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Association between Childhood Trauma and Limbic System Activation under Stress: A Study of Neurological Mechanisms for Adverse Cardiovascular Events

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Daniel Corry

B.S., Georgetown University, 2015

Thesis Committee Chair: Amit J. Shah, MD, MSCR

An abstract of

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Abstract

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By Daniel Corry

Background: Mental stress is a risk factor for cardiovascular health and adverse cardiovascular events, and trauma exposure in childhood may influence the risk of development of cardiovascular disease later in life. However, the neurological mechanisms underpinning the possible links between early trauma exposure, mental stress, and cardiovascular disease are largely unknown, although there is evidence to suggest activation of the limbic system may play a role in physiologic response to stress and increased risk of cardiovascular disease. This study aims to provide further evidence of a link between early trauma and increased activation of the limbic system later in life as a possible mechanism of cardiovascular disease risk.

Methods: Participants with coronary artery disease were recruited from three hospitals in Atlanta, Georgia for the Mental Stress Ischemia Prognosis Study. Selected participants underwent psychometric evaluation using the Early Trauma Inventory: Self-Report scale to measure childhood trauma exposure. Perfusion in selected brain regions was measured at rest and under stressful conditions to measure activation of those regions. Correlations between early trauma and perfusion were calculated, and a dose-response relationship across quintiles of early trauma score were also calculated for the amygdala and hippocampus.

Results: Mild correlations between early trauma exposure and perfusion were found in the left ($r = 0.16$) and right amygdala ($r = 0.20$), the left hippocampus ($r = 0.30$), and the right medial orbitofrontal cortex ($r = 0.17$). Subgroup analysis showed differences in correlations in the hippocampus across age, gender, and race. Both the amygdala and the hippocampus exhibited a dose-response relationship between early trauma and perfusion.

Conclusion: There is a possible association between early trauma exposure and activation of key areas of the limbic system. These associations could have implications for neurological interventions to prevent cardiovascular disease. More research is needed to assess the neurologic underpinnings of physiologic response and how much these possible mechanisms affect the development of cardiovascular disease outcomes.

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I. INTRODUCTION

Mental stress has been shown to influence cardiovascular health and plays a specific role in the development of adverse cardiovascular events. In addition, adverse childhood events (ACEs) may also be linked to the development of cardiovascular disease (CVD); previous studies have noted an increased risk of hypertension, myocardial infarction (MI), and stroke later in life (1-7). This relationship between ACEs and CVD may be explained through various mechanisms, including neurologic, endocrine, and inflammatory (8). For each of these mechanisms, however, the brain likely plays a central role.

Prior research has shown a heightened physiologic response to stress among those with childhood trauma exposure; those with greater exposure to trauma may have heightened activation of certain brain regions in response to stressful tasks when compared to those with less trauma exposure (9). The neurological mechanisms underlying the association of mental stress, childhood trauma exposure, and cardiovascular health are largely unknown, though prior research has found that those with childhood trauma exposure have impaired autonomic function due to heightened hormonal responses to stressful events (10). Autonomic cardiovascular function is also associated with the limbic system of the brain and other areas associated with autobiographical memory (11). Specifically, autonomic functions may be influenced by the amygdala, as activation of the amygdala may be related to increased heart rate and decreased HRV (11). Moreover, autonomic modulation by the amygdala may work through a neurovisceral integration pathway that also involves the medial orbitofrontal cortex (mOFC), insula, and anterior cingulate cortex (ACC) (11).

The hippocampus may also influence autonomic function via neural networks connecting it to the brainstem autonomic nuclei (12). Furthermore, the hippocampus and amygdala are involved in the recollection of traumatic events; while the hippocampus is more associated with recollection of specific details, the amygdala is more involved with emotional recall to past events (13, 14). Given the possible role these brain regions have in the physiologic stress response, and their additional roles in trauma recall, they are excellent candidates for being potential mediators in the relationship of ACE's and CVD.

We tested the hypothesis that individuals with coronary artery disease with greater exposure to traumatic experiences demonstrate heightened reactivity to mental stress in the amygdala and the hippocampus compared to those with less exposure. We also tested whether individuals with coronary artery disease with greater exposure to traumatic experiences also experience heightened reactivity in the anterior cingulate cortex (ACC), the insula, and the medial orbitofrontal cortex (mOFC) in response to compared to those with less exposure.

II. METHODS

Population

Patients from the Mental Stress Ischemia Prognosis Study (MIPS) between the ages of 30 and 79 who had been diagnosed with coronary artery disease (CAD) (N=186) were included in the study. Patients in MIPS were recruited at Emory University Hospital, Grady Memorial Hospital, and the Atlanta VA Medical Center between September 2010 and September 2016. CAD was defined as having an atherosclerosis diagnosis, history of myocardial infarction, history of coronary artery bypass grafting or percutaneous coronary intervention at least one year prior to the study, or a positive nuclear stress test. Exclusion criteria included pregnancy, systolic blood pressure greater than 180 mm Hg or diastolic blood pressure greater than 110 mm Hg on the day of the test, recent acute coronary syndrome, history of a severe mental disorder including schizophrenia, psychosis, bipolar disorder, or substance dependence within the past year, history on loss of consciousness for more than one minute, history of neurological disorder such as Parkinson's disease, dementia, or stroke, or contraindications to regadenoson. Certain medications were withheld for 12 hours (calcium channel blockers, nitrates) or 24 hours (beta-adrenergic antagonists) prior to the study. Any patient for whom withholding medications was considered harmful was also excluded from the study. All participants provided written consent and the study was approved by the Emory University Institutional Review Board (IRB).

Psychometric Assessment

Patients were assessed with psychometric survey tools, including the Early Trauma Inventory-Self Report (ETISR) questionnaire, a validated instrument used to

assess general trauma and physical, emotional, and sexual abuse (15). The questionnaire was separated into four parts (General, Physical, Emotional, and Sexual). Each positive response to a question was counted as a point, and all points were added together to find the ETISR total score and subscores for the four parts of the questionnaire. The Subjective Units of Distress Scale (SUDS) was used to assess stress before and after the stress procedures. Psychiatric diagnosis was assessed using Diagnostic and Statistical Manual-IV (DSM-IV) Guidelines.

Mental Stress Testing

Participants underwent mental stress testing while brain imaging was being performed. Patients were scanned under four conditions, with two control tasks to assess baseline measures and two stressful tasks to assess physiological response to stress. Measures were taken twice during the tasks for a total of eight brain scans. Control tasks included counting out loud and talking about a neutral event. The stressful math-related task involved mentally calculating increasingly difficult math problems with addition, subtraction, multiplication, and division, while an administrator gave them negative feedback throughout the task. The stressful language-related task involved public speaking, where patients were given a scenario and were asked to respond to the scenario, while a study administrator told the patients that their speech would be evaluated for content.

Brain Imaging

Brain perfusion was assessed to quantify regional activation in response to the stressful and non-stressful (or control) tasks. Participants underwent eight positron emission tomography (PET) scans in conjunction with control and stressful tasks.

During the scan, brain blood flow was measured with the help of radiolabeled O-15 water injected into the bloodstream. During the first four scans, patients were asked to count out loud or to talk about a neutral event, with two scans performed for each task. The final four scans were performed during the stressful tasks, involving mental arithmetic and public speaking. All tasks lasted for two minutes and the radiolabeled water was injected ten seconds after the beginning of each task. Electrocardiogram and vital signs were monitored throughout the process.

Statistical Analysis

Statistical analyses were performed using SAS 9.4. All measures for brain perfusion were standardized with a mean=0 and a standard deviation=1. The primary outcomes of interest were perfusion in the selected regions of the brain: amygdala, hippocampus, ACC, insula, and mOFC. Descriptive statistics were recorded for the entire study sample and for subsamples below and above the median ETISR score. Pearson correlations between ETISR score and the selected brain regions were recorded, and partial correlations adjusting for the covariates were also calculated. Correlations across subgroups of age, gender, and race were calculated and adjusted for the other covariates. Finally, average change in brain perfusion was calculated across quintiles of ETISR score for the amygdala and hippocampus because of their roles in the recall of traumatic experiences.

III. RESULTS

A total of 176 subjects were included in this study. The mean (SD) age among participants was 62.0 (8.5) years. The study sample included 64 African-Americans (36.4%) and 55 female participants (31.2%). Additionally, 166 participants (94.3%) had at least a high school diploma or GED, and 81 participants (46.0%) reported household income greater than $50,000. The median total ETISR score was 7, and distributions of the risk factors for the populations below and above the median score can be found in Table 1.

The correlations between total ETISR score and selected brain regions can be found in Figure 1. A higher total ETISR score was weakly correlated with increased stress perfusion change in the left (r = 0.161, 95% CI: (0.003, 0.310)) and right (r = 0.198, 95% CI: (0.043, 0.346)) lobes of the amygdala, the left hippocampus (r = 0.297, 95% CI: (0.146, 0.434)), and the right mOFC (r = 0.174, 95% CI: (0.017, 0.323)). Total ETISR score and stress perfusion change were not correlated in the other selected brain regions. Adjusted correlations did not significantly differ from the unadjusted correlations.

Subgroup correlations between total ETISR score and hippocampus perfusion are shown in Figure 2. The mean stress perfusion change between left and right lobes were averaged to create the mean stress perfusion change for the hippocampus. Change in hippocampus perfusion was more highly correlated with ETISR score in participants below the age of 63 (r = 0.377, 95% CI: (0.154, 0.563)) than in participants above the age of 63 (r = 0.125, 95% CI: (-0.089, 0.329)). In addition, stress perfusion change and ETISR score were more highly correlated in females (r = 0.459, 95% CI: (0.201, 0.657)) compared to males (r = 0.207, 95% CI: (0.017, 0.381)), and in African-Americans (r = 0.385, 95% CI:

(0.134, 0.590)) compared to participants of other races (r = 0.196, 95% CI: (-0.001, 0.378)). Similarly, adjusted correlations were not different from unadjusted correlations.

Mean stress perfusion change in the amygdala across quintiles of total ETI score is shown in Figure 3. For each quintile increase in total ETI score, the stress perfusion change increased 0.030 standard deviations in the amygdala. The mean stress perfusion change in the left and right hippocampus is shown in Figure 4. The stress perfusion change increased 0.032 standard deviations in the left hippocampus and 0.014 standard deviations in the right hippocampus with each quintile increase.

IV. DISCUSSION

In this study, we found a mild positive relationship between stress-induced brain perfusion and self-reported early trauma score in both the amygdala and the hippocampus. This supports the hypothesis that early trauma exposure causes central neurologic changes in areas involving fear and the physiologic stress response which may help explain the impact of early trauma on the cardiovascular system. Additionally, early trauma exposure was an independent predictor of stress-induced brain perfusion changes despite adjustment for potential confounding by CVD risk factors.

The amygdala is associated with emotional processing in the brain and is often activated by recall of emotions from past traumatic events. Specifically, the amygdala is heavily involved in the processing of fear, which can emerge in some form as a response to stressful tasks and stimuli (16). A dose-response relationship between ETISR score and amygdala perfusion was found, suggesting that greater trauma exposure in childhood leads to greater amygdala activation to stressful stimuli many years later. Ultimately, this may lead to greater risk of CVD later in life (17).

A differing relationship between ETISR score and stress perfusion change in the left and right hippocampus was also found. In this population, the rate of increase in stress perfusion change in the left hippocampus across quintiles was more than double the rate of increase in stress perfusion change in the right hippocampus. Prior literature supports a dissociation between the left and right hippocampus in memory recall. While the right hippocampus is more involved with spatial memory, the left hippocampus has a role in episodic memory (18). It is possible, then, that episodic

memory is disproportionately evoked by mental stress challenge in those with early trauma exposure. One possibility is that the original trauma is evoked by the lab-based stress challenges, although this requires more research to elucidate.

Our subgroup analysis suggested that this relationship may be moderated by sociodemographic factors. Participants below the median age of 63 showed greater association between self-reported trauma and hippocampus perfusion than participants above the median age, which could be due to the greater effect that psychological factors have been shown to have on cardiovascular health at younger ages (19). Female participants also showed a greater association than male participants did, supporting prior literature and possibly underscoring gender differences in neurological structure and hormonal response to stress (10, 20). Additionally, the difference between the association in African-Americans and the association in participants of other races also could be due to an unmeasured stress-related factor, like discrimination, which has been shown to adversely affect cardiovascular health (21).

This study was subject to several limitations. First, findings from our sample may not be generalizable to the healthy community, given the inclusion criteria of CAD and under-representation of women. Nonetheless, CAD is a prevalent condition, and the population is high risk, which underscores the public health relevance of these findings. Second, the cross-sectional and observational nature of the study limits causal inference; thus, more research utilizing longitudinal and experimental studies is needed. Third, trauma was a self-reported measure, which may have biased our results towards the null through non-differential recall bias. Finally, this study focused on whole brain

regions, and study of smaller sub-regions of the brain were not evaluated as part of this study's scope.

Given the role of limbic system activation in adverse CVD outcomes, and the role of trauma exposure as an independent predictor of amygdala and hippocampus activation, the results from this study may inform future cardiovascular health treatments for those patients who report elevated childhood trauma exposure. Future studies researching the mechanisms behind CVD should include further evaluation of downstream physiologic effects of neurological activation, such as stress reactivity in everyday life and how much these neurologic phenomena increase CVD risk. Additionally, research into psychotherapy and other neurological interventions to reduce CVD risk should be done. Furthermore, more research should be done in patients with and without CAD to form a more generalizable population. Finally, research into the neurology of trauma and stress response, specifically the neurologic underpinnings of complex emotional processing, would be able to provide new ideas for mechanisms of trauma processing and stress response leading to pathophysiologic outcomes.

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VI. TABLES

Table 1. Demographics of the study sample.

		Total (N=176)		ETISR < 7 (N=82)		ETISR ≥ 7 (N=84)	
		Mean	SD	Mean	SD	Mean	SD
Age		61.98	8.49	63.87	8.21	60.34	8.39
		n	%	n	%	n	%
Race							
	African-American	64	36.36	27	32.93	37	39.36
	Other	112	63.64	55	67.07	57	60.64
Gender							
	Male	121	68.75	59	71.95	62	65.96
	Female	55	31.25	23	28.05	32	34.04
Education Level							
	Grade School	2	1.14	2	2.44	0	0
	Some high school (9th-11th)	8	4.55	3	3.66	5	5.32
	High school diploma or GED	39	22.16	19	23.17	20	21.28
	Associates degree/ some college/ vocational school	58	32.95	18	21.95	40	42.55
	Bachelor's degree	28	15.91	13	15.85	15	15.96
	Master's degree	23	13.07	15	18.29	8	8.51
	Doctoral degree	12	6.82	8	9.76	4	4.26
	Other	6	3.41	4	4.88	2	2.13
Income							
	< $20,000	35	20.00	12	14.81	23	24.47
	$20,000 -$34,999	28	16.00	11	13.58	17	18.09
	$35,000 - $49,999	19	10.86	8	9.88	11	11.70
	$50,000 - $99,999	41	23.43	21	25.93	20	21.28
	≥ $100,000	40	22.86	21	25.93	19	20.21
	Do not know	12	6.86	8	9.88	4	4.26

VII. FIGURES

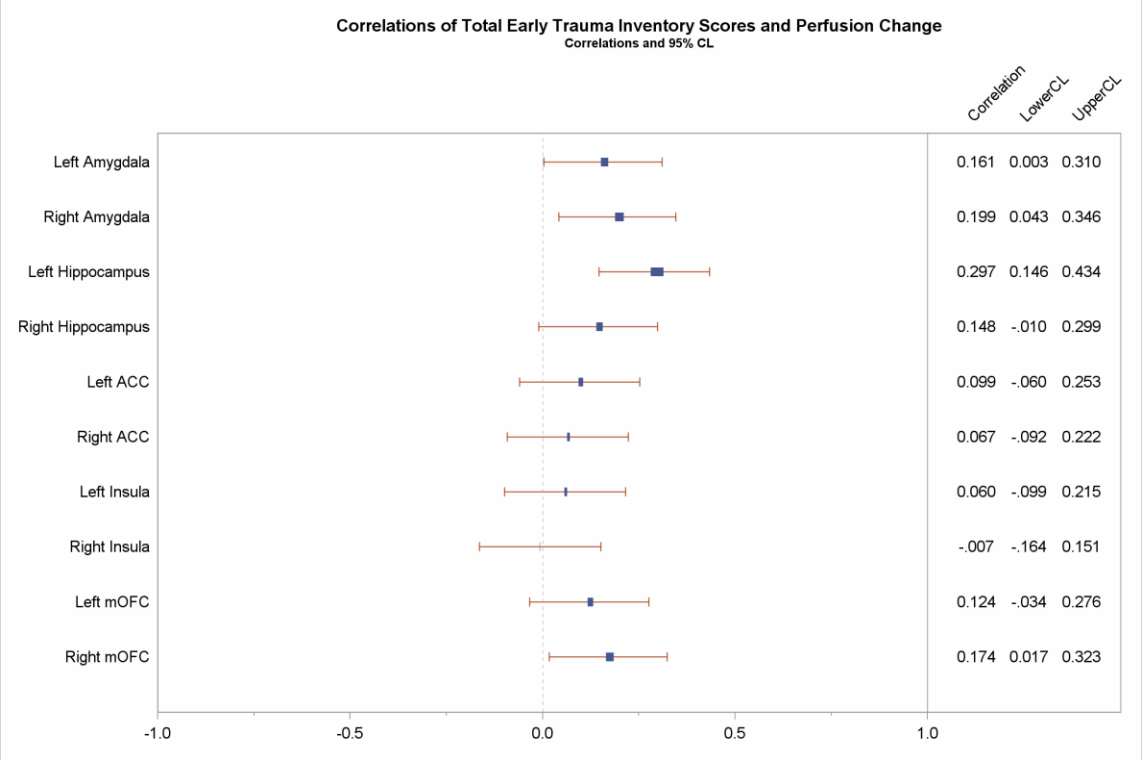

Figure 1. Correlations between total ETISR score and stress perfusion change by brain region.

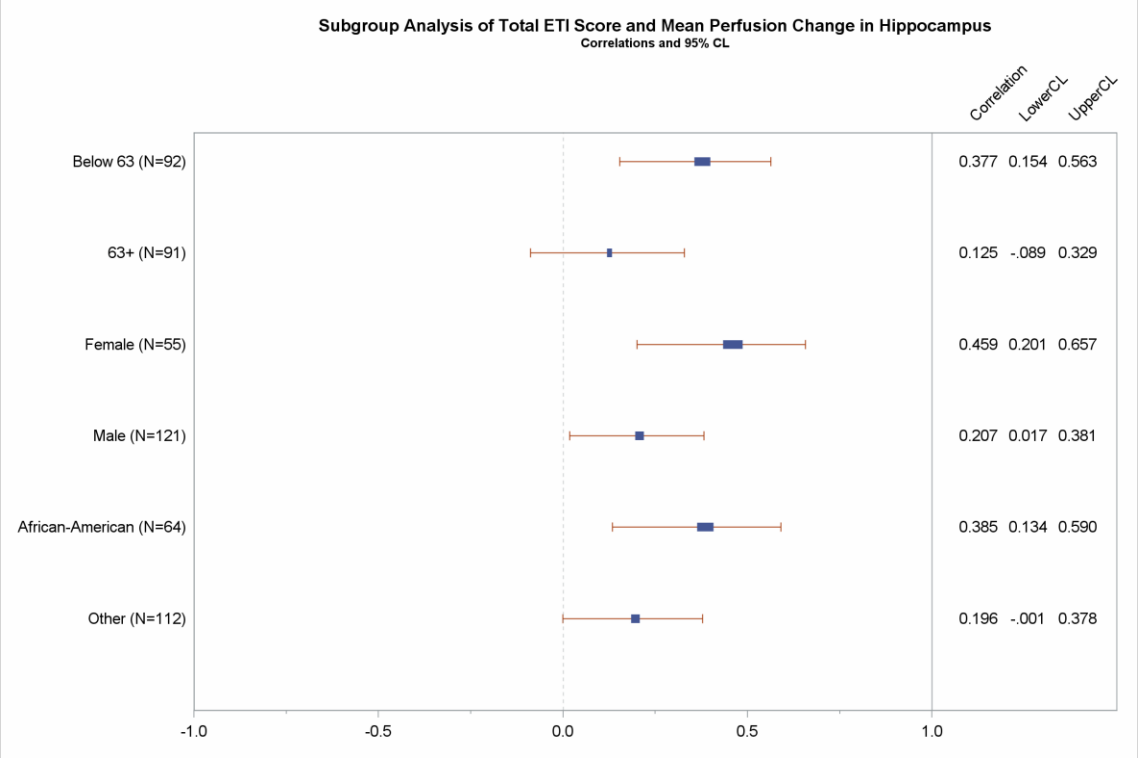

Figure 2. Subgroup correlations (age, gender, race) between ETISR score and stress perfusion change in the hippocampus.

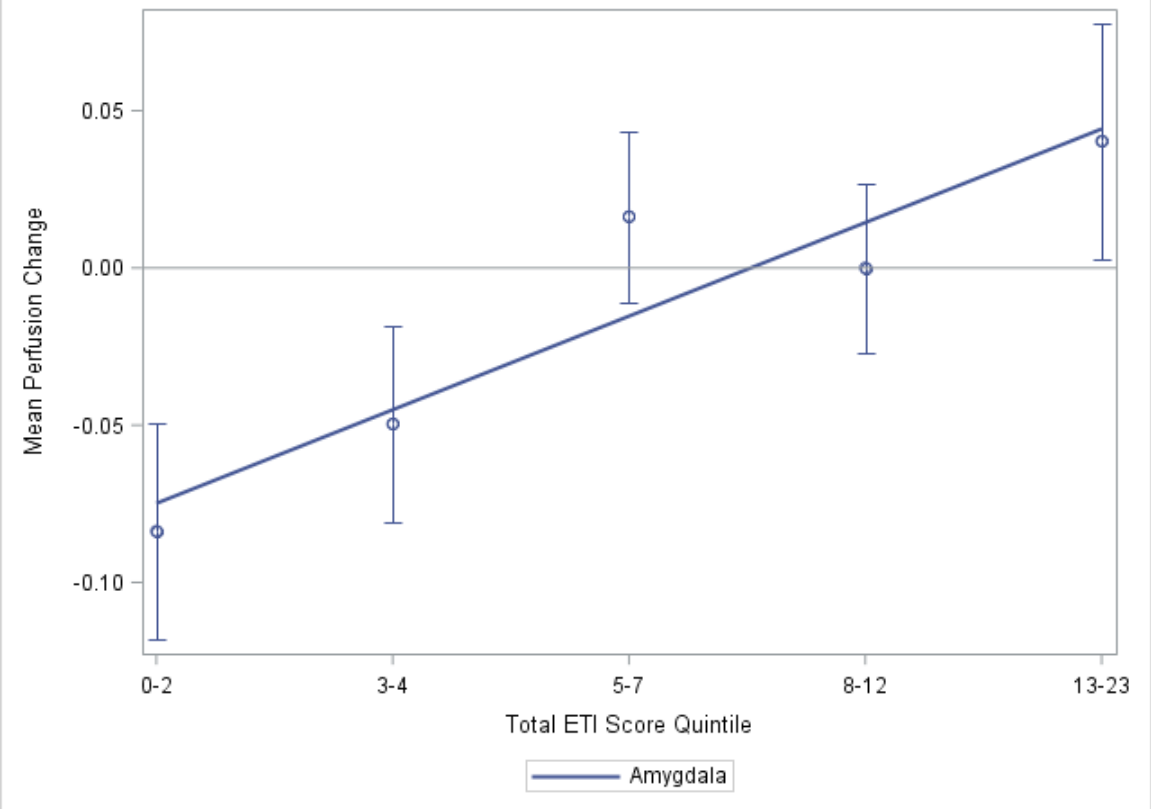

Figure 3. Mean change in amygdala perfusion across quintiles of total ETI score.

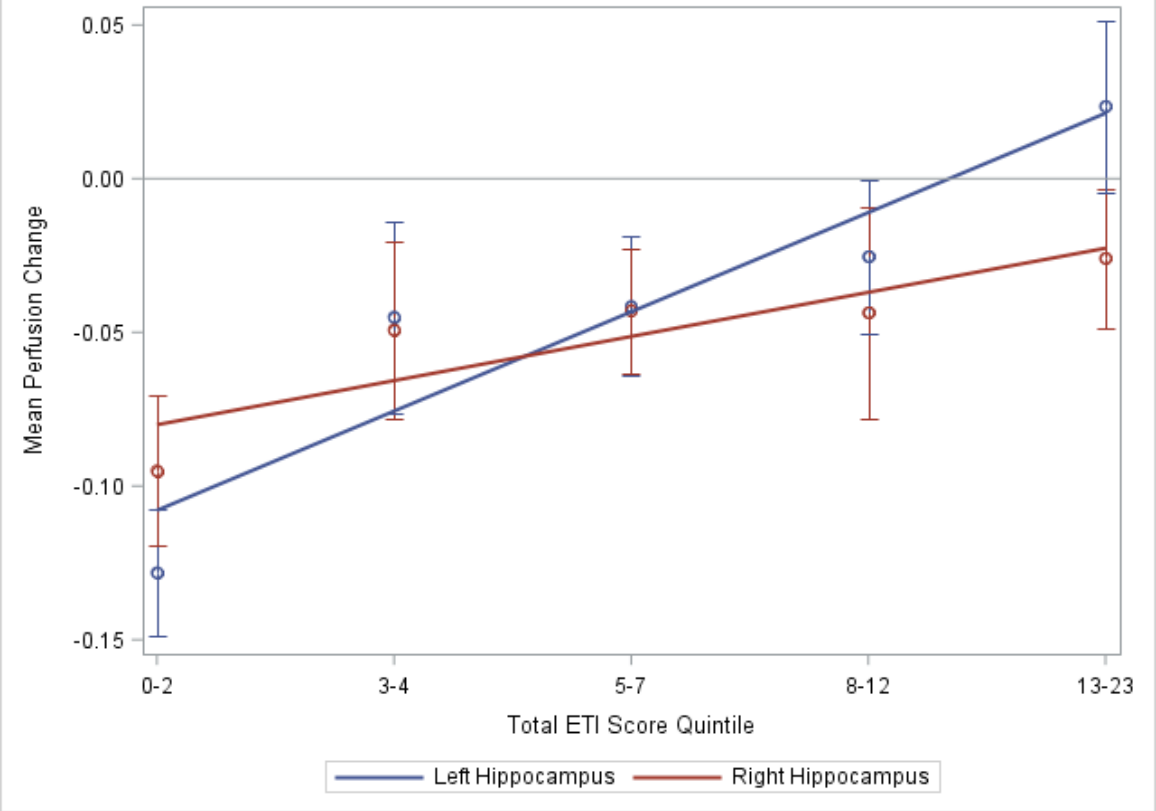

Figure 4. Mean change in left and right hippocampus perfusion across quintiles of total ETI score.