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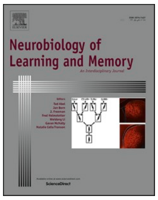

The effects of perceived stress and anhedonic depression on mnemonic similarity task performance

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ABSTRACT

Previous research has demonstrated hippocampal alterations in individuals experiencing elevated stress. The Mnemonic Similarity Task (MST) is a hippocampal-dependent task sensitive to age-related hippocampal decline, but it is unknown how performance on this task is related to one's experience of daily stress. We conducted separate discovery and replication analyses in 510 participants who completed the MST across four different Mechanical Turk studies. We hypothesized that higher scores on the Perceived Stress Scale would be associated with poorer discrimination of "lure" items from previously seen targets – a behavioral index of pattern separation – but not with recognition memory. The zero-order relationship between perceived stress and lure discrimination was not significant in the discovery or replication sample. Exploratory analyses involving anhedonic depression symptoms (from the Mood and Anxiety Symptoms Questionnaire) revealed a robust perceived stress*anhedonic depression interaction in the discovery sample that was confirmed in the replication sample. In both samples, individuals with low but not high anhedonic depression symptoms showed an inverse association between perceived stress and lure discrimination ability. Contrary to hypotheses, a similar interaction was observed for recognition memory. The novel association between perceived stress and behavioral pattern separation suggests a candidate behavioral process associated with stress-related hippocampal deficits. The specificity of this effect for individuals with low anhedonic depression symptoms – and the lack of behavioral specificity – highlight the need for additional research to unpack the clinical and neurobiological significance of these findings.

1. Introduction

Compromised function and structure of the hippocampus play a central role in stress-related psychiatric conditions, including depression (Gandy et al., 2017; Schmaal et al., 2016) and PTSD (Logue et al., 2018). Non-human research has demonstrated a causal role of chronic stressor exposure on hippocampal volume and neurogenesis (Cameron & Gould, 1994; Conrad et al., 1999; Watanabe et al., 1992), and cross-sectional human studies of PTSD and depression find greater volumetric reductions with early life adversity, longer disease duration, and greater number of depressive episodes (Sheline et al., 2003; Woon & Hedges, 2008; Treadway et al., 2015). In addition to this evidence for hippocampal deficits as a downstream consequence of stressor exposure, deficient function or structure of the hippocampus may also contribute to the emergence of stress-related psychopathology by influencing how individuals perceive and respond to stressful life events. For example, reduced hippocampal activation as measured shortly after trauma exposure predicts PTSD symptoms 3 months later (van Rooij et al., 2017), and smaller hippocampal volume predicts PTSD treatment resistance (van Rooij et al., 2015) and PTSD symptom emergence (Koch et al., 2021). Regardless of the question of causal direction, a question of great theoretical and clinical interest is how and why hippocampal deficits are associated with depression, anxiety, and posttraumatic stress.

In addressing this question, theoretical reviews have focused on the complementary hippocampal processes of pattern separation and pattern completion (Anacker & Hen, 2017; Kheirbek et al., 2012). The sparse firing patterns of adult-born dentate gyrus (DG) granule cells support the process of pattern separation, which allows novel events or stimuli to be encoded as distinct objects in memory (Yassa & Stark, 2011). In contrast, in the CA3-dependent process of pattern completion, similarities between novel events/stimuli and an existing memory

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facilitate retrieval of this stored memory, precluding these novel events or stimuli from being distinctly encoded 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 & Hen, 2017) and to activation of automatic thoughts or cognitive inflexibility in depression (Gandy et al., 2017).

Research investigating performance on a behavioral assay of pattern separation as a function of individual differences in perceived stress – a transdiagnostic risk factor for affective psychopathology (Felton et al., 2017; Kuiper et al., 1986; Lancaster et al., 2016) – can be a low-cost, high-throughput means of establishing correlational evidence for the hypothesis that deficiencies in this hippocampal-dependent information processing function predispose individuals to depression or PTSD. The mnemonic similarity task (Kirwan & Stark, 2007; Stark et al., 2013, 2019) is perhaps the most frequently deployed behavioral assay of pattern separation. In this task (Fig. 1), participants view pictures of common objects and are asked to differentiate between objects that were previously viewed (“targets”), “lure” objects that are similar yet distinct from previously seen targets, and “foil” objects that are totally dissimilar from target and lure objects. The ability to correctly identify lures as distinct from target objects reflects successful encoding of specific object details and serves as a behavioral index of pattern separation, whereas encoding the gist but not the specific details of objects results in participants incorrectly labeling lure objects as “old”. This task also provides an index of object recognition memory, believed to rely more on the adjacent perirhinal cortex (Brown & Aggleton, 2001; Diana et al., 2007). There is substantial and consistent evidence for a selective deficit in lure discrimination in healthy aging and disorders of aging, with recognition memory remaining relatively intact (for review, see Stark et al., 2019). This age-related behavioral impairment is accompanied by functional (Reagh et al., 2018; Yassa et al., 2010) and structural abnormalities (Dillon et al., 2017; Doxey & Kirwan, 2015; Yassa et al., 2010) in hippocampal DG/CA3 subregions.

In contrast to the extensive body of research on the MST in relation to aging and age-related hippocampal decline, relatively little research has investigated whether and how lure discrimination on the MST is related to individual differences in measures of perceived stress or affective symptomology. Research that has addressed this question has identified modest yet significant inverse relationships between depression symptoms and this behavioral index of pattern separation. Shelton & Kirwan (2013) reported poorer performance in participants with high vs. low depression symptoms, although their sample was quite limited in the range of symptoms. Similarly, Leal et al. (2014) reported poorer lure discrimination for lure objects in those with high relative to low depression symptoms (interestingly, these individuals also showed *greater* lure discrimination ability for negative objects). Using an adapted “object-in-context” version of the MST, Dohm-Hansen & Johannson (2020) reported an inverse relationship between lure discrimination ability and symptoms of both depression and anxiety. Bernstein et al. (2019) demonstrated an inverse relationship between trait worry (a risk factor for anxiety disorders) and lure discrimination, but only for individuals under 40 and only following a social stress induction. Additional studies utilized experimental manipulations of anxiety or stress to demonstrate how these state inductions can facilitate encoding (Balderston et al., 2017) or consolidation (Jiang et al., 2019) for lure objects, but these studies did not investigate interactions with affective symptoms.

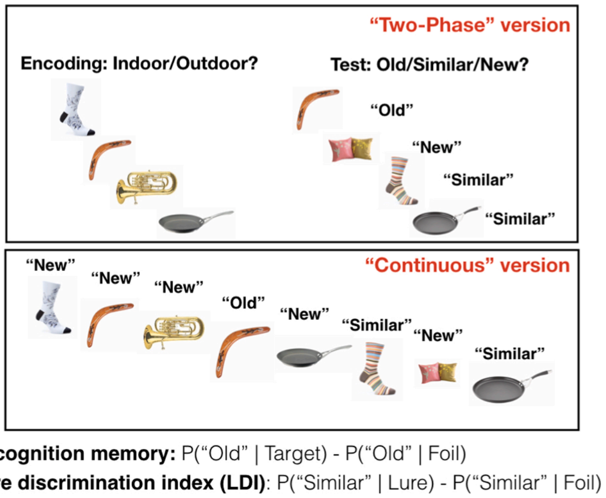

Fig. 1. Mnemonic Similarity Task schematic.

The current study utilized data from over 500 participants on Amazon’s Mechanical Turk (MTurk) to test the hypothesis that higher scores on the 10-item Perceived Stress Scale (PSS; Cohen & Williamson, 1988) would be associated with a specific deficit in lure discrimination on the MST, with no such relationship expected for recognition memory. In contrast to studies that utilized experimental manipulations of stress or anxiety (Balderston et al., 2017; Bernstein et al., 2019; Jiang et al., 2019) or examined affective symptoms in relation to pattern separation behavior for affective stimuli (Leal et al., 2014), we examined behavioral pattern separation for neutral objects during baseline conditions to investigate behavioral performance indicative of the fundamental information processing function in relation to trait-like differences in perceived stress. We additionally collected the 30-item Mood and Anxiety Symptoms Questionnaire (MASQ-30; Wardenaar et al., 2010) and tested whether this perceived stress/lure discrimination relationship would be significant while controlling for highly correlated symptoms of anhedonic depression on the MASQ-30. Exploratory analyses pooled across 2 small studies (discovery dataset; N = 95) revealed the unexpected finding that the perceived stress/lure discrimination relationship differed as a function of anhedonic depression symptoms, leading us to conduct confirmatory analyses in a replication dataset (N = 420) across 2 additional studies. This study builds on previous reports of compromised behavioral pattern separation for individuals with elevated mood or anxiety symptoms (Bernstein et al., 2019; Dohm-Hansen & Johansson, 2020; Leal et al., 2014; Shelton & Kirwan, 2013), utilizing a sample many times larger than these previous studies, which was made possible through the novel remote deployment of the MST using MTurk. This large sample allowed us to parse negative affective traits into more discrete components and to investigate unique relationships with behavioral pattern separation. The utilization of separate discovery and replication samples affords greater confidence in results that were not hypothesized a priori but that were consistent across subsamples.

2. Methods

2.1. Transparency and openness

Data and analysis code are publicly available on the Open Science Framework (https://osf.io/9gy3n/). Data were analyzed using RStudio (version 1.2.5042; RStudio Team, 2020) in the R programming environment (version 3.6.3; R Core Team, 2020). Code and supporting information for the behavioral task are available at https://github.com/uwmadison-chm/mst-labjs. Study hypotheses, study design, and analysis plans for Studies 1, 3, and 4 were pre-registered on the Open Science Framework (see “Description of Studies” for additional information), and Study 2 was not pre-registered. Sample size determinations are described in the associated pre-registrations, and data exclusions and manipulations are reported in the relevant sections below.

2.2. Description of studies

Data were collected between September 2017 - October 2020 via Amazon's Mechanical Turk (MTurk). The overall hypothesis motivating this series of studies was that elevated scores on the 10-item PSS would be associated with compromised lure discrimination ability on the MST. Although we failed to find support for this specific hypothesis across two small studies (N = 95; Study 1 pre-registered at https://osf.io/4ruvb), an exploratory analysis of these data revealed a significant interaction between PSS and the highly correlated anhedonic depression subscale on the MASQ-30 in predicting task performance (see Results). Additional pre-registered studies were conducted to follow up on this unpredicted interaction using both "continuous" (Study 3 pre-registered at https://osf.io/jq3t7) and "two-phase" versions of the MST (Study 4 pre-registered at https://osf.io/9mcby). Noting broad similarities in results across these studies, but with some study-to-study differences, we conducted the mega-analysis described here, which allowed us to maximize statistical power while controlling for variability between individual studies. We report separate results for discovery and replication analyses (Studies 1–2 and 3–4, respectively) as well as pooled results across all four studies.

2.3. Participants

We collected data on the MST from 630 participants across four studies. Demographic information for the N = 515 participants with valid MST data (see *Data Analysis* section) is provided in Table 1. The mean age of participants was 39.2 years, with few between-study differences in age distributions. Participants were primarily white (82%) and non-Hispanic (94%). Five participants completed the MST but not self-report measures, leaving a total N of 510 for analyses. For participants in each of these studies, inclusion criteria were > 50 Human Intelligence Tasks (HITs) completed with > 95% approval rate and currently residing within the United States. For Study 3, additional age qualifications were included for specific batches of HITs to enroll an equivalent number of workers younger and older than 40 with a normal age distribution. HITs were posted in batches of 25–40 at various times of day and throughout the week to capture a broad range of workers. Participants who had completed a similar task before were screened out. Participants were compensated $3 (Studies 1–2) or $5 (Studies 3–4) for this approximately 20- to 25-minute HIT.

Table 1
Participant demographics for each of 4 studies and for the entire dataset.

Study Number	1	2	3	4	TOTAL
Consented	76	32	385	178	**671**
MST data	75	32	350	173	**630**
Valid MST data	64	31	306	114	**515**
Gender					
Male	42 (66%)	17 (55%)	155 (51%)	62 (54%)	**276 (54%)**
Female	21 (33%)	14 (45%)	148 (48%)	46 (40%)	**229 (44%)**
Nonbinary	0	0	2 (1%)	1 (1%)	**3 (1%)**
Not reported	1 (2%)	0	1 (0%)	5 (4%)	**7 (1%)**
Age					
Age 18–29	27 (42%)	11 (35%)	44 (14%)	35 (31%)	**117 (23%)**
Age 30–39	23 (36%)	10 (32%)	114 (37%)	35 (31%)	**182 (35%)**
Age 40–49	9 (14%)	7 (23%)	75 (25%)	19 (17%)	**110 (21%)**
Age 50–59	3 (5%)	1 (3%)	54 (18%)	11 (10%)	**69 (13%)**
Age 60+	1 (2%)	2 (6%)	19 (6%)	10 (9%)	**32 (6%)**
Age unknown	1 (2%)	0	0	4 (4%)	**5 (1%)**
Mean age (SD)	33.7 (8.5)	36 (10.8)	40.8 (11.1)	38.5 (12.8)	**39.2 (11.4)**
Race					
American Indian	0	0	1 (0%)	1 (1%)	**2 (0%)**
Asian	6 (9%)	5 (16%)	14 (5%)	6 (5%)	**31 (6%)**
Black/African American	2 (3%)	1 (3%)	17 (6%)	7 (6%)	**27 (5%)**
White	49 (77%)	23 (74%)	252 (82%)	90 (79%)	**414 (80%)**
Other/More than one	5 (8%)	1 (3%)	19 (6%)	4 (4%)	**29 (6%)**
Unknown	2 (3%)	1 (3%)	3 (1%)	6 (5%)	**12 (2%)**
Ethnicity					
Hispanic/Latino	5 (8%)	2 (6%)	21 (7%)	4 (4%)	**32 (6%)**
Not Hispanic/Latino	57 (89%)	29 (94%)	284 (93%)	105 (92%)	**475 (92%)**
Unknown	2 (3%)	0	1 (0%)	5 (4%)	**8 (2%)**

2.4. Data collection

The behavioral task was based on PsychoPy code provided by the lab of Craig Stark (https://github.com/celstark/MST). A copy of each task version was created in Lab.js (https://lab.js.org/) using the same stimulus ordering algorithm and inputs, resulting in web-deployable version with identical inputs (https://github.com/uwmadison-chm/mst-labjs). MTurk workers who signed up for this HIT were re-directed to a Qualtrics page that included an informed consent page, followed by the Lab.js task.

Participants completed one of two versions of the MST (Fig. 1). In the "two-phase" version of this task (Stark et al., 2013), participants incidentally encode a series of pictures of objects while making an unrelated judgment about each object ("is this an indoor/outdoor object?"). They then immediately undergo a surprise recall task, and are asked whether pictures are "old", "new", or "similar" to objects seen during the encoding phase. One-third each of these pictures are identical "targets" (previously seen objects), novel "foils" (completely distinct objects), or similar "lures" (different exemplars of previously seen objects). In the "continuous" version of this task (Kirwan & Stark, 2007; Stark et al., 2015), there are not separate encoding and test phases. Instead, participants view a single stream of objects and make old/similar/new judgments throughout. Across task versions stimuli were presented for 2 s with a 0.5 s interstimulus interval. As described below ("Data analysis"), both task versions allow for the generation of behavioral indices of lure discrimination/pattern separation and recognition memory. The two-phase task version included a single encoding block and a single retrieval block, and the continuous version included a single block with no breaks. Details on the task version and image set size used in each study are provided in Table 2.

Following completion of the MST, all participants completed self-

Table 2
Study-specific task information and descriptive statistics for behavioral and self-report measures.

Study-specific task information and descriptive statistics

Study number	1	2	3	4	TOTAL
Dates	9/2017–10/2017	3/2018	11/2019	10/2020	–
Task version	two-phase	continuous	continuous	two-phase	–
Items in set	40	64	64	64	–
Mean LDI (SD)	0.42 (0.19)	0.41 (0.17)	0.4 (0.18)	0.3 (0.21)	**0.38 (0.19)**
Mean recognition memory (SD)	0.76 (0.14)	0.76 (0.14)	0.77 (0.14)	0.73 (0.15)	**0.76 (0.14)**
Mean Perceived Stress Scale (SD)	15.7 (10.6)	11.9 (8.0)	14.8 (8.9)	13.1 (8.0)	**14.4 (8.9)**
Mean Anhedonic Depression (SD)	33.1 (10.8)	27.8 (9.2)	32.6 (10.4)	30.8 (11.0)	**32.0 (10.5)**

report questionnaires including the PSS-10, the MASQ-30, and a demographics measure. The PSS-10 (Cohen & Williamson, 1988) measures the extent to which participants appraised their life circumstances over the past month as being stressful. The MASQ-30 (Wardenaar et al., 2010) is an abbreviated version of the MASQ-90 (Watson et al., 1995), developed to test a tripartite model (Clark & Watson, 1991) that parses negative affective symptoms into unique components specific to depression (anhedonic depression; MASQ-AD) and anxiety (anxious arousal; MASQ-AA), as well as non-specific symptoms of general distress (MASQ-GD). Symptoms of anhedonic depression investigated here specifically tap into the absence of positive affect experienced by participants during the past week (example items: “Felt really happy”, “Felt like I accomplished a lot”, “Felt really good about myself”).

Additional self-report questionnaires were collected for exploratory purposes and are not reported on here. The specific measures varied by study and included the Emotional Style Questionnaire (Kesebir et al., 2019), Global Physical Activity Questionnaire (Armstrong & Bull, 2006), 42-item Psychological Well-Being Questionnaire (Ryff & Keyes, 1995), 29-item PROMIS v-2.0 (Hays et al., 2018), COVID-19 impact questions (Conway et al., 2020), and an in-house measure about video game play. Notably, across all studies the first 3 questionnaires administered (in order) were the demographics questionnaire, the PSS-10, and the MASQ-30.

2.5. Data processing

The MST yields two primary indices of interest. The Lure Discrimination Index (LDI) is a behavioral proxy of pattern separation. LDI is defined as the proportion of lure items correctly identified as “similar”, corrected for response bias by subtracting foil items incorrectly identified as “similar”: P(“Similar” | Lure) - P(“Similar” | Foil). Recognition memory is defined as the proportion of target items correctly identified as “old”, corrected for response bias by subtracting foil items incorrectly identified as “old”: P(“Old” | Target) - P(“Old” | Foil).

Individuals with $>$ 25% missing behavioral responses during the “test” phase of the two-phase task (or throughout the task for the continuous version) were excluded from analysis. Outlying values for LDI and recognition memory, defined as $>$ 3 SD from the sample mean and visually distinct from the sample distribution, were excluded from analysis. Individuals with outlying values for recognition memory were also excluded from LDI analyses, as scores for recognition memory tend to be much higher and non-compliance, failure to understand task instructions, or (for testing on MTurk specifically) automated responding by “bots” is easier to identify from recognition memory scores. Negative LDI values were not excluded unless the participant was identified as an outlier for LDI or recognition memory. Of 630 total participants, data from 115 were excluded due to missing responses or behavioral outliers, resulting in a total sample of 515. Behavioral data were excluded at a higher rate for participants completing the two-phase vs. the continuous task (36% vs. 12% excluded, respectively).

2.6. Data analysis

Statistical analysis was conducted using RStudio (version 1.2.5042; RStudio Team, 2020) in the R programming environment (version 3.6.3; R Core Team, 2020). To account for the non-independence of participants from different studies, linear mixed effects analyses were conducted with a random effect of study number using the lmerTest() library with Nelder-Mead optimization. Some models did not converge, likely due to the small number of studies, in which case a linear regression analysis was conducted using lm(). Analyses were conducted separately for LDI and recognition memory as dependent variables. An initial descriptive model contained covariates for age and task version and a random effect of study number:

model1 <- lmer(LDI ~ age + taskVersion + (1 | studyNumber), REML = FALSE, control = lmerControl(optimizer =“Nelder_Mead”)).

Model 2 investigated the hypothesized relationship between the Perceived Stress Scale (PSS) and pattern separation behavior:

model2 <- lmer(LDI ~ PSS + age + taskVersion + (1 | studyNumber),

REML = FALSE, control = lmerControl(optimizer =“Nelder_Mead”)).

Model 3 included scores on the MASQ anhedonic depression scale (MASQ_AD) in a simultaneous regression with PSS scores:

model2 <- lmer(LDI ~ PSS + MASQ_AD + age + taskVersion + (1 | studyNumber),

REML = FALSE, control = lmerControl(optimizer =“Nelder_Mead”)).

The final model included an additional PSS*MASQ-AD interaction term:

model4 <- lmer(LDI ~ PSS + MASQ_AD + PSS*MASQ_AD + age + taskVersion +.

(1 | studyNumber), REML = FALSE, control = lmerControl(optimizer =“Nelder_Mead”)).

Models 3 and 4 were suggested by exploratory analyses in the discovery dataset (Studies 1–2) and were subsequently implemented in the replication dataset (Studies 3–4) as well as pooled analyses across all studies.

Data and analysis code are available on the Open Science Framework: https://osf.io/9gy3n/.

3. Results

3.1. Descriptive MST data and effects of task covariates

Table 2 contains unadjusted descriptive information for each of the MST task metrics, separately for each study and pooled across studies. Table 3 displays the raw data used to construct LDI and recognition memory indices, specifically the percentage of each image type (targets/lures/foils) categorized as “old”, “similar”, or “new”. Across all studies, LDI and recognition memory showed a modest but significant correlation ($r(513) = 0.23$, $p < 0.001$, 95% CI = [0.15, 0.31]).

The regression of LDI scores on all model covariates revealed poorer performance with increasing age ($t(510) = -2.33$, $p = 0.02$, $b = -0.0017$, 95% CI [-0.0032, −0.0002]; Fig. 2**a**) with no effect of the two-phase vs. continuous task version ($t(346.7) = -1.44$, $p = 0.23$, $b = -0.055$, 95% CI = [-0.140, −0.008]). The analogous model for recognition memory did not converge and the analysis was run using linear regression with fixed effects only. This model revealed *better* performance with increasing age ($t(507) = 2.29$, $p = 0.022$, $b = 0.0013$, 95% CI = [0.0002, 0.0057]; Fig. 2**c**) and no effect of the two-phase vs. continuous task version ($t(507) = -1.53$, $p = 0.13$, $b = -0.020$, 95% CI = -0.046, 0.0057]).

We also investigated and visualized task performance as a function of categorical age bins (under 30, 30–39, 40–49, 50–59, over 60 years old). For LDI, a slow monotonic decrease was evident, with individuals in the 30–39 age range performing better than those ages 50–59 ($t(508.0) = 2.66$, $p = 0.0008$, $b = 0.070$, 95% CI [0.018, 0.122]) and older than 60 ($t(507.8) = 2.51$, $p = 0.01$, $b = 0.090$, 95% CI [0.019, 0.160]; Fig. 2**b**). Unexpectedly, individuals under age 30 had numerically but not statistically poorer performance than those in the 30–39 age range ($t(508.8) = -1.47$, $p = 0.14$, 95% CI [-0.077, 0.011]). Recognition memory was highest for individuals in the 50–59 age range, who had significantly better performance than those between ages 30–39 only ($t(504) = 2.19$, $p = 0.03$, $b = 0.043$, 95% CI [0.004, 0.082]; Fig. 2**d**).

3.2. Relationships between perceived stress, anhedonic depression, and mnemonic discrimination

In a discovery dataset (Studies 1–2, N = 94 with valid MST and self-report data), we did not observed the hypothesized inverse relationship between perceived stress and LDI scores in a fixed effects model

Table 3
Mean (SD) percentage of each image type endorsed as “old”, “similar”, or “new”. Correct response option for each trial type is indicated with a *.

Study	Targets			Lures			Foils		
	Old*	Similar	New	Old	Similar*	New	Old	Similar	New*
Study 1	79.9% (12.7)	15.0% (9.7)	5.2% (6.6)	34.7% (13.5)	54.3% (16.5)	11.0% (10.4)	2.9% (3.8)	11.4% (9.8)	85.7% (11.1)
Study 2	78.7% (12.9)	12.3% (7.7)	9.0% (7.7)	33.1% (10.7)	51.4% (15.4)	15.5% (11.4)	1.8% (2.8)	9.3% (6.4)	88.8% (7.7)
Study 3	78.7% (13.0)	12.0%(8.7)	9.3% (9.2)	36.8% (14.6)	47.0% (16.8)	16.2% (12.4)	2.1% (2.8)	7.2% (6.9)	90.7% (8.1)
Study 4	77.9% (13.2)	15.4% (9.6)	6.7% (8.2)	39.7% (16.2)	46.7% (18.1)	13.6% (10.4)	4.5% (5.4)	16.5% (10.7)	79.0% (13.9)
All Studies	**78.7% (13.0)**	**13.1% (9.1)**	**8.2% (8.8)**	**37.0% (14.7)**	**48.1% (17.1)**	**14.9% (11.8)**	**2.7% (3.8)**	**9.9% (9.1)**	**87.4% (11.1)**

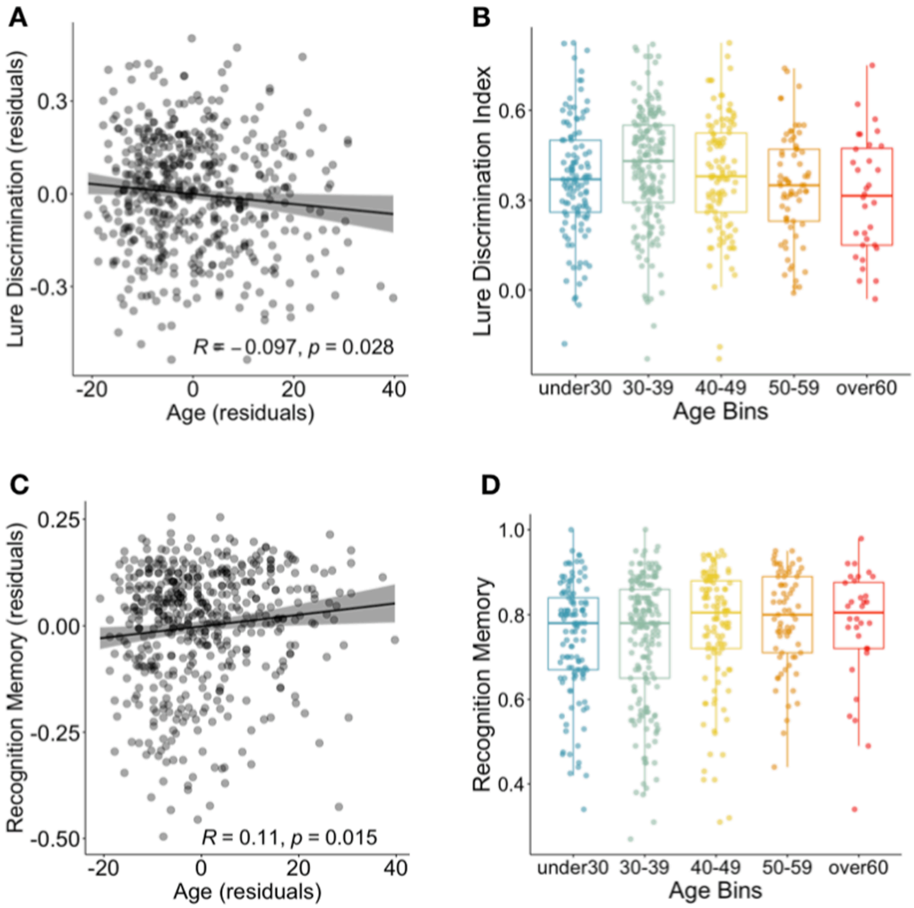

Fig. 2. Scores for the lure discrimination index (A-B) and recognition memory (C-D) as a function of age. Panels (A) and (C) show continuous age-performance relationships controlling for the influence of task version. Panels (B) and (D) show unadjusted values for categorically defined age bins.

controlling for age and task version ($t(90) = -0.51$, $p = 0.61$, $b = -0.001$, 95% CI [-0.005, 0.003]; Fig. 3**a**). Scores on the Perceived Stress Scale were highly correlated with MASQ anhedonic depression symptoms ($r(92) = 0.76$, $p < 0.001$, 95% CI [0.65, 0.83]). Considering this high correlation and the potential for suppression effects (Watson et al., 2013), we conducted an exploratory analysis in which we simultaneously regressed LDI scores on perceived stress and MASQ anhedonic depression scores. This simultaneous regression revealed significant effects of both perceived stress and anhedonic depression on LDI scores, but in *opposite* directions: perceived stress was negatively associated with lure discrimination when controlling for anhedonic depression ($t(89) = -3.37$, $p = 0.001$, $b = -0.009$, 95% CI [-0.014, −0.004]), whereas anhedonic depression was *positively* associated with lure discrimination when controlling for perceived stress ($t(89) = 4.05$, $p < 0.001$, $b = 0.010$, 95% CI [0.005, 0.016]). The additional inclusion of a perceived stress*anhedonic depression interaction term revealed a significant interaction ($t(88) = 2.95$, $p = 0.004$, $b = 4.7*10^{-4}$, 95% CI [$1.5*10^{-4}$, $7.9*10^{-4}$]), which was subsequently decomposed using a median split of anhedonic depression scores (Fig. 3**b**). Participants with low depression symptoms showed the hypothesized negative relationship between perceived stress and LDI scores ($r(49) = -0.41$, $p = 0.003$, 95% CI [-0.62, −0.15]), but this relationship was absent in those with elevated anhedonic depression symptoms ($r(41) = -0.07$, $p = 0.68$, 95% CI [-0.36, 0.24]).

We next attempted to replicate this unpredicted interaction in a unique dataset of 416 participants with valid MST and self-report data (Studies 3–4). Once again, there was no relationship between perceived stress and LDI scores across the replication dataset ($t(412) = -0.41$, $p = 0.33$, $b = -0.0004$, 95% CI [-0.003, 0.002; Fig. 3**c**). In a simultaneous regression, we again observed opposing relationships for perceived stress and anhedonic depression on lure discrimination scores (perceived stress: $t(411) = -3.28$, $p = 0.001$, $b = -0.004$, 95% CI [-0.007, −0.002]; anhedonic depression: ($t(411) = 4.71$, $p < 0.001$, $b = 0.005$, 95% CI [0.003, 0.007]). In this independent sample of 416 participants, we replicated the perceived stress*anhedonic depression interaction ($t(410) = 2.17$, $p = 0.03$, $b = 2.1*10^{-4}$, 95% CI [$2.0*10^{-5}$, $3.9*10^{-4}$]), with a significant perceived stress-LDI relationship at low ($r(211) = -0.22$, $p = 0.001$, 95% CI [-0.34, −0.09]) but not high levels of anhedonic

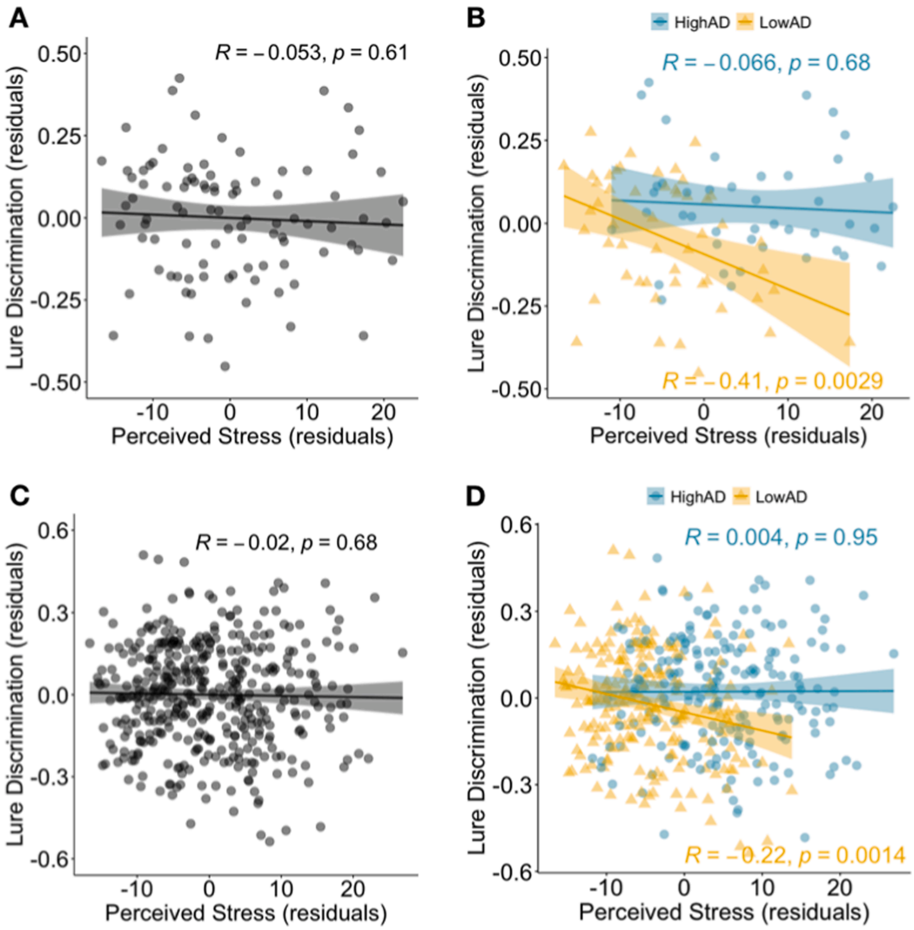

Fig. 3. Relationships between perceived stress and lure discrimination. In a discovery sample (N = 94), there was no main effect of perceived stress on lure discrimination (A). A significant perceived stress*anhedonic depression (AD) interaction was characterized by a significant inverse relationship at low (yellow triangles) but not high (blue circles) levels of anhedonic depression (B). The same pattern of results was observed in the larger replication sample (N = 416; C-D). Plots reflect residualized values adjusted for age and task version.

depression ($r(201) = 0.00$, $p = 0.95$, 95% CI [-0.13, 0.14]; Fig. 3**d**).

Collapsing across all participants provides a more robust estimate of effect sizes across studies and task versions and allows for the inclusion of a random effect to account for the non-independence of participants within study. Across all participants, there was no relationship between perceived stress and LDI scores ($t(509.1) = -0.52$, $p = 0.60$, $b = -0.0005$, 95% CI [-0.002, 0.001], but there was a significant perceived stress*anhedonic depression interaction ($t(503.5) = 3.18$, $p = 0.002$, $b = 0.0003$, 95% CI [0.0001, 0.0004]). The perceived stress-LDI relationship was significant at low ($r(323) = -0.28$, $p < 0.0001$, 95% CI [-0.39, −0.16]) but not high levels of anhedonic depression ($r(255) = -0.03$, $p = 0.65$, 95% CI [-0.15, 0.09]). The perceived stress*anhedonic depression interaction remained significant when adding as a covariate anxious arousal scores, as indicated in our preregistration ($t(502.5) = 2.73$, $p = 0.007$, $b = 0.0002$, 95% CI [0.0001, 0.0004]).

3.3. *Relationships between perceived stress, anhedonic depression, and recognition memory*

Finally, we ran an analogous regression model in the pooled sample of all participants using recognition memory as the dependent variable. We conceptualized this as a control analysis as we did not expect this non-hippocampal-dependent process to show associations with perceived stress. As was the case for LDI scores, recognition memory was not associated with perceived stress in a fixed effects regression analysis (the linear mixed effects model did not converge) with covariates of age, test modality, and task version ($t(506) = -1.31$, $p = 0.19$, $b = -0.0009$, 95% CI [-0.002, 0.0005]). Contrary to hypotheses, we observed a similar perceived stress*anhedonic depression interaction for recognition memory as for LDI ($t(504) = 3.87$, $p = 0.0001$, $b = 0.0002$, 95% CI [0.0001, 0.0004], again reflecting a significant inverse relationship between perceived stress and recognition memory for low ($r(251) = -0.20$, $p = 0.001$, 95% CI [-0.32, −0.08]) but not high levels of anhedonic depression ($r(255) = 0.01$, $p = 0.92$, 95% CI [-0.12, 0.13]). In addition to this analysis in the pooled dataset, a significant perceived stress*anhedonic depression interaction was observed in the discovery ($t(88) = 2.76$, $p = 0.007$, $b = 0.0004$, 95% CI [0.0001, 0.0006]) and replication samples ($t(410) = 2.58$, $p = 0.01$, $b = 0.0004$, 95% CI [0.001, 0.0003]).

4. Discussion

In a mega-analysis of 510 individuals from 4 different online (MTurk) studies, we identified a relationship between greater perceived stress and poorer performance on a behavioral index of pattern separation, a relationship that was specific to individuals with low levels of anhedonic depression symptoms. Prior neuroimaging studies have identified reduced hippocampal volume for individuals reporting elevated perceived stress (Gianaros et al., 2007; Zimmerman et al., 2016) or inflated threat appraisals (Grupe et al., 2019). The present results provide complementary behavioral evidence for a fundamental hippocampal information processing function that may be compromised in individuals who experience greater stress in their day-to-day lives. However, this finding comes with two important caveats.

First, this inverse relationship was only observed for individuals reporting relatively lower levels of anhedonic depression on the MASQ-30 and was absent for individuals with relatively higher anhedonic depression symptoms. The median MASQ-AD scores used to arbitrarily define “low” and “high” depression scores for discovery and replication samples were 29 and 32, respectively, values that easily exceed a suggested cut-off (23) for differentiating healthy and psychiatric individuals in a large Dutch study (Schulte-van Maaren et al., 2012). Although this level of symptoms may seem surprising, previous MTurk research with comparable sample sizes also identified mean depression and social anxiety scores in the clinical range (Arditte et al., 2016). This exploratory inverse relationship for individuals with relatively low anhedonic depression symptoms was replicated in a larger, independent group of participants with a pre-registered analysis plan. Scores on the PSS and MASQ-AD were highly correlated, and when controlling for perceived stress, individuals with greater anhedonic depression symptoms showed *increased* task performance. This pattern of results does not fit neatly with theories of impaired neurogenesis in depression (Gandy et al., 2017), or with previous studies that have reported a relationship between greater depression symptoms and impaired lure discrimination for neutral objects and/or scenes (Dohm-Hansen & Johansson, 2020; Leal et al., 2014; Shelton & Kirwan, 2013).

One possible way to account for our apparently conflicting results is the presence of multiple underlying psychological processes that exert differential effects on lure discrimination ability. The studies cited above utilized broad symptom measures that combine multiple aspects of depressive symptomology, whereas we utilized a measure of depressive symptoms that specifically indexes symptoms of anhedonia and low positive affect. The MASQ was developed in order to parse highly overlapping symptoms of anxiety and depression, allowing for the independent assessment of symptoms of somatic anxiety and hyperarousal versus anhedonia and low positive affect (Clark & Watson, 1991; Watson et al., 1995). In our data, the MST appears to provide a behavioral knife that slices the broad domain of negative affective symptoms into endophenotypes better characterized by negative appraisals of stress (associated with lure discrimination impairments) versus anhedonia (associated with enhanced lure discrimination ability). As reviewed by Dillon and Pizzagalli (2018), a variety of memory biases, each with distinct proposed neural mechanisms, have been characterized in depression. In addition to impaired recollection and pattern separation for neutral information (proposed to reflect stress-related reductions in neurogenesis), these also include impaired encoding and consolidation for rewarding events (proposed to reflect stress-related inhibition of midbrain dopamine signaling) and enhanced retrieval for negative memories (proposed to reflect stress-related amygdala sensitization). Although this framework does not provide a clear explanation for our surprising result linking anhedonia symptoms to enhanced behavioral pattern separation, it underscores the diverse neurophysiological changes resulting from chronic stress and the equivalently diverse corresponding mnemonic biases that depend on the affective content of to-be-remembered information.

To further complicate matters, because we only utilized a single behavioral task, we cannot definitively conclude that the mnemonic discrimination aspect of this task *per se* is responsible for the opposing behavioral relationships with perceived stress and anhedonic depression symptoms. Enhanced lure discrimination for neutral stimuli could reflect perceptual or attentional biases, the affective interpretation of stimuli, or some other unspecified factors. For example, prior research has identified enhanced lure discrimination for *negative* images with increasing depression symptoms (Leal et al., 2017); perhaps individuals with elevated anhedonic depression symptoms in our sample interpreted some "neutral" images as negative, thus contributing to enhanced mnemonic discrimination. Although our results provide intriguing and novel evidence that highly correlated yet conceptually distinct symptom clusters have opposing relationships with behavioral pattern separation, this phenomenon would be more fully elucidated through a broader behavioral battery, involving both neutral and affective stimuli, and in particular using behavioral assays sensitive to reward processing and anhedonia (Bilderbeck et al., 2020; Dillon et al., 2014; Treadway et al., 2009).

A second caveat is that a similar perceived stress*anhedonic depression interaction as was observed for LDI was also observed for recognition memory. One of the attractive features of the MST is that it provides dissociable metrics for lure discrimination (proposed to rely on pattern separation computations in the DG region of the hippocampus) and recognition memory (proposed to be independent of hippocampal pattern separation; Brown & Aggleton, 2001; Kirwan et al., 2012; Stark et al., 2019). The non-specificity of relationships between perceived stress and these two behavioral metrics provides equivocal support for the hypothesized neurobiological mechanism that motivated this work: namely, that stress-induced alterations to hippocampal neurogenesis impair pattern separation, which relies on sparse input of adult-born granule cells in the DG (Yassa & Stark, 2011). The lack of behavioral specificity may, for example, suggest involvement of the adjacent CA3 subfield, which receives pattern separation computations from DG and which is 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 & Stark, 2011). There may also be extra-hippocampal explanations for deficient performance at higher levels of stress. For example, individuals experiencing greater stress may exhibit decreased attention or executive processing that diminishes performance on a variety of cognitive tasks. It is important also to keep in mind that the MST is only a *proxy* for hippocampal pattern separation, and that neuroimaging outcomes should be leveraged for studies that seek to provide more definitive conclusions about links between the hippocampus and perceived stress.

As alluded to above, the observation that opposing relationships with lure discrimination emerged only in a multiple regression model suggests a classic case of "reciprocal suppression", in which two highly correlated variables (PSS and MASQ-AD) have opposing relationships with a criterion variable (LDI scores), such that the inclusion of MASQ-AD strengthens the relationship between PSS and LDI. Watson and colleagues ((Watson et al., 2013)) provided several examples of suppression effects with different symptom measures that replicated across samples (as we observed here), noting that such suppression allows one to "see another component within a scale—one that does not overlap with the suppressor—more clearly." In other words, there may be a more discrete psychological component contained within the PSS that is negatively associated with LDI, and when accounting for shared variance in PSS and MASQ-AD that suppresses the effect of this component, this relationship was made apparent. One potentially problematic feature of suppression effects is the presence of multicollinearity, as indicated by a high variance inflation factor (VIF), which can introduce instability in the estimate of regression coefficients. In simultaneous regressions involving PSS and MASQ-AD, the VIF for both regressors was below a commonly used cut-off of 5.0 for discovery and replication samples, mitigating concerns of multicollinearity (Akinwande et al., 2015).

Although not the primary goal of this paper, the collection of MST data in an entirely online sample (using Amazon MTurk) provides initial validation of this task for remote research, as well as descriptive data for a large sample of online participants (Table 2). MTurk and similar online data collection platforms allow for rapid, high-throughput data collection, and we demonstrate here that different versions of the MST can be feasibly administered outside of the lab with equivalent (or better) performance as has been observed in published laboratory studies (Stark et al., 2013). Notably, due to poor performance or non-compliance, we excluded data from nearly 20% of participants who completed the MST. In particular, we excluded data from far more participants who completed the study-test version (36%) compared to the continuous version (12%). Many of these participants were excluded due to performance at or near chance for recognition memory, suggesting that future studies conducted in remote samples should implement more robust attentional checks – or more engaging and/or ecologically valid task versions – to maximize attention to task and retain more participants.

The absence of attentional checks raises the possibility that our results may be influenced by automated "bots" or inattentive participants

(Buchanan & Scofield, 2018). Infiltration by bots likely accounted for many of the excluded behavioral responses, and because chance guessing results in scores of 0 for both recognition memory and LDI (due to the correction for response bias), we are confident that most if not all of these bots' responses were removed from the data prior to analysis. The potential that our results are influenced by workers completing self-report questionnaires with careless/insufficient effort (C/IE) is a more significant concern, as this can result not just in added noise to the data, but in systematic biases that can inflate correlations between behavioral outcomes and symptom measures (Zorowitz et al., 2021). Although we cannot definitively exclude the possibility that C/IE participants influenced our results, secondary analyses suggest the pattern of responding for the self-report measures of interest in our analyses does not follow the general pattern of C/IE responding described by Zorowitz et al. (2021). First, the most marked differences in symptom score distributions between attentive and C/IE participants were observed for measures with low overall rates of endorsement, which is not the case for the normally distributed PSS-10 (Cohen & Janicki-Deverts, 2012; Nordin & Nordin, 2013) or the MASQ-AD, which typically has *high* overall endorsement rates prior to reverse-scoring (Wardenaar et al., 2010). Second, C/IE responding is typically associated with a bias toward the right half of survey responses; due to reverse-scoring for all MASQ-AD items, this pattern of responding would manifest in a *leftward* shift (i.e., lower levels of anhedonic depression). In contrast, the observed distribution of MASQ-AD scores was relatively enriched at the upper end, as mean scores were well above published normative values (Schulte-van Maaren et al., 2012) and only 64/510 participants in the combined sample scored below 20 (out of a possible range of 10–50). Third, the fact that MASQ-AD scores are reverse-scored allows us to examine correlations with non-reverse-scored questionnaires measuring related constructs, with the assumption that C/IE responding would be reflected in inconsistent responding across measures. This was not the case in our data. For example, in Study 4 we collected the PROMIS depression subscale, which was correlated at $r = 0.55$ with MASQ-AD scores following behavioral data screening. In contrast, in participants with excluded behavioral data – reflecting the extreme in C/IE responding – the correlation was strong and *negative* ($r = -0.59$). In addition, after excluding outlying behavioral responses, observed correlations with MASQ-AD were generally consistent with published values (Watson et al., 1995) for the other MASQ subscales, anxious arousal ($r = 0.18$; published norms: $r = 0.25$–0.38) and general distress ($r = 0.68$; published norms: $r = 0.58$–0.68). Finally, we conducted sensitivity analyses in the pooled sample excluding the 12 participants with the most inconsistent responses between MASQ-AD and MASQ-GD subscales and replicated our key findings, suggesting that results are robust to C/IE responders (see analysis code for details: https://osf.io/9gy3n/).

Pooled across studies and controlling for the influence of task version, we replicated the consistent observation of relatively worse lure discrimination with increasing age (Stark et al., 2013, 2015, 2019). This effect was quite modest in size ($r_{\text{partial}}(508) = -0.10$, 95% CI [-0.18, −0.01]), which may partially be a reflection of our generally younger sample. Specifically, 59% of our sample was under age 40 and only 6% of our sample was older than 60. In earlier work characterizing the MST object task (Stark et al., 2013), a much more robust age effect was observed ($r = -0.48$), but performance did not show a consistent decline until after age 40 and dropped off sharply after age 60 (individuals over the age of 60 comprised half of the sample in that study). Although it was not a significant difference, we observed numerically lower LDI scores for individuals younger than 30 compared to those in the 30–39 age range, which weakened the overall linear age trend. Previous research has shown that age-dependent improvements in mnemonic discrimination continue throughout childhood and into young adulthood (Rollins & Cloude, 2018), and the poorer performance we observed for the youngest adults may point to a continued bias toward pattern completion vs. pattern separation, or reliance on gist memory, even further into young adulthood. It may also be the case, however, that younger adults in our sample were less attentive to the task or less familiar with some of the "common" objects used in this task.

A notable difference from prior work looking at age effects was a significant *positive* relationship between age and recognition memory, which was again quite modest in size ($r_{\text{partial}}(508) = 0.11$, 95% CI [0.02, 0.19]. Our large sample size may allow for the detection of subtle age-related gains in recognition that previous, smaller studies were underpowered to detect (even with the 510 participants in this analysis, a post-hoc power calculation shows we have only 70% power to detect a correlation of the magnitude observed). Higher recognition memory scores in older adults may to some extent represent the flip side of lower LDI scores. In our pooled dataset, participants older than 60 were equivalently likely to label lures as "old" (44.4%) as they were "similar" (40.2%). In contrast, participants younger than 40 labeled lures as "similar" 50.3% of the time and as old only 34.0% of the time. This over-reliance on gist memory in older adults may have induced a response bias toward "old" that was manifest in relatively higher performance for recognition memory. This is but one speculative explanation for this unexpected result, and our data and analysis code are available online (https://osf.io/9gy3n/) should interested readers wish to conduct their own analyses to address this or other outstanding questions in this large online dataset.

As the hypotheses driving this study are predicated on adult hippocampal neurogenesis and its impairment in individuals experiencing chronic stress, and the hypothesized resultant impact on pattern separation, we would be remiss to not mention recent high-profile papers rekindling the debate regarding whether hippocampal neurogenesis does indeed occur in the adult human brain (e.g., Sorrells et al., 2018; Moreno-Jiménez et al., 2019). We are persuaded by a comprehensive review of the direct and indirect evidence in support of continued neurogenesis throughout the human lifespan (Lucassen et al., 2020). The authors argue that "an absence of evidence is not evidence of absence", and discuss crucial differences in tissue processing, post-mortem delay, patient health information, and other factors that may have contributed to the absence of evidence for adult neurogenesis in Sorrels et al (2018). Nevertheless, critical questions remain regarding the extent to which cells born at different ages and maturing at different rates contribute to dentate function in humans, and more research is needed to elucidate the directionality and magnitude of relationships between hippocampal neurogenesis, cognitive decline, and mood and anxiety disorders (Lucassen et al., 2020).

In summary, a mega-analysis of 510 individuals across 4 different MTurk studies provided evidence of a relationship between greater perceived stress and impaired performance on a quick, simple, low-cost behavioral task that taxes the hippocampal-dependent process of pattern separation. Impaired performance for individuals high in perceived stress suggests a candidate behavioral process that may be implicated in previous studies demonstrating links between elevated perceived stress and reduced hippocampal volume (Gianaros et al., 2007; Zimmerman et al., 2016). This finding was only observed for individuals with relatively low scores on a scale of anhedonic depression, indicating that this test of mnemonic discrimination is sensitive to particular endophenotypes of affective symptoms. Future research that combines this task with additional behavioral assays and neuroimaging measures will be critical for illuminating the specificity of behavioral deficits for individuals high in perceived stress, and for testing the hypothesis that compromised hippocampal structure or function mediate the relationship between elevated perceived stress and deficient lure discrimination.

CRediT authorship contribution statement

Daniel W Grupe: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing – original draft, Visualization, Project administration, Funding acquisition. **Dan Fitch:** Methodology, Software, Validation, Writing – review & editing. **Nathan J. Vack:**

Methodology, Software, Validation, Writing – review & editing. **Richard J. Davidson:** Resources, Writing – review & editing, Supervision, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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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 conflicts to report.

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