

**Exploring the Functional Neural Correlates of Perceived Stress: A Machine Learning Approach**

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Appraisals of perceived psychological stress vary widely between individuals and are associated with chronic disease risk and poor health outcomes. However, the brain systems that may connect perceived stress and physical health outcomes remain unclear. Accordingly, the present study tested whether whole-brain resting-state functional connectivity patterns would predict individual differences in perceived stress. Participants (N = 417; 53% female; aged 30-54) completed the 10-item Perceived Stress Scale and underwent a 5-minute resting-state functional magnetic resonance imaging (fMRI) scan. Functional connectivity (FC) was computed between areas distributed across the brain. Using cross-validated and multivariate machine learning methods, we found that whole-brain resting-state FC patterns failed to predict individual differences in perceived stress, but they successfully predicted age. These results suggest that individual differences in self-reports of perceived stress may not relate reliably to resting-state FC patterns.

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# **1 Introduction**

## **1.1 Perceived stress**

According to a stage model of stress and disease (Cohen et al., 2016), events and contexts that are appraised as stressful, that is, demands that are threatening and taxing to one's ability to cope (Lazarus, 1966), lead to affective (emotional), behavioral, and physiological responses that may culminate in increased risk for physical disease (Cohen et al., 1995). Taken together, these responses are thought to comprise major dimensions of states of psychological stress. Psychological stress itself is typically assessed by self-report inventories (e.g., Perceived Stress Scale (PSS) (Cohen et al., 1983). Not all individuals, however, appraise the same events or contexts similarly, and hence there is wide variation across individuals on measures of perceived psychological stress (hereafter "perceived stress"). Importantly, these individual differences in perceived stress associate with commensurate variation in biological and behavioral risk factors for disease (e.g., inflammation, health-damaging coping behaviors, etc.), as well as clinical conditions and outcomes (e.g., cardiovascular, cerebrovascular, metabolic and other diseases, etc.) (Cohen et al., 2007; Dimsdale, 2008; Everson-Rose & Lewis, 2005; Kivimäki et al., 2023; Kivimäki & Steptoe, 2018; Knight et al., 2021; Ng & Jeffery, 2003; Weiss, 1972; Yusuf et al., 2004).

A long-standing yet untested assumption of all models of psychological stress and physical health is that the brain links stress appraisals with 'downstream' or emergent biological and behavioral responses that comprise stressful experiences and influence health (Cohen et al., 2016). But the brain systems and functional neural metrics that may relate to individual differences in perceived stress have yet to be fully characterized. As such, the present study tested whether individual differences in perceived stress associate reliably with patterns of whole-brain activity reflecting functional interrelationships between distributed brain areas (functional connectivity), as well as whether there are patterns of functional connectivity between specific brain areas that consistently contribute to the prediction of individual differences in perceived stress.

## **1.2 Functional neural correlates of perceived stress**

It is unlikely that the functional neural correlates of perceived stress can be localized to a single brain region. Rather, given its complexity and multidimensionality, perceived stress is more plausibly

represented by distributed patterns of brain activity. This notion of distributed neural correlates aligns with conceptual views on the psychological constructs of value, reward, and affect, among others, which have been associated with (or predicted by) multivariate activity patterns across multiple brain regions. While some studies have identified different regions distributed across the brain whose functional activity may associate with specific components of a complex psychological process (e.g., computation of expected value; processing of action values) (Knutson, 2005; E. J. Shin et al., 2021), others have used distributed multivariate patterns to classify/predict such processes (e.g., value, saliency, and category encoding; affective processing) (Baucom et al., 2012; Bush et al., 2017; Chang et al., 2015; Z. Zhang et al., 2017). Broadly speaking, the literature suggests that distributed functional neural correlates are more appropriate and biologically plausible for modeling and predicting complex, multidimensional psychological processes or constructs – both within and between individuals.

Further, it is unlikely that a single brain region could be identified wherein functional activity would reliably or uniformly relate to the multiple dimensions or biobehavioral elements of perceived stress. Rather, it may be that functional activity in multiple interacting brain systems relates to these emergent features and their interactions (e.g., labelling an event or context as threatening, coordination of neuroendocrine and physiological changes, regulation of affect, selection of coping behaviors, etc.). As such, the functional neural correlates of perceived stress – itself an aggregate of multiple underlying components – may be reflected by interactions between distributed brain regions, as computed by *functional connectivity* (FC).

FC metrics broadly encompass time-dependent statistical associations between spatially distant regions (Friston, 2011), measured either in the presence of a task (task-based FC) or during rest (resting-state FC). Additionally, FC metrics are thought to reflect the functional organization of the brain – an interpretation that is based on the assumption that regions whose activity is statistically related are part of a *network*, or a group, ensemble, or collective system of structures that may be involved in social, cognitive, affective, and behavioral processes. Importantly, these networks tend to be relatively stable across time (Gratton et al., 2018). FC metrics vary widely between individuals (Laumann et al., 2015; Mueller et al., 2013; D. Wang et al., 2015) and have been used to reveal brain-phenotype relationships in a number of different domains (Greene et al., 2020). Thus, insofar as FC is able to characterize distributed activity across interacting brain systems, then it is possible that FC metrics may be plausible candidates to identify the functional neural correlates of individual differences in perceived stress.

More specifically, an organizing hypothesis of the present study is that the functional neural correlates of perceived stress are likely to relate to activity between multiple prefrontal and medial temporal regions that are involved in the affective, behavioral, and physiological dimensions of perceived stress.

These regions include the ventromedial prefrontal cortex, anterior insula, anterior cingulate cortex, amygdala, and hippocampus. Several of these regions are components of anatomically and functionally interconnected brain systems that are implicated in neuroendocrine, visceromotor, and behavioral phenomena (Benarroch, 1993; Gianaros & Wager, 2015; Ginty et al., 2017; Koban et al., 2021; McEwen & Gianaros, 2010; Saper, 2002; Thayer et al., 2009; Vaccarino et al., 2021), including processes relevant to perceived stress. Evidence supporting these speculations will be presented next.

### **1.3 Candidate brain systems for the neural representation of perceived stress**

#### **1.3.1 Ventromedial prefrontal cortex (vmPFC)**

Anatomically, the medial prefrontal cortex (mPFC) encompasses the medial section of the prefrontal cortex and extends into the orbitofrontal cortex. It connects limbic (including amygdala) and visceral (including the hypothalamus and periaqueductal gray in the brainstem) systems via afferent and efferent pathways, some of which are bidirectional (Gianaros & Wager, 2015; Koban et al., 2021). Given these interconnections, the mPFC is thought to be an important area for emotion regulation and integration of affective and physiological signals (Price, 2007). According to one view, the ventromedial PFC (vmPFC) may play an important role in linking psychological processes, including stress appraisals, to affective, behavioral, and physiological factors related to disease risk (Hänsel & von Känel, 2008; Koban et al., 2021). More specifically, the vmPFC is activated during self-referential processing, including during reflection about personality traits and judgment of mental/emotional states (Denny et al., 2012; Northoff et al., 2006). vmPFC activity also correlates with measures of stressor-evoked autonomic reactivity, including heart rate, heart rate variability, blood pressure, and skin conductance (Beissner et al., 2013; Gianaros et al., 2017). Further, Wager and colleagues also showed that decreases in right vmPFC activity in response to social evaluative threat (one determinant of perceived stress) predicted increases in stress-related heart rate reactivity (Wager et al., 2009). And Orem and colleagues found that stressor-evoked vmPFC activity was positively associated with self-reported stress (Orem et al., 2019). Further evidence in support of this view comes from studies in cardiovascular disease (CVD) patients, showing associations between stressor-evoked brain activity in mPFC regions and exaggerated stress reactivity patterns, as well as CVD risk factors and outcomes (Bremner et al., 2018; Moazzami, Wittbrodt, Alkhalaf, et al., 2020; Moazzami, Wittbrodt, Lima, Levantsevych, et al., 2020; Moazzami, Wittbrodt, Lima, Nye, et al., 2020; Shah et al., 2019).

### **1.3.2 Anterior insula (AI)**

The insula is the cortical demarcation between the frontal, parietal, and temporal lobes. It has many afferent and efferent connections to other cortical, limbic, and visceral systems (including all of the regions of interest discussed here), establishing it as a hub for visceromotor-sensory integration (Augustine, 1996; Oppenheimer & Cechetto, 2016; Wager & Barrett, 2017). The anterior region of the insula (AI) in particular is thought to be involved in the processing of exteroceptive/interoceptive signals and emotional stimuli, as well as the maintenance of emotional and physiological homeostasis (Craig, 2009; Lindquist et al., 2012; Oosterwijk et al., 2012; Oppenheimer & Cechetto, 2016; X. Wang et al., 2019). The AI may also be involved in the pathophysiology of post-traumatic stress disorder (PTSD), and it exhibits volumetric and functional alterations that may relate to the symptoms experienced by trauma-exposed individuals (Hopper et al., 2007; Jeong et al., 2019; Nicholson et al., 2016; Pitman et al., 2012; Y. Zhang et al., 2016). As it relates to stress processing in non-clinical populations, AI activity has been associated with subjective and physiological measures of stress reactivity. Wang and colleagues showed that stressor-evoked changes in cerebral blood flow in the right ventral PFC and the left AI were positively associated with perceived stress ratings; and that stress-related increases in cerebral blood flow in the right AI and ACC was sustained during stress recovery among participants reporting high levels of perceived stress (J. Wang et al., 2005). AI activity has also been positively associated with stressor-evoked changes in blood pressure (Gianaros et al., 2005), and individuals showing a blunted pattern (i.e., low magnitude) of cardiovascular stress reactivity also showed corresponding stressor-evoked hypoactivity in the AI and the amygdala (Ginty et al., 2013). Finally, stress-related reductions in baroreflex sensitivity have been associated with increased activation of the AI (Gianaros et al., 2012).

### **1.3.3 Anterior cingulate cortex (ACC)**

The anterior cingulate cortex (ACC) is anatomically situated between the prefrontal and limbic regions of the brain. Its subregions have functionally relevant differences: the subgenual ACC (sgACC) is thought to be involved in autonomic control, while the pregenual ACC (pACC) appears to be involved in emotion-autonomic integration (Vogt, 2005, 2009; Vogt et al., 1995). Thus, like the AI, the ACC is thought to be a hub for the integration of emotional stimuli and viscerosensory signaling (Allman et al., 2006; Critchley, 2005; Medford & Critchley, 2010; Stevens et al., 2011), and may also be involved in the pathophysiology of PTSD and mood disorders (H. J. Chen et al., 2019; Connolly et al., 2013; Drevets et al., 2008; Holsen et al., 2011; Kennis et al., 2015; L. M. Shin et al., 2001, 2007). The ACC subregions have been associated with stress-related visceromotor control. In rodents, stimulation of the pACC elicits a blood

pressure response in rodents (Burns & Wyss, 1985). And in marmosets, overstimulation of the sgACC reduces heart rate variability, alters stress-related cortisol release, and increases vigilance to threat (Alexander et al., 2020). Similar associations are seen in the human neuroimaging literature. Wager and colleagues showed that increases in a dorsal region of the pACC in response to social evaluative threat predicted increases in stress-related heart rate reactivity (Wager et al., 2009). Further, stressor-evoked activity in the perigenual ACC (a subregion of the pACC), among other regions involved in cardiovascular control, has been shown to be positively associated with blood pressure reactivity in humans (Gianaros et al., 2005, 2007).

### **1.3.4 Amygdala**

The amygdala, an allocortical cell complex located in the medial temporal lobe, is thought to be a central structure for fear conditioning (LeDoux, 1994). Stressful stimuli are perceived and processed by the sensory integration areas in the thalamus and cortex. These signals are then transmitted to the amygdala, which has connections to motor areas in the brainstem and the paraventricular nucleus of the hypothalamus – brain systems that coordinate a physiological response to stress. Thus, the amygdala is thought to play a role in modulating the emotional processing of stress, as well as in stressor-evoked cardiovascular reactivity. Orem and colleagues showed that the amygdala is engaged in the context of emotional responses to an fMRI-based stress induction, such that increased amygdala activity associates with a greater skin conductance response (Orem et al., 2019). Gianaros and colleagues found that among individuals exposed to an acute fMRI-based stressor, those who exhibited an exaggerated pattern of stressor-evoked blood pressure reactivity showed greater activation and lower gray matter volume in the amygdala, as well as greater amygdala-perigenual ACC FC (Gianaros et al., 2008), although the latter findings have yet to be replicated. Additionally, greater heart rate and cardiac output reactivity during acute stress was associated with lower gray matter volume in the amygdala (and hippocampus) (Trotman et al., 2019). Further, the amygdala also appears to also be involved in the processing of stressors in a more chronic, ambient context. Perceived stress, as assessed by the PSS, has been shown to be positively associated with amygdalar volume and activity at rest (Caetano et al., 2021; Tawakol et al., 2017). And among breast cancer survivors, greater levels of perceived stress was associated with greater left amygdala reactivity to social threat (Leschak et al., 2020). Finally, Hölzel and colleagues showed that reduction in perceived stress following an 8-week stress reduction intervention was associated with decreased right basolateral amygdala grey matter density (Hölzel et al., 2010). Critically, given this role, the amygdala also appears to be a key player in the neurobiological mechanisms linking stress and CVD risk. Several studies have shown associations between

amygdalar activity and increased CVD risk factors (e.g., adiposity, arterial inflammation, subclinical atherosclerosis) and events (Dar et al., 2019; Gianaros et al., 2009; Ishai et al., 2019; Tawakol et al., 2017).

### **1.3.5 Hippocampus**

The hippocampus is also located in the medial temporal lobe, adjacent to the amygdala, and plays a well-established role in learning and memory. This structure has a high concentration of receptors for glucocorticoids (e.g., cortisol), which are released on activation of the HPA axis, and is involved in the negative feedback loop that downregulates HPA activity to terminate the stress response (J. J. Kim & Diamond, 2002). This connection with the HPA axis makes it susceptible to stress-related functional (e.g., impaired performance on memory tasks, impaired synaptic plasticity) and morphological (e.g., decreased volume) changes (E. J. Kim et al., 2015; J. J. Kim & Diamond, 2002; McEwen & Akil, 2020). Given its connection with prefrontal and other limbic areas, the hippocampus may also be an important region for integrating (potentially stressful) experiences with physiological responding and mediating biobehavioral processes relevant to health (McEwen & Akil, 2020; McEwen & Gianaros, 2010).

## **1.4 Stress-related functional connectivity**

### **1.4.1 vmPFC connectivity**

Ginty and colleagues showed that exposure to an acute fMRI-based psychological stressor (i.e., preparation of a speech they were told they would later be randomly assigned to deliver) was associated with increased connectivity of the vmPFC with the amygdala, insula, and ACC (Ginty et al., 2019). Similarly, among cortisol “responders”—those participants showing a peak in cortisol following stress exposure—enhanced amygdala FC with multiple regions, including the mPFC, was associated with stress exposure and recovery (Quaedflieg et al., 2015). The literature on stress-related changes in vmPFC-amygdala connectivity is inconsistent, however, as Hanson and colleagues showed that among adolescents, early life stress such as childhood poverty, as well as more recent life stress, was associated with decreased vmPFC-amygdala resting-state FC (Hanson et al., 2019). More globally, Eisenbarth and colleagues used a machine learning approach to show that a multivariate pattern of brain activity comprising the vmPFC, insula, dorsal ACC, and other regions related to emotion regulation and visceromotor control predicted

individual differences in heart rate and skin conductance responses to social evaluative threat (Eisenbarth et al., 2016).

#### **1.4.2 AI and ACC connectivity**

As suggested above, the AI and the ACC interact across a range of biological, behavioral, and psychological processes. Further, they are both key hubs within a so-called ‘salience network’, which is posited to be involved in processing and integrating “homeostatically relevant” stimuli (Seeley, 2019). Thus, it is unsurprising that their connectivity patterns are associated with stress-related processing. Findings among PTSD patients, for example, suggest that connectivity of these regions may be disrupted in the context of extreme experiences of psychological stress (H. J. Chen et al., 2019; Kennis et al., 2015; Y. Zhang et al., 2016). Perhaps most relevant to perceived stress from the PTSD literature is the finding that individuals exposed to combat stress (i.e., deployment to war) showed increased insular connectivity with the amygdala, and that the connectivity patterns of the amygdala with the insula and the dorsal region of the ACC is moderated by *perceived* threat, not actual threat exposure (van Wingen et al., 2011). Among non-clinical populations, exposure to an fMRI-based stressor increased FC of an AI subregion with regions involved in autonomic control, including the perigenual ACC, amygdala, midbrain, PAG, and pons (Gianaros et al., 2012). Also, sgACC-insula resting-state FC decreased following stress exposure among individuals with high self-reported resilience (Shao et al., 2018). Archer and colleagues found that among female participants, perceived stress was positively associated with bilateral ACC-middle cingulate resting-state FC (Archer et al., 2018).

#### **1.4.3 Amygdala connectivity**

Quaedflieg and colleagues suggested that changes in FC within amygdala-based networks was associated with exposure to and recovery from acute stress (Quaedflieg et al., 2015). Findings from a host of other studies are in line with this pattern of sustained alterations of amygdala connectivity in the aftermath of stress. van Merle and colleagues showed that amygdala resting-state FC with the dorsal ACC, dorsal insula, and a subregion of the pons (a brainstem region that relays sensory and motor information) remained enhanced immediately after acute stress exposure (van Marle et al., 2010). Veer and colleagues showed that stress-related increases in amygdala FC with the vmPFC and PCC/precuneus (a subcortical limbic region implicated in self-referential processing and memory) were sustained up to 1 hour following stress exposure (Veer et al., 2011). Vaisvaser and colleagues (2013) showed a similar pattern of results,

with a sustained stress-related increase in amygdala-hippocampal resting-state FC observable up to 2 hours following stress exposure for both cortisol responders and non-responders (Vaisvaser et al., 2013). Furthermore, the PTSD literature suggests that some of the amygdala connectivity patterns described above may be reversed in trauma-exposed individuals, including enhanced resting-state FC with the insula and reduced resting-state FC with the hippocampus (Rabinak et al., 2011; Sripada et al., 2011). In addition to these short-lived effects, amygdala connectivity is also modulated by chronic stress. Caetano and colleagues found that perceived stress was positively associated with resting-state FC between the amygdala and frontal cortical regions also involved in stress processing, including the superior and middle frontal gyri (Caetano et al., 2022). Additionally, Taren and colleagues showed that perceived stress was positively associated with greater bilateral amygdala-sgACC resting-state FC, and that a brief mindfulness meditation intervention reduced this coupling (Taren et al., 2015).

#### **1.4.4 Hippocampus connectivity**

Among healthy adult males exposed to the dexamethasone-suppression/corticotrophin-releasing hormone stimulation (dex/CRH) test, an assessment of HPA axis function, resting-state FC between the left and right hippocampal regions was negatively associated with HPA axis dysregulation (Kiem et al., 2013). More specifically, lower connectivity predicted greater stimulated cortisol levels in response to the dex/CRH test – an indication of a reduced ability to downregulate the physiological stress response when faced with a challenge. Patterns of resting-state FC within hippocampal subregions were associated with prospective memory deficits in college students exposed to chronic stress (J. Chen et al., 2019). Using a machine learning approach, Goldfarb and colleagues used stressor-evoked hippocampal connectivity patterns to predict subjective feelings of stress (Goldfarb et al., 2020). They found that stress-related increases in hippocampal connectivity with brain regions involved in the regulation of the physiological stress response formed a positive predictive network that predicted feeling more stressed, whereas connectivity with brain regions associated with threat processing formed a negative network that predicted feeling less stressed. Finally, Archer and colleagues found that among female participants, greater perceived stress was associated with decreased hippocampus resting-state FC with the precuneus and middle frontal gyrus (Archer et al., 2018).

### **1.4.5 Network affiliations**

Taken together, the evidence presented thus far suggests that individual differences in perceived stress may relate to FC among brain systems that appear to be involved in the biological, behavioral, and psychological aspects of stress. Accordingly, the primary prediction tested here is that resting-state FC patterns – particularly reflecting activity across the vmPFC, AI, ACC, amygdala, and hippocampus – will correlate with individual differences in perceived stress. Critically, each of these brain regions are components of large-scale intrinsic brain networks that exhibit reliable and correlated activity at rest. Most notably, many are subsumed by the so-called ‘salience network’ (Seeley, 2019); the ‘default mode network’, presumptively involved in self-referential thought and mind-wandering (Raichle, 2015; Xu et al., 2016); and the so-called ‘allostatic’ network, which is hypothesized to support the processing of interoceptive (bodily) signals in the service of homeostatic regulation (Kleckner et al., 2017). Recent evidence suggests that some of these networks, and their interactions, associate with individual differences in perceived stress. Using a connectome-based predictive modelling approach, Liu and colleagues showed that among college-aged adults, individual differences in perceived stress during the COVID-19 pandemic was predicted by resting-state FC patterns within and between key nodes of the default mode and salience networks, including the parahippocampal gyrus, precuneus, orbital gyrus, and thalamus (Liu et al., 2021).

### **1.5 Knowledge gaps addressed by the present study**

To date, only one study has directly addressed the primary question at issue in the present study; namely, whether resting-state FC patterns predict individual differences in perceived stress (Liu et al., 2021). Moreover, the most relevant studies are characterized by methodological limitations that preclude inferences about reliable functional neural correlates of individual differences. To begin, nearly all prior studies in this area have used a mass-univariate analytic approach, which aims to determine brain activity given the presence of a certain set of variables (i.e., change in brain activity in voxels upon stress exposure). This approach would be suitable for predicting variability in brain activity from variability in perceived stress, for example (Varoquaux & Thirion, 2014). However, predicting psychological state from brain activity necessitates a reversal of this analytic approach (i.e., determine the level of perceived stress given patterns of activity in brain regions). Thus, the mass-univariate analytic approach creates a context for the *reverse inference fallacy*, or inferring the presence of a psychological process from patterns of brain activity. Another drawback of the mass-univariate analytic approach, which has been commonly

implemented in brain-wide association studies, is the increased risk of finding spurious effects due to the large number of statistical tests run and comparisons made. These multiple comparisons are often corrected for using various error-rate adjustments, but if inadequately handled can lead to inflated effect sizes, thus contributing to replication failures (Marek et al., 2022). Further, many studies use a region-of-interest (ROI) analytic approach, in which one or more brain regions are selected *a priori* for analysis. Although ROI approaches can help to simplify the analysis by paring down the number of statistical tests conducted (Poldrack, 2007), they are limiting in that by focusing on only one or a few brain regions, the contributions of unexamined brain regions will not be detected and the corresponding results being potentially biased or selective.

An additional limitation is that task-based connectivity paradigms may limit the ability to reliably identify functional neural correlates of individual difference measures. More specifically, while they have been used to model brain-phenotype relationships (and in some cases, even better than resting-state paradigms (Greene et al., 2020), in the context of stress-related processing, task paradigms may evoke measures of brain activity that lack acceptable psychometric properties, such as high test-retest reliability or internal consistency. In the absence of strong psychometric properties, further correlations of functional neural activity with other individual difference measures are problematic. Lastly, in trying to determine whether perceived stress can be predicted from task-evoked brain activity, it may be difficult to disentangle whether the evoked brain activity corresponds to an acute “stress perception” or other components of the stress response (e.g., affective, cognitive, physiological) that may be transient and tied to the specific task used for modeling.

As such, the present pre-registered study aimed to determine whether individual differences in perceived stress are reliably predicted by a whole-brain resting-state FC pattern. To achieve this, we used a multivariate machine learning approach, which combined predictor dimensionality reduction, penalized regression, and cross-validation. In the predictive model, all functional connections, or *edges*, in the whole-brain resting-state pattern were used to predict individual differences in perceived stress. Using nested cross-validation, the model was iteratively trained and tested using subsets of study participants. Critically, testing was always done on an out-of-sample subset not used for training. This allowed us to evaluate the model’s predictive ability, and to determine whether it is generalizable, that is, whether it could be used to predict outcomes on novel datasets (Rosenbusch et al., 2021).

## 2. Method

### 2.1 Participants

All participants provided written informed consent, and experiments were conducted in accordance with protocols approved by the University of Pittsburgh Institution Review Board. Before access to the data was granted, the study hypotheses and analytic plan were [pre-registered](#) through the Open Science Framework. Participants were recruited as part of two projects: the Pittsburgh Imaging Project (PIP; N = 331, age 30-51) and Phase II of the Adult Health and Behavior project (AHAB; N = 107, age 30-54). Eligibility was based on the following exclusion criteria: history of chronic medical illness (e.g., diabetes, cancer, emphysema, rheumatological conditions, etc.), cardiovascular or cerebrovascular disease, or psychiatric or neurological disorder; use of medications with known cardiovascular or autonomic effects; use of psychotropic medications; presence of standard MRI contraindications (i.e., claustrophobia, presence of metal in or on the body/history of metal exposure); pregnancy; consumption of  $\geq 5$  servings of alcohol 3 or more times/week; treatment for hypertension, or having a resting blood pressure greater than 140/60 mmHg; left-handedness; and color-blindness. Given that the fMRI data acquisition protocol was identical for both studies, PIP and AHAB participants were combined to maximize statistical power. To retain as much of the full sample as possible, missing values on variables of interest ( $<1\%$ ) were median imputed. Twenty-one participants with mean framewise displacement (FWD; a measure of head motion over time during fMRI data acquisition) of  $\geq 0.5$  mm were excluded from the analyses. The final analytic sample was 417 participants.

### 2.2 Perceived stress

Perceived stress was assessed using the 10-item Perceived Stress Scale (PSS-10). This scale offers a global measure of the extent to which a person appraises their life events over the last month as stressful. An example item is, “In the last month, how often have you been upset because of something that happened unexpectedly?”. For each item, participants rate the frequency with which they have experienced the feeling or thought described on a scale from 0 (Never) to 4 (Very Often). It has both high internal reliability ( $\alpha = .85$  in PIP,  $\alpha = .89$  in AHAB) and high test-retest reliability ( $ICC > .70$ ) (Lee, 2012). The PSS has been shown to be a better predictor of health outcomes (e.g., life event scores, depressive and physical

symptomatology, anxiety, health behaviors) than more specific life event scales (Cohen et al., 1983). The highest score on the PSS-10 is 40, and higher scores indicate higher levels of perceived stress.

### 2.3 fMRI acquisition and preprocessing

fMRI data for both PIP and AHAB were acquired by a 3 T Trio TIM whole body MRI scanner (Siemens, Erlangen, Germany), equipped with a 12-channel phased-array head coil. Participants laid in the scanner for 5 minutes with their eyes open while blood-oxygen level-dependent (BOLD) images with a gradient-echo EPI sequence were acquired using the following parameters: TR = 2,000 ms, TE = 28 ms, flip angle = 90 degrees, field-of-view = 205 x 205 mm<sup>2</sup>, matrix size = 64 × 64 mm<sup>2</sup>, 39 slices, and 3 mm isotropic voxels. Slices were obtained an interleaved sequence in the inferior-to-superior direction, yielding 150 total BOLD images. The first three images were discarded to allow for magnetic equilibration. T1-weighted 3D magnetization-prepared rapid gradient echo (MPRAGE) neuroanatomical images were acquired over a duration of 7 min 17 s with the following parameters: FOV = 256 × 208 mm<sup>2</sup>, matrix size = 256 × 208 mm<sup>2</sup>, TR = 2,100 ms.

The following procedures were adapted from a separate analysis carried out on the PIP dataset (Kraynak et al., 2019). Resting-state BOLD data was preprocessed using the CONN toolbox (Whitfield-Gabrieli & Nieto-Castanon, 2012) following a standard fMRI preprocessing pipeline, with steps including realignment using a six-parameter rigid-body transformation, co-registration to the T1-weighted structural image; normalization to MNI space. Additionally, to further reduce noise in the data, the following additional preprocessing steps were implemented: (1) temporal bandpass filtering ( $0.009 \text{ Hz} < f < 0.08 \text{ Hz}$ ); (2) spatial smoothing of functional images using a 6-mm full-width-at-half-maximum (FWHM) Gaussian kernel; and (3) regression of motion and physiological noise in a model including regressors derived from the 6 parameters from the realignment step and regressors for CSF and white matter (Power et al., 2011).

The denoised data were then segmented into 200 parcels, based on a whole-brain fMRI parcellation (Craddock et al., 2011). Resting-state derived atlases are preferred over the standard anatomical atlases (e.g., AAL). First, the anatomical/cytoarchitectural homogeneity of regions as defined by the standard atlases does not necessarily extend to patterns of connectivity. Different subregions of a given structure may be networked with distinctly different regions, and thus may be implicated in different cognitive functions (Craddock et al., 2011). Thus, atlases like the AAL may not be suitable for resting-state FC analyses. Finally, functional connectivity was computed in the CONN toolbox using the ROI-to-ROI

approach. For each pair of parcels, bivariate Pearson correlation coefficients were computed for the BOLD timeseries. These coefficients were then transformed using Fisher's Z transformation. The upper triangle of the resulting connectivity matrix consisted of 19,900 correlations (edges) per participant.

## 2.4 Machine learning analyses

All statistical analyses were performed using R Statistical Software (v4.2.0; R Core Team 2022), utilizing the caret (v 6.0-93; Kuhn, 2022) and glmnet (v 4.1-6; (Friedman et al., 2010) packages. We used a multivariate penalized regression approach to test whether perceived stress was predicted by a whole-brain resting-state FC pattern. In this analysis, all 19,900 edges served as the multivariate predictor variables and PSS score was the outcome variable. First, to reduce the dimensionality and address the multicollinearity of the input data, principal components analysis was applied to the normalized and scaled edges. This operation transformed the input features (i.e., the edges) to the principal component space whose dimensionality was  $n - 1$ , with  $n$  being the number of participants within a given training set split. Next, perceived stress was regressed on to the principal components using penalized regression models. Our primary model was the elastic net model because it combines the penalty terms of the lasso (L1) and ridge (L2) regression models. Briefly, when applied, these penalties shrink high variance beta coefficients to or toward zero, respectively. These effects are modulated by two hyperparameters: a shrinkage parameter lambda ( $\lambda$ ) which determines how much penalization is applied (ranges from 0 -  $\infty$ ); and a mixing parameter alpha ( $\alpha$ ) which determines the ratio of L1 and L2 penalties ( $\alpha = 0$  for ridge (L2),  $\alpha = 1$  for lasso (L1),  $0 < \alpha < 1$  for elastic net). We also ran ridge regression as our secondary model, given its treatment of multicollinearity, as it reconciles correlated predictors by shrinking them near each other rather than removing one of them from the model (Khalaf & Shukur, 2005). Lasso regression, on the other hand, proved to be too stringent in this analysis context, removing too many features and thus preventing the model from converging (results not reported here; available on request) (Zou & Hastie, 2005).

Nested  $k$ -fold cross-validation was implemented, where the model's predictive ability was assessed within the outer loop and the model hyperparameters were optimized within the inner loop (Korjus et al., 2016). In the outer loop, 10-fold cross-validation was implemented, such that the dataset was partitioned into 10 nonoverlapping subsets of equal size. At each fold, all but one of these subsets was used for model training (training set) and the held-out subset was used for model testing (i.e., testing set). Moreover, the training set was passed to the inner loop for hyperparameter tuning, where a range of  $\lambda$  and  $\alpha$  values were tested via grid search to find the optimal parameters; namely, those values that minimize the prediction

error (RMSE). Within this inner loop, 5-fold cross-validation was implemented with the same data partitioning process described above. For the elastic net model, a range of 100  $\lambda$  values from 0-100 and 3  $\alpha$  values from 0-1 were tested. For the ridge model, a range of 100  $\lambda$  values from 0-25 were tested and  $\alpha$  was fixed at 0. The hyperparameter tuning process was repeated 3 times to test the reliability of the resulting model performance metrics. These optimized hyperparameters were then used to train the model and generate predictions in the held-out testing set from the outer loop.

The final predictive performance of each model concatenated across the outer folds was summarized by multiple metrics, per recommendations on best practices for reporting predictive modelling results (Poldrack et al., 2020). The differences between predicted and observed PSS scores was summarized by the Root Mean Squared Error (RMSE) and Mean Absolute Error (MAE) values. The proportion of variance in the predicted values explained by the observed values was summarized by the coefficient of determination ( $R^2$ ), which was computed using the sums of squares formula. The association between predicted and observed PSS scores was summarized by the Pearson correlation coefficient, along with the corresponding  $p$  value and 95% CI.

As an exploratory analysis and pipeline check, we tested whether age was predicted by the whole-brain resting-state FC pattern, as this has been found previously (Kandaleft et al., 2022; Tsvetanov et al., 2016; Vergun et al., 2013). The models and approach were identical to those described above, except that age was used as the outcome variable.

## 3 Results

### 3.1 Sample characteristics and associations among model variables

Table 1 outlines characteristics of the analytic sample ( $n = 417$ ). Participants were a mean age of 41 years old, 53% female, and 24.2% non-White (see Table 1). Participants with FWD outlier values reported higher perceived stress than those included in the analyses (17.8 versus 13.8,  $t(22) = 2.86$ ,  $p = .009$ ), but they did not differ on age. Participants in PIP and AHAB did not differ on age, perceived stress, or FWD. Age was correlated with FWD ( $r = .12$ ,  $p = .019$ ), but not perceived stress. Female participants were slightly older than male participants (42.00 years versus 40.01 years),  $t(411) = -2.997$ ,  $p = .003$ , but there were no sex differences in PSS score or FWD.

### 3.2 Predictive modelling results

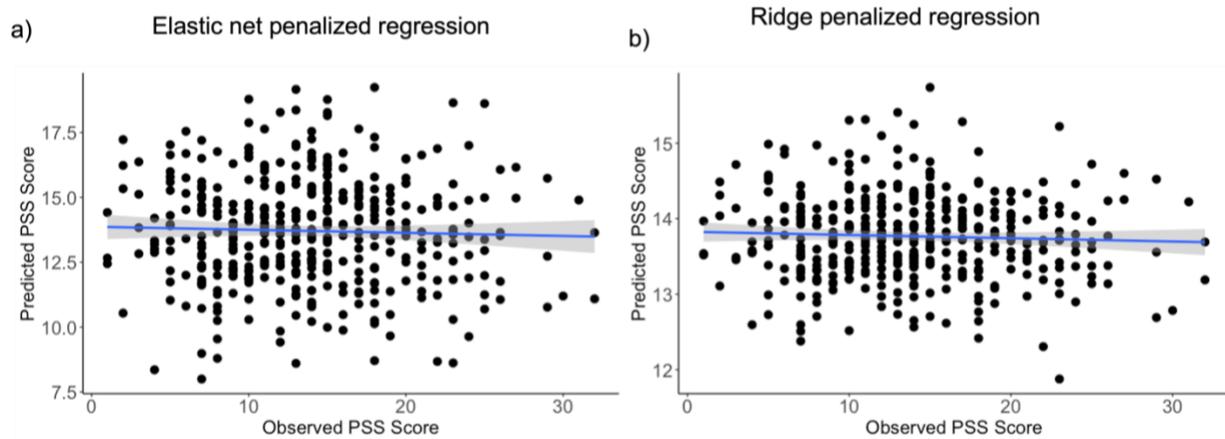
Using a cross-validated penalized regression approach, we found that the models predicting perceived stress performed poorly. As shown in Figure 1, nested cross-validation showed that perceived stress predicted by the whole-brain resting-state FC pattern was not significantly correlated with observed PSS scores, elastic net:  $r = -.035$ ,  $p = .479$ , 95% CI [-.131 .061], RMSE = 6.441,  $R^2 = .001$ , MAE = 5.095; ridge:  $r = -.046$ ,  $p = .346$ , 95% CI [-.142 .050], RMSE = 6.049,  $R^2 = .002$ , MAE = 4.810. These results do not appear to differ by sex or cohort, though stratified analyses were not run to retain the highest possible sample size (see Figures 3-6 in Appendix).

We also found that while the performance metrics for the models predicting age were equally as poor, the association between age predicted by the whole-brain resting-state FC pattern and observed age was significant, elastic net:  $r = 0.193$ ,  $p < .0001$ , 95% CI [.099 .284], RMSE = 6.661,  $R^2 = 0.037$ , MAE = 5.715; ridge:  $r = .197$ ,  $p < .0001$ , 95% CI [0.103 0.287], RMSE = 6.613,  $R^2 = 0.039$ , MAE = 5.814 (see Figure 2).

**Table 1: Analytic Sample Characteristics – N = 417 (95%)**

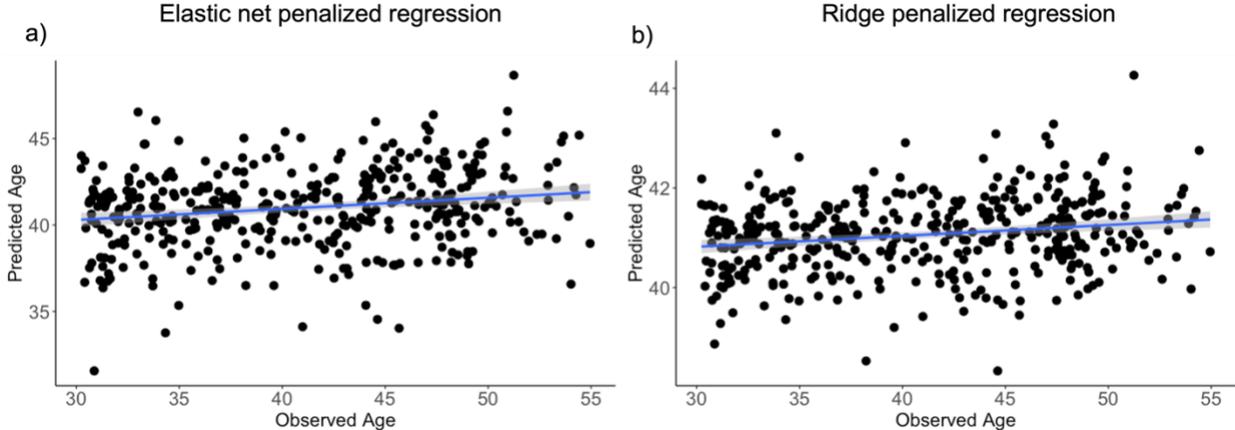
Characteristics	AHAB (N = 106)	PIP (N = 311)	Overall (N = 417)
Female (%)	62.3	49.8	53
Race (%)			
White	83	73.3	75.8
Black	12.3	20.6	18.5
Asian	4.7	4.2	4.3
Native American	0	1	.7
Bi/Multi-racial	0	1	.7
Other	0	0	0
Age (years)	41.9 (7.99)	40.8 (6.23)	41 (6.73)
PSS score (out of 40)	13.7 (6.08)	13.8 (5.99)	13.6 (6.00)
Framewise displacement (mm)	.16 (.08)	.17 (.09)	.17 (.08)

Values reflect mean (standard deviation), unless otherwise noted.



**Figure 1: Whole-brain resting-state FC patterns do not predict PSS scores**

Relationship between observed and predicted PSS score for two multivariate penalized regression models – (a) elastic net and (b) ridge. The blue solid line and gray shading represent the line of best fit and the corresponding 95% confidence interval, respectively.



**Figure 2: Whole-brain resting-state FC patterns predict age**

Relationship between observed and predicted age for two multivariate penalized regression models – (a) elastic net and (b) ridge. The blue solid line and shading represent the line of best fit and the corresponding 95% confidence interval, respectively.

## 4 Discussion

In the present study, we do not demonstrate that individual differences in perceived stress are reliably predicted by a whole-brain resting-state FC pattern. Cross-validated, multivariate penalized regression models performed poorly, and predicted values did not significantly associate with observed values (Figure 1). However, these models did successfully predict age in this sample (Figure 2). Our results suggest that the functional neural correlates of perceived stress may not be characterized by patterns of resting-state FC. Below, we speculate about potential explanations for these findings, including differences in how resting-state FC and perceived stress are operationalized and measured; methodological differences from previous work; robustness of the statistical approach; and low statistical power.

While resting-state FC and perceived stress, as measured in the present study, both exhibit reliable individual differences, it could be that they are conceptually distinct from one another and thus may not be meaningfully relatable to each other in this context. Perceived stress, for example, is thought to reflect a cumulative “cognitive average” of stress appraisals over the last month. Resting-state FC, on the other hand, is thought to reflect spontaneously evoked intrinsic brain activity that may be context independent with respect to fluctuating stress appraisals over the past month. Thus, resting-state FC could be capturing underlying processes that may be unrelated to those presumably reflected in the PSS score and may not be the best measure for modelling individual differences in perceived stress. As such, future studies might reconcile these conceptual and operational differences by using an adapted protocol that is in line with the so-called “third-wave” of human neuroimaging research, which combines the flexibility afforded by resting-state paradigms with the structure of task-based paradigms to improve the interpretability of our results and deepen our understanding of brain-phenotype relationships (Finn, 2021). In this vein, rather than completing an unstructured resting-state scan, participants could instead receive instructions that mirror the items on the PSS (e.g., “During this resting period, think about how unpredictable/uncontrollable/overloading your life experiences over the last month have been.”). This instruction manipulation may evoke the same cognitions and engage the relevant appraisal processes that are presumably at play during the completion of the PSS, enabling a more direct comparison, in the service of more precisely characterizing the functional neural correlates of perceived stress.

The null findings observed here could be due to methodological differences between our study and the existing literature. First, Liu and colleagues used a sample of college-aged adults newly experiencing a novel global pandemic (mean age of 19.14 years across the three datasets), while our sample consisted of midlife adults studied prior to this historical epoch (mean age of 41 years) (Liu et al., 2021). Thus, it may

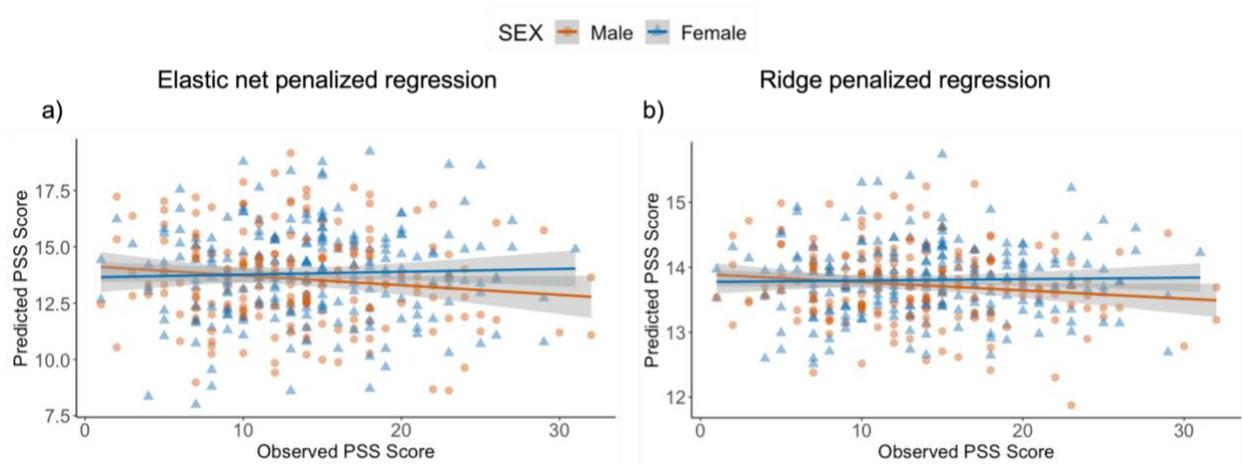
be that the association between perceived stress and resting-state FC is an age-dependent effect or one affected by ambient levels of commonly experienced psychological stress. Moreover, perceived stress appears to decrease with age normatively, with self-reported levels peaking in young adulthood and gradually decreasing into midlife (Almeida et al., 2022; Cohen & Janicki-Deverts, 2012). Additionally, age-related changes in resting-state FC dynamics are characterized by reduced connectivity within large-scale networks (including the default mode and salience networks) and enhanced connectivity between them (Damoiseaux et al., 2008; Jockwitz & Caspers, 2021; Varangis et al., 2019). Differences in the resting-state scan protocols between studies may also account for the discrepancy in results; while Liu et al had an 8-minute, eyes-open resting-state scan, our protocol included a 5-minute, eye-closed resting-state scan (Liu et al., 2021). There is evidence suggesting that both scan length and eye state can modulate the reliability and strength of the connectivity measures obtained. For example, compared to shorter scans (~5 minutes), scans of moderate length (~12 minutes) can improve the reliability and consistency of the resulting FC measures by up to 20% and 36%, respectively (Birn et al., 2013). And FC of the primary visual area with the salience and default mode networks differs depending on eye state during a resting-state scan, suggesting that eye state modulates brain activity configuration (Costumero et al., 2020).

Further, differences in statistical approach, coupled with low statistical power, may also explain the failure to replicate the previously published effect. Liu and colleagues used leave-one-out cross-validation (LOOCV), while we used nested  $k$ -fold cross-validation (Liu et al., 2021). In LOOCV, the model is trained on all but one datapoint in the sample, then that datapoint is used for model testing. Though this approach is exhaustive, using almost the entire sample to train the model and thus producing unbiased estimates, the variance between the resulting model predictions tends to be high, increasing the risk of overfitting (James et al., 2014). Conversely, nested  $k$ -fold cross-validation (described above) attempts to rectify this bias-variance tradeoff by separating the model tuning and model testing processes (Cawley & Talbot, 2010; Korjus et al., 2016). Thus, it may be the more robust approach to using resting-state FC to model individual difference variables, as demonstrated by the model's successful prediction of age in our exploratory analyses (Figure 2). Additionally, though the sample size in Liu et al was double that of the present study ( $n = 817$  versus  $n = 417$ ), it may be the case that both studies are underpowered to detect a replicable effect. By some accounts, multivariate brain-wide association studies require large sample sizes, possibly upwards of 1000 participants, to yield replicable results, although some show replicable effects in small to moderate samples (e.g.,  $n = 75 - 500$ ) (Marek et al., 2022; Spisak et al., 2023; Tervo-Clemmens et al., 2023).

In conclusion, our results suggest that whole-brain resting-state FC patterns do not reliably predict individual differences in perceived stress, contrary to previous work (Liu et al., 2021). It remains unclear

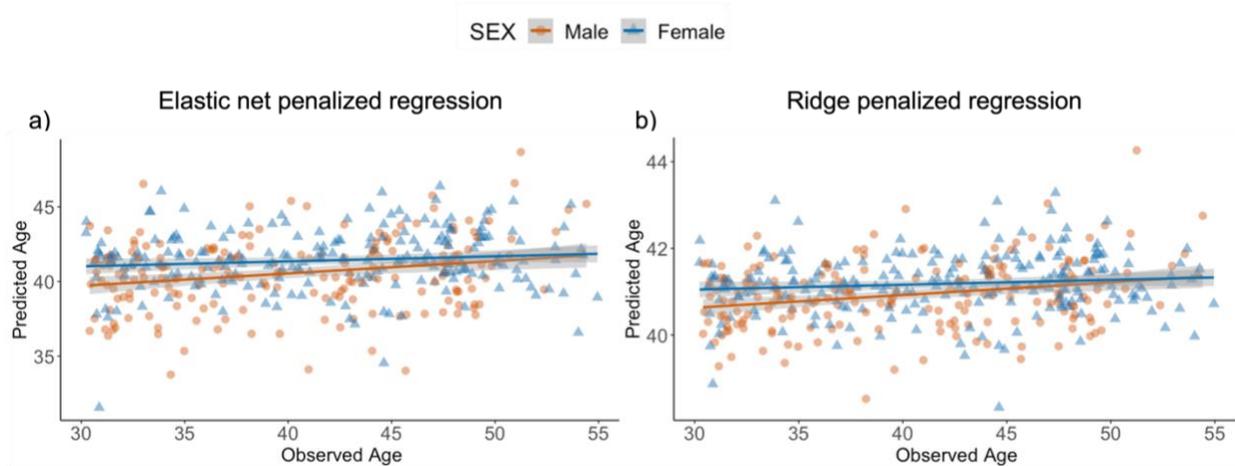
whether these results are due to inconsistencies between studies with respect to measurement of model variables, lifespan considerations, methodological approaches, or low statistical power. Future studies using different imaging assessment methods or possibly different markers of psychological stress (e.g., biological) are warranted to better understand the role of the brain in linking stress and physical health outcomes.

## Appendix A Appendix A: Predictive modelling results, stratified by sex



**Figure 3: Penalized regression model results for PSS score, by sex**

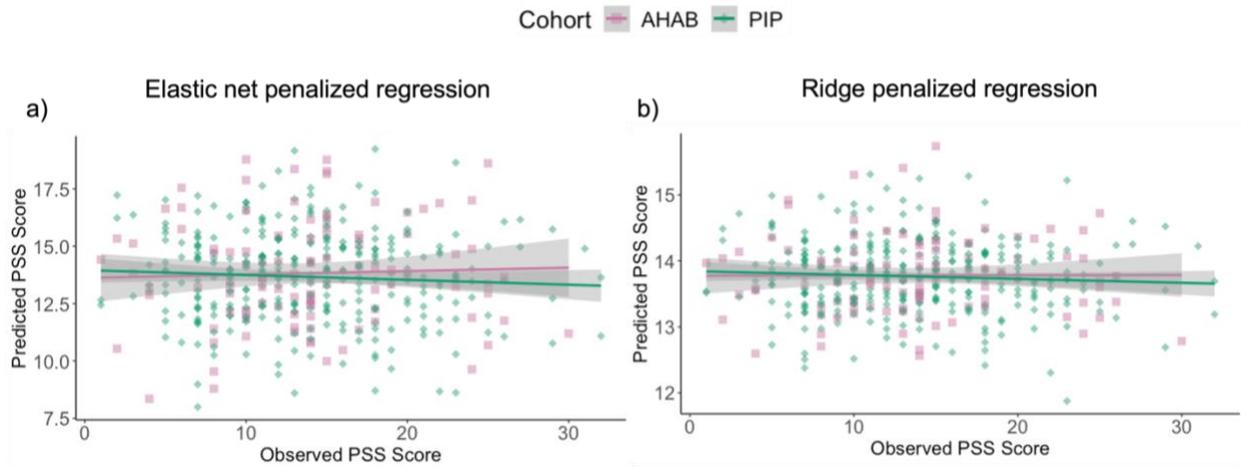
Relationship between observed and predicted PSS score for (a) elastic net and (b) ridge penalized regression models, stratified by sex. Orange circles represent male participants and blue triangles represent female participants. Solid colored lines with shading represent the line of best fit and the corresponding 95% confidence interval.



**Figure 4: Penalized regression model results for age, by sex**

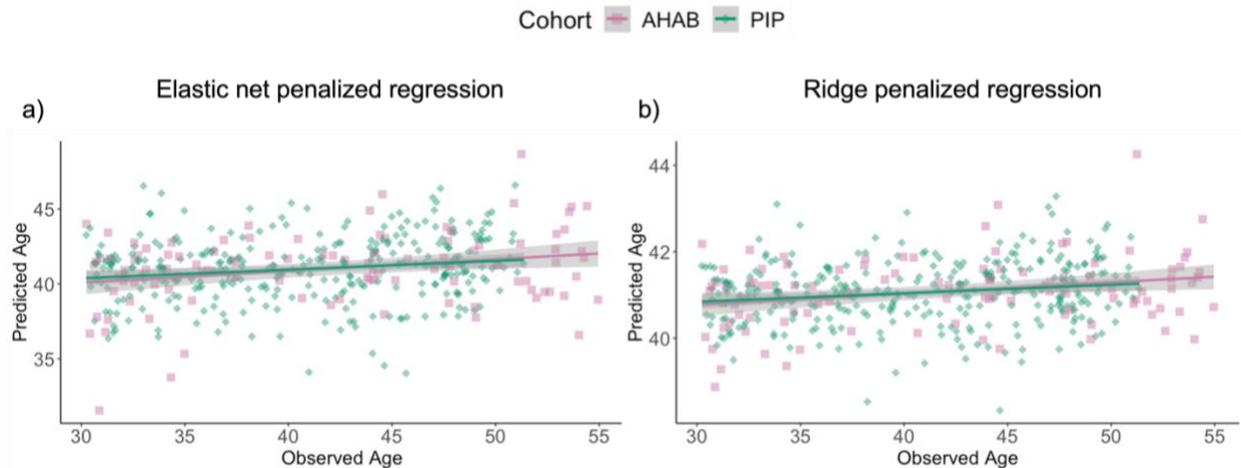
Relationship between observed and predicted age for (a) elastic net and (b) ridge penalized regression models, stratified by sex. Orange circles represent male participants and blue triangles represent female participants. Solid colored lines with shading represent the lines of best fit and the corresponding 95% confidence interval.

## Appendix B Predictive modelling results, stratified by cohort



**Figure 5: Penalized regression model for PSS score, by cohort**

Relationship between observed and predicted PSS score for (a) elastic net and (b) ridge penalized regression models, stratified by cohort. Pink squares represent AHAB participants and green diamonds represent PIP participants. Solid colored lines with shading represent the lines of best fit and the corresponding 95% confidence interval.



**Figure 6: Penalized regression model results for age, by cohort**

Relationship between observed and predicted age for (a) elastic net and (b) ridge penalized regression models, stratified by cohort. Pink squares represent AHAB participants and green diamonds represent PIP participants. Solid colored lines with shading represent the lines of best fit and the corresponding 95% confidence interval.

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