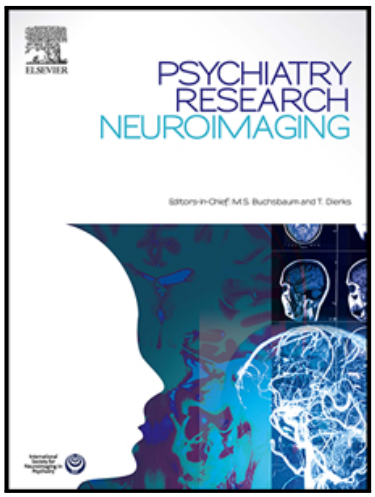

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Neural Correlates Linking Trauma and Physical Symptoms

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Highlights

- Trauma patients showed greater physical health symptoms and decreased prefrontal but increased hippocampal responses to stress than controls.
- More frequent physical symptoms were associated with an increased left hippocampal response to stress.
- Trauma may increase physical health symptoms by compromising hippocampal function, which could also increase vulnerability to comorbid stress- and pain-related disorders.

Abstract

Trauma and chronic pain frequently co-occur, but the underlying neurological mechanisms are poorly understood. The current study investigated the neural correlates of stress and physical symptoms in trauma patients using functional magnetic resonance imaging (fMRI) and follow-up smartphone surveys. Participants were 10 patients diagnosed with Trauma- and Stressor-Related Disorders and 18 demographically-matched healthy controls who completed a fMRI stress provocation task in which they viewed stressful and neutral-relaxing images. Subsequently, participants completed daily smartphone surveys which prospectively monitored their stress and physical symptoms for 30 days. The trauma group experienced a significantly higher frequency of physical symptoms than controls during the follow-up period. During stress, trauma patients exhibited increased activity in the hippocampus, insula, and sensorimotor areas, but decreased activity in the ventromedial prefrontal cortex (vmPFC), lateral prefrontal cortex (LPFC), and dorsal striatum relative to controls. In all participants, higher physical symptom frequency was significantly associated with a hyperactive left hippocampal response to stress. The current study reports that trauma is characterized by greater physical symptoms and decreased prefrontal but increased limbic responses to stress. Our findings suggest that trauma may increase physical health symptoms by compromising hippocampal function, which could also increase vulnerability to stress- and pain-related disorders.

Keywords: trauma; stress; pain; physical symptoms; fMRI; hippocampus

1. Introduction

Trauma, although primarily conceptualized as a psychiatric disorder, is often accompanied by pain and physical health symptoms (Pacella et al., 2013; Ryder et al., 2018). In fact, trauma and chronic pain are highly co-occurring conditions, with comorbidity rates in the United States reaching as high as 50% in veteran populations (Fishbain et al., 2017). It has previously been suggested that chronic stress and pain are mutually reinforcing wherein the symptoms of one can exacerbate the symptoms of the other, and vice versa (Asmundson et al., 2002; Sharp & Harvey, 2001). As a potential explanation, prior studies have suggested the framework of *allostatic load* (Abdallah & Geha, 2017; Lunde & Sieberg, 2020), which refers to the ―wear and tear‖ induced by chronic stress on bodily systems which can eventually lead to physical health problems (McEwen, 1998, 2007). Consistent with this, a national epidemiologic survey conducted in the U.S. found that Post-Traumatic Stress Disorder (PTSD) patients had disproportionately high rates of various medical conditions compared to controls (Pietrzak et al., 2011).

However, there remain significant gaps in our understanding of the neural mechanisms underlying the link between stress, trauma, and pain. A prior study from our group with healthy community individuals found that cumulative trauma and adversity were associated with a greater likelihood of physical health symptoms and an altered neural response to stress (Seo, Tsou, et al., 2014). Specifically, hypoactivity in the ventromedial prefrontal cortex (vmPFC) and hyperactivity in the hippocampus explained the link between high cumulative stress and physical symptoms (Seo, Tsou, et al., 2014). The vmPFC is known to be involved in emotion regulation (Golkar et al., 2012; Ochsner et al., 2002), while the hippocampus is involved in stress, memory (Kim & Diamond, 2002; Lupien & Lepage, 2001), and modulation of immune function (Devi et al., 2004; Xiong et al., 2016). These findings suggest that an overactive hippocampal response to stress resulting from decreased vmPFC regulatory control may underlie the link between trauma and physical symptoms.

Although our prior study provided insight into the neural mechanisms of stress and physical pain in healthy individuals, it did not examine this phenomenon in trauma patients who are more likely to display stronger stress-related symptoms.

Furthermore, prior trauma studies measuring pain have been constrained by a retrospective approach to tracking pain and physical symptoms (Langford et al., 2018; Noel et al., 2016). A prospective approach where participants are tracked in real-time and in real-life settings can minimize participants' recall bias (Shiffman et al., 2008) and yield more accurate data on stress and health-related symptoms (Smyth & Stone, 2003). These studies emphasize the need for prospective measures of physical symptoms to better understand the link between trauma and pain.

To extend our findings in community individuals from Seo, Tsou, et al. (2014) to clinical populations, the present study examined the associations between neural correlates of stress and prospectively measured physical symptoms in trauma patients and demographically-matched healthy controls. We used functional magnetic resonance imaging (fMRI) combined with a prospective follow-up method that tracked daily stress and physical symptoms in real-life settings via smartphone surveys. For stress manipulation during fMRI, we used a sustained stress provocation task that has been well-validated in prior neuroimaging studies (Goldfarb et al., 2020; Goldfarb et al., 2019; Sinha et al., 2016). Based on our prior results (Seo, Tsou, et al., 2014), we hypothesized that trauma patients would experience greater physical symptoms than healthy controls and exhibit altered activation of the vmPFC and hippocampus in response to stress exposure. In addition, we predicted that the degree of the altered vmPFC and hippocampal responses to stress would be associated with greater physical health symptoms.

2. Methods

2.1 Participants

Participants were 28 community adults (aged 19-48), including 10 individuals with trauma and 18 demographically-matched healthy controls (Table 1). No significant differences in age, sex, race, education, or intelligence were found between trauma patients and healthy controls (all *p*'s > 0.05). Participants were recruited through advertisements placed on social-networking sites and in local newspapers as well as flyers posted on community bulletin boards in the greater New Haven area.

Participants in the control group were healthy individuals with no past or current Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5) diagnoses for any mental health disorders. Participants in the trauma group met current DSM-5 criteria for Trauma- and Stressor-Related Disorders, as determined by the Structured Clinical Interview for DSM-5 (SCID-5; First (2015)). One participant in the trauma group met lifetime—but not current—criteria for a DSM-5 trauma-related disorder. However, this participant exhibited significant trauma-related symptoms and had last experienced a traumatic event approximately one year prior to study participation and was thus included in the study. Given the high rate of comorbidity between trauma and other psychiatric disorders (Brady et al., 2000), the presence of other DSM-5 psychiatric diagnoses was non-exclusionary. All comorbid non-trauma-related DSM-5 diagnoses are presented in Table 1.

In order to ensure that results would not be influenced by the presence of physical disorders, potential participants were excluded if they had any significant medical conditions (e.g., seizures, thyroid disorders, cardiovascular diseases). Other exclusion criteria included MRI-related issues (e.g., claustrophobia, metal in body), history of head trauma, current pregnancy, and use of psychiatric medications. Additional eligibility criteria included the ability to read English and provide informed written and verbal consent. All study procedures

were reviewed and approved by the Human Investigation Committee of the Yale School of Medicine.

2.2 Study procedure

Interested participants were initially screened over the phone to determine their eligibility. Eligible participants completed 3-4 intake appointments where they provided informed consent and completed additional in-person intake screenings. Participants also completed the Shipley Institute of Living Scale (Shipley, 1940) to assess their cognitive aptitude and intelligence (IQ). The Structured Clinical Interview for DSM-5 (SCID-5; First (2015)) was administered to determine whether participants met DSM-5 criteria for any current Trauma- and Stressor-Related Disorders. Upon completion of intake procedures, participants were scheduled for a functional magnetic resonance imaging (fMRI) scan session from 8:00am to 10:00am. All participants were instructed to abstain from using any drugs and/or medications for 48 hours prior to their fMRI scan to minimize drug-related confounding factors. Alcohol and drug abstinence were verified by breathalyzer and urine tests administered shortly before each scan. During the fMRI scan session, participants completed a well-validated stress provocation task (adapted from Sinha et al. (2016)) in which they were exposed to stressful and neutral-relaxing scenes. After completion of the fMRI scan, participants were prospectively followed with daily smartphone surveys that monitored their daily stress and physical symptoms for 30 consecutive days.

2.3 fMRI experimental task

During the fMRI scan, participants completed a stress provocation task (adapted from Sinha et al. (2016); see Figure 1), which was administered with E-Prime 2.0 (Psychology Software Tools, Inc.). The stress provocation task included stressful and neutral-relaxing visual stimuli in a fMRI block design, with each condition presented in a separate block (Figure 1). Condition order was randomized across participants. Stressful images (e.g., scenes

of violence, injury, and terror) were selected from the International Affective Picture System (IAPS; Lang et al. (1997)). Neutral-relaxing images (e.g., scenes of nature and people relaxing) were selected from validated pictures sets (Blaine et al., 2020; Goldfarb et al., 2020; Sinha et al., 2016). Pre-task ratings for mean valence (1 = negative to 9 = positive) and arousal (1 = calm/relaxed to 9 = aroused/excited) were $M_{valence}$ = 2.34 (*SD* = 0.63) and $M_{arousal}$ = 6.00 (*SD* = 0.83) for stress images, and $M_{valence}$ = 6.07 (*SD* = 0.40) and $M_{arousal}$ = 3.63 (*SD* = 0.47) for neutral-relaxing images.

The fMRI stress provocation task (Goldfarb et al., 2020; Goldfarb et al., 2019; Sinha et al., 2016) consisted of two randomly ordered blocks in which participants were exposed to either stressful or neutral-relaxing scenes (Figure 1). In each block, participants completed three sequential phases: baseline, provocation, and recovery. During the baseline phase, blank gray images with central fixation cross were displayed for three runs (Runs 1-3). During the provocation phase, participants viewed either stressful or neutral-relaxing images for six runs (Runs 4-9). In each run, 11 images were shown in succession for 5 seconds each with a 1-second interstimulus interval (ISI), for a total of 66 seconds (1.1 minutes) per run. The level of emotional intensity of images was matched across the six provocation runs in each condition, verified by no statistical differences in IAPS normative ratings of valence or arousal, as previously described (Blaine et al., 2020; Sinha et al., 2016). During the recovery phase (4 minutes), participants were asked to stay still and relax and were not shown any images as they were scanned. In-between blocks (stress followed by neutral-relaxing, or vice versa), a 2-minute progressive relaxation recording was played to ensure that physiological levels returned to baseline, as described in previous work (Seo et al., 2013; Sinha et al., 2016). After each baseline/provocation run and after the recovery phase, participants were asked to provide ratings of their stress (1 = not at all stressed to 9 = extremely stressed) and

arousal (1 = calm/relaxed to 9 = aroused/excited) using the Self-Assessment Manikin method (SAM; Bradley and Lang (1994)) and two-button fMRI response pads.

2.4 Daily smartphone surveys

After the fMRI scan session, participants completed daily smartphone surveys over a 30-day follow-up period where they reported their daily stress and physical symptoms. The surveys were programmed and administered using a HIPAA-compliant smartphone application (MetricWire Inc., ON, Canada). Participants received each daily survey at 5:00pm (EST) on their smartphone devices. This time of day was selected to sync up with the end of the standard business day to maximize compliance rates. Participants were given a seven-hour window from 5:00pm to 2:00am of the next calendar day to complete each daily survey, which required approximately 10-15 minutes of their time. On the daily survey, participants were asked whether they had experienced any physical symptoms since completing the previous day's survey including: –headache,‖ –stomachache/indigestion,‖ –chest pain,‖ –allergy symptoms,‖ –dizziness/fainting feeling,‖ –shortness of breath,‖ –fatigue/weakness,‖ –muscle aches/pain,‖ –cold symptoms/flu,‖ and –other.‖ Choosing –other‖ prompted participants to specify any additional physical symptoms. Frequency of physical symptoms was indexed by the number of days on which at least one physical symptom was reported (mean: 10.9 days, range: 0-29 days). Participants were also asked to rate their daily stress levels using a sliding scale ranging from 1 to 100 (1 = not at all stressed; 100 = extremely stressed). The daily protocol achieved a very high rate of survey compliance (91.4%). No significant differences in compliance rates were observed between trauma patients and healthy controls, $t(26) = 0.46$, $p = 0.65$.

2.5 fMRI data acquisition

MRI data were acquired using a T2*-sensitive gradient-recalled single-shot echo-planar pulse sequence on a 3T Siemens Prisma MRI system equipped with a standard

Physical Symptom	Trauma (n = 10)	Control (n = 18)
Headache	61	53
Stomachache/Indigestion	16	11
Chest pain	3	3
Allergy symptoms	25	6
Dizziness/Fainting feeling	27	3
Shortness of breath	7	1
Fatigue/Weakness	56	9
Muscle aches/pain	66	43
Cold symptoms/Flu	20	16
Other		
Bursitis	0	1
Clenched jaw	2	0
Shakiness	1	0
Itching/Eczema	3	0
Unspecified	2	1
Total**	289	147

Note: $^{**}p < 0.01$. Trauma patients endorsed a significantly higher quantity of daily physical symptoms than controls. Each count denotes each instance that a physical symptom was reported on a daily survey. The overall survey compliance rate over the 30-day follow-up period was 91.4%, with no significant difference observed between trauma patients and healthy controls.

Figure Captions

Figure 1. *fMRI task design.* The fMRI stress provocation task (adapted from Sinha et al. (2016)) consisted of two blocks representing the stress and neutral-relaxing conditions. Condition order was counterbalanced across participants. Each block consisted of three phases: baseline, provocation, and recovery. During the baseline phase, blank gray images with central fixation cross were displayed for three runs (Runs 1-3). During the provocation phase, participants viewed either stressful or neutral-relaxing images for six runs (Runs 4-9). During each run, 11 images (or gray blanks) were shown in succession for 5 seconds each with a 1-second interstimulus interval (ISI), for a total of 66 seconds (1.1 minutes) per run. During the recovery phase (4 minutes), participants were asked to relax and were not shown any images. Participants were asked to rate their stress and arousal using two-button fMRI response pads. Stress (1 = not at all stressed to 9 = extremely stressed) and arousal (1 = calm/relaxed to 9 = aroused/excited) ratings were collected after each baseline and provocation run and after each recovery phase.

Fig. 1

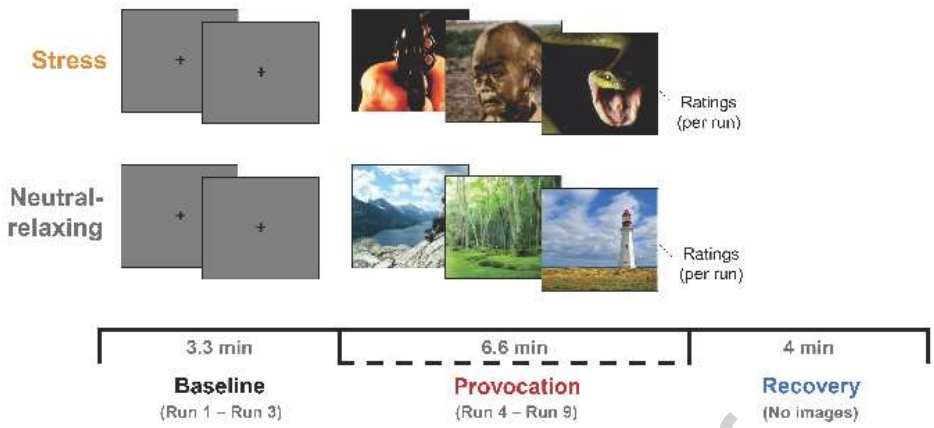


Figure 2. *fMRI task ratings.* (a) Stress Ratings: Both trauma patients and healthy controls reported significantly higher stress ratings during stress provocation than at baseline ($p <$ 0.01). However, only trauma patients exhibited elevated stress ratings after stress recovery relative to baseline ($p < 0.05$). (b) Arousal Ratings: Both trauma patients and healthy controls reported significantly higher arousal ratings during stress provocation than at baseline ($p <$ 0.01). *Note*: $^{*}p < 0.05$, $^{**}p < 0.01$. Error bars represent ± 1 standard error (SE) of the mean.

Fig. 2

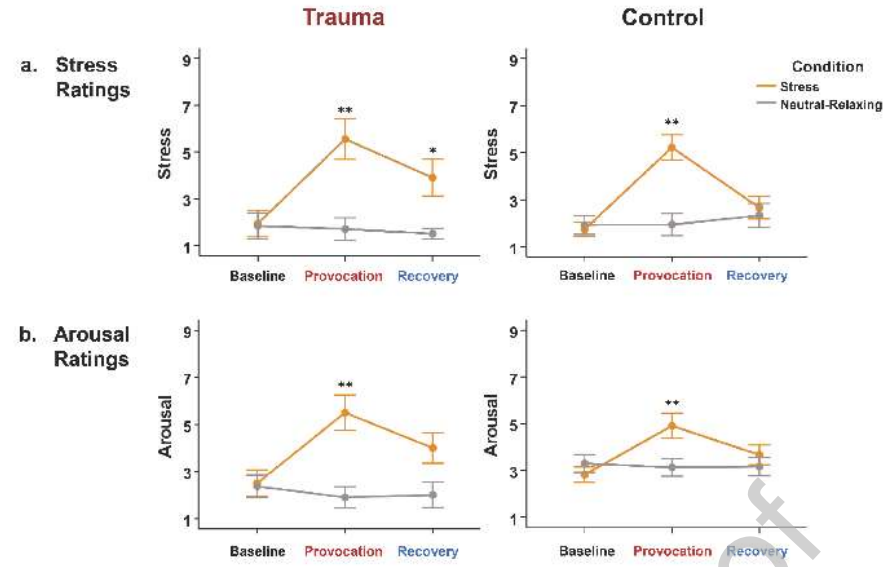


Figure 3. *Physical symptoms and stress.* After the fMRI scan, participants completed daily smartphone surveys monitoring their stress and physical symptoms over a 30-day follow-up period. (a) Trauma patients experienced a higher frequency of physical symptoms (indexed by the number of days on which at least one physical symptom was reported) compared to healthy controls, $t(26) = 3.57$, $p < 0.01$. (b) In all participants, higher fMRI stress ratings after stress recovery were associated with a greater number of days with physical symptoms in the follow-up period ($\beta = 0.48$, $p = 0.01$). *Note*: $^{**}p < 0.01$. Error bars represent ± 1 standard error (SE) of the mean.

Fig. 3

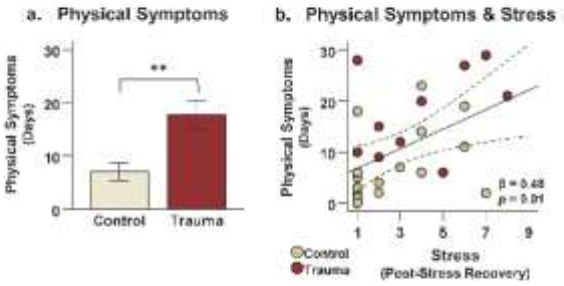


Figure 4. *fMRI results.* Whole-brain voxel-based analysis indicated significant group differences in the fMRI BOLD response to stress. (a) Group differences during stress provocation (Trauma − Control): Trauma patients, relative to controls, showed decreased activity in the ventromedial prefrontal cortex (vmPFC), lateral prefrontal cortex (LPFC), temporal lobe (superior, middle, and inferior temporal gyri), and dorsal striatum (caudate and globus pallidus) but increased activity in the left hippocampus, right insula, occipital cortex (visual association areas), parietal lobe (angular and supramarginal gyri), fusiform gyrus, primary motor cortex, and midcingulate cortex ($p < 0.001$, $\check{U} < 0.05$, whole-brain family-wise error corrected). A blue/purple color denotes decreased brain activity (Trauma < Control), while a yellow/red color denotes increased brain activity (Trauma > Control). (b) The fMRI BOLD response to stress provocation relative to baseline are displayed by group ($p < 0.001$, $\check{U} < 0.05$, whole-brain family-wise error corrected).

Note: R = Right; L = Left; vmPFC = ventromedial prefrontal cortex; LPFC = lateral prefrontal cortex; Hippo = hippocampus; GP = globus pallidus; ITG = inferior temporal

gyrus; MTG = middle temporal gyrus; STG = superior temporal gyrus; FG = fusiform gyrus; SMG = supramarginal gyrus; AG = angular gyrus; Visual = visual association areas; PM = primary motor cortex; MCC = midcingulate cortex.

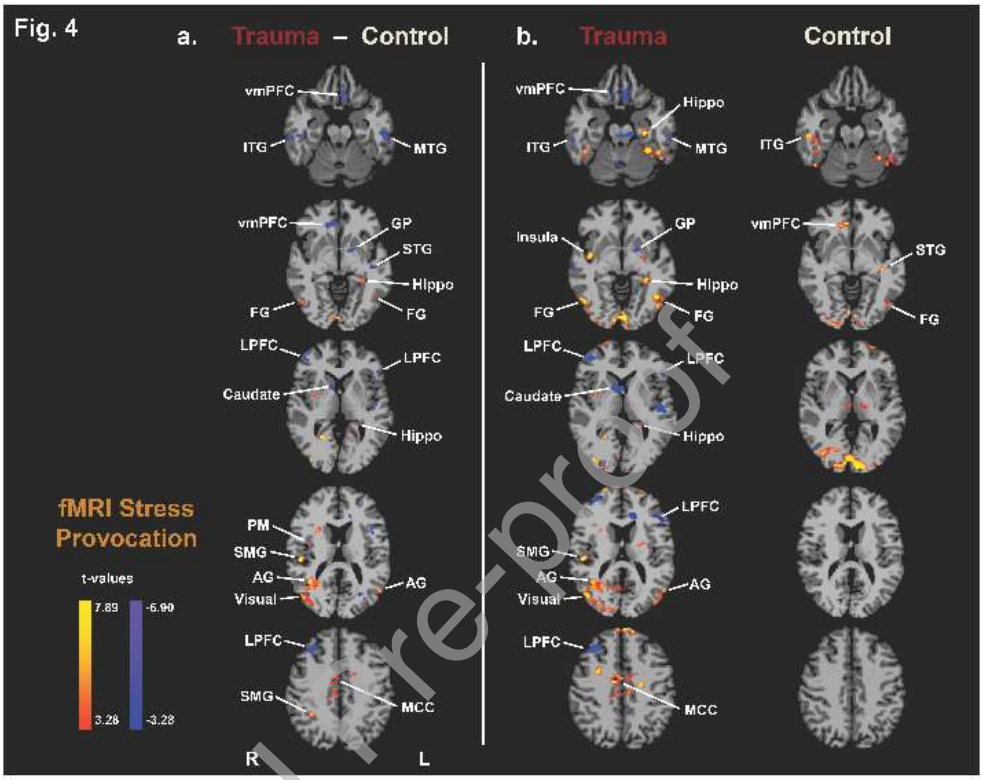
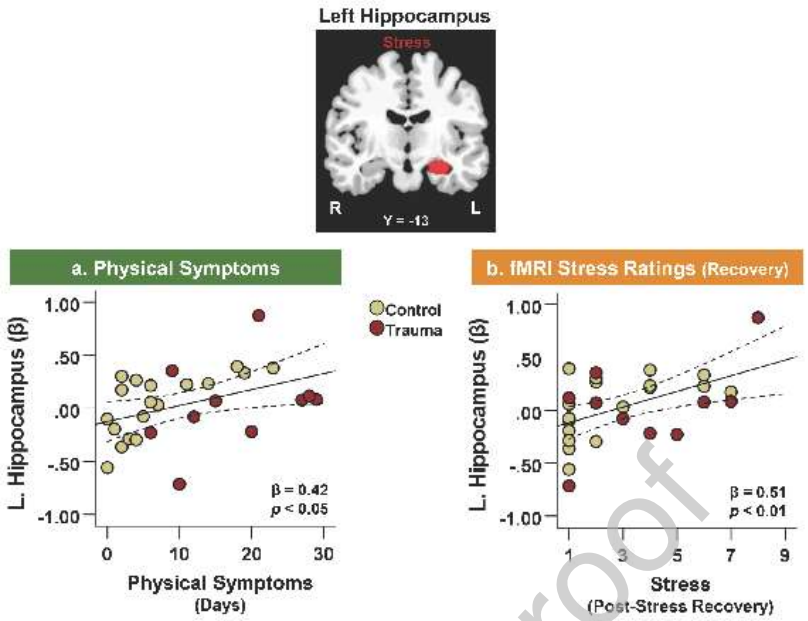


Figure 5. *Neural correlates of physical symptoms and stress.* Left hippocampal activity during fMRI stress provocation was positively associated with (a) number of days with physical symptoms over the 30-day follow-up period ($\beta = 0.42$, $p < 0.05$) and (b) fMRI stress ratings after stress task recovery ($\beta = 0.51$, $p < 0.01$).

Fig. 5



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