

## Perceived stress associations with hippocampal-dependent behavior and hippocampal subfield volume<sup>☆</sup>

Daniel W. Grupe<sup>a,b,\*</sup>, Alexandra L. Barnes<sup>a</sup>, Lauren Gresham<sup>a</sup>, Andrew Kirvin-Quamme<sup>a</sup>, Elizabeth Nord<sup>a</sup>, Andrew L. Alexander<sup>b,c,d</sup>, Heather C. Abercrombie<sup>a,b</sup>, Stacey M. Schaefer<sup>a,b</sup>, Richard J. Davidson<sup>a,b,d,e</sup>

<sup>a</sup> University of Wisconsin-Madison Center for Healthy Minds, 625 W Washington Ave, Madison, WI, 53703, USA

<sup>b</sup> University of Wisconsin-Madison Waisman Laboratory for Brain Imaging and Behavior, 1500 Highland Ave, Madison, WI, 53705, USA

<sup>c</sup> University of Wisconsin-Madison Department of Medical Physics, 1111 Highland Ave, Madison, WI, 53705, USA

<sup>d</sup> University of Wisconsin-Madison Department of Psychiatry, 6001 Research Park Blvd, Madison, WI, 53719, USA

<sup>e</sup> University of Wisconsin-Madison Department of Psychology, 1202 W Johnson St, Madison, WI, 53706, USA

### ARTICLE INFO

#### Keywords:

Perceived stress  
Stress reactivity  
Hippocampus  
Behavioral pattern separation  
Asymmetry

### ABSTRACT

**Background:** Individual differences in stress appraisals influence trajectories of risk and resilience following exposure to chronic and acute stressors. Smaller hippocampal volume may contribute to elevated stress appraisals via deficient pattern separation, a process depending on dentate gyrus (DG)/CA3 hippocampal subfields. Here, we investigated links between perceived stress, DG/CA3 volume, and behavioral pattern separation to test hypothesized mechanisms underlying stress-related psychopathology.

**Methods:** We collected the Perceived Stress Scale (PSS) and ratings of subjective stress reactivity during the Trier Social Stress Test (TSST) from 71 adult community participants. We obtained high-resolution T2 MRI scans and used Automatic Segmentation of Hippocampal Subfields to estimate DG/CA3 volume in 56 of these participants. Participants completed the mnemonic similarity task, which provides a behavioral index of pattern separation. Analyses investigated associations between perceived stress, DG/CA3 volume, and behavioral pattern separation, controlling for age, gender, hemisphere, and intracranial volume.

**Results:** Greater PSS scores and TSST subjective stress reactivity were each independently related to poorer behavioral pattern separation, together accounting for 15% of variance in behavioral performance in a simultaneous regression. Contrary to hypotheses, DG/CA3 volume was not associated with either stress measure, although exploratory analyses suggested a link between hippocampal volume asymmetry and PSS scores.

**Conclusions:** We observed novel associations between laboratory and questionnaire measures of perceived stress and a behavioral assay of pattern separation. Additional work is needed to clarify the involvement of the hippocampus in this stress-behavior relationship and determine the relevance of behavioral pattern separation for stress-related disorders.

### 1. Introduction

An estimated 90% of U.S. adults have been exposed to traumatic life events (Kilpatrick et al., 2013), yet resilient responses to extreme stress and trauma are the exception rather than the rule (Bonanno, 2004). A host of psychosocial, socioeconomic, and structural factors largely outside of one's control contribute to different trajectories of risk and

resilience, including early life adversity (Hughes et al., 2017; Nelson et al., 2020), social support before and after challenging life events (Boscarino, 1995; Brown, 2008; Paykel, 1994), and structural determinants of mental health disparities (Shim, 2021). In addition to these external factors, individual differences in subjective stress appraisals are a crucial intervening factor between negative life events and long-term psychological outcomes, including the development of

<sup>☆</sup> These results were previously presented at the 2021 meeting of the Society of Biological Psychiatry (virtual meeting). The pre-peer review version of this manuscript has been uploaded to the Open Science Framework (<https://osf.io/ez6tq/>).

\* Corresponding author. University of Wisconsin-Madison Center for Healthy Minds, 625 W Washington Ave, Madison, WI, 53703, USA.

E-mail address: [grupe@wisc.edu](mailto:grupe@wisc.edu) (D.W. Grupe).

<https://doi.org/10.1016/j.ynstr.2022.100469>

Received 26 April 2022; Received in revised form 13 June 2022; Accepted 5 July 2022

Available online 8 July 2022

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posttraumatic stress disorder (PTSD) and depression (King et al., 1995, 2008; Kuiper et al., 1986; Lancaster et al., 2016). Identifying neurobiological and behavioral mechanisms of perceived stress is crucial for research on preventive interventions, particularly if movement on proximal target mechanisms can be shown to confer distal psychological benefits (Insel et al., 2010).

A brain region of special interest in this regard is the hippocampus, which is relatively smaller in individuals with PTSD (Logue et al., 2018) and depression (Schmaal et al., 2016). Even in the absence of psychopathology, elevated perceived stress is associated with smaller hippocampal volume (Gianaros et al., 2007; Grupe et al., 2019; Zimmerman et al., 2016). One interpretation of these correlational data is that stressful and traumatic life events have a deleterious effect on hippocampal structure. Indeed, influential non-human research has demonstrated that chronic stressor exposure results in atrophy of the CA3 region of the hippocampus (Conrad et al., 1999; Watanabe et al., 1992) and decreased adult neurogenesis in the adjacent dentate gyrus (DG; Watanabe et al., 1992). In addition, prospective neuroimaging studies suggest that hippocampal impairments may predispose individuals for stress-related psychopathology; for example, reduced hippocampal activation shortly after trauma exposure predicts PTSD symptoms 3 months later (van Rooij et al., 2017), and smaller hippocampal volume in police recruits predicts the emergence of PTSD symptoms following subsequent trauma exposure (Koch et al., 2021).

The information processing function of pattern separation has been put forth as a candidate mechanism linking compromised hippocampal integrity to elevated risk of mood and anxiety disorders (Anacker and Hen, 2017; Kheirbek et al., 2012; Liberzon and Abelson, 2016). Successful pattern separation, as instantiated by sparse firing patterns of adult-born DG granule cells transmitted to the downstream CA3 subfield (Yassa and Stark, 2011), allows similar incoming information to be distinctly encoded and represented in the brain. For individuals with an information processing bias favoring pattern completion over pattern separation, novel events or objects that share features with fearful, threatening, or otherwise negative memories can (inappropriately) activate these existing memory traces, which may contribute to fear generalization in PTSD (Anacker and Hen, 2017) and activation of automatic thoughts or cognitive inflexibility in depression (Gandy et al., 2017).

The mnemonic similarity task (MST; Kirwan and Stark, 2007; Stark et al., 2019, 2013) provides a behavioral proxy of this information processing function. The MST and related tasks have been used to demonstrate behavioral pattern separation alterations in aging and disorders of aging (Stark et al., 2019) that correspond to reductions in the volume of DG/CA3 subfields (Dillon et al., 2017; Doxey and Kirwan, 2015; but see Bennett et al., 2019). Comparatively little research has investigated whether and how behavioral pattern separation is related to individual differences in perceived stress or affective symptomatology, although several studies in participants with elevated depression symptoms have reported deficits in pattern separation behavior (Bernstein and McNally, 2018; Dohm-Hansen and Johansson, 2020; Leal et al., 2014b; Shelton and Kirwan, 2013) and DG/CA3 pattern separation signaling (Leal et al., 2014a). In a mega-analysis of over 500 participants recruited via Amazon Mechanical Turk, we recently identified an inverse relationship between scores on the Perceived Stress Scale (PSS (Cohen and Williamson, 1988); and behavioral pattern separation on the MST (Grupe et al., 2022).

The current study is the first to integrate previously demonstrated pairwise relationships between smaller hippocampal volume, greater perceived stress, and impaired behavioral pattern separation. Assessing each of these variables in the same participants allows for a novel test of the hypothesis that compromised behavioral pattern separation helps account for the relationship between smaller hippocampal volume and greater perceived stress. We tested the following three pre-registered hypotheses:

- H1.** Perceived stress will be negatively correlated with a behavioral index of pattern separation
- H2.** Perceived stress will be negatively correlated with volume of the DG/CA3 regions of the hippocampus
- H3.** The relationship between greater DG/CA3 volume and lower levels of perceived stress will be mediated by greater performance on the behavioral pattern separation task

We conducted analogous analyses using recognition memory scores on the MST, which we hypothesized would show weaker associations with perceived stress and DG/CA3 volume, as this process is believed to rely on the perirhinal cortex to a greater extent than the hippocampus (Brown and Aggleton, 2001; Diana et al., 2007).

In addition to testing a novel mediation model linking hippocampal volume, behavioral pattern separation, and perceived stress, the current study is novel in examining behavioral and hippocampal volumetric correlations with two distinct subjective stress indices. We examined trait-like perceived stress for daily life stressors using the PSS – higher scores on which have previously been linked to reduced hippocampal volume (Gianaros et al., 2007; Zimmerman et al., 2016) and impaired pattern separation behavior (Grupe et al., 2022) – as well as subjective state measures of stress reactivity on the Trier Social Stress Test (TSST; Kirschbaum et al., 1993). While the PSS has high external validity as it assesses perceived stress in daily life, the TSST has high internal validity and reflects a more “pure” appraisal process as participants are exposed to an highly controlled, robust laboratory stressor. While the TSST has previously been used to experimentally manipulate cognitive and mnemonic performance – including, notably, a demonstration of enhanced pattern separation for negative objects encoded prior to TSST exposure (Cunningham et al., 2018) – the current study is unique in examining the relationship between subjective stress reactivity during the TSST and pattern separation behavior assessed in a separate session.

Our analysis of hippocampal subfields utilized an automated machine learning process and high-resolution (0.4 mm in-plane) T2-weighted structural data to isolate individual hippocampal subfields and test the specificity of hypothesized relationships to DG/CA3 subfields. One previous study in 116 older adults identified an inverse relationship between PSS scores and DG/CA3 subfields using a different segmentation approach in FreeSurfer (Zimmerman et al., 2016), although the authors’ use of 1 mm<sup>3</sup> isotropic structural data for hippocampal subfield segmentation has been cautioned against (Wisse et al., 2021). In the current study, we sought to replicate this relationship in a broader age range and with higher resolution structural data, and to extend these findings using a behavioral pattern separation task in the same participants. After identifying a striking L > R asymmetry in DG/CA3 subfields, we conducted additional exploratory analyses relating the degree of DG/CA3 asymmetry to both subjective stress measures. While unplanned, these analyses provide an additional contribution to an extant literature linking asymmetry in hippocampal volume to cognitive function and stress resilience.

## 2. Methods and materials

Hypotheses and the data analysis plan were pre-registered on the Open Science Framework (<https://osf.io/vyfu8>) after data collection but prior to analysis. Deviations from this pre-registration and unregistered hypotheses are noted below. This pre-registration was submitted in July 2020 during an indefinite hold on data collection due to the COVID-19 pandemic. The most substantive deviation from the pre-registration was the decision to conduct analyses using data from 78 participants enrolled prior to the pandemic, instead of the 116 participants initially proposed in our pre-registration. As a result, our power to detect effects of magnitude  $r = 0.30$  at  $p < 0.05$  – roughly the magnitude of previously reported perceived stress associations with hippocampal volume (Gianaros et al., 2007; Zimmerman et al., 2016) and behavioral pattern

separation (Grupe et al., 2022) – fell from 0.86 to 0.62 in our final MRI sample of 56. Despite this loss in power, combining data collected prior to March 2020 with data collected in the post-pandemic world would introduce multiple confounds, particularly given the focus of this paper on stress appraisals.

### 2.1. Participants

Participants were recruited from Dane County (WI) and surrounding communities using newspaper and web advertisements, flyers, and email recruitment lists. Informed consent was obtained from 78 participants between the ages of 25–65 (mean age  $\pm$  SD = 40.4  $\pm$  12.9; 49 women, 28 men, 1 nonbinary; 3 American Indian, 7 Asian, 5 Black, 3 multiracial, and 60 white; 4 Hispanic, 74 non-Hispanic). Exclusionary criteria included medication changes in the previous 4 weeks, contraindications to MRI, history of head trauma or neurological disorders, pregnancy, current chronic infectious disease or cancer, diagnosis of a manic disorder, and use of antipsychotics, mood stabilizers, or systemic steroids. Study procedures were approved by the University of Wisconsin-Madison Health Sciences IRB.

### 2.2. Data collection

Data were collected across two study visits as part of a larger investigation of individual differences in emotional style and its biological, behavioral, cognitive, and clinical correlates. Study data were managed using Research Electronic Data Capture (REDCap) tools hosted at the UW-Madison School of Medicine and Public Health (Harris et al., 2009). The first visit included informed consent procedures, psychophysiological recordings, computerized behavioral tasks, biological sample collection, questionnaires, and TSST administration. The second laboratory visit occurred  $17.2 \pm 9.4$  days (range = 10–74) following visit 1 (MRI analyses were unaffected by the inclusion of a covariate corresponding to days between visits). At visit 2, participants completed an MRI scan, additional computerized tasks and questionnaires, and the Structured Clinical Interview for DSM-5 (SCID-5). Over 1/3 of the participants who completed the SCID-5 (23/66) met diagnostic criteria for a depressive disorder ( $n = 5$ ), anxiety disorder ( $n = 16$ ), obsessive compulsive disorder ( $n = 2$ ), or a trauma/stress-related disorder ( $n = 6$ ; some participants received more than one diagnosis). Controlling for diagnostic status or excluding these participants had no impact on findings unless otherwise noted (see section 3.3).

#### 2.2.1. Mnemonic similarity task

The Mnemonic Similarity Task (MST; Kirwan and Stark, 2007; Stark et al., 2019, 2013, Fig. 1) provides behavioral indices of pattern separation ability and recognition memory. The task was based on code from the lab of Craig Stark (<https://github.com/celstark/MST>) and delivered using PsychoPy v1.85.4 on desktop computers. Data were obtained from 76/78 participants at visit 1. Participants viewed a continuous stream of

objects (2000 ms presentation, 500 ms interstimulus interval) and indicated whether each object was “old”, “new”, or “similar” to previously seen objects. Images came from one of six randomly selected stimulus sets, each of which consisted of 192 unique objects. The task consisted of 320 total object presentations: 192 novel objects (or “foils”), 64 identical repeats (“targets”), and 64 similar “lures” (distinct exemplars of previously seen objects). Total task duration was approximately 14 min with no breaks.

#### 2.2.2. Trier Social Stress Test

The TSST, a social evaluative stressor that consistently elicits robust psychological and physiological stress responses (e.g., Hellhammer and Schubert, 2012), was administered at the end of visit 1. The TSST consisted of a 5-min preparatory period, a 5-min impromptu speech, and a 5-min mental arithmetic test in front of a panel of judges. Participants rated present-moment stress on a 1–10 scale at baseline (Sample 1, before entering the room), anticipation (Sample 2, following the preparatory period), and reactivity (Samples 3–4, following the speech and arithmetic tests). Valid stress ratings were obtained from 75/78 participants. We obtained saliva samples for cortisol measurement throughout the TSST and recovery periods, and in secondary analyses we tested whether cortisol reactivity was associated with MST performance (see Supplementary Materials for details). We obtained continuous psychophysiological data using a wireless BIOPAC BioNomadix system for exploratory purposes (data not presented here).

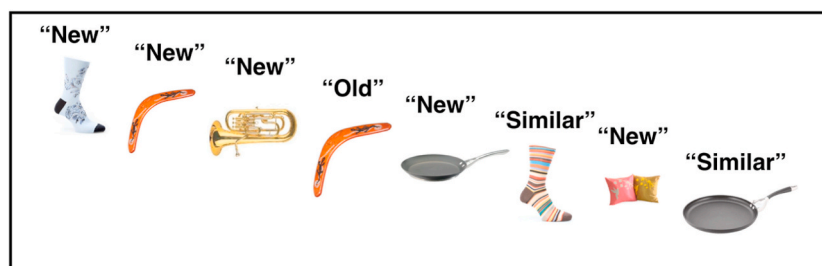
#### 2.2.3. Self-report

The 10-item Perceived Stress Scale (PSS-10; Cohen and Williamson, 1988), which measures the extent to which participants appraised life circumstances over the past month as stressful, was obtained from 71/78 participants during visit 1. For secondary analyses, our pre-registration included anxiety and depression scores from the computer-adaptive version of the Patient-Reported Outcomes Measurement Information System (PROMIS; Pilkonis et al., 2011). Due to missing data for participants who did not complete visit 2, we instead used the 8-item short-form PROMIS anxiety and depression measures, which were collected from all 78 participants during screening.

#### 2.2.4. Magnetic resonance imaging

During visit 2, MRI data were obtained from 59/78 individuals who completed visit 1. Of the other 19 individuals, 4 dropped out prior to visit 2; 5 declined the MRI scan due to claustrophobia during a simulated scan; 2 failed MRI safety screening on the day of the scan; and 8 were unable to complete MRI visits due to the COVID-19 pandemic.

MRI data were acquired on a GE MR750 3 T scanner with a 32-channel Nova Medical coil using parallel imaging. MPnRAGE (Kecksemeti et al., 2016) with retrospective motion correction was used to obtain motion-corrected, 1.0 mm isotropic T1-weighted images (TR = 4.9 ms, TE = 1.8 ms, flip angles = 4°/8° [first 304/remaining 82 views], 200 axial slices, acquisition time = 9:01). We used a modified version of the



**Recognition memory:**  $P(\text{“Old”} \mid \text{Target}) - P(\text{“Old”} \mid \text{Foil})$

**Lure discrimination index (LDI):**  $P(\text{“Similar”} \mid \text{Lure}) - P(\text{“Similar”} \mid \text{Foil})$

Fig. 1. Mnemonic Similarity Task schematic.

“high-resolution in-plane thick-slab” approach described previously (Ekstrom et al., 2009; Yushkevich et al., 2015b) to acquire a T2-weighted sequence, with oblique coronal images spanning the length of the hippocampus (TR = 7200 ms, TE = 76 ms, flip angle = 150°, 30 slices, 0.4 mm × 0.4 mm in-plane, 2.0 mm slice thickness, acquisition time = 6:29). Because anatomical changes unfold slowly along the long axis relative to other axes, this approach allows for the identification of distinct hippocampal subfields with a relatively brief acquisition time.

### 2.3. Data processing

#### 2.3.1. Mnemonic similarity task

We generated two behavioral indices from MST data. The Lure Discrimination Index (LDI), a behavioral proxy of pattern separation, was defined as the proportion of lure items correctly identified as “similar”, corrected for response bias by subtracting foil items incorrectly identified as “similar”:  $P(\text{“Similar”} \mid \text{Lure}) - P(\text{“Similar”} \mid \text{Foil})$ . Recognition memory was defined as the proportion of target items correctly identified as “old”, again corrected for response bias:  $P(\text{“Old”} \mid \text{Target}) - P(\text{“Old”} \mid \text{Foil})$ . No participants had data excluded based on pre-registered criteria for missing data or outlying values.

#### 2.3.2. TSST stress reactivity

Our pre-registered index of subjective stress on the TSST was the difference between stress ratings from baseline to reactivity, although we did not specify which of two reactivity metrics would be used. To generate more stable estimates of stress reactivity, we averaged the post-speech and post-arithmetic stress ratings, which were highly correlated across participants ( $r(74) = 0.78, p < 0.001$ ). We calculated cortisol area under the curve with respect to ground ( $AUC_g$ ) using the baseline and two reactivity samples (Fig. S1; see Supplementary materials for details). Subjective stress reactivity and cortisol reactivity on the TSST were not significantly related to each other ( $r(64) = -0.19, p = 0.12$ ).

#### 2.3.3. Hippocampal subfield segmentation and volume estimation

T1 and T2 images were visually inspected prior to image processing, resulting in the exclusion of one participant due to incorrectly acquired images. The other 58 participants had valid data with T2 images spanning the entire length of the hippocampus. T2/T1 images were provided as input to the Automatic Segmentation of Hippocampal Subfields (ASHS) processing pipeline (Yushkevich et al., 2015a; <https://sites.google.com/view/ashs-dox/>). We utilized an existing multi-atlas library (Bennett et al., 2019) that assigned each hippocampal voxel to CA1, DG/CA2/CA3, or the subiculum (Fig. 3a). Following manual review of QA images, we excluded data from two participants with poor segmentation results, resulting in a final sample of 56 for hippocampal analyses. We extracted intracranial volume and subfield volume estimates using Joint Label Fusion and Corrective Learning algorithms (Wang and Yushkevich, 2013), ignoring intensity information and only using shape/positional information.

### 2.4. Data analysis

Statistical analysis was conducted using RStudio v1.2.5042 (RStudio Team, 2020) in the R programming environment (version 3.6.3; R Core Team, 2020). Linear regression was used to test the hypothesis that greater subjective stress would be associated with lower LDI scores (controlling for age and gender). Analogous control analyses were conducted using recognition memory scores as the dependent variable. Secondary analyses for the TSST examined whether cortisol reactivity was associated with LDI scores independent of the effect of subjective stress reactivity. Effect sizes are expressed as partial eta-squared ( $\eta_{\text{partial}}^2$ ), reflecting the variance explained by the predictor of interest controlling for other model predictors.

To test for hypothesized inverse relationships between perceived stress and DG/CA3 subfield volumes, multilevel regression analyses

were conducted with a random effect of participant and repeated measures for left and right hemispheres, with covariates of age, gender, hemisphere, and estimated intracranial volume. Control analyses were conducted for additional subfields (CA1 and subiculum) not expected to show correlations with perceived stress. We conducted analogous (non-registered) analyses between LDI scores and each of these hippocampal subfields to see if we would replicate previously reported inverse associations between DG/CA3 volume and behavioral pattern separation (Dillon et al., 2017; Doxey and Kirwan, 2015; but see Bennett et al., 2019).

We conducted causal mediation analysis using the `mediate()` function from the R “mediation” library, using bootstrapping with 5000 iterations. Separate models were used to test the indirect effect of DG/CA3 subfields on PSS and TSST stress through the hypothesized mediator of LDI scores. Mediation analyses were conducted separately for left and right DG/CA3 subfields as conducting mediation analyses with multi-level models was not feasible.

## 3. Results

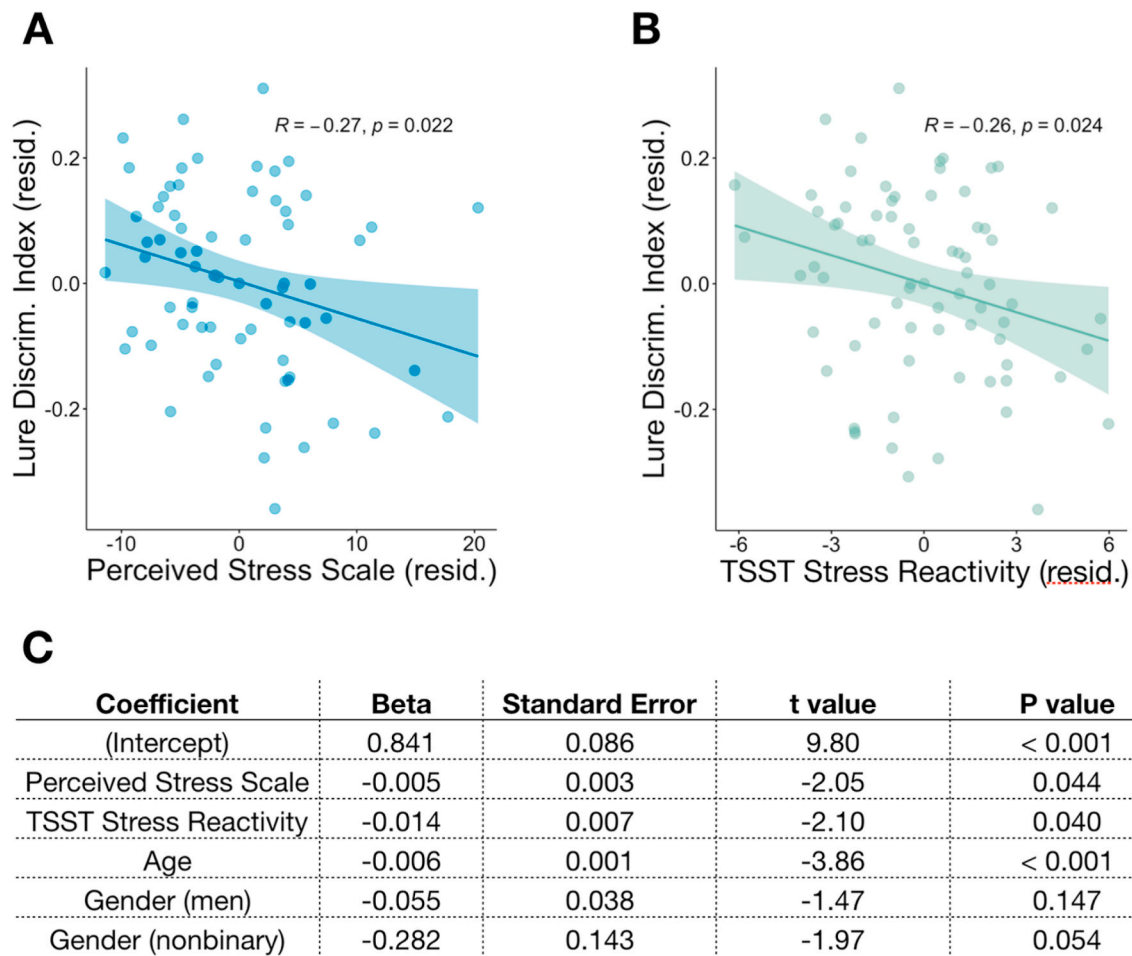
### 3.1. Elevated perceived stress and greater subjective stress reactivity are independently associated with compromised behavioral pattern separation

Separate regression analyses related LDI scores on the mnemonic similarity task, a behavioral measure of pattern separation, to perceived stress on the PSS and TSST (see Figs. S2a–b for distributions). Controlling for age and gender, elevated PSS scores were associated with lower LDI scores ( $t(65) = -2.29, p = 0.03, b = -0.006, 95\% \text{ CI} [-0.011, -0.001], \eta_{\text{partial}}^2 = 0.03$ ; Fig. 2a). Contrary to hypotheses, a similar (non-significant) relationship was seen for recognition memory, thought to be independent of DG/CA3 subfields ( $t(65) = -1.81, p = 0.08, b = -0.003, 95\% \text{ CI} [-0.006, 0.000], \eta_{\text{partial}}^2 = 0.05$ ; Fig. S3a).

Elevated subjective stress reactivity on the TSST was also associated with lower LDI scores ( $t(69) = -2.27, p = 0.03, b = -0.015, 95\% \text{ CI} [-0.029, -0.002], \eta_{\text{partial}}^2 = 0.09$ ; Fig. 2b). In contrast to the PSS, the TSST relationship showed behavioral specificity, with no relationship between subjective stress reactivity and recognition memory ( $t(69) = 0.39, p = 0.70, b = 0.002, 95\% \text{ CI} [-0.007, 0.010], \eta_{\text{partial}}^2 = 0.00$ ; Fig. S3b). Follow-up analyses suggested that this relationship was driven primarily by stress ratings during the reactivity period ( $t(70) = -1.88, p = 0.06$ ) rather than baseline stress ( $t(69) = 0.97, p = 0.34$ ). No association was observed between cortisol reactivity and LDI scores, whether examined in isolation ( $t(62) = 0.41, p = 0.69$ ) or in a model including subjective stress reactivity ( $t(59) = -0.03, p = 0.98$ ; see Supplementary Analyses).

Notably, PSS scores were uncorrelated with TSST subjective stress reactivity ( $r(67) = 0.12, p = 0.32$ ; Fig. S2c), suggesting that appraisals of daily life stressors are orthogonal to reactivity to this robust, controlled laboratory stressor. Moreover, PSS was more strongly correlated with PROMIS depression ( $r = 0.59$ ) and anxiety ( $r = 0.51$ ) than was TSST stress reactivity ( $r = 0.22$  and  $0.11$ , respectively), suggesting these two measures differentially reflect trait-like negative affectivity vs. stressor reactivity. Importantly, in a simultaneous regression analysis, these two subjective stress measures accounted for significant and non-overlapping variance in LDI scores (PSS:  $t(62) = -2.05, p = 0.044$ ; TSST:  $t(62) = -2.10, p = 0.040$ ; Fig. 2c). Stepwise regression analyses showed that, after accounting for age and gender, PSS and TSST stress reactivity together accounted for 15% of the variance in LDI scores. Each of these relationships remained significant when including PROMIS anxiety and depression scores as covariates, as indicated in pre-registered secondary hypotheses (PSS-LDI:  $t(60) = -2.49, p = 0.016$ ; TSST-LDI:  $t(60) = -2.22, p = 0.030$ ).

Each of the above analyses controlled for age, which showed a significant negative association with LDI scores ( $r(74) = -0.37, p < 0.001$ ) but not recognition memory ( $r(74) = 0.08, p = 0.49$ ). Age also showed a trend-level negative relationship with PSS ( $r(69) = -0.21, p = 0.08$ ). We



**Model fit:  $F(6,62) = 5.188, p < 0.001, \text{adjusted } R^2 = 0.238$**

**Fig. 2.** (A) Increased Perceived Stress Scale scores were associated with significantly lower Lure Discrimination Index (LDI) scores on the Mnemonic Similarity Task, controlling for age, gender, and subjective stress reactivity to the Trier Social Stress Test (TSST). (B) Similarly, TSST stress reactivity was associated with significantly lower LDI scores, controlling for age, gender, and Perceived Stress Scale scores. (C) Full results of the linear regression model.

conducted an unregistered exploratory regression analysis that included an age\*PSS interaction term, which revealed significant moderation of the PSS-LDI relationship by age ( $t(64) = 2.13, p = 0.04, b = 0.0004, 95\% \text{ CI } [-0.011, -0.001], \eta^2_{\text{partial}} = 0.03$ ). A post-hoc median split on age showed a robust inverse relationship between PSS and LDI for individuals younger ( $r(31) = -0.48, p = 0.005$ ) but not older than the median age of 35 ( $r(34) = -0.07, p = 0.67$ ). In contrast, the TSST stress-LDI relationship was not moderated by age ( $t(68) = -0.70, p = 0.49$ ).

### 3.2. Perceived stress is unrelated to DG/CA3 hippocampal subfield volume

Given significant relationships with LDI scores, we hypothesized that PSS and/or TSST stress reactivity would be inversely related to volume of DG/CA3, subfields implicated in pattern separation, controlling for age, gender, intracranial volume, and brain hemisphere. Contrary to hypotheses, DG/CA3 volume did not account for significant variance in PSS scores ( $t(55) = -0.78, p = 0.44, b = -1.8, 95\% \text{ CI } [-6.5, 2.8], \eta^2_{\text{partial}} = 0.01$ ; Fig. 3b) or TSST stress reactivity ( $t(54) = -0.11, p = 0.91, b = -0.6, 95\% \text{ CI } [-10.3, 9.2], \eta^2_{\text{partial}} = 0.00$ ; Fig. 3c). Null relationships were also observed for volume of the CA1, subiculum, and whole hippocampus (all  $|ts| < 1.3, \text{ all } ps > 0.2$ ; Fig. S4).

We also tested the association between LDI scores and DG/CA3 subfield volume, and the volume of subfields not expected to correlate

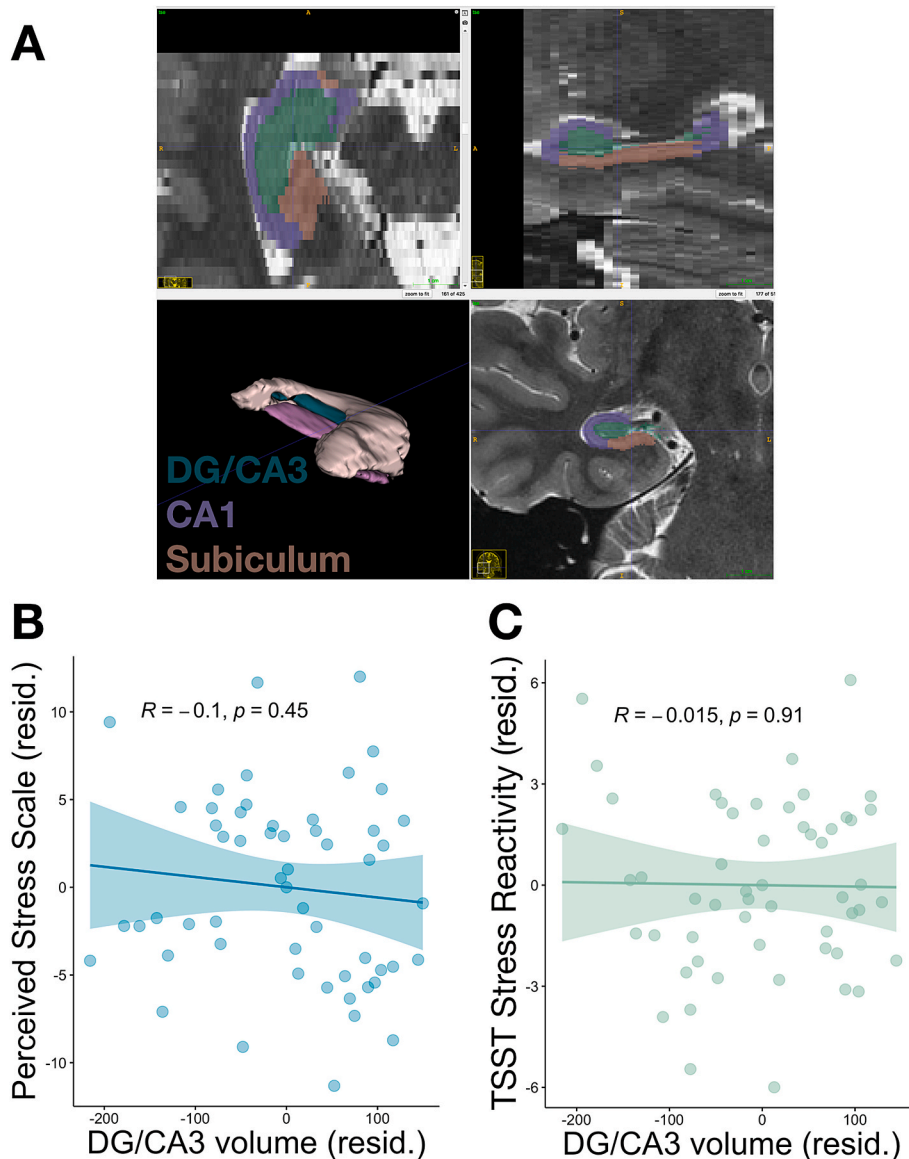
with behavioral performance. LDI scores were not associated with the volume of DG/CA3 ( $t(56) = 0.33, p = 0.74, b = 27.8, 95\% \text{ CI } [-138.6194.2], \eta^2_{\text{partial}} = 0.00$ ) or with CA1, subiculum, or the whole hippocampus (all  $|ts| < 0.7, \text{ all } ps > 0.5$ ).

Despite the absence of significant relationships between DG/CA3 volume and either stress measure or LDI scores, we conducted pre-registered mediation analyses to test the indirect effect of DG/CA3 volume on perceived stress as mediated by LDI scores. For both PSS and TSST stress reactivity, the confidence intervals for the indirect effect of DG/CA3 volume on stress included zero, indicating the absence of hypothesized mediation by behavioral pattern separation (all  $p$  values  $> 0.6$ ).

### 3.3. DG/CA3 subfield asymmetry is associated with individual differences in perceived stress

Regression analyses revealed a striking left  $>$  right asymmetry in the volume of DG/CA3 subfields (PSS regression:  $t(55) = 4.28, p < 0.001, b = 34.5, 95\% \text{ CI } [18.7, 53.0], \eta^2_{\text{partial}} = 0.25$ ;

TSST regression:  $t(54) = 4.94, p < 0.001, b = 38.2, 95\% \text{ CI } [23.0, 53.4], \eta^2_{\text{partial}} = 0.31$ ; Fig. 4a; Table S1). In exploratory analyses, we tested the relationship between DG/CA3 volumetric asymmetry (rather than absolute volume) and these two stress measures. Following prior research (Milne et al., 2018), we calculated a laterality index to quantify



**Fig. 3.** (A) Representative hippocampus segmentation results showing voxels labeled as dentate gyrus (DG)/CA3 (green), CA1 (purple), and subiculum (orange). In regression analyses controlling for age, gender, hemisphere, and estimated intracranial volume, DG/CA3 volume was not associated with Perceived Stress Scale scores (B) or subjective stress reactivity on the Trier Social Stress Test (TSST; C). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

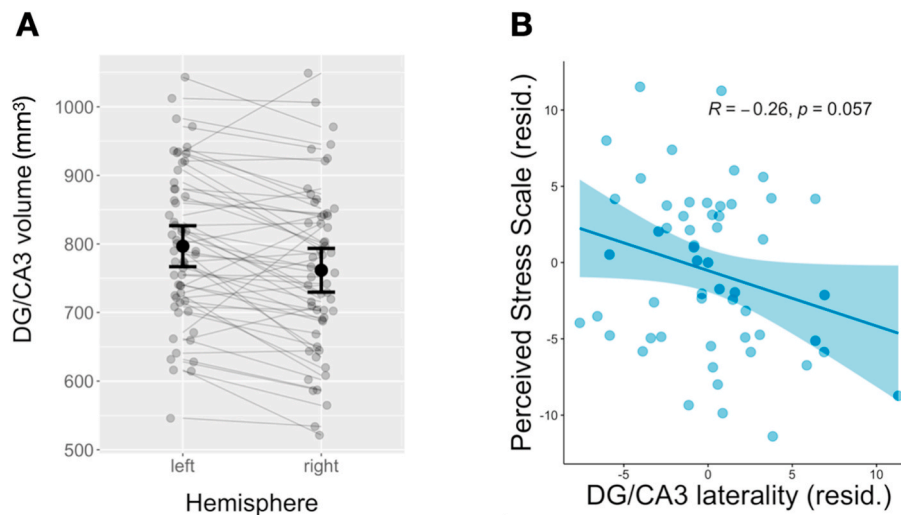
the degree of asymmetry as a percentage of total volume:  $[\text{right volume} - \text{left volume}] / [\text{right volume} + \text{left volume}] * 100$ . Controlling for age and gender, DG/CA3 asymmetry was associated at a trend level with PSS scores, such that individuals with greater right > left laterality reported lower perceived stress ( $t(50) = -1.88, p = 0.066, b = -0.18, 95\% \text{ CI } [-0.38, 0.01], \eta^2_{\text{partial}} = 0.09$ ; Fig. 4b). This relationship became significant when including a covariate for SCID mood, anxiety, or stress disorder diagnoses ( $t(49) = -2.00, p = 0.050$ ) or only including participants without such a diagnosis ( $t(33) = -2.13, p = 0.041$ ). No relationship was observed for TSST stress reactivity ( $t(49) = -1.18, p = 0.244, b = -0.24, 95\% \text{ CI } [-0.65, 0.17], \eta^2_{\text{partial}} = 0.02$ ). Follow-up analyses underscored that it was the asymmetry ratio and not the volume of either subfield driving the relationship with PSS, as the association with PSS did not approach significance for either the right ( $t(49) = -1.24, p = 0.221, b = -3.30, 95\% \text{ CI } [-8.65, 2.05], \eta^2_{\text{partial}} = 0.06$ ) or left DG/CA3 ( $t(49) = -0.14, p = 0.886, b = -0.37, 95\% \text{ CI } [-5.59, 4.84], \eta^2_{\text{partial}} = 0.00$ ).

In contrast to DG/CA3, there were no significant associations between asymmetry of CA1, subiculum, or the whole hippocampus – each of which exhibited right > left asymmetry (Table S1) – and PSS or TSST stress reactivity (all  $|ts| < 0.7$ , all  $ps > 0.5$ ).

#### 4. Discussion

Our results provide novel evidence that subjective appraisals of stress – both state appraisals of a robust laboratory stressor (the TSST) and trait appraisals of a questionnaire life stress measure (the PSS) – are independently associated with a hippocampal-dependent behavioral index of pattern separation. The novel relationship with TSST stress reactivity (which in secondary analyses was independent of stress-induced cortisol changes) was specific to pattern separation behavior, with no association for recognition memory (which, for objects, relies more on perirhinal cortex than the hippocampus; Brown and Aggleton, 2001; Diana et al., 2007). In contrast, PSS scores were inversely correlated with both pattern separation and (at a trend level) recognition memory, consistent with results of a mega-analysis of Mechanical Turk studies (Grupe et al., 2022). An exploratory analysis revealed moderation of the PSS-LDI relationship by age, with a robust negative association for younger but not older adults, suggesting that associations with perceived stress may be obscured by the robust age-related decline in mnemonic discrimination ability (Stark and Stark, 2017).

Notably, PSS scores were unrelated to subjective stress reactivity on the TSST, and these two stress measures accounted for unique and significant variance in behavioral pattern separation scores. The PSS has



**Fig. 4.** (A) Volume of dentate gyrus (DG)/CA3 subfields showed significant left > right asymmetry in the whole sample, with substantial between-participant variability. (B) Greater right > left asymmetry of DG/CA3 volume was associated with a trend-level reduction in Perceived Stress Scale scores, controlling for age and gender.

high external validity, but scores may reflect differential stressor exposure in addition to individual differences in appraisal processes. In contrast, while the TSST has lower external validity due to being delivered in a laboratory setting, stress ratings for this highly controlled stressor are less confounded by differences in stressor exposure. Consistency in results across these two stress assessments suggests that behavioral pattern separation is associated with a core stress appraisal process, and that observed relationships are not a reflection of the specific way in which we measured these appraisals or confounding variables that we did not measure. At the same time, because these two measures of stress accounted for unique variance in behavior, our results do not merely replicate prior links between behavioral pattern separation and perceived stress (Grupe et al., 2022), but extend this work by highlighting a distinct relationship with reactivity to a robust laboratory stressor. In contrast to the PSS, TSST stress ratings were not associated with depression or anxiety scores, suggesting that deficient pattern separation may contribute to increased stress reactivity independent of its associations with negative mood or depression symptoms (Bernstein and McNally, 2018; Dohm-Hansen and Johansson, 2020; Leal et al., 2014a; Shelton and Kirwan, 2013).

Contrary to hypotheses, there were no associations between either PSS or TSST subjective stress reactivity and volume of DG/CA3 hippocampal subfields (or other subfields). This finding is at odds with reports of negative correlations between perceived stress questionnaires and hippocampal volume, measured using voxel-based morphometry (Gianaros et al., 2007) or volumetric analysis of the whole hippocampus (Lindgren et al., 2016) and hippocampal subfields (Zimmerman et al., 2016). Two of these studies (Gianaros et al., 2007; Lindgren et al., 2016) tracked perceived stress repeatedly over a 20-year period, and the mean age of these samples (ranging from 50.8 to 79.4 years) was markedly higher than our sample (40.4 years). Our cross-sectional assessment of perceived stress in relatively younger adults may not capture the long-term impact of chronic perceived stress on hippocampal volume. Relationships between perceived stress and hippocampal volume may emerge only as hippocampal volume declines later in life, highlighting the importance of longitudinal assessments of perceived stress and hippocampal volume over the lifespan. Longitudinal research may also help clarify the directionality of relationships between greater psychological stress and compromised behavioral pattern separation. We have argued that deficient pattern separation may influence stress appraisals and increase risk for stress-related psychopathology, but stress also has detrimental effects on cognitive and mnemonic function. Repeated

assessments of pattern separation behavior, exposure to naturalistic and experimental stressors, and perceptions of these stressors may provide insight into the directionality of effects that cannot be inferred from our correlational design.

Despite null findings between stress appraisals and hippocampal subfield volume, exploratory asymmetry analyses suggested that relatively larger right DG/CA3 volume was associated with lower PSS scores. Previous studies of whole-hippocampus volume found R > L asymmetry to be associated with greater cognitive and executive function (Milne et al., 2018; Woolard and Heckers, 2012) and fewer subjective reports of cognitive decline, an early clinical indicator of dementia (Yue et al., 2018). The left hippocampus may be more sensitive to the effects of chronic stress: rodents exposed to chronic stressors showed earlier volume reductions for left compared to right hippocampus (Rahman et al., 2016), and volumetric reductions in adults with a history of child maltreatment are generally stronger for the left hippocampus (Teicher et al., 2012). In soldiers scanned prior to deployment, greater R > L asymmetry in hippocampal volume was prognostic of lower PTSD symptoms for those experiencing greater combat stressor exposure (Cobb et al., 2021). Relative R > L hippocampal asymmetry may thus be a prognostic marker of stress resilience, and our results suggest the potential importance of DG/CA3 asymmetry specifically for more adaptive stress appraisals. Due to the exploratory nature (and statistical insignificance) of this finding, however, these results should be interpreted with caution until confirmed in an independent sample.

#### 4.1. Limitations and future directions

As indicated above, our final sample was smaller than planned, as the COVID-19 pandemic necessitated a year-long shutdown in in-person data collection during which we conducted pre-registered analyses. With 56 participants for hippocampal subfield analyses, we only had 62% power at  $p < 0.05$  to detect effects of comparable magnitude ( $r = 0.3$ ) to published reports linking the PSS and hippocampal volume (whereas our planned sample size of 99 afforded 86% power at  $p < 0.05$ ). Although our proposed mediation model was not supported, we interpret this null result with caution and hope that future studies with larger samples can conduct well-powered tests of this model, while also attempting to replicate exploratory asymmetry findings.

ASHS offers a methodological advantage over FreeSurfer and other segmentation protocols in its mapping of individual brains to the most similar atlas brains at a local level, and the use of high-resolution T2

images provides us with a high degree of confidence in the assignment of voxels to one of three subfields. This high sensitivity, however, is accompanied by less specificity as we utilized a published atlas (Bennett et al., 2019) that combines DG and CA3 subfields. Consensus internal segmentation rules for these adjacent, anatomically similar subfields have not yet been established (Olsen et al., 2019), and the authors of this atlas cautioned against fine-grained subfield discrimination that may provide a false sense of specificity (C. Stark, personal communication). Because CA3 has been implicated in both pattern completion and pattern separation processes, depending on the state of the network and the input received from DG (Leutgeb et al., 2007; Yassa and Stark, 2011), combining these subfields may obscure relationships that are specific to pattern separation.

A third limitation is our treatment of stress appraisals in a vacuum, ignoring the context of participants' environments and life experiences. The contribution of individual differences in stress appraisals to variance in psychological outcomes may be dwarfed by extra-individual factors that can directly impact appraisal processes or negatively affect mental health through additional pathways. The influence of external factors on trajectories of risk and resilience – including early life adversity (Hughes et al., 2017; Nelson et al., 2020), social support before and after challenging life events (Boscarino, 1995; Brown, 2008; Paykel, 1994), and structural determinants of mental health disparities (Shim, 2021) – is not accounted for here. It is critical for future research in this area to carefully measure and account for the broader context of participants' lives, so that research on stress and trauma bears on the vast mental health disparities that result from inequitable socioeconomic and structural conditions.

#### 4.2. Conclusions

Research on neurobiological and behavioral mechanisms of perceived stress provides a foundation for developing and studying preventive interventions that enhance the function of underlying circuitry, rather than reactive treatments focused on symptom reduction. Our results linking behavioral pattern separation, trait-like appraisals of daily life stressors, and subjective state reactivity to a robust laboratory stressor suggest a potential behavioral target for research on preventive behavioral interventions that enhance psychological resilience by modifying appraisals of stressors, such as cognitive and mindfulness-based therapies (Beck, 1976; Teasdale et al., 2000). Because pattern separation behavior is a malleable process sensitive to behavioral interventions (Clemenson et al., 2020; Clemenson and Stark, 2015; Kolarik et al., 2020), an intriguing direction for future research is testing whether interventions that modify stress appraisals elicit corresponding improvements in behavioral pattern separation (or vice versa).

#### CRedit authorship contribution statement

**Daniel W. Grupe:** Conceptualization, Methodology, Formal analysis, Data curation, Visualization, Funding acquisition, Writing – original draft. **Alexandra L. Barnes:** Investigation, Data curation, Writing – review & editing. **Lauren Gresham:** Project administration, Writing – review & editing. **Andrew Kirvin-Quamme:** Investigation, Data curation, Writing – review & editing. **Elizabeth Nord:** Investigation, Data curation, Writing – review & editing. **Andrew L. Alexander:** Resources, Supervision, Writing – review & editing. **Heather C. Abercrombie:** Methodology, Formal analysis, Writing – review & editing. **Stacey M. Schaefer:** Conceptualization, Supervision, Project administration, Funding acquisition, Writing – review & editing. **Richard J. Davidson:** Conceptualization, Resources, Supervision, Funding acquisition, Writing – review & editing.

#### Declaration of competing interest

Dr. Richard Davidson is the founder and president, and sits on the

board of, the non-profit organization Healthy Minds Innovations, Inc. The other authors have no disclosures to report.

#### Data availability

Data will be made available on request.

#### Acknowledgements

**Funding:** This study was supported by funding from the National Institute of Mental Health (K01-MH117222 to DWG and R01-MH043454 to RJD and SMS). This study was also supported in part by a core grant to the Waisman Center from the National Institute of Child Health and Human Development (P50-HD105353), and by the Clinical and Translational Science Award (CTSA) program through the NIH National Center for Advancing Translational Sciences (UL1-TR002373). The content is solely the responsibility of the authors and does not necessarily represent the official views of NIH.

The authors extend their gratitude to Jeanne Harris, John Koger, Michael Anderle, Ron Fisher, Steve Kecskemeti, Scott Mikkelsen, and the Survey of the Health of Wisconsin for assistance with participant recruitment and data collection; the TSST judges for their fiercely neutral judgment; Dan Fitch and Nate Vack for support with behavioral task development and implementation; and Craig and Shauna Stark for input on the behavioral task and hippocampal segmentation methods.

#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.yinstr.2022.100469>.

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