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Examining the Effects of Exercise on Pattern Separation and the Moderating Effects of Mood Symptoms

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Aerobic exercise has broad cognitive benefits. One target of interest is enhanced memory. The present study explored pattern separation as a specific memory process that could be sensitive to acute and regular exercise and clinically significant for disorders (e.g., depression) characterized by cognitive-affective deficits and hippocampal impairment. In a within-subjects design, participants ($N = 69$) attended two visits during which they repeated a behavioral pattern separation task at rest and after an activity (cycling, stretching). Regular exercise habits, demographics, mood and anxiety symptoms, and recognition memory capacity were also measured. More regular exercise predicted better resting pattern separation, $t(62) = 2.13$, b = 1.74, $p = .037$. Age moderated this effect, $t(61) = 2.35$, b = .25, $p = .02$; exercise most strongly predicted performance among middle-age participants. There was no main effect of activity condition on post-activity performance, $t(61) = .67$, $p = .51$. However, with significant heterogeneity in reported mood symptoms and regular exercise habits, there was a three-way interaction between condition, regular exercise, and depression, $t(55) = 2.08$, b = .22, $p = .04$. Relative to stretching, cycling appears to have enhanced the benefit of regular exercise for pattern separation performance; however, this was evident among participants with mild to no symptoms of depression, but absent among participants with moderate to severe symptoms. Results have implications for how exercise might protect against declines in pattern separation. Future research should explore exercise's potential as a prevention tool or early intervention for pattern separation and related clinical outcomes.

Keywords: mnemonic discrimination; pattern separation; exercise; depression; mood

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REGULAR AND EVEN SINGLE SESSIONS of aerobic exercise have broad cognitive benefits (Hillman, Erickson, & Kramer, 2008). Behavioral pattern separation is one such exciting and measurable target. Pattern separation is a component process of episodic memory, touching on encoding and resolving interference between memories, and is supported by the dentate gyrus of the hippocampus (Yassa & Stark, 2011). At the computational or neurobiological level, pattern separation is a process that reduces neural overlap in how two entities are represented. Behaviorally, this allows for two similar entities—in theory, visual stimuli, physical sensations, or other experiences—to be perceived as distinct (Kheirbek & Hen, 2014; Sahay et al., 2011). Behavioral measures of pattern separation appear to track the underlying neural activity (Stark, Yassa, Lacy, & Stark, 2013; Yassa et al., 2011). Poor pattern separation could contribute to psychopathology, and emotional disorders in particular, such as depression. Depression and related disorders are characterized by overgeneral memory, overgeneralized emotional learning, and inflexible or global negative beliefs and appraisals (Carver & Ganellen, 1983; Gibbs & Rude, 2004; Lissek, 2012; Williams et al., 2007). Difficulty overcoming or resolving memory interference, i.e. poor pattern separation, could contribute to the onset or maintenance of such pathology (Kheirbek & Hen) and partially explain the association between hippocampal deficits and disorder risk and course (DeCarolis & Eisch, 2010).

Importantly, this relationship is likely bidirectional. Just as poor pattern separation could increase emotional vulnerability, declines in this cognitive capacity could also be attributable to the prolonged strain of emotional disorders. For example, in the case of depression, low pre-morbid episodic memory performance predicts future mood episodes (Airaksinen, Wahlin, Forsell, & Larsson, 2007), and the occurrence of mood episodes appears to have further consequences for episodic memory (Gorwood, Corruble, Falissard, & Goodwin, 2008; Zakzanis, Leach, & Kaplan, 1998). Relatedly, early impairments in the hippocampus denote risk and predict onset (e.g., Chen, Hamilton, & Gotlib, 2010), and course (akin to chronic stress in this region) predicts continued declines therein (e.g., Singh & Gotlib, 2014).

Functionally, aerobic and resistance exercise—both regular training and single sessions—can lead to related cognitive gains, such as in general episodic memory (Kattenstroth, Kalisch, Holt, Tegenthoff, & Dinse, 2013; Weinberg, Hasni, Shinohara, & Duarte, 2014). One of many possible and important pathways is through sustained or enhanced volume and function of the hippocampus (Erickson et al., 2009; Griffin et al., 2011; Ma, 2008). Exercise appears to facilitate neuroplasticity, especially in the dentate gyrus of the hippocampus, contributing to enhanced hippocampal function, learning, and memory (Kandola, Hendrikse, Lucassen, & Yücel, 2016; Pereira et al., 2007; Ryan & Nolan, 2016). This candidate mechanism is highly relevant for disorders or diseases that adversely affect hippocampal function, such as depression, anxiety, and dementia. Targeted changes in the hippocampus or to hippocampally dependent cognitive functions may support exercise-related boosts to psychological well-being, and reductions in risk for and symptoms of depression and anxiety (Cotman, 2002; Ernst, Olson, Pinel, Lam, & Christie, 2006). However, an understanding of the specific and immediate downstream cognitive and behavioral effects remains limited. For this reason, the present study focuses on behavioral pattern separation. Determining exercise's precise cognitive targets and specific, resultant behavioral phenomena could improve exercise and related interventions as well as highlight modifiable causal mechanisms of emotional disorders.

In animal models, chronic stress (e.g., isolation, impoverished environment) and aging reliably worsen pattern separation (Schloesser, Lehmann, Martinowich, Manji, & Herkenham, 2010; Wilson et al., 2003; Wilson, Gallagher, Eichenbaum, & Tanila, 2006). Similar declines occur in older humans and nonhuman primates (Sahay et al., 2011). Encouragingly, an enriched environment and voluntary exercise each attenuate this decline in animal models (Aimone et al., 2014; Bekinschtein, Oomen, Saksida, & Bussey, 2011). In one study, aged mice with access to a running wheel performed as well on a fear-based contextual discrimination task—a behavioral measurement of pattern separation—as did young mice, with both groups outperforming aged mice without access to exercise (Wu, Luna, & Hen, 2015). These effects emerged despite the fact that neurogenesis in the aged exercising mice remained significantly lower than in the young mice. Additionally, running did not improve all learning processes; rather, the benefit seemed specific to certain demanding cognitive abilities. The effects of long-term exercise programs on ability to discriminate between familiar, novel, and similar stimuli have begun to be replicated in humans as well (Dery et al., 2013). In a recent cross-sectional study, physical fitness and regular physical activity were also associated with greater pattern separation performance among young adults (Suwabe, Hyodo, Byun, Ochi, Fukuie, et al., 2017).

Overall, there is compelling preliminary research linking habitual aerobic exercise and pattern separation. To date, the few studies examining pattern separation and exercise have largely focused on long-term exercise and older adults. Therefore, the present study addressed two primary aims. First, we explored whether more regular physical activity would similarly predict superior pattern separation performance, even in relatively younger participants. The study sample included participants ranging from young adulthood through middle age. We expected to see a main effect of regular exercise, such that individuals engaging in regular moderate or vigorous exercise would outperform peers who were less active or sedentary. We also hypothesized that this effect would be especially pronounced among older participants; long-term exercise may buffer against age-related declines in this domain, thus gaps in performance among active and sedentary individuals should increase with age.

Second, we experimentally tested whether acute aerobic exercise could alter pattern separation performance. In other cognitive domains, studies show that a single session of moderate aerobic exercise can yield post-activity improvements, such as memory and executive function, paralleling stable improvements occurring over time with regular physical activity (Ferris, Williams, & Shen, 2007; Hillman, Snook, & Jerome, 2003; Hogervorst & Riedel, 1996; Kamijo et al., 2009). Acute aerobic exercise could plausibly alter performance, for example, as multiple studies have demonstrated that brain-derived neurotrophic factor (BDNF) levels temporarily increase following single sessions of moderate to vigorous exercise (Gustafsson et al., 2009; Tang, Chu, Hui, Helmeste, & Law, 2008); BDNF, a protein that is highly concentrated in the hippocampus, has also been linked to pattern separation capacity (e.g., Bekinschtein et al., 2011). Thus, we hypothesized that participants would perform better on a behavioral pattern separation task after one session of moderate aerobic exercise (cycling) relative to one session of static stretching. To our knowledge, only one study has examined acute exercise and mnemonic discrimination, and results demonstrated improvements following 10 minutes of activity relative to 10 minutes of rest (Suwabe, Hyodo, Byun, Ochi, Yassa, et al., 2017). To bolster confidence in the results, we included three methodological improvements: (a) an active control condition (stretching) to isolate the effects of *aerobic* exercise; (b) a measure of general memory capacity to probe for specific effects on pattern separation; and (c) an assessment of regular exercise habits to test whether effects were influenced by fitness level.

Finally, we were interested in how exercise might benefit pattern separation for people varying in their level of psychopathological risk, given the hypothesized relevance of pattern separation for emotional disorders. Researchers have suggested that improving pattern separation may prevent or even reduce symptoms of emotional disorders (Kheirbek & Hen, 2014). However, clinical symptoms that result in cognitive deficits or tax cognitive capacity may attenuate the beneficial effects of exercise. Because worsening symptoms can co-occur with weakened cognitive performance, acute aerobic exercise may not prove uniformly beneficial for individuals at varying levels of risk for an emotional disorder. Results could provide clues as to when interventions might be most effective or what magnitude of effects can be expected from adjusting doses or timescales. We hypothesized that participants experiencing significant symptoms of emotional disorders could require a higher dose of exercise, and thus the effect of a single session of exercise on pattern separation performance could be lessened relative to participants denying depression or anxiety.

Methods

SUBJECTS

Adults (N = 69) between the ages of 18 and 49 were recruited from the community (51 women, M_{age} = 31.38, SD = 8.02). To avoid potential confounds, we restricted eligibility to participants without a history of head injury, cognitive impairment, or neurologic disorder, contraindications to exercise, and current antidepressant medication use that could alter neurogenesis. Self-reported ethnic and racial composition of the sample included 4.35% Hispanic or Latino, 60.87% Caucasian or White, 18.84% African American or Black, 13.04% Asian or Asian American, 1.45% Native American or American Indian, 4.35% multiracial, and 1.45% other. The study was approved by Harvard University's Committee on the Use of Human Subjects. Participants provided written informed consent before beginning any study procedures.

PROCEDURE

Participation was divided across two visits separated by 1 week (± 1 day). At each visit participants completed a behavioral pattern separation task twice, once before and once after an activity (stretching or cycling). In a within-subjects design, all participants were to complete both types of visits; the order of activities was randomized and counterbalanced across participants.

BASELINE MEASURES

After the informed consent process, participants completed a battery of questionnaires including demographics (e.g., gender, education), mood symptoms, and exercise habits. Participants' height and weight were measured at baseline in order to calculate body mass index (BMI). Mood symptoms in the past week were captured by the three subscales—depression, anxiety, and stress—of the Depression Anxiety Stress Scales, 21-item (DASS-21; Lovibond & Lovibond, 1995). Example depression items include sad or low mood, feelings of worthlessness, and anhedonia. Example anxiety items include somatic symptoms (e.g., racing heart), situational anxiety, general anxiety, and panic. Example stress items include irritability, fidgeting, tension, and heightened startle response. Higher scores on each subscale indicate more frequent or severe symptoms. We used the third item from the George Non-Exercise Test (GNET; George, Stone, & Burkett, 1997) to assess participants' exercise habits. Scores on this measure can range from "avoid walking or exertion" to "vigorous activity; run over 25 miles per week or spend over 8 hours per week in comparable physical activity." Finally, state-level affect was assessed at baseline, pre- and post-activity, and at the end of the study via the valence and arousal items of the Self-Assessment Manikin (SAM; Lang et al., 1993; Suk & Irtel, 2006). In this nonverbal, self-report measure, participants identify the icons of a human-like figure that best correspond to their current levels of emotional arousal and valence, respectively.

MNEMONIC SIMILARITY TASK (MST)

Behavioral pattern separation (or mnemonic discrimination) was assessed via the two phases of the MST, which serves as a behavioral proxy to tax and thus measure hippocampal pattern separation (Stark et al., 2013; Yassa et al., 2011). In Phase 1, participants saw a series of 128 everyday objects one at a time and judged whether each belonged indoors or outdoors by pressing one of two designated keys. In Phase 2, participants saw a second series of everyday objects and judged whether each was old or an exact repetition from Phase 1 ("targets"), similar but not exactly the same as an earlier image ("lure"), or new ("foil"). Participants saw a few example trials before completing the test phase. Sixty-four images from each category were presented. Images were on screen for 2 seconds with an inter-stimulus interval of 0.5 seconds. Two scores were derived from accuracy on Phase 2 of the MST. A lure discrimination index (LDI or pattern separation score) was calculated as the difference between correct similar ratings given to lures minus incorrect similar ratings given to foils. The latter corrects for a potential response bias to use the similar rating. A traditional recognition memory score was calculated as the difference in the percentage of targets correctly labeled old versus incorrectly labeled new. Lower scores on both indices indicated worse performance. Reaction times were also recorded. At each visit, in between the first and second MST, participants underwent the experimental manipulation.

EXPERIMENTAL CONDITIONS

Participants were randomly assigned to the aerobic exercise condition (cycling) or active control condition (stretching).

Cycling

Participants engaged in sustained, moderate aerobic exercise for 30 minutes (4 minutes warmup, 26 minutes sustained 60%–70% estimated maximum heart rate). Heart rate was monitored with a Polar heart rate monitor worn around the chest. Resting, maximum, and average heart rate were recorded. The experimenter monitored for adherence. Prior research has demonstrated that 20–30 minutes of activity is sufficient to induce immediate (though temporary) bursts in BDNF (Etnier et al., 2016; Ferris et al., 2007) and benefits for cognitive function (Brisswalter, Collardeau, & Rene, 2002; Lambourne & Tomporowski, 2010; Pontifex, Hillman, Fernhall, Thompson, & Valentini, 2009). Participants' heart rate had to return to within 10% of baseline resting heart rate before they could begin the second MST.

Stretching

Participants were led through 30 minutes of light stretching. At 5-minute intervals participants were provided with different instructions about how to be stretching (e.g., neck and shoulder stretches) and the experimenter monitored for adherence. This condition served as an active control condition. Active, but nonaerobic, it isolated the effects of aerobic activity. Participant heart rate also had to be within 10% of baseline resting heart rate before continuing on to the second MST.

STATISTICAL ANALYSES

Independent sample *t*-tests and one-way analyses of variance (ANOVAs) assessed whether level of regular physical activity or baseline LDI score differed by gender, race, ethnicity, or education level, and bivariate regressions assessed differences by age, BMI, depressive, anxious, and stress-related symptoms, and baseline measures of valence and arousal.

Linear mixed models assessed the relationship between self-reported level of regular exercise and baseline LDI scores (i.e. pre-activity MST). Additional models tested the interaction of habitual exercise with age and clinical symptoms (DASS-Depression, DASS-Anxiety, and DASS-Stress scores), and controlled for baseline recognition memory performance and any demographic or clinical characteristic that emerged as significantly related to LDI score.

Before examining the effects of physical activity on pattern separation performance, we performed a manipulation check to confirm that resting heart did not differ by randomized condition, but average heart rate during the assigned activity did. Additionally, to ensure that changes in affect (valence, arousal) did not account for any experimental results, we also examined if there were differences in self-reported affect by condition at any time point via two-way ANOVAs.

To examine the effects of acute exercise on pattern separation performance, we computed linear mixed models in which condition served as a fixed predictor —both alone and as an interaction term with regular exercise habits— and post-activity LDI as the outcome variable. Analyses were repeated controlling for age, concurrent recognition memory, and any demographic or clinical characteristic that emerged as significantly related to LDI score. Finally, we explored three-way interactions between condition, regular exercise, and clinical symptoms (DASS-Depression, DASS-Anxiety, and DASS-Stress scores). Specifically, we examined whether different types of symptoms would moderate the effects that regular and acute exercise could have on LDI scores. MST scores that were greater than 2.5

standard deviations above or below the mean were excluded from all analyses. Additionally, we adjusted each set of analyses by using the Benjamini-Hochberg procedure (false discovery rate = .05) to account for multiple comparisons.

Results

Baseline characteristics of the sample are included in Table 1. Less frequent and intense regular exercise was associated with older age, $F(1, 67) = 12.14$, $p < .001$, B = -.12, greater anxiety (DASS-Anxiety), $F(1, 67) = 5.89$, $p = .02$, B = -.78, and higher BMI, $F(1, 67) = 5.37$, $p = .02$, B = -.69. Exercise habits were not associated with gender, ethnicity, race, education, DASS-Depression, DASS-Stress, or baseline state affect (valence, arousal). Baseline LDI scores did not differ by race, DASS-Depression, -Anxiety, or -Stress score, BMI, baseline valence, or baseline arousal (*p*s > .05). Better (i.e., higher) LDI scores were associated with younger age, $F(1, 67) = 7.95$, $p = .006$, $B = -.77$, female gender, $F(1, 67) = 6.04$, $p = .02$, and not identifying as Hispanic or Latino, $F(2, 66) = 5.27$, $p = .008$ (Hispanic or Latino vs. Not Hispanic or Latino, $p = .006$; Hispanic or Latino vs. Unknown or not reported, $p = .02$; Not Hispanic or Latino vs. Unknown or not reported, $p = .92$; *p*-values were adjusted by using the Benjamini-Hochberg procedure). Though education level was also a significant predictor of baseline LDI

Table 1
Demographic and Baseline Characteristics of the Sample

	Whole Sample	Regular Exercise	
	N (%)	Mean ± *SD*	*p*
Gender			.38
Female	51 (73.91)	4.98 ± 2.34	
Male	18 (26.09)	4.39 ± 2.79	
Ethnicity			.74
Hispanic/Latino	3 (4.35)	4.0 ± 1.73	
Not Hispanic/Latino	61 (88.41)	4.82 ± 2.50	
Unreported	5 (7.25)	5.4 ± 2.51	
Race			.12
Caucasian/White	42 (60.87)	5.45 ± 2.70	
African America/Black	13 (18.84)	3.83 ± 1.90	
Asian American/Asian	9 (13.04)	3.89 ± 1.36	
Native American/American Indian	1 (1.45)	7.0	
Mixed Race	3 (4.35)	3.67 ± .58	
Other/Unreported	1 (1.45)	2.0	
Education			.38
High school diploma/GED	3 (4.35)	4.0 ± 2.0	
Some college	16 (23.19)	5.44 ± 2.80	
Technical school/Associates Degree	2 (2.90)	4.0 ± 2.83	
College Diploma	19 (27.54)	4.0 ± 1.53	
Graduate/Professional Degree	29 (42.03)	5.18 ± 2.73	
	Whole Sample	**Regular Exercise**	
	Mean ± *SD*	**B**	***p***
Age	31.38 ± 8.02	-.12	< .001
DASS-Depression	7.04 ± 8.45	-.37	.37
DASS-Anxiety	5.77 ± 6.76	-.78	.02
DASS-Stress	10.38 ± 9.70	-.30	.54
BMI	25.73 ± 6.19	-.69	.02
Regular Exercise	4.91 ± 2.40		
Valence	6.13 ± 1.58	.09	.29
Arousal	2.91 ± 1.95	.03	.75

Note. *p*-values were derived from *t*-tests and one-way ANOVAs for categorical variables and bivariate regressions for continuous variables. In all cases, regular exercise, as measured by item 3 of the George Non-Exercise Test, was entered as the criterion variable. DASS = Depression Anxiety Stress Scales (Depression, Anxiety, and Stress subscales), BMI = Body mass index (kg/m^2).

score, *F*(4, 64) = 2.84, *p* = .03, no pairwise comparisons survived correction.

REGULAR EXERCISE AND PATTERN SEPARATION

More regular exercise predicted better resting LDI scores, *t*(62) = 2.13, b = 1.74, SE = .82, *p* = .037. This held controlling for recognition memory, gender, and ethnicity, *t*(59) = 2.26, b = 1.61, SE = .71, *p* = .028. When age was included, a significant interaction effect emerged, *t*(61) = 2.35, *p* = .02, b = .25, SE = .11, such that age moderated the effect of regular exercise habits on pattern separation performance (Figure 1). This interaction also held controlling for recognition memory, gender, and ethnicity, *t*(58) = 3.29, *p* = .002, b = .30, SE = .09. Simple slopes analyses suggest that this positive relationship between regular exercise and LDI score is driven by older participants. The effect was nonsignificant for individuals 1 *SD* below the mean, *p* = .74, but was a trend at the mean, b = 1.64, *p* = .06, and significant at 1 *SD* above the mean, b = 3.64, *p* = .01. When the Benjamini-Hochberg procedure was applied, the main effect of regular exercise on resting LDI scores was reduced to a trend (*p* = .06), but the interaction between regular exercise and age survived. DASS-Depression, DASS-Anxiety, and DASS-Stress scores did not emerge as significant moderators, *p*s > .05.

Furthermore, more regular exercise predicted faster reaction times on trials when lures were accurately identified, *t*(62) = 3.28, *p* = .002, b = -19.86, SE = 6.05. This effect held controlling for recognition memory, gender, and ethnicity, *t*(62) = 3.01, *p* = .003, b = -18.46, SE = 6.13. This effect survived correction. No such relationship was found between regular exercise and overall average reaction time, *t*(63) = .68, *p* = .50, or between regular exercise and reaction time on lure items in general, *t*(63) = 1.21, *p* = .23. Similarly, a significant regular exercise-by-age interaction effect was found for reaction time to correctly identify lures, *t*(61) = 2.05, *p* = .04, B = -1.66, SE = .81 (Figure 2). Simple slopes analyses revealed no effect of regular exercise for participants 1 *SD* below the mean for age, *p* = .40, but significant effects at the mean, b = -20.27, *p* = .003, and 1 *SD* above, b = -33.65, *p* = .002. This interaction effect held controlling for recognition memory, gender, and ethnicity, *t*(61) = 2.06, *p* = .04, B = -1.69, SE = .82. With the Benjmani-Hochberg procedure, this interaction effect was reduced to a trend (*p* = .07). Again, this effect was unique to correctly identifying lures as no significant relationships were found with overall reaction time, *t*(62) = .99, *p* = .32, or reaction time for lures in general, *t*(62) = .62, *p* = .53. DASS-Depression, DASS-Anxiety, and DASS-Stress scores did not emerge as significant moderators, *p*s > .05.

ACUTE EXERCISE AND PATTERN SEPARATION

As intended by the manipulation, although resting heart rate did not differ by condition, *F*(1,63) = .01, *p* = .92, average heart rate during the activity portion of the study did differ, *F*(1,62) = 289.25, *p* < .001; participants experienced greater average heart rate

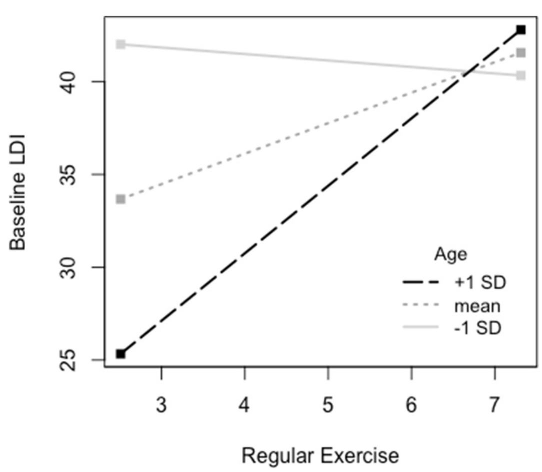

FIGURE 1 Age by regular exercise habits interaction predicting baseline pattern separation performance*Note*. Regular Exercise derived from item 3 on the George Non-Exercise Test; higher scores indicate more intense and frequent regular exercise. LDI = lure discrimination index, derived from the Mnemonic Discrimination Task (MST); higher scores indicate better performance.

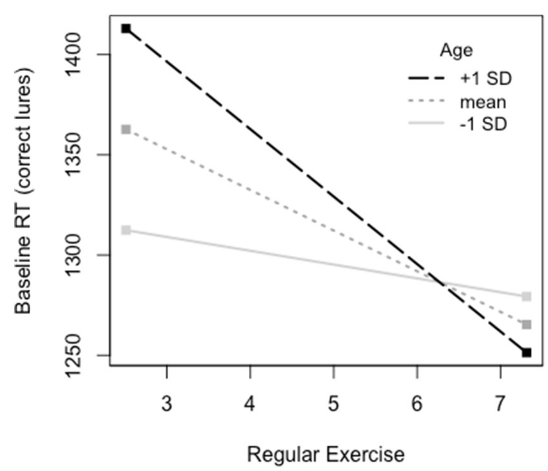

FIGURE 2 Age by regular exercise habits interaction predicting reaction times for correctly identifying lures in the baseline behavioral pattern separation task*Note*. Regular Exercise derived from item 3 on the George Non-Exercise Test; higher scores indicate more intense and frequent regular exercise. RT = reaction time responding correctly to lures in the Mnemonic Discrimination Task (MST); lower scores indicate faster reaction times.

while cycling (M_{cycle} = 116.08, SD = 10.03) than while stretching ($M_{stretch}$ = 86.28, SD = 14.48). Additionally, there was no main effect of condition, main effect of time point, or interaction between condition and time point on valence or arousal, *p*s > .05.

Post-activity LDI scores did not differ by condition (stretching, cycling), $t(61) = .67$, $p = .51$. There was also no significant interaction between condition and regular exercise habits, $t(59) = .53$, $p = .60$. Additionally, reaction times did not differ by condition overall, $t(62) = 1.72$, $p = .09$, for lures, $t(62) = 1.46$, $p = .15$, or for correctly identified lures, $t(61) = .23$, $p = .82$. Condition by regular exercise interactions were also nonsignificant predictors of overall reaction time, $t(60) = 1.77$, $p = .08$, reaction time to lures, $t(60) = .85$, $p = .40$, and reaction time for correct lures, $t(59) = .84$, $p = .41$. Results remained unchanged controlling for age, recognition memory, gender, and ethnicity, *p*s > .05.

A significant three-way interaction emerged for condition by regular exercise by depression severity (DASS-Depression) in predicting LDI scores, $t(55) = 2.08$, $p = .04$, b = .22, SE = .11 (Figure 3). Simple slopes tests clarified this interaction. Regardless of the level of DASS-Depression severity, when regular exercise was low (i.e. 1 *SD* below the mean), there were no effects of condition, *p*s > .05. This suggests that there were no differences in the impact of one session of stretching versus cycling on LDI score among inactive participants. There were significant effects for condition when DASS-Depression scores were low and regular exercise was at the mean, b = -7.09, $p = .006$, or 1 *SD* above, b = -11.69, $p = .007$. There were no significant effects for condition when DASS-Depression scores were at the mean, *p*s > .05. Finally, there were significant effects for condition when DASS-Depression scores were high (i.e., 1 *SD* above the mean) and regular exercise was at the mean, b = 6.69, $p = .03$, or 1 *SD* above, b = 11.22, $p = .03$. This pattern suggests that among regular exercises experiencing no or mild symptoms of depression (DASS-Depression < 7), the cycling condition yielded better LDI scores than the stretching condition. However, for those experiencing moderate symptoms of depression (DASS-Depression $\geq$ 7), there are no differences between activities, and for those experiencing severe symptoms of depression (DASS-Depression $\geq$ 11), performance in the stretching condition exceeded that in the cycling condition. Results should be interpreted with caution as the three-way interaction did not survive correction ($p = .12$). No such effects emerged for DASS-Anxiety, $t(55) = 1.65$, $p = .10$, or DASS-Stress, $t(55) = .81$, $p = .42$. No effects emerged for reaction times indices, *p*s > .05.

Discussion

Data revealed a positive relationship between more frequent and intense regular exercise and performance on the pattern separation task (MST). Importantly, this was in a heterogeneous sample of both young and middle-aged adults and including participants with a range emotional symptoms or risk (i.e., more than one third of participants reported symptoms of depression or anxiety above the clinical threshold). This pattern emerged both for accuracy in differentiating similar items from

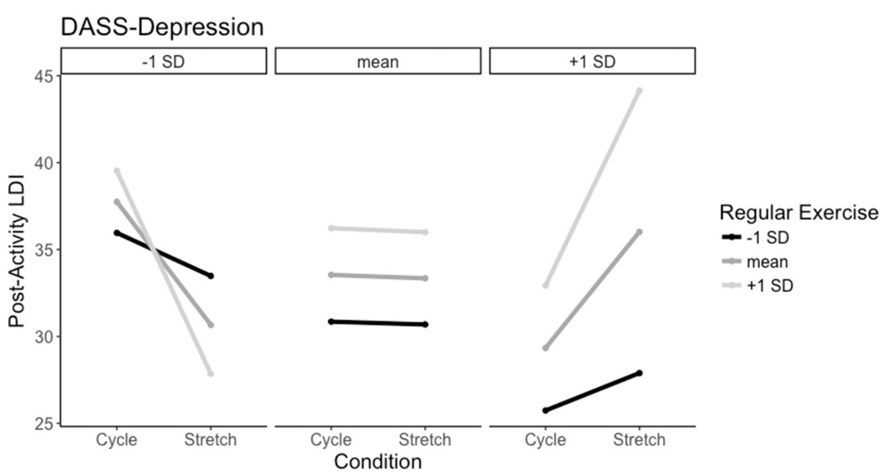

FIGURE 3 Condition by regular exercise habits by depression interaction predicting post-activity behavioral pattern separation performance *Note.* DASS = Depression Anxiety Stress Scales (Depression, Anxiety, and Stress subscales); higher scores indicate more severe depression. Regular Exercise derived from item 3 on the George Non-Exercise Test; higher scores indicate more intense and frequent regular exercise. LDI = lure discrimination index, derived from the Mnemonic Discrimination Task (MST); higher scores indicate better performance.

old and new ones as well as for reaction time on such trials. Correlational findings are consistent with early evidence that regular exercise could benefit pattern separation performance among middle-aged and young adults in addition to older adults (Dery et al., 2013; Suwabe, Hyodo, Byun, Ochi, Fukuie, et al., 2017). As such, this study contributes to claims that a physically active lifestyle supports cognitive function across the lifespan and can specifically enhance mnemonic discrimination, which may reflect greater cognitive flexibility.

Effects on both accuracy and reaction time were most robust among middle-aged participants relative to their younger counterparts. Long-term exercise can prevent hippocampal decline more so than facilitate hippocampal growth across the lifespan (Firth et al., 2018). Thus, if we consider MST performance as a marker of hippocampal function (Stark et al., 2013; Yassa et al., 2011), it is unsurprising that effects of regular exercise on pattern separation would be greater among older participants. Without intervention, they are more likely to exhibit detectable—and increasing—atrophy or dysfunction in these regions due to aging (Driscoll et al., 2003). As some individuals experience a buffer from habitual physical activity, the gap in pattern separation capacity, as with other cognitive abilities, between sedentary and active individuals widens with age. This implies that individuals could experience the greatest exercise-related benefits and subsequently sustained pattern separation capacity if they engaged in regular aerobic exercise from a young age; early activity should support hippocampal development (Chaddock et al., 2010; Sibley & Etnier, 2003) and protect against early stress-related damage and declines (Dik, Deeg, Visser, & Jonker, 2003; Lupien et al., 2007). However, the present study did not include neuroimaging or related measures, and thus the neuromechanisms of this age effect remains an open question with alternative possibilities.

Among young adults, although accuracy on the MST did not differ by level of regular exercise, there was a signal for speed in differentiating the similar stimuli; this is evidence of potential early separations in performance among younger participants varying in exercise habits. It is possible that slower reaction times indicate more effort or difficulty with the task. It is also possible that the effects of such differences could accumulate or be exacerbated in challenging conditions (e.g., stress, dual tasks) and have consequences for sedentary individuals, including increasing risk for developing emotional disorders. This is particularly important as young adulthood is a high-risk time for psychopathology (Kessler et al., 2007). Additional experimental and complementary longitudinal research would be necessary to confirm these interpretations. Furthermore, the present data are cross-sectional and thus cannot confirm that exercise history is causing variation in behavioral pattern separation performance. It is possible that the relationship between regular exercise and pattern separation is due to a third variable, such as general physical health or low life stress, or that high pattern separation reflects one of many cognitive strengths that can support a healthy, active lifestyle. In reality, the nature of this relationship is likely complex and bidirectional. More longitudinal and intervention research is needed to unpack true causal connections and the mechanisms underlying these observations.

The second aim of the present study was to investigate potential temporary boosts in pattern separation performance following acute aerobic exercise. In a within-subjects design, we did not find a main effect of cycling relative to stretching. This conflicts with preliminary findings from Suwabe and colleagues, who found that 10 minutes of moderate cycling, relative to rest, enhanced mnemonic discrimination in young adults (Suwabe, Hyodo, Byun, Ochi, Yassa, et al., 2017). There are, however, important differences between the two experimental designs that could influence the diverging results. For example, the present study compared 30 minutes of moderate cycling to 30 minutes of stretching; it is possible that stretching, unlike resting, also produces positive changes to MST performance or that 10-minute and 30-minute sessions have significantly different effects. Additionally, the present sample included a wider range of ages, mood symptoms, and exercise habits, potentially lessening the likelihood of identifying a main effect. Differences suggest that exercise dose and characteristics of the individual likely moderate the impact that a single session of exercise could have on pattern separation. More research, beyond these two early studies, is necessary to resolve these questions.

Given the hypothesized effects of regular exercise on MST performance and the wide range of exercise habits represented in the sample, we also considered the interaction between acute and regular exercise. The expected relationship, whereby a single session of aerobic exercise enhances the effect of regular physical activity on mnemonic discrimination, was only evident when mood symptoms were also considered. Importantly, when a stringent correction for multiple comparisons was applied, this 3-way interaction was no longer significant at $p < .05$. Thus, we interpret results cautiously and propose that further research is needed to explore resulting hypotheses. It is possible that one session of cycling could prove sufficient to further boost the relationship between regular exercise and pattern separation relative to stretching, but only among individuals reporting no or mild symptoms of depression. However, no such augmentation effect occurred for participants experiencing moderate symptoms of depression and the effect was ostensibly reversed for participants experiencing severe symptoms of depression. Notably, clinical symptoms in the past week did not moderate the effect of regular exercise on resting pattern separation. Adding more comprehensive measures of clinical symptoms would be important in future research to tease apart how habitual exercise and past or present diagnoses interact to effect pattern separation across the lifespan. For example, the current measures could not differentiate individuals experiencing low mood for just the past week from those experiencing such symptoms for the past year. As such, regular exercise may be insufficient to overcome the deleterious effects of longstanding mood episodes. The present pattern of results can still help us to generate hypotheses about how exercise might best be used as an intervention and why.

One compelling, proposed biological mechanism of the effect of exercise on pattern separation involves BDNF. BDNF contributes to the function of the central nervous system, promotes synaptic and structural plasticity and cell survival, and reduces neurodegeneration. Higher levels of BDNF are associated with improved cognitive functioning, particularly memory and learning (Cirulli, Berry, Chiarotti, & Alleva, 2004; Egan et al., 2003). BDNF has been conceptually linked to the dentate gyrus and pattern separation performance because of its experimentally demonstrated role in memory consolidation and persistence, contextual fear and avoidance learning, and object recognition (Bekinschtein et al., 2013; Bekinschtein, Oomen, et al., 2011). More directly, blocking BDNF function in the dentate gyrus during encoding (i.e., when pattern separation is understood to occur), but not retrieval, interferes with performance on a spontaneous location recognition task. Importantly, this interference only occurs when the two locations to be differentiated are similar (i.e., requiring pattern separation), and no interference is observed when the two locations being tested are dissimilar (Bekinschtein, Oomena, et al., 2011). In rodent models, both enriched environment and voluntary exercise enhance BDNF expression in the hippocampus (Bekinschtein, Oomena, et al., 2011). New evidence suggests that BDNF expression may occur on an as-needed basis, such as when pattern separation is implicated. In rats, BDNF expression in the dentate gyrus spontaneously and significantly increases when the animals explore two similar environments, but not when they explore two dissimilar ones (Bekinschtein et al., 2013; Bekinschtein, Oomena, et al., 2011). Thus, regular exercise may build up this reserve.

Reduced BDNF expression is thought to leave a person more vulnerable to the neurobiological consequences of stress in part by failing to adequately support the hippocampus in its negative feedback role for the HPA axis. Excess glucocorticoids, often resulting from stress exposure, may further deplete BDNF expression (Chen et al., 2006). Lower levels of BDNF are also associated with risk for or diagnosis of depression and related disorders (Bocchio-Chiavetto et al., 2010; Karege et al., 2005; Szuhany, Smits, Asmundson, & Otto, 2014). Physical activity, however, is known to enhance BDNF expression or release, particularly in the hippocampus (Gómez-Pinilla et al., 2002; Szuhany, Bugatti, & Otto, 2015). Critically and in line with the above results, regular exercise increases resting BDNF levels and post-exercise bursts of BDNF are larger among regular exercisers compared to sedentary peers (Szuhany et al., 2015). Exercise may buffer against stress-induced declines in BDNF availability or expression and subsequently support adaptive stress responses and regulation. This is one plausible pathway through which aerobic activity prevents the development or worsening of emotional symptoms and disorders (Harvey et al., 2017; Ströhle, 2009). Participants in the present study with moderate to severe depression could be experiencing significant strain on their BDNF system or reserve such that one session of exercise was insufficient to yield effects. Furthermore, for individuals with severe symptoms, stretching appeared more advantageous than cycling. One possible explanation is that depression is frequently characterized by low energy and motivation. As such, stretching could have been physically taxing enough to induce cognitive benefits and cycling could have been too intense or aversive; although results are mixed, some research has shown that acute high intensity exercise is less beneficial than moderate activity for cognition and may even be detrimental in some cases (Chang, Kim, Jung, & Kato, 2017; Eich & Metcalfe, 2009).

Future follow-up studies would benefit from addressing additional limitations of the present project. First, although the MST provides low cost, noninvasive, behavioral evidence of underlying hippocampal function, it is not equivalent to direct measurement of activity within the dentate gyrus. Thus, replicating behavioral findings with complementary imaging and other biological measures is an important next step. Relatedly, exercise affects a host of biological and psychological systems; examining interacting effects among these various systems (e.g., cardiovascular health, motivation, and self-esteem) was outside the scope of the present study, but could conceivably influence results. Furthermore, we only considered the effects of 30 minutes of moderate cycling. As alluded to above, additional research is needed to examine different modalities, intensities, and durations of physical activity. Finally, variations in future experimental designs would further isolate the pathways by which exercise (and mood) impact pattern separation; future experiments could, for example, delay the retrieval phase (i.e., Phase 2) within the study visit or to a later date, vary when a participant exercises relative to completing the MST, or use new, emotional stimuli as exercise effects for cognition may be greater for valenced than neutral targets (Weinberg et al., 2014).

CONCLUSIONS

Despite these limitations, results provide novel insight into how regular and acute exercise impact memory and cognition, and the malleability of pattern separation in particular. In the context of past research on emotional disorders, aging, and cognition, our results help to generate new hypotheses for how exercise, and other interventions, might be used to protect pattern separation and build resilience against emotional disorders. As cognitive and emotional health worsen, larger or more regular doses of exercise or another intervention are likely required to yield positive effects, and the plausible aim may be stabilizing rather than regaining cognitive function. Results suggest that exercise's buffering effect may be strongest the longer one has been physically active and before significant mood symptoms develop; both of these moderators highlight how exercise could be viewed as potentially most potent as a prevention tool or early intervention for pattern separation and related outcomes.

Conflict of Interest Statement

The authors declare that there are no conflicts of interest.

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