**

**Denotes significant at p<0.05; ASAB=assigned sex at birth; BMI=body mass index

However, there was a significant IL-6 reactivity by sociality interaction (see Table 4.4). Simple slopes analyses revealed that the slope for IL-6 reactivity was significantly different for social trials (b=34.93, SE=15.40, p=0.03) but not monetary trials (b=24.94, SE=15.40, p=0.11). In other words, greater IL-6 reactivity was associated with more reaction time variability for social incentive trials specifically (see figure 2).

Figure 4.2. Plot of interaction between IL-6 reactivity and sociality on reaction time variability.



There was also a significant IL-6 reactivity by magnitude interaction. Simple slopes analyses did not specify whether the associations with IL-6 reactivity were specific to high versus low incentive trials (ps>0.10). Visual inspection of the interaction plots suggests that at higher levels of IL-6 reactivity, low and high incentive trials were both associated with greater reaction time variability (see figure 4.3).

Figure 4.3. Plot of interaction between IL-6 reactivity and magnitude on reaction time variability.

The exploratory 3- way interaction between IL-6 reactivity, incentive type, and magnitude was also significant (see table 4). Simple slopes analyses revealed that the slope for IL-6 reactivity was significantly different for high social incentive trials (b=34.93, SE=15.40, p=0.03) but not for low social, high monetary, or low monetary incentives (ps>0.10). In other words, participants who experienced larger increases in IL-6 were more variable in their go responses for trials where the potential reward was time viewing a picture of a smiling close other (see figure 4.4).

Figure 4.4. Interaction between IL-6 reactivity, sociality, and magnitude on reaction time variability.

Discussion

While the association between low-grade inflammation and cognition has received much attention, comparatively fewer studies have explored the effect of acute increases in inflammation on cognitive functioning in humans. Thus, in the current study, we examined the impact of an inflammatory challenge on response inhibition, a key subcomponent of executive function. Using a within-subjects design, we examined performance on an incentivized response inhibition task both before and after receiving the influenza vaccine. We found that greater increases in IL-6 in response to the vaccine were associated with an increase in errors of commission (failures to inhibit a prepotent response) on the GNG task. To our knowledge, this is the first experimental demonstration of inflammation-related alterations in response inhibition. This is important given that response inhibition is a critical skill for navigating daily life with implications for self-regulatory health behaviors.

These results expand upon the cross-sectional studies of inflammation and cognitive function and suggest that effects may not be limited to Alzheimer's and dementia-related diseases. While the majority of research exploring links between inflammation and cognition has been limited to aging and dementia-related cognitive changes, these results suggest that acute increases in inflammation may be relevant to cognitive functioning across the lifespan. Another contribution to the literature involves the ability to disentangle the effects of inflammation from other age-related changes that often confound studies of inflammation and cognition. Notably, peripheral inflammatory markers increase with age and heightened levels can relate directly and indirectly to dementia risk via their role in the development and progression of other conditions also known to influence cognitive function. Therefore, while the association is known, specificity regarding the direction of effects between inflammation and cognition is still

questioned. We are showing that an acute increase in inflammation is related to response inhibition, strengthening conclusions that can be drawn about the causal nature between inflammation and cognition. Furthermore, given our within-subjects design, we are able to address some of the issues with correlational studies, such as controlling for the potential effects of individual differences on response inhibition and enhancing sensitivity to detect effects even among this young, relatively healthy sample of participants.

How might inflammation engender deficits in response inhibition? Though the present study doesn't address this question directly, prior work provides insight into plausible mechanisms. Indeed, preclinical evidence demonstrates that inflammation in the periphery can access the brain to influence neural processes associated with cognitive control and motivated behavior (see Haroon et al., 2012 & Dooley et al., 2018 for reviews). Pro-inflammatory cytokines, such as interleukin-6, can alter molecular and cellular aspects of cognition (McAfoose & Baune, 2009) via neuron-to-glia communication (Jurgens & Johnson, 2012; Wohleb et al., 2013), neurogenesis (Hueston et al., 2017; McKim et al., 2016), neuroplasticity (Delpech et al., 2015; Calabrese et al., 2014), long-term potentiation (Wohleb & Delpech, 2017), and neurotransmitter systems (Dantzer et al., 2008; Zhu et al., 2006). Evidence suggests that one key mechanism linking inflammation and neurocognitive function is via the dopaminergic neurotransmitter systems. Dopaminergic signaling is important for response inhibition through well-established effects in the striatum and cortex (Westbrook et al., 2021). The basal ganglia, a region within the striatum supplied with high levels of dopamine, has been found to regulate the cognitive proactive and reactive processes needed during the Go/No-Go task (Beste et al., 2010; Criaud et al., 2021). Together, these findings suggest possible neurobiological mechanisms for the observed link between inflammation and executive functioning; future neuroimaging

research is needed to examine these possibilities in humans and to establish the neurobiological pathways through which peripheral inflammation may influence executive functioning.

Contrary to expectations, we did not find a relationship between increases in IL-6 following the vaccine and accuracy on the GNG task and as a function of incentive type. There are many possible reasons for this null interaction effect. First, the fact that we observe a main effect of inflammation on no-go trial task performance but do not find moderation by incentive type supports the notion that inflammation "breaks the link" between incentives and task performance, regardless of incentive type. Along these lines, a recent meta-analysis exploring the links between response inhibition and reward found that rewards are associated with improvements in response inhibition (Burton et al., 2021). In our data, we see that inflammation was related to poorer response inhibition despite the presence of rewards. This suggests that inflammation might have mitigated the positive effect that rewards typically have on response inhibition tasks. However, we did not have a no-incentive condition, so this hypothesis would require follow-up testing to explore whether the relationship between inflammation and accuracy on the current task was due to the presence of incentives for all trials.

Other decisions regarding task parameters may have potentially affected the patterns of associations observed. Indeed, a recent paper notes that there are several aspects of task design that may influence participants' performance on incentivized cognitive control paradigms (Chiew et al., 2021). Specifically, task difficulty and task length are both found to moderate the association between reward and response inhibition. A follow-up study should explore whether lengthening the task, decreasing the ratio between go- and no-go trials, enhancing the incentives, and/or shortening the reaction time window are associated with a different pattern of associations with inflammation. Relatedly, recent work suggests that both the expectations of reward (Herrera

et al., 2019) and the probability of acquiring the reward importantly guide an individual's allocation of cognitive control at the start of tasks (Fromer et al., 2021). Indeed, participants in Fromer et al. (2021) showed more cognitive control when the potential gain and the likelihood of successfully obtaining the gain were highest. Thus, a future study ought to explore whether changes in gain likelihood would be significantly modulate the association between by inflammatory reactivity and response inhibition.

To that point, several studies exploring the connection between inflammation and reward processing suggest that the link between inflammation and motivated behavior may be more about effort expenditure than reward sensitivity per se. For example, a prior study with rodents showed that higher levels of inflammation were associated with an overall decrease in task engagement, similar to that observed here. However, they also found that rodents with the highest levels of inflammation actually performed better on high effort/high reward tasks, suggesting that inflammation may make individuals more likely to save their energy/effort for tasks that are likely to generate a large reward (Vichaya et al., 2014). Similarly, increases in IL-6 to the influenza vaccine in humans were associated with a lower likelihood of choosing to complete hard trials in the Effort expenditure for rewards task (Boyle et al., 2019). In the current study, we did not manipulate effort or task difficulty. In all, the null findings from this study raise several questions for a line of research exploring whether and how inflammation may modulate the relationship between motivation and cognitive processes.

The present findings should be interpreted in light of the study's limitations. For instance, the lack of a placebo/sham vaccine control group limits the ability to make any causal inferences from our data. While we entered statistical controls in our models (i.e., controlling for baseline inflammation and task accuracy), future experimental work ought to unpack the causal

relationship between increases in inflammation and incentive response inhibition. Additionally, it is possible that the sample size was too small to be generalizable, particularly considering that our sample comprised undergraduate students under the age of 25. Although our sample is larger than other studies published in this area, it is possible that sample size decreased our power to detect smaller effects of interest, including the critical three-way (inflammation by sociality by magnitude) interaction. It is also important to consider that this study only focused on changes in one pro-inflammatory cytokine, IL-6, and there may be other cytokines that could mediate the relationship between inflammatory reactivity and response inhibition. As such, the results of this study should be interpreted with caution.

Although large-scale epidemiological studies suggest that inflammation may be associated with cognitive impairments, there have been few experimental studies exploring links between inflammation and cognitive functioning. Given the importance of response inhibition for daily life functioning and self-regulatory health behaviors, the current study examined whether response inhibition, a component of executive function, was impaired following a mild-inflammatory challenge. Results showed that higher increases in interleukin-6 after the influenza vaccine were associated with lower accuracy on no-go trials, regardless of reward sociality or magnitude. To our knowlede, these findings are the first to demonstrate that increased inflammation is associated with impaired response inhibition. These findings highlight the potential role of inflammation on executive function and suggest that further experimental work is needed to better understand the complex relationship between inflammation and cognition.

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CHAPTER 5: GENERAL DISCUSSION

The current dissertation aims to contribute empirical support for the assertions that affective processing is significantly influenced by prior experiential and internal physiological information. The first study found that one's contextual history may differentially shape how the brain processes affective information by demonstrating that the activity and connectivity of the allostatic interoceptive network varied by socioeconomic position. Study 2 explored inflammation as one source of physiological information that can influence affective processing finding that levels of systemic inflammation were associated with less activity to positive content in subcortical regions. Then, in study 3, I examined how shifting inflammation may alter affective processing via changes in motivated behavior. Overall, inflammation altered performance on an executive functioning task regardless of the potential type of gain. By investigating how affective processing integrates prior external information (study 1) and internal physiological information (studies 2 & 3), the current set of studies enhances the field's understanding of the constituent elements, the brain utilizes to generate affective experiences and guide behavior. In what follows, the general discussion will describe themes that emerged across studies, discuss the implications of the studies, and conclude with a summary of research directions for this author.

Shared Themes Across Studies

Theme # 1: Context shapes reactivity to positive affective stimuli

Across all three studies, my findings highlight the crucial role of context in shaping reactivity to positive affective stimuli. These findings offer significant contributions to the field of affective neuroscience, which has traditionally focused on the study of individual sensitivity to negative affective stimuli while neglecting positive non-monetary stimuli. Moreover, investigations into the impact of inflammation on affective processing have primarily centered around sensitivity to monetary rewards, predominantly within clinical samples. However, the current analyses have revealed compelling evidence that both SES and inflammation profoundly influence responses to positive non-monetary stimuli. Notably, in study 2, reactivity to positive stimuli emerged as a more salient factor than reactivity to negative stimuli, challenging the prevailing emphasis on negative affect. These findings are consistent with prior work that underscores the benefits of positive affect on well-being, including enhanced resilience, strengthened social connections, and improved psychological well-being (Tugade et al., 2004; Cohen & Pressman, 2006).

These findings contribute significantly to the affective processing literature, as few studies have explored associations between positive affect and socioeconomic position or inflammation. Among the only two known studies that have examined associations by SEP, both found a positive association between SEP and neural responses to positive stimuli, such individuals with lower SEP showed blunted activity in the amygdala and insula to happy infant faces (Kim et al., 2017) and blunted activity in several subcortical regions (e.g., caudate, hippocampus) to positive scenes (Silverman et al., 2009). While informative, both studies had limitations pertaining to sample characteristics that reduced the generalizability of the findings.

For example, only 15 participants were included in the Silverman et al. (2009) sample, and all individuals that were included were young adults (M_{age}=24). Moreover, the participants in Kim et al.'s (2017) were all first-time mothers who were within six months of giving birth. In study 1 within the current dissertation, the sample was larger and more inclusive of age (range= 35-76) and socioeconomic position (less than high school through graduate degree earner) to address concerns of generalizability. Among this sample, lower SEP was associated with greater activity in several regions, including corticostriatal regions such as the caudate, nucleus accumbens, and ventral-mPFC. Given that regions within the caudate nucleus are linked to associative learning (Delgado et al., 2004) and shifts in behavior to maximize potential gains (Haruno et al., 2004), this enhanced activity to positive stimuli among individuals with lower SEP may suggest greater attention and preparation for gain. A lower-SEP context may engender enhanced vigilance and preparation to secure potential gains in environments with fewer resources and greater uncertainty (Gonzalez et al., 2016; Ellis et al., 2009).

Similar to SEP, very few studies examine the link between inflammation and neural reactivity to positive stimuli. Both studies suggested that greater neural responses to positive stimuli might be related to lower levels of systemic inflammation. One study among 12 men found that greater activity in the medial prefrontal cortex (mPFC) in response to pictures of a favorite actor was related to better innate immune system functioning (Matsunaga et al., 2008). A second found that greater activity in the mPFC in response to positive autobiographical memories was related to lower inflammation (Matsunaga et al., 2013) in a sample of 10 volunteers. These studies, however, were both conducted in small samples, again limiting the generalizability of the findings. Results from study 2 in the current dissertation extend findings to a larger sample and beyond the mPFC to support an inverse relationship between

inflammation and positive affect such that higher levels of peripheral inflammation were associated with lower activation in the amygdala, hippocampus, anterior insula, and temporal pole in response to positive images (vs. neutral). Overall, this dissertation sheds light on the neurocognitive mechanisms underlying positive affect and seeks to encourage further investigation in this domain.

Theme # 2: Inflammation influences affective processing at low-grade levels

In the current studies, I have demonstrated that even subtle differences in inflammation, below the typical thresholds associated with sickness, were associated with notable influence on affective experiences. This extends prior research that mainly examines associations among more potent acute inflammatory models of sickness. In study 2, I excluded individuals who reported high levels of C-reactive protein (CRP) levels, ensuring that I focused specifically on individuals with relatively low-grade inflammation not demonstrating current illness. Similarly, in study 3, the influenza vaccine elicited minor interleukin-6 (IL-6) fluctuations that remained below the levels typically seen during illness. While distinct from the typical models of acute inflammation that engender more pronounced symptoms of sickness, the current two studies allowed us to investigate the effects of inflammation within a range more representative of everyday physiological fluctuations.

By exploring these subtle changes in affective processing linked to differences in low-grade inflammation, my research contributes to a deeper understanding of how even minor increases in inflammation can impact one's emotional life. For instance, a single unhealthy meal or a restless night of sleep, both of which can trigger mild inflammatory responses, can have influential effects on one's affective experiences throughout the day. Relatedly, an intriguing aspect of my findings is that these effects on affective processing can operate below conscious

awareness such that inflammation can subtly shape one's emotional experiences without consciously perceiving or attributing them to physiological changes. This highlights the complex interplay between physiological states and emotional responses, underscoring the need to investigate the underlying mechanisms that connect inflammation to affective processing.

Theme # 3: Context may shape cognition via changes in affective processing

Another theme arising from this set of studies is the idea that context may shape cognitive functioning, particularly through alterations in affective processing. These studies demonstrate the relevance of both experiential context (as captured by SEP in study 1) and physiological context (as measured by inflammation in study 2) in shaping cognitive mechanisms. In study 1, an intriguing finding emerged, revealing that SEP is associated with differences in the efficiency of interaction between the AIN and ECN. Specifically, individuals with lower SEP exhibited increased integration between these networks during affective processing. This observation raises important questions about how socioeconomic factors impact cognitive processes related to affective stimuli. Notably, the ECN underlies executive functioning processes during working memory, cognitive control, and attentional tasks. The findings suggest that individuals from lower SES backgrounds may display altered cognitive processes during affective tasks, potentially influencing decision-making and other affect-cognition processes, such as emotional regulation abilities. Furthermore, study 3 provides additional insights by demonstrating that participants who displayed heightened responsiveness to the inflammatory challenge exhibited reduced response inhibition across all reward conditions. Together, these studies highlight the importance of context in the link between affective and cognitive processes.

A potential system that may underlie this shared link between affect and cognition is the dopaminergic system. Previous research has elucidated the role of the basal ganglia, known for its high concentration of dopamine, in regulating proactive and reactive cognitive processes crucial for tasks involving executive functions (Beste et al., 2010; Criaud et al., 2021). Intriguingly, inflammation has been shown to directly affect basal ganglia and dopamine production, potentially influencing cognitive functioning. Moreover, lower SES has been associated with lower levels of dopamine receptors in the brain, suggesting a link between socioeconomic factors and dopaminergic functioning. Overall, these findings highlight the complex interplay between contextual factors, affective processing, and underlying neural systems, providing valuable insights into the mechanisms driving individual differences in cognitive functioning.

Limitations & Discrepancies

Moving beyond the examination of shared themes, the following section delves into the limitations and discrepancies across the studies. There are several limitations to study 3 that ought to be addressed in future studies to further the field's understanding of the mechanisms implicating inflammation with the affect-cognition link. First, an important caveat to note was that response inhibition was not assessed outside of the context of reward in this study. In other words, there were no control trials in which participants were not receiving a reward that could have been compared to trials in which there was not an affective component. This limitation poses a substantial question for future research, as it would be important to determine whether the association between inflammation and response inhibition exists regardless of the potential to win monetary or social rewards.

Additionally, results from this study are unable to fully address whether associations between inflammation and response inhibition are unique to that subdomain of cognition or whether the associations reflect impairments in a third variable not explored in this study. For example, it is unclear whether inflammation disrupts attentional processes more generally, ultimately affecting performance on a response inhibition task. Perhaps, inflammation's disruption of attentional processes more generally may suggest that inflammation disrupts cognitive functioning more broadly. Future research should further probe these mechanisms to determine the specific role inflammation may play in altering cognitive processes. To address the gaps highlighted by both limitations, I propose a study that examines the relationship between inflammation and cognitive functioning among individuals across a variety of cognitive tasks in the future directions section below.

While the findings in study 1 and study 2 shed light on the intricate neurocognitive links between socioeconomic position (SEP) and reactivity to positive stimuli, there are intriguing divergences that warrant careful consideration. Previous research consistently reports a negative association between SEP and inflammation (see Muscatell et al., 2020 for meta-analysis), such that lower SEP is associated with increases in inflammation. This link suggests a potential mediating role of inflammation in the SEP to positive affective processing relationship. In study 1, I observed that lower SEP was associated with higher activity in response to positive stimuli, while study 2 revealed that higher inflammation levels were associated with reduced activity to positive stimuli. However, if I assume that low SEP is indeed linked to higher inflammation, study 1 of this dissertation should have shown decreased activity to positive stimuli. Instead, I report an increase in activity to positive stimuli in study 1, which raises important questions regarding the underlying mechanisms at play.

There are several reasons that may explain the discrepancy between the findings. One possibility may be due to sample differences between the two studies. It is plausible that study 2 of this dissertation may have lacked sufficient variability in SEP, such that participants in that study may have been of higher SEP. In this case, the association between inflammation and reactivity to positive stimuli may not overlap between groups, given that socioeconomic variability between the samples was significantly distinct.

Furthermore, the discrepancy may stem from differences in measuring neural activity versus neural connectivity between the two studies. In study 2, participants with higher inflammation demonstrated decreased activity to positive stimuli in a cluster primarily encompassing the amygdala and hippocampus. However, whole-brain activity results from study 1 did not demonstrate a significant association between SEP and activity to positive stimuli in the amygdala and hippocampus. Study 2 did find, however, that connectivity among a network, including the amygdala and the hippocampus, did significantly differ by SEP. Perhaps, inflammatory processes may alter subcortical to cortical interactions, ultimately modulating the dynamics within and between these brain regions that ought to be further explored in future research. In support of this notion, study 2 demonstrated that while inflammation was associated with decreased activity in the hippocampus to positive stimuli, inflammation was conversely associated with increased connectivity between the hippocampus and medial prefrontal cortex, which has also been replicated in another sample (Kitzbichler et al., 2021).

Finally, it is worth noting that inflammation may not be the sole pathway through which SEP influences brain responses to positive stimuli. Other physiological pathways may link SEP to positive affect, including direct changes to neurotransmitter, endocrine, and autonomic systems that also vary by SEP. Future research should delve deeper into these factors to gain a

comprehensive understanding of the complex interplay between SES, inflammation, and neural processes underlying reactivity to positive stimuli. To address this gap, I propose a study that examines the relationship between inflammation and positive affective processing among individuals across the spectrum of SEP in the future directions section below.

Implications for health

The current studies have implications for health and have revealed valuable information regarding the mechanisms by which affective processing can contribute to poorer health. These studies identify two distinct pathways that link affective processing to health, namely, a neurobiological pathway and a behavioral health pathway.

Pathway #1: neurobiological pathway suggesting heightened and sustained AIN efficiency as a driver of poor health

Study 1 revealed that individuals with lower socioeconomic positions (SEP) exhibit enhanced transfer of affective information within regions of the allostatic interoceptive network (AIN). This heightened efficiency within the AIN has valuable implications as it facilitates attention to salient information and mobilizes the necessary physiological resources for responding appropriately (Kleckner et al., 2017; Barrett, 2017). According to global workspace theory, the neural architecture responsible for the exertion of cognitive effort during complex tasks is characterized by enhanced processing through longer connections, leading to increased global efficiency. As such, it is possible that the global workspace is activated or enhanced when individuals with lower socioeconomic positions (SEP) are attending to novel, unpredicted, affective stimuli. Sustaining this level of integration requires energy (Dehaene et al., 1998; Kitzbichler et al., 2011), and it is worth noting that prolonged elevation in global network efficiency is associated with higher metabolic costs (Bullmore & Sporns, 2012).

While increased efficiency within the AIN may prove beneficial in certain circumstances, it is essential to consider the potential long-term consequences. Chronic activation and sustained preparedness for environmental threats can take a toll on the body over time, resulting in physiological wear and tear (McEwen & Gianaros, 2010). Perhaps, one pathway to this wear and tear results from the higher metabolic costs associated with the AIN's sustained and prolonged global efficiency. The energy allocated to prepare for threats diverts resources from other vital restorative processes that the body requires for optimal functioning. In essence, this energy allocation competes with mechanisms promoting longevity, growth, and repair (Bobba-Alves et al., 2022). Consequently, the heightened efficiency within the AIN, which underlies physiological activation, may prove detrimental in the long run, potentially adversely affecting overall health and mental functioning (Colich et al., 2020).

In summary, while the enhanced transfer of affective information within the AIN among individuals with lower SEP holds immediate benefits, it is crucial to consider the potential costs in terms of long-term physiological wear and tear. Further research is needed to thoroughly evaluate the potential impact of prolonged AIN global efficiency on overall health and well-being to assess further the hypothesis that increased metabolic demands may divert resources from restorative processes. To address this gap, I propose a study that examines the relationship between AIN efficiency and metabolic health among a sample of older adults in the future directions section below.

Pathway #2: behavioral health pathway suggesting that enhanced inflammation reduces response inhibition

The current set of studies reveals an important health implication, particularly highlighted in study 3. The findings demonstrate a significant association between increased inflammation and decreased response inhibition. This finding suggests that inflammation may make executive

functioning more difficult, potentially hindering individuals' ability to engage in healthy behaviors. Indeed, response inhibition plays a crucial role in overriding urges to engage in health-reducing behaviors, allowing individuals to adhere to their health behavior goals (Allan et al., 2016). For example, one study found that dieters with stronger response inhibition were more successful at losing weight than those dieters lower in response inhibition (Hoffman et al., 2014). Relatedly, another study found that better response inhibition on the go/no-go was associated with greater correspondence between the intention to exercise and actual exercise (Hall et al., 2008).

Aligning with these findings, other studies examining the link between inflammation and decision-making have found that inflammation is associated with impulsive behavior (Gassen et al., 2019a; Gassen et al., 2019b). Relatedly, research has also found that individuals with more impulsivity-related traits have a higher white blood cell count (Sutin et al., 2012). In the other direction, another study found that engaging in regular exercise, known to reduce inflammation, is associated with a notable decrease in impulsivity (Javelle et al., 2021), further supporting the connection between inflammation and impulsive behavior. Researchers in the field postulate that the presence of inflammation may prompt individuals to prioritize immediate resource acquisition, potentially at the expense of considering long-term consequences (Gassen et al., 2019a). This hypothesis aligns with the notion that inflammation-induced alterations in cognitive processes could lead to a bias toward immediate gratification and hinder the ability to delay rewards for future benefits.

Overall, these findings contribute to the field’s understanding of the complex interplay between inflammation and decision-making, underscoring the potential impact of inflammation on impulsive behavior. Unhealthy behaviors, such as maintaining a poor diet and leading a

sedentary lifestyle, can contribute to heightened inflammation levels, thus compounding the difficulties associated with response inhibition and executive functioning. Consequently, the interplay between inflammation and response inhibition may pose challenges in engaging with health behaviors and maintaining overall well-being. Moreover, the emerging evidence supporting the beneficial effects of reducing inflammation through exercise opens up avenues for developing interventions aimed at improving impulse control and decision-making processes. Further research is needed to elucidate the underlying mechanisms and explore the potential therapeutic implications of mitigating inflammation in the context of impulsive behaviors.

Remaining Questions and Future Directions

Unanswered question #1: What is the relationship between SEP, inflammation, and positive affect?

One question that was raised by the current studies regards the link between socioeconomic position, inflammation, and reactivity to positive affective stimuli. As highlighted by the discrepant findings between study 1 and study 2 (see discussion in the above *Limitations & Discrepancies* section), it is unclear whether the association between inflammation and reactivity to positive affective stimuli is consistent across the socioeconomic gradient. Is lower socioeconomic position associated with greater inflammation that reduces reactivity to positive stimuli? Or is it that, regardless of inflammation, lower socioeconomic position is associated with greater sensitivity to positive stimuli? This is particularly important to understand as the pathway could further delineate the risk and possibility of protective factors underlying socioeconomic health inequities.

To test these questions, the first proposed study aims to decrease inflammation within individuals across the SEP gradient to examine changes in neural function to positive stimuli.

This study would be a double-blind crossover trial of naproxen, a nonsteroidal anti-inflammatory medication, where participants across the socioeconomic gradient would complete a task that measured sensitivity to positive affect (i.e., passive viewing of positive and neutral affective stimuli) in the scanner. Whole brain activity and connectivity would be compared when participants viewed positive images versus neutral images. Additionally, I would collect self-report data regarding secondary variables (i.e., stress exposure and coping behaviors) to explore potential moderating factors in the sample.

The first analytical test will assess whether neural activity to positive stimuli differed when individuals were taking naproxen versus placebo. I would then assess whether that association was moderated by between-subject differences in socioeconomic position. The results from this would answer whether the association between socioeconomic position and sensitivity to positive stimuli was mediated by inflammatory processes. The second analytical test would assess whether subcortical-cortical connectivity to positive stimuli differed when individuals were taking naproxen versus placebo. I would then assess whether that association was moderated by between-subject differences in socioeconomic position. The results from this test further clarify whether the link between subcortical activity and subcortical-cortical connectivity is directionally driven by inflammation. Finally, I would test whether secondary variables partially explained the association between SEP and sensitivity to positive stimuli. The results from this test would help probe alternative mediators regarding the SEP and sensitivity to positive stimuli association. Overall, results from this study would further clarify the SES, inflammation, and sensitivity to positive stimuli association.

Unanswered question #2: Does inflammation alter cognition via changes in motivation?

The second question raised by the current studies pertains to the link between inflammation and cognitive function. As highlighted by the limitations of study 3 (see discussion in the above *Limitations & Discrepancies* section), there are outstanding questions regarding the mechanisms involved in the reduction of response inhibition following the inflammatory challenge. Specifically, the questions include (a) the associations between inflammation and response inhibition due to disruptions in motivation and (b) whether inflammation impairs general cognitive performance or whether the link to response inhibition is unique.

To address these gaps, I propose a between-subjects, placebo-controlled inflammatory challenge study where participants complete a battery of cognitive tasks following the administration of the flu vaccine or a placebo sham vaccine. In this study, participants will complete tasks to measure response inhibition (i.e., reward GNG & Stroop), working memory (i.e., n-back), and attention (i.e., visual search). For the rewarded go/no-go task, participants will complete alternating blocks of rewarded trials and non-rewarded trials. The first analytical test will assess whether a change in IL-6 was associated with overall differences in responses on the no-go trials or whether the association varied depending on the potential for reward (vs. no reward condition). The second analytical test would assess whether IL-6 reactivity to the vaccine was associated with reduced performance across all cognitive tasks. Ultimately, the results from this study would improve granularity regarding the acute inflammation to cognition link.

Unanswered question #3: Is AIN global efficiency related to poorer physiological health?

The final question raised by the current set of studies is whether the global efficiency of the allostatic interoceptive network (AIN) is associated with longer-term physiological health.

Given that the AIN function is associated with both increased vigilance and physiological activation, AIN efficiency may require greater metabolic resources that detract from the restorative functions of the body that also require a metabolic expense (see discussion in the above *Implications for Health Pathway #1* section). With this backdrop, the resulting hypothesis is that perhaps sustained and prolonged global efficiency of the AIN may lead to enhanced biological aging.

To address this question, I propose a longitudinal examination of AIN efficiency among a sample of aging adults to examine how AIN efficiency is related to changes in physical health status. For this study, I would aim to recruit a mid-to-late-life sample of adults, given that this is a time when rapid and diverging health trajectories are more likely to emerge. Participants would complete an affective attention task in the scanner twice, approximately a year apart. During both sessions, participants will also provide information regarding their overall health which would include measurements of metabolic health. Specifically, a physical and blood sample will be collected to measure waist-to-hip ratio, blood pressure, fasting glucose, triglycerides, and cholesterol levels. Together, the values will be used to create a composite score that assesses the risk for cardiovascular disease and diabetes, also known as metabolic syndrome (Alberti et al., 2009). The study's primary analytical test would assess whether there was a significant association between the change in AIN efficiency during the affective attention task between T1 and T2 and the change in metabolic syndrome score between T1 and T2. I hypothesize that increases in AIN efficiency between visits will be associated with increased metabolic syndrome risk between visits as well. These results would support the argument that prolonged AIN efficiency may be harmful to health.

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