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Effects of Acute Aerobic Exercise on Mnemonic Discrimination Performance in Older Adults

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Abstract

Objective: Ample evidence suggests exercise is beneficial for hippocampal function. Furthermore, a single session of aerobic exercise provides immediate benefits to mnemonic discrimination performance, a highly hippocampal specific memory process, in healthy younger adults. However, it is unknown if a single session of aerobic exercise alters mnemonic discrimination in older adults, who generally exhibit greater hippocampal deterioration and deficits in mnemonic discrimination performance. **Methods:** We conducted a within subject acute exercise study in 30 cognitively healthy and physically active older adults who underwent baseline testing and then completed two experimental visits in which they performed a mnemonic discrimination task before and after either 30 minutes of cycling exercise or 30 minutes of seated rest. Linear mixed-effects analyses were conducted in which condition order and age were controlled, time (pre vs. post) and condition (exercise vs. rest) were modeled as fixed effects, and subject as a random effect. **Results:** No significant time by condition interaction effect was found for object recognition ($p=.254$, $\eta^2=.01$), while a significant reduction in interference was found for mnemonic discrimination performance following the exercise condition ($p=.012$, $\eta^2=.07$). A post-intervention only analysis indicated that there was no difference between condition for object recognition ($p=.186$, $\eta^2=.06$), but that participants had better mnemonic discrimination performance ($p<.001$, $\eta^2=.22$) following the exercise. **Conclusions:** Our results suggest a single session of moderate-intensity aerobic exercise may reduce interference and elicit better mnemonic discrimination performance in healthy older adults, suggesting benefits for hippocampal-specific memory function.

Key Words: Hippocampus, Memory, Physical Activity, Cognition, Dentate Gyrus, Cycling

Introduction

Memory decline is a pervasive complaint of older adults and can exact an enormous toll on individuals, their loved ones, and society (Livingston et al., 2020). Physical exercise is a critical lifestyle intervention for promoting healthy brain aging, particularly preserving the hippocampus and memory function (Voss et al., 2019). Meanwhile, growing evidence suggests a single session of aerobic exercise may provide immediate benefits for hippocampal integrity, function, and memory performance (Callow et al., 2021; El-Sayes et al., 2019; Hillman, Erickson, & Kramer 2008; Loprinzi et al., 2021). Specifically, a single session of low to moderate intensity aerobic exercise upregulates hippocampal BDNF expression in rats (Huang et al., 2006; Soya et al., 2007; Venezia, Quinlan, & Roth 2017) and leads to small to moderate improvements in long term episodic memory performance in humans (Labban & Etnier 2011; Loprinzi et al., 2021; Roig et al., 2013). While a single exercise session may not elicit the same magnitude of benefit for memory performance as long-term exercise training protocols, acute exercise paradigms are ideally suited to understand the temporal interactions between exercise and phases of memory (Loprinzi et al., 2021). Furthermore, understanding these mechanisms and the timeframe by which a single acute session, or dose, of exercise may promote hippocampal function and integrity is critical to understanding and optimizing long-term brain health interventions in older adults. Nevertheless, previous acute exercise studies have predominantly been conducted on younger adults and utilized non-specific cognitive tasks that only partially tap into specific hippocampal function or integrity (Griebler et al., 2022). There is a need to incorporate cognitive tasks that more directly engage and challenge the integrity of important age- susceptible episodic memory circuits to better ascertain the relationship between acute aerobic exercise and hippocampal function in older adults.

One such cognitive task is the Mnemonic Similarity Task (MST), which behaviorally has been shown to engage hippocampal circuits and integrity by placing high demands on pattern separation. During the MST participants are asked to view colored images of everyday objects and then to determine whether the images they view are new, similar, or old compared to previously encoded images. The focus of the task is on quantifying how well participants can accurately distinguish between the previously viewed (old) stimuli and newly presented but visually similar stimuli. The new stimuli, which vary in their degree of similarity to the old items, are termed 'lures' (Lacy et al., 2011). The Lure Discrimination Index (LDI) is a measure from the MST that represents the degree to which participants can successfully discriminate memories of highly similar old and new items. The LDI is the quantitative measure that operationally defines mnemonic discrimination capacity and has been strongly linked to hippocampal function (Stark, Kirwan, & Stark 2019). Episodic memory encompasses the ability to encode, store, and retrieve unique facts or events in our life and is one of the most studied subdomains of memory as it is often the first process to deteriorate in both normal and pathological aging (Harvey 2019; Tromp et al., 2015). Meanwhile, pattern separation, the process of reducing interference among memories, is thought to be a computation that supports episodic memory and is believed to be facilitated by the dentate gyrus (DG), a subfield of the hippocampus (McClelland, McNaughton, & O'Reilly 1995; Yassa & Stark 2011). Furthermore, the ability to accurately perform mnemonic discrimination and distinguish between similar experiences and event related memories is an important aspect of interacting with the world and functioning independently.

Mnemonic discrimination performance may be a useful marker of hippocampal function in older adults because the ability to behaviorally separate similar stimuli often declines earlier and more substantially during the aging process than other cognitive processes (Stark et al., 2015; Stark & Stark 2017; Voss et al., 2019). Furthermore, age-related deterioration in mnemonic discrimination performance has been strongly linked to deterioration of hippocampal subfield specific microstructure and function, particularly within the DG (Berron et al., 2016; Lacy et al., 2011; Yassa et al., 2011). One hypothesis for this age-related deterioration is due to reduced neuroplasticity within the DG (Nakashiba et al., 2012), as studies that directly stimulate neurogenesis within the DG show specific improvements in pattern separation performance (Sahay et al., 2011).

Voluntary chronic exercise is known to reliably stimulate hippocampal neurogenesis. Animal studies have found regular exercise enhances neural plasticity, particularly within the DG of rats (Van Praag,Kempermann,and Gage 1999), and can counteract age-related reductions in neural plasticity (Van Praag et al., 2005; Siette et al., 2013) and pattern separation performance (Bolz, Heigele, and Bischofberger 2015; Creer et al. 2010). In humans, exercise training is associated with increased DG perfusion (Pereira et al., 2007), DG volume (Frodl et al., 2019; Nauer et al., 2019), and better mnemonic discrimination performance (Déry et al., 2013; Heisz et al., 2017). While most studies focusing on the relationship between exercise and mnemonic discrimination performance have been conducted in younger college-aged adults, Bullock et al. (2018) found a relationship between higher cardiorespiratory fitness and LDI across the lifespan and Kovacevic et al. (2019) found that a 3 month exercise training program improved LDI scores in older adults. While a growing body of research indicates that maintaining and improving aerobic fitness may benefit mnemonic discrimination and hippocampal function, less is known about the effects of a single session of exercise on hippocampal function in older adults.

Several recent studies suggest a single short bout of light to moderate-intensity aerobic exercise can benefit mnemonic discrimination and DG function in younger adults. Suwabe et al. (2017) found that 10 minutes of moderate-intensity aerobic exercise immediately improved the discrimination of high-interference memories during the MST in 21 younger adults, but there were no benefits for traditional object recognition. Suwabe et al. (2018) similarly found 10 minutes of low to moderate-intensity aerobic exercise led to improvements on moderate and high-interference memories, but not object recognition, and led to an increase in CA3/DG activity and connectivity with several cortical regions (left angular gyrus, left fusiform gyrus, and left perirhinal cortex) in 16 younger adults. Finally, Bernstein et al. (2019) found that 30 minutes of moderate-intensity aerobic exercise improved LDI in young to middle-aged adults with low depressive symptoms. Importantly, all three studies only tested mnemonic discrimination after the exercise intervention, and all three focused on young to middle-aged adults. Far fewer studies have tested the acute effects of exercise on memory in older adults (Roig et al., 2013), which is surprising given older adults are more likely to experience memory deterioration and, therefore, may experience greater or differential benefits from acute exercise than younger adults (Chang et al., 2012; Etnier, Vance, & Ueno 2021; Griebler et al., 2022).

Two studies have explored the relationship between acute exercise and episodic memory in older adults. Segal et al. (2012) found that 6 minutes of moderate-intensity aerobic exercise increased the number of words recalled on the Rey Auditory Verbal Learning Task (RAVLT) in healthy older adults (Segal, Cotman, & Cahill 2012). In addition, Etnier et al. (2021) recently showed that 20 minutes of moderate-intensity aerobic exercise led to better word recall on the RAVLT in healthy older adults. It is important to note however, that both studies incorporated post intervention only study designs, which permits comparisons between the exercise and rest conditions, but does not provide measures of change in memory performance from pre- to post-condition. Additionally, these two previous studies measured episodic memory with the RAVLT, which also involves language processing and verbal learning (Schoenberg et al., 2006). Meanwhile, the MST is a modified object recognition task and the LDI measure is a more sensitive and specific proxy of hippocampal function and aging than RAVLT scores due to its more robust demand on mnemonic discrimination (Holden & Gilbert 2012; Stark et al., 2013, 2019). Therefore, understanding the effects of acute exercise on mnemonic discrimination performance via the MST in older adults, while incorporating a pre- and post-exercise study design could better explain the relationship between an acute bout of exercise and hippocampal function and integrity.

The purpose of this study was to determine the effects of an acute bout of moderate-intensity aerobic exercise on mnemonic discrimination performance (measured via LDI on the MST) in healthy older adults. Based on previous studies reporting on the effects of acute aerobic exercise on LDI in younger adults (Bernstein & Mcnally 2019; Suwabe et al., 2017, 2018) and previous studies suggesting the benefits of acute exercise for memory may be even more pronounced in older adults (Chang et al., 2012; Etnier et al., 2021; Roig et al., 2013), we hypothesized that acute aerobic exercise would lead to higher LDI scores compared to a seated rest control condition. However, given previous studies focusing on MST performance have only employed or reported post-intervention results, we predict that there will be an interactive effect for mnemonic discrimination from pre- to post-intervention between the two conditions, but do not propose a specific directional hypothesis.

Methods

Participants

Forty-one physically active older adults (ages, 60-89 years) were recruited from the local community to participate in the study in accordance with the Helsinki Declaration. Participants were excluded if they reported a history of stroke, diabetes, untreated high blood pressure, neurological disease, major psychiatric disorder, had any contraindications to exercising on a bike, or were less physically active (less than 3 days/week of moderate intensity physical activity). Six participants dropped out before completing the study, leading to a final sample of 35. All participants completed a baseline session, a rest session, and an exercise session (order of Rest vs. Exercise counterbalanced across participants; see **Figure 1)**.

[INSERT FIGURE 1 HERE]

Submaximal Exercise Stress Test

Participants performed a submaximal stress test on a cycle ergometer (Corival, Lode, Netherlands) and respiratory gases were monitored via open-circuit spirometry (True One 2400 integrated metabolic system). Briefly, a staged ramp protocol (Cress and Meyer 2003) was employed where, following a two-minute warm up at 25W, an initial 30W resistance was set and increased by 10W/min until termination criteria was reached. Throughout the test heart rate (Polar H9, Polar) and measures of ventilation including rate of oxygen (O2) consumption, rate of carbon dioxide (CO2) production, and the respiratory exchange ratio (RER; CO2 production/O2 consumption) were collected, while the ratings of perceived exertion (RPE; 6-20 scale administered with instructions consistent with (Borg 1982; Cook et al., 1997)) scale was used to monitor subjective effort every minute. Tests were terminated upon attainment of 85% of participant's age predicted maximal heart rate response (220-Age), participant's request, or observations of exercise contraindications.

Mnemonic Similarity Task (MST)

The MST (Stark et al., 2013) was performed on a computer at five different time points and consists of an encoding and retrieval phase. During the encoding phase participants were shown 128 colored images of everyday objects, one at a time, for 2.5 s each (.5 s Interstimulus Interval) and then asked to indicate whether the object was an “indoor” or “outdoor” item. Immediately following the encoding phase, participants were shown a short 2-minute video that provided instructions for the retrieval phase. Participants then immediately performed the retrieval phase in which they were shown 192 colored images one at a time and were asked to identify whether the items were “old”, “similar”, or “new” with a button press. Of the 192 items, 64 were repeats from the encoding phase (targets), 64 were similar but not identical to an image in the encoding phase (lures), and 64 were new images (foils). Trial types were presented randomly and separate stimulus sets were used for each test (Set 1 for the practice condition and Sets 2-5 counterbalanced across conditions). A total of 5 sets were used, with each set being equivalent in terms of the mnemonic similarity of their lures. Specifically, each lure image varied in its degree of similarity and was previously empirically ranked by assessing the false alarm rates (% old response) in a separate population (Lacy et al., 2011). These lures were then divided into 5 lure bins based on false alarm rates and each set was given an equal number of lures for each bin (Stark et al. 2013). Given our sample consisted of older adults, we implemented the self-paced version of the MST in which participants were shown an image for 2 s, after which time the screen went blank, and then the program waited for a button response before continuing (Stark et al., 2015). Two primary measures were obtained from the MST. The first was a traditional object recognition memory measure which was calculated as the rate of “Old” responses to repeats, minus “Old” responses to foils (Old | Target – Old | Foil) to account for response bias. The second measure was LDI, a measure of mnemonic discrimination, which was calculated as the rate of “Similar” responses to Lures minus “Similar” responses to new objects (Similar | Lure – Similar | foil) to again control for response bias.

Baseline Testing

Prior to the two experimental day visits, participants attended the baseline testing session. Upon arrival, participants provided written informed consent approved by Institutional Review Board. They then completed the Mini-Mental State Examination (MMSE), a 30-point questionnaire used to screen for global cognitive impairment, and demographic and baseline questionnaires to determine health history, physical activity (Stanford 7-day Physical Activity Recall questionnaire; (Sallis et al., 1985)), anxiety symptoms (Geriatric Anxiety Scale; (Segal et al., 2010)), and depression symptoms (Geriatric Depression Scale; (Yesavage et al., 1983)). Finally, participants performed Set 1 of the MST to allow for familiarization with the task and to minimize practice effects during the following two experimental visits (Stark et al., 2015).

Exercise and Rest Conditions

At least 48 hours after the baseline testing day, all participants underwent counterbalanced control (seated rest) and exercise conditions on separate days, with each participant completing both experimental visits at the same time in the morning each day. Participants were asked to refrain from performing moderate to vigorous physical activities within 24 hours of testing, to eat a consistent breakfast, and to refrain from consuming coffee the morning of testing. All participants verbally confirmed that they followed the provided instructions at the beginning of each visit. Upon arrival participants completed the MST (Sets (2-5) and condition order (Exercise or Rest first) were counterbalanced across participants). Then participants completed either 20-minutes of moderate intensity aerobic exercise or 30 minutes of seated rest. During both the exercise and rest condition participants' heart rate (HR), RPE, and subjective valence (pleasantness) and arousal ratings (Self Assessment

Manikin (SAM) (Bradley and Lang 1994)) were taken every 5 minutes. For the moderate intensity aerobic exercise condition, participants warmed up for the first 5 minutes and cooled down for the last 5 minutes of the 30 minute session. During the middle 20 minutes of the moderate intensity exercise session participants were instructed to exercise at a subjective rating of perceived exertion of 13 to 15 on the Borg 6-20 RPE scale (associated with a verbal anchor of “somewhat hard” to “hard”) and were permitted to adjust the resistance on the cycle ergometer in order to maintain a consistent relative moderate intensity. After a 5-minute seated cooldown period, participants completed a different set of the MST.

Statistical Analysis

As a manipulation check, paired t-tests were conducted to determine differences in HR, RPE, valence, and arousal between the exercise and rest conditions. First, we looked at the relationship between age and pre-intervention LDI and object recognition performance using a linear mixed-effects model while controlling for gender. To determine the effects of acute exercise on memory performance, we next compared the change in object recognition and LDI performance between the two intervention conditions with a linear mixed-effects model in which participant ID was a random effect and Condition (exercise vs rest) by Time (pre vs post) was modeled as a fixed interaction effect. Main effects of Condition and Time were further reported for both object recognition and LDI scores. To control for any variance related to the age of the participant and order of conditions, Order and Age were included in the model as fixed effects. To compare our findings to previous studies using only post-intervention designs and to further determine the effects on object recognition and LDI performance, we performed a post-intervention only analysis with Order, Age, and Condition modeled as fixed effects and participant ID as a random effect. Finally, to compare our results to previous studies in younger (Suwabe et al., 2018) and older adults (Segal et al., 2012), we conducted a post-hoc analysis to determine whether exercise-induced differences (Exercise minus Rest) in arousal levels were associated with exercise-induced differences (Exercise minus Rest) in post-intervention LDI scores using a Pearson correlation. To accomplish this, we ran a Pearson correlation on differences in arousal scores between the exercise and rest condition with differences in post condition LDI scores between exercise and rest. Statistical significance was set to an a priori threshold of $p<0.05$. All statistical analyses were performed using the R 4.0.1 statistical package.

Results

Participants

Of the 35 participants who completed all study protocols, four participants (2 males and 2 females) were excluded from further analysis due to exceptionally poor performance (< 50%) on MST's traditional object recognition memory component and one additional (male) participant was excluded due to a failure to use the "similar" response button at least ten times. These criteria have been similarly employed to remove participants that were not following task instructions (Kolarik,Stark,and Stark 2020). A final sample size of 30 participants were included in the analyses (see **Table 1**).

"Participants were physically active, with an average 7 day metabolic equivalent (MET) of 56.5 hours and with all participants getting at least 8.3 MET hours (consistent with physical activity guidelines of 150 minutes of moderate intensity physical activity per week (Kaminsky & Montoye 2014)). Additionally, participants were cognitively healthy (MMSE>26) and did not have major depressive (GDS<12) or anxiety (GAS<22) symptoms." (Page 12/13)

[INSERT TABLE 1 HERE]

Age and Baseline Behavioral Performance

While controlling for gender, we found that pre-intervention LDI scores (F(1,30)=5.08, p=.032), but not object recognition scores (F(1,30)=0.684, p=.415), were negatively associated with age.

Experimental Manipulation Check

As expected, HR (t(59)=22.21, p<.001), RPE (t(59)=39.20, p<.001), and arousal (t(59)=-5.82, p<.001) were significantly higher during the exercise condition compared to the seated rest condition, see **Table 2**. There were no significant differences in valence (t(59)=-0.37, p=.709) values between conditions.

[INSERT TABLE 2 HERE]

Time by Condition Analysis

While controlling for the Order and participant Age, the interaction effect of Time by Condition on object recognition performance was not significant (F(1,90)=1.32, p=.254, η^2=.01). Furthermore, there was no significant main effect of condition (F(90,1)=537. ,p =.770), but there was a significant main effect of Time with participants on average performing better post-intervention (F(1,90)=1.32, p=.004, η^2=.09). Additionally, while there was no difference in pre-exercise vs rest (t(93)=0.23, p=.992) or for post-exercise vs rest object recognition performance (t(93)=-.13, p=.561), there was a significant increase in object recognition performance from pre- to post-exercise (t(93)=2.88, p=.025) (**Figure 2**). With respect to LDI performance, there was a significant main effect of Time (F(1,90)=4.20, p=.04, η^2=.04), but not Condition (F(1,90)=2.17, p=.144), with participants on average performing worse post-intervention compared to pre-intervention. Furthermore, there was a significant interaction effect of Time by Condition on LDI performance (F(1,90)=6.65, p=.012 η^2=.07). Specifically, while pre-rest LDI was not significantly different from pre-exercise LDI (t(93)=0.77, p=.868), there was a significant decline in LDI from pre-rest to post-rest (t(93)=-3.22, p=.010). Additionally, there was no significant decline in LDI from pre-exercise to post-exercise (t(93)=0.37., p=.983) (**Figure 2**).

[INSERT FIGURE 2 HERE]

Post Intervention Analysis

While controlling for condition Order and participant Age, the post-intervention analysis showed no significant effect of Condition on post-condition object recognition performance (F(1,30)=1.83, p=.186, η^2=.06). Meanwhile, LDI was significantly higher following exercise compared to rest (F(1,30)=8.29, p<.001, η^2=.22), see **Figure 3**.

Arousal and Post Condition Behavioral Performance

We found a significant increase in self-rated arousal in the last 10 minutes of the exercise condition compared to the rest condition (t(59) = -5.88, p-value <.001), see **Table 2**. However, exercise-induced differences in post-intervention LDI scores were not associated with exercise-induced differences in self-rated arousal levels (r=.044, p=.817).

Discussion

The primary purpose of this study was to determine if moderate-intensity aerobic exercise alters mnemonic discrimination performance in healthy older adults. In a group of 30 healthy older adults, we found that a 30-minute session of moderate-intensity aerobic exercise did not have a significant interactive effect or main effect of Condition on object recognition. However, acute exercise led to better maintenance of LDI scores from pre- to post-condition performance compared to the seated rest condition. Exercise also resulted in a significantly higher post-exercise LDI score compared to after seated rest. Additionally, we found that pre-intervention LDI scores were negatively related to age. These results suggest moderate-intensity aerobic exercise may promote better hippocampal specific function via reduced interference and better mnemonic discrimination of similar objects in healthy older adults.

Age and Mnemonic Discrimination

LDI scores on the two pre-intervention tasks were negatively related to age which is consistent with numerous previous studies (Stark et al., 2013, 2015; Stark & Stark 2017), showing that aging is associated with poorer discrimination of similar objects on the MST task, but not with object recognition. We further explored this relationship and found that age was negatively associated with correctly identifying lure images and was positively associated with incorrectly identifying a lure image as a repeated image, suggesting a worsening ability to discriminate images with increased age and indicating a shift in older age from behavioral pattern separation to pattern completion (Nauer, Schon, & Stern 2020). Critically, there was no significant relationship between age and object recognition performance (i.e., identifying a repeated image correctly). This is consistent with widely reported age-specific effects on mnemonic discrimination that cannot be attributed to age-related differences in object recognition memory (Holden et al., 2013; Stark et al., 2013).

These behavioral findings corroborate previous computational and animal findings. Specifically, computational and animal models of pattern separation propose that newborn neurons within the DG of the hippocampus are critical for distinguishing between highly similar information and storing the information as separate and distinct representations (Kesner & Rolls 2015; Marr 1971; Rolls & Kesner 2006). Furthermore, aging rodents (Kuhn, Dickinson-Anson, & Gage 1996) and potentially humans (Kempermann et al., 2018; Moreno-Jiménez et al., 2019) appear to exhibit fewer newborn neurons within the DG. Meanwhile, reductions in newborn DG neurons are directly associated with poorer pattern separation performance in rodents (Creer et al., 2010; Sahay et al., 2011). In humans, it is not possible to directly measure DG neurogenesis, and thus, we can not definitively determine the underlying mechanisms for this relationship. Additionally, a recent study suggests that LDI deficits are significantly associated with deficits in visual perception (Davidson et al., 2019) and thus, age related deficits in visual perception could be partially contributing to our finding of an age and behavior relationship.

Acute Exercise and Object Recognition Performance

Interestingly, while we found an improvement in object recognition from pre to post-intervention, we found no interactive effect or main effect of condition for object recognition performance. This suggests that acute exercise does not significantly affect simple object recognition performance for healthy older adults when compared to seated rest. Notably, the MST's measure of object recognition provides a valuable comparison to mnemonic descrimination, as object recognition is considered to be less heavily implicated in hippocampal function (Stark et al., 2019), given it is relatively robust to aging and in those who have sustained hippocampal damage (Kirwan et al., 2012; Stark et al., 2013). This finding aligns with previous acute exercise studies that have examined mnemonic discrimination performance in younger adults. For example, Suwabe et al. (2017, 2018) reported improvements in mnemonic discrimination performance but not object recognition. Furthermore, Bernstein et al. (2019) did not report a significant effect of acute moderate-intensity aerobic exercise on object recognition performance compared to a stretching condition. Taken together, this suggests the effects of acute aerobic exercise on memory and hippocampal function, at least for visual objects, may be somewhat specific to mnemonic discrimination performance.

Mnemonic Discrimination Interaction Effect

We found LDI scores were better maintained following the exercise condition but decreased after rest. Furthermore, we found a main effect of time in which participants had worse LDI scores during the post-intervention test than the pre-intervention test, likely predominantly driven by the rest condition. While decreased or maintained performance may seem counterintuitive to the expected increase in performance after exercise (or due to practice), this finding suggests participants were further challenged when performing the task for a second time in the post-intervention task, which required disentangling similar images in the context of extra interference induced by the previously viewed images from the pre-intervention task. Notably, participants performed different versions of the task at each time point with entirely different images that did not overlap with each other (Stark et al., 2019). Previous work by Stark and colleagues (2015) has shown that the MST can be used repeatedly in the same person to determine changes in performance over time. However, these previous studies performed repeat tests using different temporal spacings (either immediately or days between tests) and often compared standard vs. overt instructions during the encoding phase, to try to determine the effects of repeated testing on performance (Kolarik et al., 2020; Stark et al., 2015). However, previous work has not compared repeated task performance within the moderate time window we employed (approximately 35 minutes). Interestingly, however, we had numerous cases in which participants provided unsolicited feedback after the experimental session had ended that they found the post-condition version of the task more challenging than the pre-condition version due to interfering memories of the pre-condition task images. While the main effect of reduced LDI scores over time might suggest that reductions in post-condition task performance could be due to some level of interference, future studies will need to specifically test whether repeated testing over short time intervals negatively affects LDI performance.

Nevertheless, we did find an interaction effect in which participants' LDI scores were maintained from pre to post-test for the exercise but not the rest condition. Previous acute exercise studies focusing on the MST and mnemonic discrimination have thus far only performed post-intervention study designs (Suwabe et al., 2017, 2018) or failed to report pre to post-intervention results (Bernstein & Mcnally 2019). Additionally, while several previous studies have found that the effects of acute exercise were dependent on the degree of lure similarity in healthy younger adults (Suwabe et al., 2017, 2018), we did not find that the degree of lure similarity interacted significantly with treatment condition in our older adult sample (see Supplemental Table 1 and Supplementary Figure 1). Interestingly, previous work by Segal et al. (2012) found 6 minutes of walking after viewing a set of emotional images led to elevated endogenous norepinephrine and better recall of emotional image details in older adults, suggesting exercise may retrogradely enhance memory consolidation of images. Concerning our current findings, this could mean participants who performed exercise between the two sets of MST tasks may remember more details of previously depicted images, and thus, be more resistant to interference from the previously viewed images during the post-intervention test phase.

In support of this hypothesis, Etnier et al. (2021) recently tested the effects of acute exercise timing on RAVLT performance in healthy older adults. They found 20 minutes of moderate-intensity aerobic exercise improved the number of words recalled in healthy middle-aged and older adults. Specifically, they found that an exercise prior condition led to the greatest improvement in words recalled and that this improvement was specific to the short-term (Trial 1), learning portion (Trials 1-5), and the retroactive interference portion (Trial 7) of the RAVLT, but not for the proactive interference trial (Trial 6) (Etnier et al., 2021). This suggests that while acute aerobic exercise may not affect verbal recall on an interference list, it did lead to significantly better post interference recall, and suggests that aerobic exercise might help overcome interference issues when performing memory tasks. However, it is also important to note that there was not a significant improvement in LDI from pre to post exercise condition. Given our control condition consisted of 30 minutes of quite seated rest, which has the potential to elicit negative emotional and cognitive effects, could be leading to a reduction in LDI. Yet, there were no differences in subjective measures of pleasantness (valence) between the exercise and rest condition and differences in arousal between the two conditions were not related to differences in LDI scores. Thus, our data do not support the view that unpleasant emotion or boredom of the rest condition explains the memory performance differences between the conditions. Nevertheless, future studies should consider implementing more active or engaging control conditions to better determine if benefits in MST performance are specific to a single session of exercise.

Post Exercise Improvements

Previous studies looking at the effects of acute aerobic exercise on mnemonic discrimination in younger adults have only reported post-condition effects. We took the same approach and found that following the 20 minutes of moderate-intensity aerobic exercise, older adults had significantly higher LDI scores compared to following the seated rest condition. This finding is in line with three previous studies conducted in healthy younger adults, all of which found 10-30 minutes of light to moderate-intensity aerobic exercise on a cycle ergometer led to better LDI scores via improvements in the discrimination of mnemonically similar objects (Bernstein & Mcnally 2019; Suwabe et al., 2017, 2018). Furthermore, previous work has shown an inverted-U-shaped dose-response relationship, where moderate-intensity aerobic exercise between 15-30 minutes appears to be optimal for eliciting benefits in complex cognitive processes, including memory (Chang et al., 2012; Hacker et al., 2020). It is important to note that acute exercise paradigms are ideally suited to understand the temporal interactions between exercise and phases of memory. In particular, looking at the effects of exercise before the encoding phase and the incorporation of retrieval shortly after suggests these effects may be more specific to encoding mechanisms (Loprinzi et al., 2021). However, to truly disentangle these effects from storage/consolidation, a study that specifically compares pre-encoding vs post encoding interventions (between the encoding and test phase) would be needed. Nevertheless, these potential benefits are relevant given that numerous previous studies conducted in college-aged adults have shown that exercising shortly before, but not during or after a memory task leads to improvements in both short and long-term memory (Firth et al., 2018; Labban & Etnier 2011; Sng, Frith, & Loprinzi 2018). Etnier et al. (2021) similarly found improvements in short and long-term memory performance on the RAVLT in healthy older adults when employing a similar length (20 minutes) and intensity (moderate) of acute aerobic exercise in middle and older-aged adults. Interestingly, we found a relatively large positive effect of exercise on post-condition LDI scores (η^2=.22), which is consistent with effects reported in older adults by Etnier et al. (2021). Unfortunately, previous acute exercise studies on mnemonic discrimination in younger adults did not report effect sizes for direct comparisons (Bernstein & Mcnally 2019; Suwabe et al., 2017, 2018). However, our finding of a relatively large effect size supports our previous hypothesis, which may relate the premise that older adults have more room to benefit from behavioral interventions given they are theorized to have less cognitive reserve, and younger adults have greater potential for performance ceiling effects (Chang et al., 2012; Etnier et al., 2021; Loprinzi et al., 2021; Reuter-Lorenz &

Park 2014). However, since our study includes older adults from a relatively narrow age range, future studies are needed to determine if age moderates this effect.

Strengths and limitations

Our study is the first to show, in healthy older adults, effects of moderate-intensity aerobic exercise on a highly hippocampal specific and age susceptible mnemonic discrimination task. Furthermore, this is the first study to measure and compare MST performance before and after an exercise and control intervention, providing more rigorous insight into the effects of aerobic exercise on mnemonic discrimination. By accounting for baseline LDI scores, we were able to determine how participants' performance changed over time. However, our study sample was predominantly white, well-educated, and female, making it challenging to generalize at the population level. Furthermore, our volunteers were all physically active individuals, who may respond differently to a single exercise session compared to more sedentary individuals.

Conclusions

In conclusion, this is the first study to show effects of a single 30-minute session of moderate-intensity aerobic exercise on mnemonic discrimination in healthy older adults relative to rest. We found exercise led to better discrimination of similar objects and better maintenance of mnemonic discrimination capacity than following the seated rest control condition. Furthermore, and consistent with the literature, we found that baseline mnemonic discrimination was negatively related to age in our sample. Our results suggest a single session of moderate-intensity aerobic exercise may provide benefits for hippocampal-specific memory function and thus, provide evidence for exercise as a safe and easy-to-implement intervention to maintain healthy cognitive function.

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References

American College of Sports Medicine. 2013. *ACSM's Guidelines for Exercise Testing and Prescription*. 8th ed. edited by Lippincott Williams & Wilkins.

Bernstein, Emily E., and Richard J. Mcnally. 2019. *Examining the Effects of Exercise on Pattern Separation and the Moderating Effects of Mood Symptoms*. Vol. 50. doi: 10.1016/j.beth.2018.09.007.

Berron, David, Hartmut Schütze, Anne Maass, Arturo Cardenas-Blanco, Hugo J. Kuijf, Dharshan Kumaran, and Emrah Düzel. 2016. "Strong Evidence for Pattern Separation in Human Dentate Gyrus." *Journal of Neuroscience* 36(29):7569–79. doi: 10.1523/JNEUROSCI.0518-16.2016.

Bolz, Leoni, Stefanie Heigele, and Josef Bischofberger. 2015. "Running Improves Pattern Separation during Novel Object Recognition." *Brain Plasticity (Amsterdam, Netherlands)* 1(1):129–41. doi: 10.3233/BPL-150010.

Borg, G. A. 1982. "Psychophysical Bases of Perceived Exertion." *Medicine and Science in Sports and Exercise* 14(5):377–81.

Callow, Daniel D., Junyeon Won, Alfonso J. Alfini, Jeremy J. Purcell, Lauren R. Weiss, Wang Zhan, and J. Carson Smith. 2021. *Microstructural Plasticity in the Hippocampus of Healthy*

Older Adults After Acute Exercise. Vol. 53. Lippincott Williams and Wilkins.

Chang, Y. K., J. D. Labban, J. I. Gapin, and J. L. Etnier. 2012. “The Effects of Acute Exercise on Cognitive Performance: A Meta-Analysis.” *Brain Research* 1453:87–101. doi: 10.1016/j.brainres.2012.02.068.

Cook, Dane B., Patrick J. O’Connor, Steven A. Eubanks, Jerome C. Smith, and Ming Lee. 1997. “Naturally Occurring Muscle Pain during Exercise: Assessment and Experimental Evidence.” *Medicine and Science in Sports and Exercise* 29(8):999–1012. doi: 10.1097/00005768-199708000-00004.

Creer, David J., Carola Romberg, Lisa M. Saksida, Henriette Van Praag, and Timothy J. Bussey. 2010. “Running Enhances Spatial Pattern Separation in Mice.” *Proceedings of the National Academy of Sciences of the United States of America* 107(5):2367–72. doi: 10.1073/pnas.0911725107.

Cress, M. Elaine, and Mary Meyer. 2003. “Maximal Voluntary and Functional Performance Needed for Independence in Adults Aged 65 to 97 Years.” *Physical Therapy* 83(1):37–48. doi: 10.1093/PTJ/83.1.37.

Davidson, Patrick S. R., Petar Vidjen, Sara Trincao-Batra, Charles A. Collin, and Angela Gutchess. 2019. “Older Adults’ Lure Discrimination Difficulties on the Mnemonic Similarity Task Are Significantly Correlated With Their Visual Perception.” *The Journals of Gerontology. Series B, Psychological Sciences and Social Sciences* 74(8):1298–1307. doi: 10.1093/GERONB/GBY130.

Déry, Nicolas, Malcolm Pilgrim, Martin Gibala, Jenna Gillen, J. Martin Wojtowicz, Glenda Macqueen, and Suzanna Becker. 2013. “Adult Hippocampal Neurogenesis Reduces Memory Interference in Humans: Opposing Effects of Aerobic Exercise and Depression.”

Frontiers in Neuroscience 7:66. doi: 10.3389/FNINS.2013.00066.

El-Sayes, Jenin, Diana Harasym, Claudia V. Turco, Mitchell B. Locke, and Aimee J. Nelson. 2019. “Exercise-Induced Neuroplasticity: A Mechanistic Model and Prospects for Promoting Plasticity.” *Neuroscientist* 25(1):65–85.

Etnier, Jennifer L., Jarod C. Vance, and Aiko Ueno. 2021. “Effects of Acute Exercise on Memory Performance in Middle-Aged and Older Adults.” *Journal of Aging and Physical Activity* 29(5):753–60. doi: 10.1123/JAPA.2020-0208.

Firth, Joseph, Brendon Stubbs, Davy Vancampfort, Felipe Schuch, Jim Lagopoulos, Simon Rosenbaum, and Philip B. Ward. 2018. “Effect of Aerobic Exercise on Hippocampal Volume in Humans: A Systematic Review and Meta-Analysis.” *NeuroImage*. doi: 10.1016/j.neuroimage.2017.11.007.

Frodl, Thomas, Katharina Strehl, Angela Carballedo, Leonardo Tozzi, Myles Doyle, Francesco Amico, … Veronica O’Keane. 2019. “Aerobic Exercise Increases Hippocampal Subfield Volumes in Younger Adults and Prevents Volume Decline in the Elderly.” *Brain Imaging and Behavior* 1–11. doi: 10.1007/s11682-019-00088-6.

Griebler, Nathália, Nadja Schröder, Milena Artifon, Michele Frigotto, and Caroline Pietta-Dias. 2022. “The Effects of Acute Exercise on Memory of Cognitively Healthy Seniors: A Systematic Review.” *Archives of Gerontology and Geriatrics* 99:104583. doi: 10.1016/J.ARCHGER.2021.104583.

Hacker, Sebastian, Winfried Banzer, Lutz Vogt, and Tobias Engeroff. 2020. “Acute Effects of Aerobic Exercise on Cognitive Attention and Memory Performance: An Investigation on Duration-Based Dose-Response Relations and the Impact of Increased Arousal Levels.” *Journal of Clinical Medicine* 9(5):1380. doi: 10.3390/jcm9051380.

Harvey, Philip D. 2019. “Domains of Cognition and Their Assessment.” *Dialogues in Clinical Neuroscience* 21(3):227. doi: 10.31887/DCNS.2019.21.3/PHARVEY.

Heisz, Jennifer J., Ilana B. Clark, Katija Bonin, Emily M. Paolucci, Bernadeta Michalski, Suzanna Becker, and Margaret Fahnestock. 2017. “The Effects of Physical Exercise and Cognitive Training on Memory and Neurotrophic Factors.” *Journal of Cognitive Neuroscience* 29(11):1895–1907. doi: 10.1162/jocn_a_01164.

Hillman, Charles H., Kirk I. Erickson, and Arthur F. Kramer. 2008. “Be Smart, Exercise Your Heart: Exercise Effects on Brain and Cognition.” *Nature Reviews Neuroscience* 9(1):58–65. doi: 10.1038/nrn2298.

Holden, Heather M., and Paul E. Gilbert. 2012. “Less Efficient Pattern Separation May Contribute to Age-Related Spatial Memory Deficits.” *Frontiers in Aging Neuroscience* 4(MAY):1–6.

Holden, Heather M., Chelsea Toner, Eva Pirogovsky, C. Brock Kirwan, and Paul E. Gilbert. 2013. “Visual Object Pattern Separation Varies in Older Adults.” *Learning and Memory* 20(7):358–62. doi: 10.1101/lm.030171.112.

Huang, A. M., C. J. Jen, H. I. F. Chen, L. Yu, Y. M. Kuo, and H. I. F. Chen. 2006. “Compulsive Exercise Acutely Upregulates Rat Hippocampal Brain-Derived Neurotrophic Factor.” *J Neural Transm* 113:803–11. doi: 10.1007/s00702-005-0359-4.

Kaminsky, Leonard A., and Alexander H. K. Montoye. 2014. “Physical Activity and Health: What Is the Best Dose?” *Journal of the American Heart Association* 3(5). doi: 10.1161/JAHA.114.001430.

Kempermann, Gerd, Fred H. Gage, Ludwig Aigner, Hongjun Song, Maurice A. Curtis, Sandrine

Thuret, … Jonas Frisén. 2018. “Human Adult Neurogenesis: Evidence and Remaining Questions.” *Cell Stem Cell* 23(1).

Kesner, Raymond P., and Edmund T. Rolls. 2015. “A Computational Theory of Hippocampal Function, and Tests of the Theory: New Developments.” *Neuroscience and Biobehavioral Reviews* 48:92–147. doi: 10.1016/j.neubiorev.2014.11.009.

Kirwan, C. Brock, Andrew Hartshorn, Shauna M. Stark, Naomi J. Goodrich-Hunsaker, Ramona O. Hopkins, and Craig E. L. Stark. 2012. “Pattern Separation Deficits Following Damage to the Hippocampus.” *Neuropsychologia* 50(10):2408. doi: 10.1016/J.NEUROPSYCHOLOGIA.2012.06.011.

Kolarik, Branden S., Shauna M. Stark, and Craig E. L. Stark. 2020. “Enriching Hippocampal Memory Function in Older Adults Through Real-World Exploration.” *Frontiers in Aging Neuroscience* 0:158. doi: 10.3389/FNAGI.2020.00158.

Kuhn, H. Georg, Heather Dickinson-Anson, and Fred H. Gage. 1996. “Neurogenesis in the Dentate Gyrus of the Adult Rat: Age-Related Decrease of Neuronal Progenitor Proliferation.” *Journal of Neuroscience* 16(6):2027–33. doi: 10.1523/JNEUROSCI.16-06-02027.1996.

Labban, Jeffrey D., and Jennifer L. Etnier. 2011. “Effects of Acute Exercise on Long-Term Memory.” *Research Quarterly for Exercise and Sport* 82(4):712–21. doi: 10.1080/02701367.2011.10599808.

Lacy, Joyce W., Michael A. Yassa, Shauna M. Stark, L. Tugan Muftuler, and Craig E. L. Stark. 2011. “Distinct Pattern Separation Related Transfer Functions in Human CA3/Dentate and CA1 Revealed Using Highresolution FMRI and Variable Mnemonic Similarity.” *Learning and Memory* 18(1):15–18. doi: 10.1101/lm.1971111.

Livingston, Gill, Jonathan Huntley, Andrew Sommerlad, David Ames, Clive Ballard, Sube Banerjee, … Naaheed Mukadam. 2020. "Dementia Prevention, Intervention, and Care: 2020 Report of the Lancet Commission." *The Lancet* 396(10248):413–46. doi: 10.1016/S0140-6736(20)30367-6.

Loprinzi, Paul D., Marc Roig, Jennifer L. Etnier, Phillip D. Tomporowski, and Michelle Voss. 2021. "Acute and Chronic Exercise Effects on Human Memory: What We Know and Where to Go from Here." *Journal of Clinical Medicine 2021, Vol. 10, Page 4812* 10(21):4812. doi: 10.3390/JCM10214812.

Marr, D. 1971. "Simple Memory: A Theory for Archicortex." *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences* 262(841):23–81. doi: 10.1098/rstb.1971.0078.

McClelland, James L., Bruce L. McNaughton, and Randall C. O'Reilly. 1995. "Why There Are Complementary Learning Systems in the Hippocampus and Neocortex: Insights from the Successes and Failures of Connectionist Models of Learning and Memory." *Psychological Review* 102(3):419–57. doi: 10.1037/0033-295X.102.3.419.

Moreno-Jiménez, Elena P., Miguel Flor-García, Julia Terreros-Roncal, Alberto Rábano, Fabio Cafini, Noemí Pallas-Bazarra, … María Llorens-Martín. 2019. "Adult Hippocampal Neurogenesis Is Abundant in Neurologically Healthy Subjects and Drops Sharply in Patients with Alzheimer's Disease." *Nature Medicine* 25(4).

Nakashiba, Toshiaki, Jesse D. Cushman, Kenneth A. Pelkey, Sophie Renaudineau, Derek L. Buhl, Thomas J. McHugh, … Susumu Tonegawa. 2012. "Young Dentate Granule Cells Mediate Pattern Separation, Whereas Old Granule Cells Facilitate Pattern Completion." *Cell* 149(1):188–201. doi: 10.1016/j.cell.2012.01.046.

Nauer, Rachel K., Matthew F. Dunne, Chantal E. Stern, Thomas W. Storer, and Karin Schon. 2019. “Improving Fitness Increases Dentate Gyrus/CA3 Volume in the Hippocampal Head and Enhances Memory in Young Adults.” *Hippocampus* hipo.23166. doi: 10.1002/hipo.23166.

Nauer, Rachel K., Karin Schon, and Chantal E. Stern. 2020. “Cardiorespiratory Fitness and Mnemonic Discrimination across the Adult Lifespan.” *Learning & Memory* 27(3):91–103. doi: 10.1101/lm.049197.118.

Pereira, Ana C., Dan E. Huddleston, Adam M. Brickman, Alexander A. Sosunov, Rene Hen, Guy M. McKhann, … Scott A. Small. 2007. “An in Vivo Correlate of Exercise-Induced Neurogenesis in the Adult Dentate Gyrus.” *Proceedings of the National Academy of Sciences of the United States of America* 104(13):5638–43. doi: 10.1073/pnas.0611721104.

Van Praag, Henriette, Gerd Kempermann, and Fred H. Gage. 1999. “Running Increases Cell Proliferation and Neurogenesis in the Adult Mouse Dentate Gyrus.” *Nature Neuroscience* 2(3):266–70. doi: 10.1038/6368.

Van Praag, Henriette, Tiffany Shubert, Chunmei Zhao, and Fred H. Gage. 2005. “Exercise Enhances Learning and Hippocampal Neurogenesis in Aged Mice.” *Journal of Neuroscience* 25(38):8680–85. doi: 10.1523/JNEUROSCI.1731-05.2005.

Reuter-Lorenz, Patricia A., and Denise C. Park. 2014. “How Does It STAC up? Revisiting the Scaffolding Theory of Aging and Cognition.” *Neuropsychology Review* 24(3):355–70. doi: 10.1007/s11065-014-9270-9.

Roig, Marc, Sasja Nordbrandt, Svend Sparre Geertsen, and Jens Bo Nielsen. 2013. “The Effects of Cardiovascular Exercise on Human Memory: A Review with Meta-Analysis.”

Neuroscience and Biobehavioral Reviews 37:1645–66. doi: 10.1016/j.neubiorev.2013.06.012.

Rolls, Edmund T., and Raymond P. Kesner. 2006. “A Computational Theory of Hippocampal Function, and Empirical Tests of the Theory.” *Progress in Neurobiology* 79(1):1–48. doi: 10.1016/j.pneurobio.2006.04.005.

Sahay, Amar, Kimberly N. Scobie, Alexis S. Hill, Colin M. O’Carroll, Mazen A. Kheirbek, Nesha S. Burghardt, … René Hen. 2011. “Increasing Adult Hippocampal Neurogenesis Is Sufficient to Improve Pattern Separation.” *Nature* 472(7344):466–70. doi: 10.1038/nature09817.

Sallis, James F., William L. Haskell, Peter D. Wood, Stephen P. Fortmann, Todd Rogers, Steven N. Blair, … Ralph S. Paffenbarger. 1985. “Physical Activity Assessment Methodology in the Five-City Project.” *American Journal of Epidemiology* 121(1):91–106. doi: 10.1093/oxfordjournals.aje.a113987.

Schoenberg, Mike R., Kyra A. Dawson, Kevin Duff, Doyle Patton, James G. Scott, and Russell L. Adams. 2006. “Test Performance and Classification Statistics for the Rey Auditory Verbal Learning Test in Selected Clinical Samples.” *Archives of Clinical Neuropsychology* 21(7):693–703. doi: 10.1016/J.ACN.2006.06.010.

Segal, Daniel L., Andrea June, Matthew Payne, Frederick L. Coolidge, and Brian Yochim. 2010. “Development and Initial Validation of a Self-Report Assessment Tool for Anxiety among Older Adults: The Geriatric Anxiety Scale.” *Journal of Anxiety Disorders* 24(7):709–14. doi: 10.1016/j.janxdis.2010.05.002.

Segal, Sabrina K., Carl W. Cotman, and Lawrence F. Cahill. 2012. “Exercise-Induced Noradrenergic Activation Enhances Memory Consolidation in Both Normal Aging and

Patients with Amnestic Mild Cognitive Impairment." *Journal of Alzheimer's Disease* 32(4):1011–18. doi: 10.3233/JAD-2012-121078.

Siette, Joyce, R. Frederick Westbrook, Carl Cotman, Kuldip Sidhu, Wanlin Zhu, Perminder Sachdev, and Michael J. Valenzuela. 2013. "Age-Specific Effects of Voluntary Exercise on Memory and the Older Brain." doi: 10.1016/j.biopsych.2012.05.034.

Sng, Eveleen, Emily Frith, and Paul D. Loprinzi. 2018. "Temporal Effects of Acute Walking Exercise on Learning and Memory Function." *American Journal of Health Promotion* 32(7):1518–25. doi: 10.1177/0890117117749476.

Soya, Hideaki, Toru Nakamura, Custer C. Deocaris, Akiyo Kimpara, Miho Iimura, Takahiko Fujikawa, … Takeshi Nishijima. 2007. "BDNF Induction with Mild Exercise in the Rat Hippocampus." doi: 10.1016/j.bbrc.2007.04.173.

Stark, Shauna M., C. Brock Kirwan, and Craig E. L. Stark. 2019. "Mnemonic Similarity Task: A Tool for Assessing Hippocampal Integrity." *Trends in Cognitive Sciences*. doi: 10.1016/j.tics.2019.08.003.

Stark, Shauna M., and Craig E. L. Stark. 2017. "Age-Related Deficits in the Mnemonic Similarity Task for Objects and Scenes." *Behavioural Brain Research* 333:109–17. doi: 10.1016/j.bbr.2017.06.049.

Stark, Shauna M., Rebecca Stevenson, Claudia Wu, Samantha Rutledge, and Craig E. L. Stark. 2015. "Stability of Age-Related Deficits in the Mnemonic Similarity Task Across Task Variations." *Behavioral Neuroscience* 129(3):257–68. doi: 10.1037/bne0000055.

Stark, Shauna M., Michael A. Yassa, Joyce W. Lacy, and Craig E. L. Stark. 2013. "A Task to Assess Behavioral Pattern Separation (BPS) in Humans: Data from Healthy Aging and

Mild Cognitive Impairment." *Neuropsychologia* 51(12):2442–49. doi: 10.1016/j.neuropsychologia.2012.12.014.

Suwabe, Kazuya, Kyeongho Byun, Kazuki Hyodo, Zachariah M. Reagh, Jared M. Roberts, Akira Matsushita, … Hideaki Soya. 2018. "Rapid Stimulation of Human Dentate Gyrus Function with Acute Mild Exercise." *Proceedings of the National Academy of Sciences* 201805668. doi: 10.1073/pnas.1805668115.

Suwabe, Kazuya, Kazuki Hyodo, Kyeongho Byun, Genta Ochi, Michael A. Yassa, and Hideaki Soya. 2017. "Acute Moderate Exercise Improves Mnemonic Discrimination in Young Adults." *Hippocampus* 27(3):229–34. doi: 10.1002/hipo.22695.

Tromp, D., A. Dufour, S. Lithfous, T. Pebayle, and O. Després. 2015. "Episodic Memory in Normal Aging and Alzheimer Disease: Insights from Imaging and Behavioral Studies." *Ageing Research Reviews* 24:232–62. doi: 10.1016/J.ARR.2015.08.006.

Venezia, A. C., E. Quinlan, and S. M. Roth. 2017. "A Single Bout of Exercise Increases Hippocampal *Bdnf* : Influence of Chronic Exercise and Noradrenaline." *Genes, Brain and Behavior* 16(8):800–811. doi: 10.1111/gbb.12394.

Voss, Michelle W., Carmen Soto, Seungwoo Yoo, Matthew Sodoma, Carmen Vivar, and Henriette van Praag. 2019. "Exercise and Hippocampal Memory Systems." *Trends in Cognitive Sciences* 23(4):318–33. doi: 10.1016/j.tics.2019.01.006.

Yassa, M. A., A. T. Mattfeld, S. M. Stark, and C. E. L. Stark. 2011. "Age-Related Memory Deficits Linked to Circuit-Specific Disruptions in the Hippocampus." *Proceedings of the National Academy of Sciences* 108(21):8873–78. doi: 10.1073/pnas.1101567108.

Yassa, Michael A., and Craig E. L. Stark. 2011. "Pattern Separation in the Hippocampus."

Trends in Neurosciences 34(10):515–25. doi: 10.1016/j.tins.2011.06.006.

Yesavage, JA, TL Brink, TL Rose, O. Lum, V. Huang, M. Adey, and VO Leirer. 1983. “Development and Validation of a Geriatric Depression Screening Scale: A Preliminary Report.” *Journal of Psychiatric Research* 37–49. doi: 10.1016/0022-3956(82)90033-4.

Tables

Table 1. Participant Demographic Information (n = 31).

		Total sample (n=31)
		Mean (SD)
Demographics		
	Age (years)	70.2 (6.1)
	Sex	23 Female, 8 Male
	Education (n,(%), ≥ Graduate School)	20 (67%)
Health		
	Height (cm)	166.6 (8.9)
	Weight (kg)	71.3 (14.1)
	BMI (kg/m^2)	25.7 (4.3)
	$HR_{resting}$ (bpm)	68.7 (10.9)
Cardiorespiratory Fitness and Leisure-Time Physical Activity		
	VO_{2peak} (kg/ml/min)	21.2 (6.1) [a]
	7-day Physical Activity Energy Expenditure (MET-hours/week)	56.5 (27.7) [b]
Cognitive Status, Depression, and Anxiety		
	MMSE	29.8 (.4) [c]
	Geriatric Depression Score	3.1 (4.6) [d]
	Geriatric Anxiety Score	4.6 (3.7) [e]

Notes: bpm = beats per minute; RHR = Resting Heart Rate; HR_{max} = Maximum Age predicted heart rate; MMSE = Mini Mental State Examination. kg/ml/min = kilogram per milliliter per minute. MET = ratio of working metabolic rate relative to energy at rest. 7-day Energy Expenditure = the total MET- hours completed in the last 7 day period. MET is a unit of energy expenditure relative to the resting metabolic rate. VO_{2peak} = Peak oxygen consumption estimated from submaximal exercise stress test. [a] American College of Sports Medicine 50th percentile for peak oxygen consumption of older adults aged 60+ is approximately 30 (male) & 27 (female). [b] American Heart Association physical activity guidelines suggest 8.3-16.66 MET-hours/week for significant health benefits. [c] MMSE scores below 27 indicate potential mild cognitive impairment. [d] Geriatric Depression Scores between 9-15 indicate moderate to severe depression symptoms. [e] Geriatric Anxiety Scores between 16-63 indicate moderate to severe anxiety symptoms.

Table 2. Experimental condition outcomes and manipulation check.

Measure	Mean (SD)		
	Rest	Exercise	p
HR (BPM)	65.6 (9.4)	117.4 (16.9)	**<.001**
RPE (Borg 6-20 scale)	6.5 (1.0)	13.53 (0.9)	**<.001**
Valence	2.5 (0.9)	2.4 (0.8)	.709
Arousal	3.0 (0.9)	3.7 (1.2)	**<.001**
Reaction Time (milliseconds)	1700 (449)	1687 (467)	.557

Notes: SD = Standard Deviation. Measures of HR = heart rate; BPM = beats per minute; RPE = rating of perceived exertion. Valence = subjective measure of valence; Arousal = subjective measure of arousal; All measures were averaged and compared over the final 10 minutes of the moderate intensity exercise session (minutes 15-25 of the experimental conditions). Reaction Time = the average response time (in milliseconds) that participants took for each response during the test phase of the MST. Average participant heart rate in the final 10 minutes of the exercise condition was approximately 78% (SD 11%) of age predicted maximal heart rate. This is consistent with a moderate to hard intensity rating based on ACSM guidelines (American College of Sports Medicine, 2013).

Supplementary Table 1: Interaction Effects of Condition and Time by Lure Similarity

Lure Similarity Bins	F (df)	p-value
Lure Bin 1	F (1,90) = 0.762	.385
Lure Bin 2	**F (1,90) = 4.04**	**.047**
Lure Bin 3	**F (1,90) = 4.30**	**.041**
Lure Bin 4	F (1,90) = 3.24	.075
Lure Bin 5	F (1,90) = 0.683	.411

Notes: Results from a linear mixed effects analysis of Condition (Exercise vs Rest) and Time (Pre vs Post) on LDI Bin scores while controlling for Age and Order of condition. Lure Bins ranked from 1 (most similar) to 5 (least similar). F(df) = F-value (degrees of freedom).

Figures

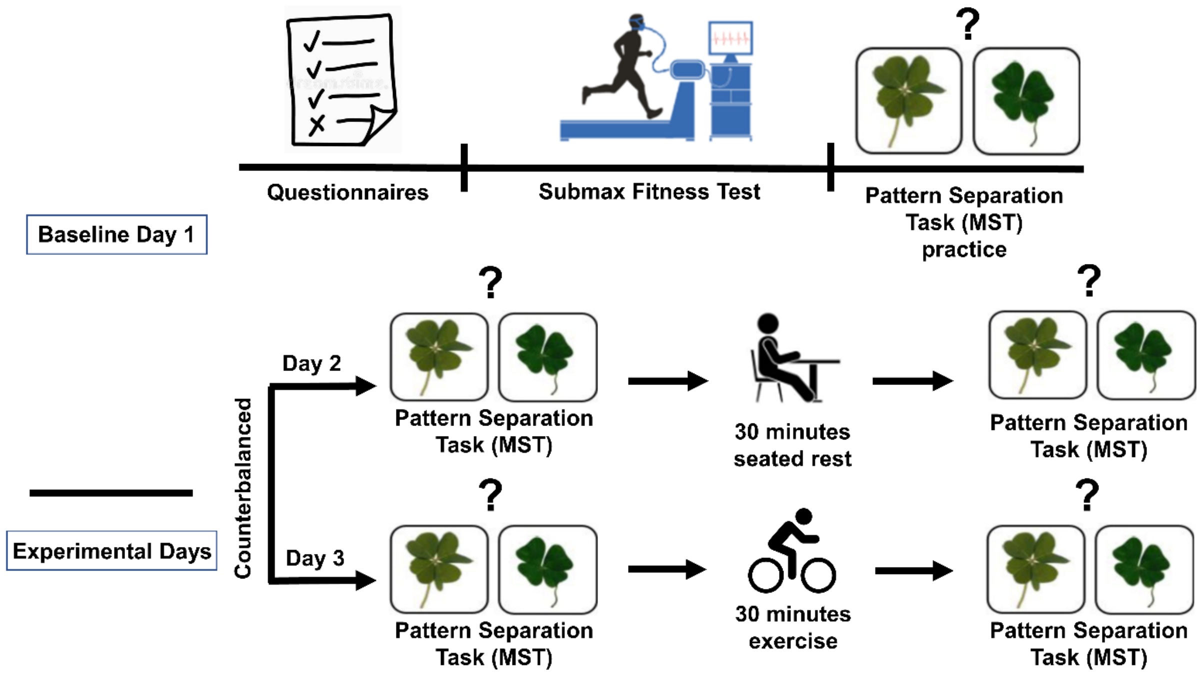


Figure 1: Graphical depiction of study design. Note, all participants completed all three days and all conditions with only the order of experimental conditions varying across participants. Comparisons between rest and exercise are therefore within-participant.

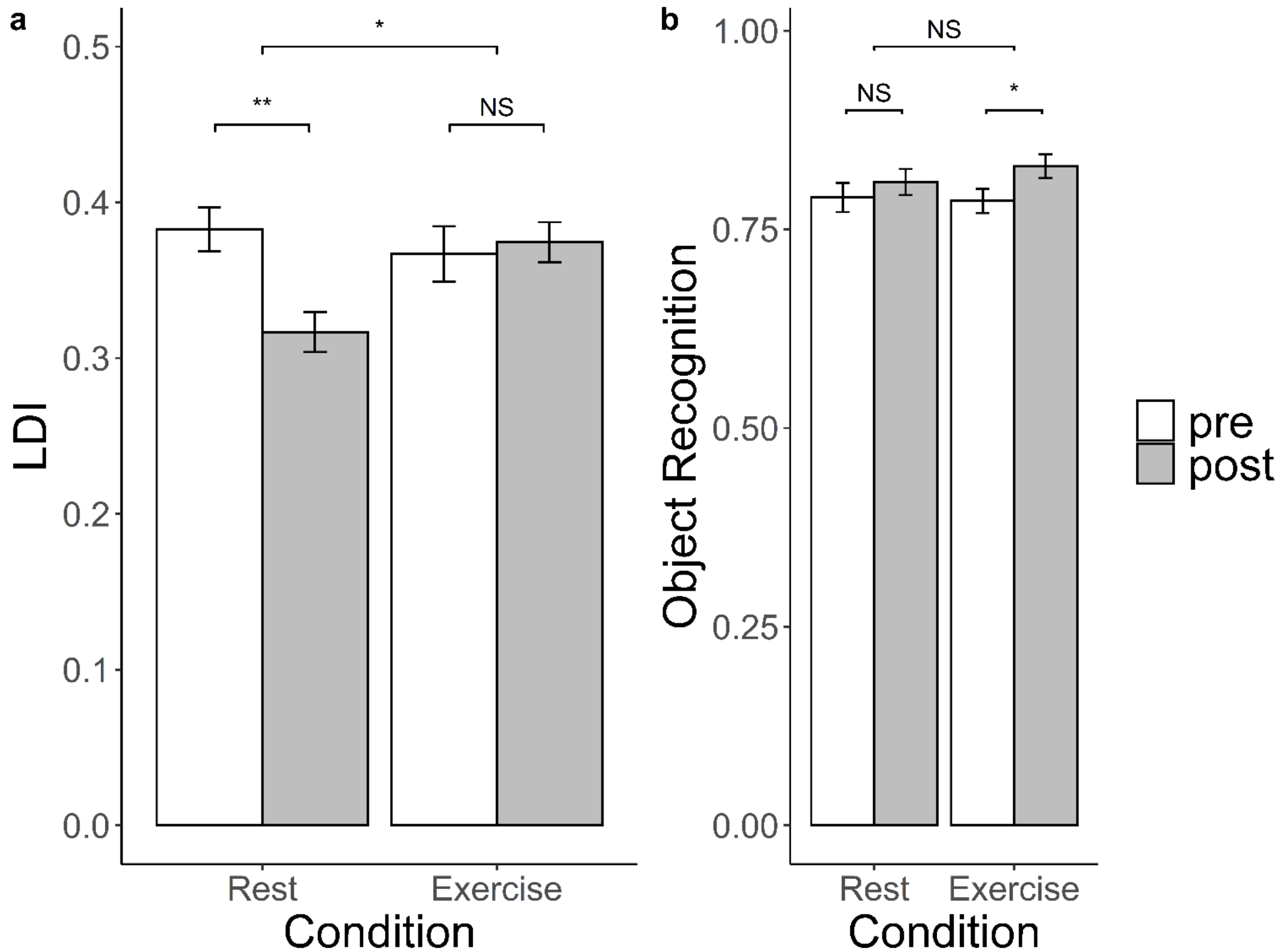


*Figure 2: Panel a) depicts raw LDI (Lure Discrimination Index) score before and following both the exercise and rest condition (error bars = 1 SEM). * Indicates a significant interactive effect of Time (pre vs. post) by Cond (exercise vs rest) on LDI performance while controlling for condition Order and participant Age. ** Indicates a significant decrease in LDI from pre to post rest while NS indicates a non significant difference in LDI scores from pre to post exercise. Panel b) depicts raw Object Recognition performance before and following both the exercise and rest condition (error bars = 1 SEM). * Indicates a significant increase in object recognition from pre to post exercise while NS indicates a non significant difference in object recognition scores from pre to post rest and a non significant interactive effect. *p<.05; **p<.01; NS (p>.05).*

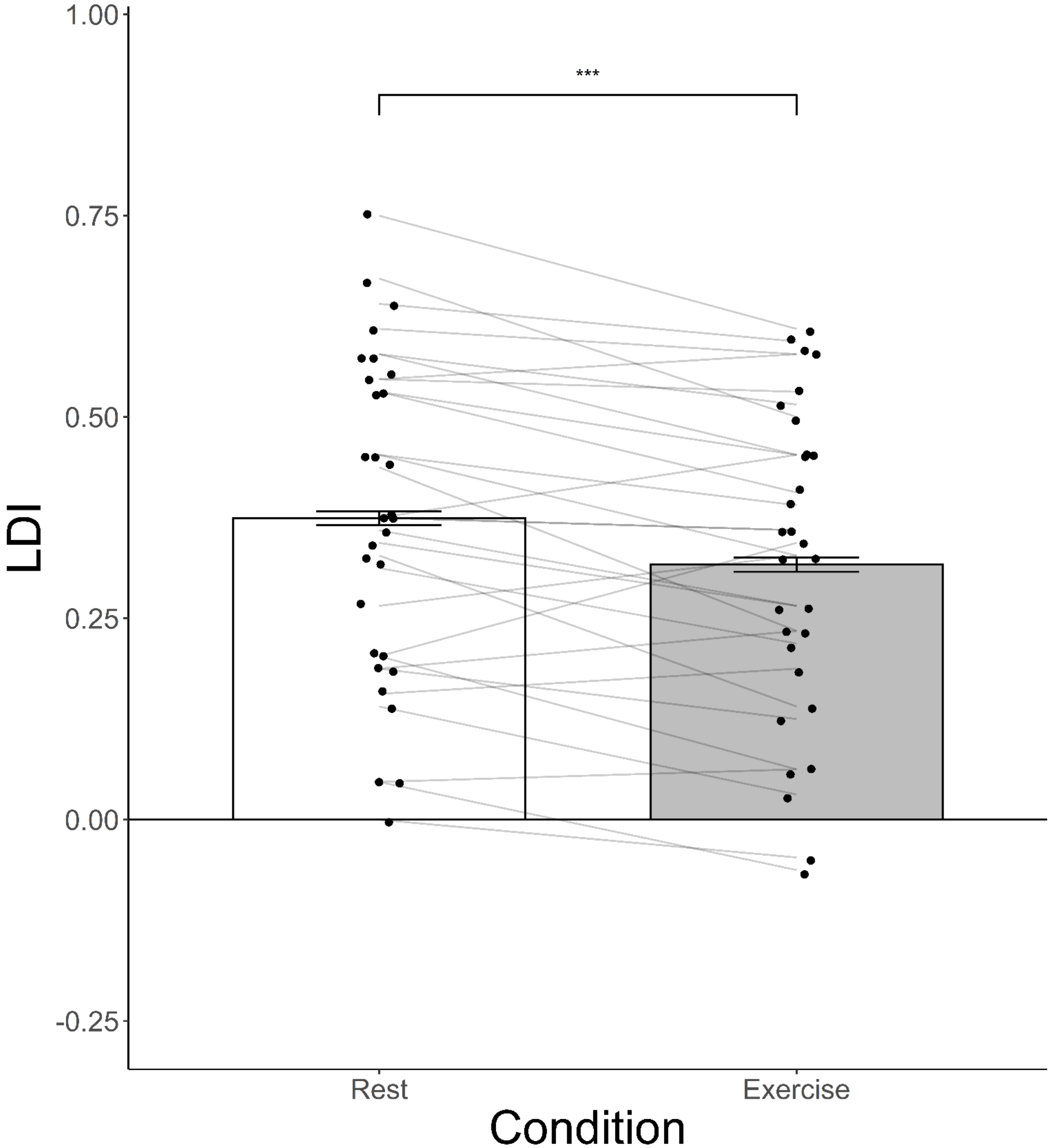
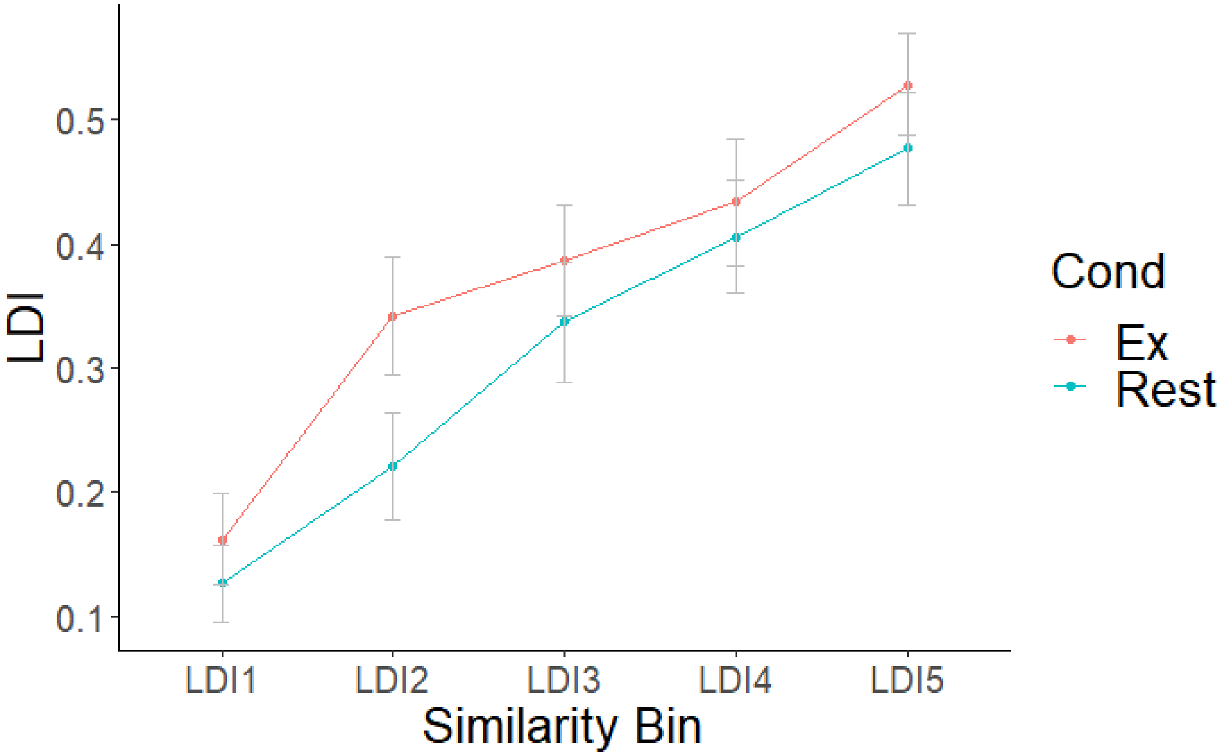


*Figure 3: Bar graph of raw LDI (Lure Discrimination Index) performance following both the exercise and rest condition (error bars depict standard errors). *** Indicates a main effect of Condition (Exercise vs Rest) on LDI performance while controlling for condition Order and participant Age. *** p<.001.*



Supplementary Figure 1: Line graph showing LDI scores following the Exercise and Rest condition and varying across lure similarity bins. With similarity bins scaling from 1 (most similar) to 5 (least similar).