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Exploring the Effects of Depression and Physical Activity on Pattern Separation Performance

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Doctor of Philosophy

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ABSTRACT

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Cognitive performance declines in depression and increases with physical activity. These changes may in part be due to changes in the level of neurogenesis (the generation and survival of adult-born neurons), which decreases with depression and increases with physical activity. Pattern separation (the formation of distinct neural representations of incoming information through orthogonalizing similar patterns of activation) has also been linked to neurogenesis. This project explores pattern separation within these two populations through three experiments.

Experiment 1. Previous research has found impaired pattern separation among individuals with higher depression scores, but who have not been diagnosed with Major Depressive Disorder (MDD). This experiment sought to expand these findings and evaluated behavioral differences during the performance of a continuous recognition pattern separation task among women with MDD and age- and education-matched controls. It was hypothesized that clinically depressed participants would have lower pattern separation scores and would be more likely to incorrectly identify lure stimuli as "old". Contrary to this prediction, clinically depressed participants had higher pattern separation scores, while controls were more likely to misidentify lure items as "old".

Experiment 2. While there are many known benefits of regular physical activity, the majority of individuals in the United States do not engage in the recommended levels of fitness training. Furthermore, there have only been a limited number of studies evaluating the effect physical activity may have on cognitive abilities and neurological components and none have evaluated what effect the recommended levels of fitness may have on these areas. The second experiment evaluated differences between individuals with varying levels of physical activity using functional magnetic resonance imaging (fMRI) during the performance of a continuous recognition pattern separation task. It was hypothesized that participants with self-reported higher levels of physical activity would have greater activation in the CA3/dentate gyrus subregions of the hippocampus than those with lower fitness levels and sedentary individuals. Surprisingly, there were no activation differences across groups.

Experiment 3. The final experiment explored diffusion tensor imaging (DTI) differences in physical activity levels with the same sample used in Experiment 2. It was hypothesized that participants with self-reported higher levels of physical activity would have indications of increased white matter integrity compared to those with lower fitness levels and sedentary individuals. There were significant differences across groups in DTI measures of white matter integrity (axial diffusivity or AD) in bilateral cingulum, the left temporal middle gyrus, and the right uncinate fasciculus.

Keywords: pattern separation, depression, physical activity, fMRI, DTI

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Chapter 1: Literature Review

The study of long-term memory traditionally has been broken down into two main categories: declarative and non-declarative. Declarative memory involves "conscious recollection about facts and events" (Squire, 2004, p. 173), while non-declarative memory involves performance-based behavior, such as habits and skills, simple conditioning, and priming (Squire, Stark, & Clark, 2004). Declarative memory involves the encoding of relationships between items and events, and can be further divided into semantic memory, which deals with facts of the world, and episodic memory, which deals with personal experiences of the world (Squire, 2004). A particularly unique feature of declarative memory is its "ability to detect and encode what is unique about a single event" (Squire, 2004, p. 174). While non-declarative memory has been related to many brain structures, such as the neocortex, striatum, and cerebellum, declarative memory has been isolated to the diencephalon and medial temporal lobe structures (Squire, 2004). Within the medial temporal lobe, information from the poly-modal association areas in the neocortex projects onto perirhinal and parahippocampal cortices, these cortical regions then project onto the entorhinal cortex, which in turn projects to the hippocampus (Squire et al., 2004). The perirhinal cortex is associated with visual memory; the parahippocampal cortex is associated with spatial memory; and the hippocampus is believed to be critical for tasks that involve "relating or combining information from multiple sources" (Squire et al., 2004, p. 286).

Pattern Separation

A particularly interesting phenomenon associated with declarative memory that has become more popular in the research literature in recent years is pattern separation. Pattern separation involves the formation of distinct neural representations of incoming stimuli and is

often associated with orthogonalizing similar or partially overlapping patterns of activation in order to reduce interference (Carr, Rissman, & Wagner, 2010; Gilbert & Kesner, 2006; Kesner, 2012; Yassa & Stark, 2011). This is in contrast to pattern completion, whereby previously stored representations are retrieved and used to fill-in or reconstruct partially presented representations (Chen, Olsen, Preston, Glover, & Wagner, 2011; O'Reilly & Norman, 2002; Yassa & Stark, 2011). The ability to pattern separate has been proposed to be especially important for memory encoding accuracy (Clelland et al., 2009). According to the Complementary Learning Systems model, there are two separate, but interactive, specialized memory systems: the neocortical system, which is believed to slowly create general representations of environmental elements; and the hippocampal system, which is believed to be involved in quickly and automatically creating connections between existing cortical representations (O'Reilly & Norman, 2002). These same authors have shown that both neocortical and hippocampal networks demonstrate pattern separation capabilities; however, the hippocampal network is engaged in a larger amount of pattern separation and assigns these nonoverlapping representations to the CA3 (Norman & O'Reilly, 2003). The hippocampus is especially capable of pattern separation due to its much sparser levels of neuronal firing, compared to those in the neocortex, which produces a decrease in overlap between representations (O'Reilly & Norman, 2002). The hippocampus uses compressed representations in order to carry out pattern separation capabilities and this compression takes place in the connections leading to the hippocampus (McClelland, McNaughton, & O'Reilly, 1995). This allows the hippocampal network to engage in fast learning processes, enabling it to "link the situation, action, and outcome together into a single memory trace" (McClelland et al., 1995, p. 453). When one of these linked elements is presented later on it prompts the hippocampus to retrieve the entire memory through pattern completion

(McClelland et al., 1995). This ability of the hippocampus to create pattern-separated representations of stimuli allows it to engage in rapid learning without "suffering catastrophic interference" (Norman & O'Reilly, 2003, p. 613). However, as the similarity in input patterns increases, the ability of the hippocampus to create distinct representations may become limited (Norman & O'Reilly, 2003).

Neural correlates of pattern separation. The primary hippocampal inputs derive from the entorhinal cortex, parahippocampal cortex and perirhinal cortex converging in the CA3 subregion. While the primary hippocampal output to the neocortex originates in CA1 and projects to subiculum, entorhinal cotex, and parahippocampal structures and to the prefrontal cortex (Rolls & Kesner, 2006). One specific hippocampal input, the perforant pathway, originates in the entorhinal cortex and projects to the dentate gyrus (DG) granule cells. The granule cells then project to the CA3 cells via the mossy fibers and the CA3 cells provide input to each other via recurrent collateral projections and also to the CA1 cells via the Schaffer collaterals. Additionally, CA1 cells also receive projections directly from the entorhinal cortex (Rolls & Kesner, 2006). Entorhinal cortical neurons also have weaker collaterals that go directly to CA3, bypassing the DG, which has led some to speculate that these projections are used in recalling information; in contrast, the DG-CA3 mossy fiber pathway is believed to be involved in creating novel pattern-separated representations onto CA3 neurons, which supports new learning and reduces interference (Yassa & Stark, 2011). Rolls and Kesner (2006) suggest that the hippocampus is involved in both spatial and non-spatial memory due to the one-stage autoassociation memory process, which occurs in the CA3 subregion. This autoassociation memory processes both spatial and episodic information and constructs arbitrary simultaneous neural patterns representing the various stimuli input from the environment, which are associated

together as one event. The sparse, but non-redundant representation required for autoassociation in the CA3 cells is made possible by the granule cells within the DG, which have a competitive learning process that allows separation of similar inputs to the hippocampus. It is essential that a competitive network precede the CA3 autoassociative network to allow for the storing of separate memories. This competitive system within the hippocampus is believed to be the crux of spatial pattern separation. Thus, the DG and the CA3 subregions may be involved in creating distinct representations (i.e., pattern separation) by changing their rates of firing when changes in input patterns are small (Yassa & Stark, 2011).

Evidence supporting hippocampal-dependent pattern separation. Several studies have provided support for these various models. For example, Kirwan, Shrager, and Squire (2009) found that activity within the medial temporal lobe could reflect the actual status of whether an item is old or new, rather than participants' reports of oldness or newness. They scanned participants while they were viewing new and old words (based on a previously studied list) and tested their recognition memory by having them indicate whether or not each word was old or new on a six-point confidence scale. FMRI activity in the hippocampus and parahippocampal gyrus increased as a function of increasing confidence for targets (correctly identifying a repeat item as old), but not with increasing confidence for foils (mistakenly identifying a similar item as old). This finding suggests that the brain was aware of whether or not a word was new or old independent of participants' overt behavior. This may reflect the hippocampus' ability to create distinct representations of old and new items (i.e., pattern separation) and provide support that this process occurs automatically.

Bakker, Kirwan, Miller, and Stark (2008) sought to differentially determine which subregions of the hippocampus in humans are involved in pattern separation and which are

involved in pattern completion. They used a continuous recognition fMRI task consisting of new, repeated, and lure objects (lure stimuli consisted of similar versions of previously shown objects) and asked participants to identify whether each object was typically found indoors or outdoors. Using this indirect task, the authors hypothesized that lure stimuli would generate one of two types of activity within hippocampal subregions which could then be used to infer pattern separation or pattern completion processes. If lures generated a similar level of activity as new objects for a given subregion it would be involved in pattern separation. In contrast, if lures generated a similar activity level as repeated objects a given subregion would be involved in pattern completion. Although high-resolution fMRI scans were performed in this study, resolution is still not sufficient enough to distinguish between CA3 and DG subregions of the hippocampus; therefore, these two regions were combined in the analyses. Hippocampal activity in the CA3/DG subregions was very similar for both lure and novel stimuli, demonstrating a bias towards pattern separation, while activity favoring pattern completion was observed in the CA1 subregion as well as several other MTL regions (e.g., entorhinal and parahippocampal cortices).

Lacy, Yassa, Stark, Muftuler, and Stark (2011) predicted that CA3/DG activity would be similar for small changes in stimuli and first presentations of stimuli and this would proceed in a step-wise manner, while CA1 activity would vary in a continuous manner with stimulus change. Similar to the task conducted by Bakker et al. (2008), Lacy et al. (2011) had participants engage in an incidental encoding task in which they viewed images of objects and indicated whether the objects were typically found indoors or outdoors. The images consisted of either new images, repetitions of previously shown images, or images that were similar to previously shown images. Patterns of activity in the right CA1 were consistent with pattern completion while activity patterns in the bilateral CA3/DG region were consistent with pattern separation. Furthermore, the

CA1 region demonstrated graded activity changes to stimuli, which varied from no activity (when viewing repeated images) to small levels of activity (when viewing highly similar images) to moderate activity levels (when viewing images that were low in similarity) to high levels of activity (when viewing first presentations of images). In contrast, the CA3/DG region had high activity levels for images that were highly similar. While the CA1 region showed incremental changes in activity as stimulus input variability increased, the CA3/DG region was highly sensitive to even very small changes between stimuli. Thus, these regions have distinct transfer functions for pattern separation activities, with CA1 responding incrementally and being more resistant to small changes, while the CA3/DG area responds in a stepwise manner and is sensitive to small changes. These results are in alignment with the prediction from computational models that the DG is primarily involved in pattern separation processes.

After reviewing the hippocampal pattern separation literature, Yassa and Stark (2011) conclude that there is abundant evidence for the DG being critical for pattern separation. The DG and CA3 play an important role in pattern separation processes with the dorsal DG facilitating spatial pattern separation and the dorsal CA1 facilitating pattern separation for visual objects (2012). Schmidt and associates (Schmidt, Marrone, & Markus, 2012) state that there is compelling evidence (anatomical, electrophysiological, and lesion data) for the role of the "dentate gyrus as a critical mediator of pattern separation" (p. 57). Even small changes in stimuli result in changes in DG neuronal recruitment (Schmidt et al., 2012). While it has been demonstrated that the medial temporal lobe, and specifically the hippocampus, are critical for creating distinct representations, there is still variability with which hippocampal subregions are responsible for pattern separation processes.

Interference and amnesia. Amnesic patients with hippocampal damage have provided strong support for the idea that pattern separation is tied to the hippocampus. Computational models of hippocampal function (McClelland et al., 1995; O'Reilly & Norman, 2002) predict a specific pattern of impairments when damage is limited to the hippocampus; specifically, a disproportionate impairment in pattern separation, behaviorally demonstrated as increased susceptibility to inter-stimulus interference. Harry, Postans, and Umla-Runge (2013) theorize that medial temporal lobe damage reduces the ability to discriminate between complex-featured stimuli and the medial temporal lobe structures which function normally (i.e., non-damaged structures) act as shields against interference and allow for the formation and preservation of overlapping representations. When considering cases of amnesia with a wide range of etiologies, it is apparent that amnesic patients are indeed more susceptible to interference than matched controls (for review, see Lustig & Hasher, 2001). Hippocampal amnesics are able to overcome this increased susceptibility to interference if their memory is probed in an appropriate way. Holdstock et al. (2002) describe the case of patient YR, who suffered selective adult-onset hippocampal damage. In tests of recognition memory, YR is unimpaired relative to matched controls for single items when tested in both forced choice and yes/no recognition formats (Holdstock, Gutnikov, Gaffan, & Mayes, 2000; Mayes, Holdstock, Isaac, Hunkin, & Roberts, 2002; Mayes et al., 2001). However, when target and lures were made more similar (i.e. interference was increased), YR's yes/no item recognition is impaired relative to controls (Holdstock et al., 2002), indicating a pattern separation deficit (but see Bayley, Wixted, Hopkins, & Squire, 2008). Duff et al. (2012) also demonstrated that when inter-stimulus similarity increased, patients with hippocampal damage were differentially impaired in a memory task relative to matched controls. Specifically, they used semantic stimuli to show that these patients

have slower reductions in word counts for similar items and use more words when describing similar items (compared to dissimilar items), providing support for the hippocampus' role in pattern separation.

Neurogenesis and pattern separation. It is widely accepted that neurogenesis occurs in the adult brain in two distinct regions: the olfactory bulb and the hippocampus, specifically within the DG (Eriksson et al., 1998; Gage, 2002; Kaplan & Hinds, 1977). Adult neurogenesis within the hippocampus may serve a function for pattern separation and different neurogenesis levels may represent adaptations to changes in cognitive demands based on environmental stimuli (Sahay, Wilson, & Hen, 2011). Alternatively, the ability to correctly identify comparable visual objects as "similar" in pattern separation tasks requires hippocampal neurogenesis for ideal functionality (Déry et al., 2013). Cerebral blood flow (CBV) has been linked to angiogenesis (Dunn et al., 2004) and neurogenesis (Palmer, Willhoite, & Gage, 2000; Pereira et al., 2007) and CBV in the DG has been tied to a pattern separation-dependent task evaluating visual pattern recognition performance (Brickman, Stern, & Small, 2011).

Computational models have proposed that future environmental encoding is contingent upon the generation of specialized granule cell groups within the DG and these newly developed granule cells are dependent upon neuronal activity levels in order to survive and mature (Aimone, Wiles, & Gage, 2009). In this neurogenesis-based model, fully mature adult-born DG neurons are critical for the hippocampal system's ability to progress from novel to familiar environmental responses (Aimone et al., 2009). Evidence in support of this hypothesis comes from Clelland et al. (2009) who used two separate methods for ablating hippocampal neurogenesis. While mice were able to learn challenging object-place associations, they were impaired on a spatial pattern separation task for low, but not high, stimuli separations. A recent

review concluded that activity patterns within the DG are congruent with the idea of granule cell 'retirement' or the notion that adult-born granule cells begin as extremely excitable cells, but as they mature they become more inhibited and ultimately reach a state in which they no longer respond to stimuli (Schmidt et al., 2012).

The varying levels of neurogenesis within the DG represent a long-term adaptive response to environmental differences achieved by altering between pattern separation and pattern completion processes (Sahay, Wilson, et al., 2011). Nakashiba et al. (2012) created transgenic mice to evaluate the effects of old versus new DG granule cells on pattern separation tasks. New granule cells were required for correctly distinguishing between similar environments in pattern separation tasks, but old granule cells were not necessary. Furthermore, old granule cells were necessary for standard performance in pattern completion tasks, while new granule cells were not. The adult-born granule cells have a critical period of a few weeks during which time they are selective for pattern separation processes by creating new CA3 attractor states and as these cells mature they take on pattern completion processes through previously existing CA3 attractor states (Nakashiba et al., 2012). Decreases in DG neurogenesis may interfere with pattern separation and create a bias towards pattern completion (Sahay, Wilson, et al., 2011) and computational models predict that both chronic and acute decreases in neurogenesis (due, for example, to aging and stress respectively) may significantly affect memory formation (Aimone et al., 2009).

This project examined the putative role of neurogenesis on pattern separation by considering two factors that influence neurogenesis levels: depression and physical activity. These studies explored behavioral, structural, and functional components of pattern separation

and evaluated how specific populations with assumed variable levels of neurogenesis respond to pattern separation paradigms.

Chapter 2: Exploring Pattern Separation in Women with Major Depressive Disorder (Experiment 1)

Depression has been tied to declines in multiple cognitive processes, including memory deficits, and with reductions in hippocampal structure volumes. Cognitive deficits are frequently correlated with reductions in hippocampal volumes in individuals with mood disorders (Brown, Rush & McEwen, 1999; MacQueen & Frodl, 2011) and the most severe cognitive impairment has been found with measurements of memory that are specifically tied to hippocampal structures (MacQueen & Frodl, 2011). Some have speculated that hippocampal damage in depressed patients may result from an excess of corticosteroids and since the hippocampus provides negative feedback to the HPA axis, a damaged hippocampus may result in even further elevations in cortisol leading to a downward spiral of cognitive impairment (Brown, Rush, & McEwen, 1999; Campbell & MacQueen, 2004). However, MacQueen and Frodl (2011) found that memory deficits in depressed older adults were associated with reductions in bilateral hippocampal volumes, but not in cortisol levels or the current or past level of depressive symptoms. Furthermore, deficits in attention, learning and memory, and executive function continued six months after treatment even with individuals who were in full remission.

During the first or first few episodes of depression, reversible hippocampal damage results in cognitive dysfunction; however, with additional episodes or chronic depression this damage becomes permanent (Brown et al., 1999). MacQueen et al. (2003) compared structural images of first-episode, never-treated, depressed individuals, multiple-episode depressed individuals, and healthy control individuals and found that individuals with multiple depressed episodes had reductions in bilateral hippocampal volumes, while individuals with a single episode of depression did not. Both single-episode and multiple-episode depressed individuals

had impairments in memory recollection tasks that are hippocampus-dependent. Additionally, hippocampal volume reductions transpire early in the course of depression, although not before the first episode of depression, and these reductions occur rapidly during the first few years of depression followed by a plateau. Several meta-analyses have found reduced hippocampal volumes in patients with long-lasting depression and concluded that the critical factor associated with detecting hippocampal volume reduction was depression duration (Campbell, Marriott, Nahmias, & MacQueen, 2004; McKinnon, Yucel, Nazarov, & MacQueen, 2009). One study found hippocampal volume reductions in depressed individuals who either have the illness for longer than two years or have more than one episode of depression (McKinnon et al., 2009). Furthermore, there were differences in children, middle-aged, and older adults, but not in young adults, and hippocampal volume reductions were highest in depressed individuals with moderate illness durations compared with extensive illness durations.

Deficits in adult-born hippocampal neurogenesis may be one of the primary causes of depression; with evidence showing that hippocampal neurogenesis is required for antidepressants to be an effective treatment (Surget et al., 2008). Hippocampal neurogenesis may be necessary for the successful treatment of depression, but the disruption of neurogenesis may not necessarily be required for the onset of depression (Mahar, Bambico, Mechawar, & Nobrega, 2014; Sahay & Hen, 2007). More recently, Eisch and Petrik (2012) have proposed a "neurogenic interactome" model for depression which "consists of key endocrine and neurochemical signaling cascades, reciprocal connections among brain regions that control adult neurogenesis, and their major downstream influences on behavior" (p. 73). Hippocampal neurogenesis and its control over mood and memory is more interrelated than previously supposed and further speculations suggest that pattern separation tasks may be critical to recognizing initial symptoms of

depression (Eisch & Petrik, 2012). Their model states that "both direct and indirect anatomical connections…influence adult neurogenesis in a dynamic manner… [and] alterations in neurogenesis reciprocally influence the connecting regions" (p. 74). Because strong and unpredictable stress often acts as a precursor to depression and is known to decrease adult-born neurogenesis, pattern separation functions may also be impaired when experiencing stress. This disruption in pattern separation processes will interfere with an individual's ability to distinguish and manage future incoming stressful events, thus creating an ongoing vicious cycle.

Two recent studies evaluated pattern separation performance and depression scores in individuals who had not been diagnosed with depression (Déry et al., 2013; Shelton & Kirwan, 2013). Shelton and Kirwan (2013) used a continuous recognition pattern separation task similar to the one used by Bakker et al. (2008) during which individuals were shown a series of color photographs of everyday objects one at a time. These objects consisted of new, repeat, and similar objects; however, instead of making an indoor/outdoor judgment, participants were asked to identify each object as either "new", "old", or "similar". Individuals with lower depression scores performed better on the pattern separation task and were less likely to misidentify similar items as "old" than those with higher depression scores. These findings are consistent with a neurogenic-reduction hypothesis of depression, that neurogenesis is critical for pattern separation performance. Déry et al. (2013) used a modified version of the pattern separation task previously used (Kirwan & Stark, 2007) to further evaluate delays of learning and contextual elements. These authors incorporated an outdoor scene behind the objects and presented the objects in a study/test block manner. Participants with lower depression scores had enhanced pattern separation abilities and were more likely to identify similar items as "similar" rather than "old". Both groups had improved pattern separation performance when there was increased temporal

spacing and contextual changes between presentations. They suggested that individuals with lower depression scores had an increased number of available adult-born cells in the DG, which contributed to their improved pattern separation abilities.

Experiment 1 of the current project evaluated behavioral performance in a continuous recognition pattern separation task among women diagnosed with Major Depressive Disorder (MDD). This study sought to extend the findings of previous studies, which used healthy individuals and spilt them into "higher" and "lower" groups based on a median split from a depression assessment (Déry et al., 2013; Shelton & Kirwan, 2013), to evaluate pattern separation performance in a clinically depressed population. Experiment 1 utilized the same pattern separation task used by Shelton and Kirwan (2013). It was hypothesized that clinically depressed participants would have lower overall pattern separation scores and would be more likely to incorrectly identify similar items as "old" compared to control participants.

Method

Participants. Twenty-one participants (all women) with MDD were recruited through the Brigham Young University (BYU) Counseling Center. An additional 20 healthy individuals (all women) served as the control group and were recruited through from the BYU community. This study was conducted in collaboration with a clinical psychology laboratory on campus and participants were limited to only women to address the specific clinical hypotheses these researchers had for their study. No gender differences have previously been found with this behavioral task (C. B. Kirwan, personal communication, August 20, 2012); thus, the inclusion of a female-only sample is unproblematic. All participants were given a structured clinical interview (i.e., the MINI International Neuropsychiatric Interview, M.I.N.I.; Sheehan et al., 1998) to ensure they either met diagnostic criteria for MDD and no other psychiatric disorder for

the MDD participants, or did not meet any diagnostic criteria for the control participants. Exclusion criteria for all participants included an age of less than 18 or greater than 25 years, cardiovascular disease, use of vasoactive medications, alcohol or drug abuse, history of electroconvulsive therapy (ECT) treatment, head injury or any physiological or neurological disorders, and MRI incompatibility. Participants also participated in MRI scanning as part of another study and were compensated $20 for each MRI scanning session (two sessions for all participants with MDD and 10 of the control participants; one session for the other 10 control participants).

Two MDD participants were removed from data analyses, one due to equipment errors and one because she was a non-native English speaker. Three control participants were also removed from data analyses, one because she had previously participated in a study that used the same behavioral task, one because she reported falling asleep during the task (and analysis of her behavioral data confirmed this report), and one due to a self-reported history of seizures. Thus, final groups submitted for data analyses consisted of 19 MDD participants and 17 control participants (see Table 1). These groups did not differ by education (MDD M=12.47, SD=1.17; Control M=12.47, SD=1.13; $t(34)=-.01$, $p = .994$) or age (MDD ages 18-23, M=20.00, SD=1.63; Control ages 18-23, M=20.65, SD=1.27; $t(34)=.20$, $p = .197$). None of the control participants reported a history or current diagnosis of psychiatric disorders or medication use. All of the MDD participants met diagnostic criteria for MDD, with four reporting a history of MDD, which began during their teen years. Only one of the MDD participants reported current use of medication (Prozac); however, she was in the process of weaning off this medication.

Questionnaires and psychological measures. All participants completed an online survey, which included demographic information and the Beck Depression Inventory (BDI-II;

Beck, Steer, & Brown, 1996) to determine the severity of depression symptoms. This measure consists of 21 groups of statements and individuals were instructed to select one statement from each group that best described their feelings during the previous two weeks. Participants were administered the Rey Auditory Verbal Learning Test (RAVLT; Rey, 1964) to assess verbal memory performance and the Test of Premorbid Functioning (TOPF; Wechsler, 2001) to assess general cognitive ability. In addition, participants completed a dietary questionnaire as part of a separate ongoing study.

Behavioral procedure. The behavioral task used in Experiment 1 was the same task used by Shelton and Kirwan (2013) with a minor variation in stimulus presentation time. Participants were seated approximately two feet from a laptop computer and the task was carried out using the Psychophysics Toolbox for Matlab (Brainard, 1997; Kleiner, Brainard, & Pelli, 2007). In this task, participants were shown a series of color photographs of everyday objects one at a time. Some of the objects were only shown once (foils), some objects appeared twice (repeats), and some objects consisted of paired images that were visually and conceptually similar (lures). This database of lure images has been previously tested for similarity (Kirwan & Stark, 2007) and were found to be the most similar to their related pairs. The use of lure items has been hypothesized to enhance interference and result in an increased need for pattern separation (Kirwan & Stark, 2007; Toner, Pirogovsky, Kirwan, & Gilbert, 2009). For each object shown, participants were asked to identify (by pressing one of three buttons) whether it was "new" (if they did not remember seeing the image before), "similar" (if they remembered seeing an image that was similar to, but not exactly the same as the present image), or "old" (if they remembered previously seeing the exact same image). The delay between the first presentation and repeated presentation of lure or repeated objects varied with a mean lag of 19 trials. Six blocks of 108

stimuli, for a total of 648 images, were presented and, unlike the paradigm previously used (Shelton & Kirwan, 2013) where participants were given unlimited time to make a selection, participants in this study were required to respond within 2.5s, after which time the stimulus was replaced by a blank screen for .5s followed by the next stimulus.

Results

Pattern separation scores were calculated in Microsoft® Excel® for Mac 2011 (Version 14.4.4; Redmond, WA) by taking the proportion of "similar" responses to lure stimuli and correcting for participants' response bias (estimated by subtracting the proportion of "similar" responses to foil stimuli; i.e., p("similar"|lure) – p("similar"|foil); see Déry et al., 2013; Kirwan et al., 2012; Kirwan & Stark, 2007; Shelton & Kirwan, 2013). These scores were then analyzed in SPSS (Version 21; Armonk, NY) with an independent samples *t*-test to compare pattern separation performance between groups (MDD and controls). This analysis revealed a significant difference in pattern separation scores between MDD (M=.6396, SD=.13) and control (M=.5255, SD=.13) groups; $t(34)=-2.62$, $p = .013$. Surprisingly, these results revealed that the MDD participants had higher pattern separation scores than the control participants rather than lower pattern separation scores as originally hypothesized.

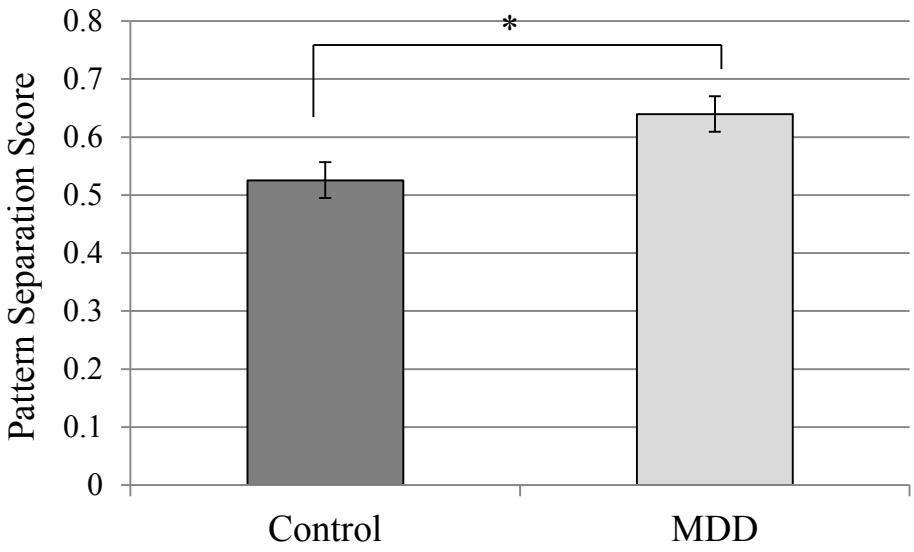


Figure 1. Plot of pattern separation scores (p("similar"|lure) – p("similar"|foil) for control and MDD participants in Experiment 1.Analysis revealed significant difference between groups; $t(34)=-2.62$, $p = .013$. Error bars depict *SEM*.

Next, to determine whether participants would be more likely to engage in successful pattern separation verses pattern completion (determined as responding "old" to a lure stimulus), a generalizability score was calculated with the following formula: (p("similar"|lure) – p("similar"|foil)) – (p("old"|lure) – p("old"|foil); Shelton & Kirwan, 2013). These scores were also analyzed in an independent samples *t*-test, which also revealed a significant difference between MDD (M=.3960, SD=.23) and control (M=.1862, SD=.24) groups; $t(34)=-2.66$, $p = .012$. Thus, the MDD participants were more likely to engage in pattern separation and the control participants were more likely to engage in pattern completion.

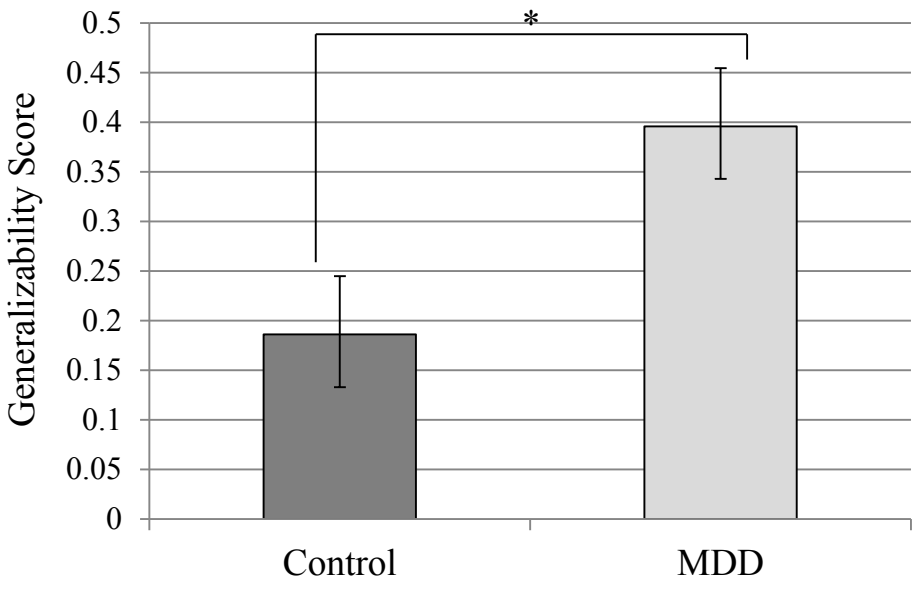


Figure 2. Plot of generalizability scores (p("similar"|lure) – p("similar"|foil)) – (p("old"|lure) – p("old"|foil) for control and MDD participants in Experiment 1. Analysis revealed significant difference between groups; $t(34)=-2.66$, $p = .012$. Lower scores suggest a bias towards pattern completion, while higher scores suggest successful engagement in pattern separation. Error bars depict *SEM*.

Correct responses for each of the stimulus types (i.e., responding "new" to foil stimuli, "old" to repeat stimuli, and "similar" to lure stimuli) were analyzed using a one-way ANOVA, with group (MDD and controls) as the between-group factor and response-stimulus type (new-foil, old-repeat, and similar-lure) as the dependent variables. No significant differences were found for the new-foil ($F(1, 34) = .863$; $p = .359$; partial $\eta^2 = .025$) or old-repeat comparisons ($F(1, 34) = .023$; $p = .879$; partial $\eta^2 = .001$); however, there were significant differences for the similar-lure comparison ($F(1, 34) = 6.800$; $p = .013$; partial $\eta^2 = .167$). Descriptive statistics revealed that participants with MDD were more likely to correctly respond to the lure stimuli (MDD M=.6683, SD=.13; control M=.5621, SD=.11).

To evaluate the types of errors that were performed in response to lure stimuli, another one-way ANOVA was conducted, with group (MDD and controls) as the between-group factor and error type (i.e., responding "old" and "new" to lure stimuli) as the dependent variables.

Results revealed a significant effect for "old" responses to lure stimuli ($F(1, 34) = 6.165$; $p = .018$; partial $\eta^2 = .153$), but not for "new" responses to lure stimuli ($F(1, 34) = .322$; $p = .574$; partial $\eta^2 = .009$). Descriptive statistics show that for the "old" responses to lure stimuli, control participants were more likely to make this error (M=.3488, SD=.12) than MDD participants (M=.2528, SD=.11).

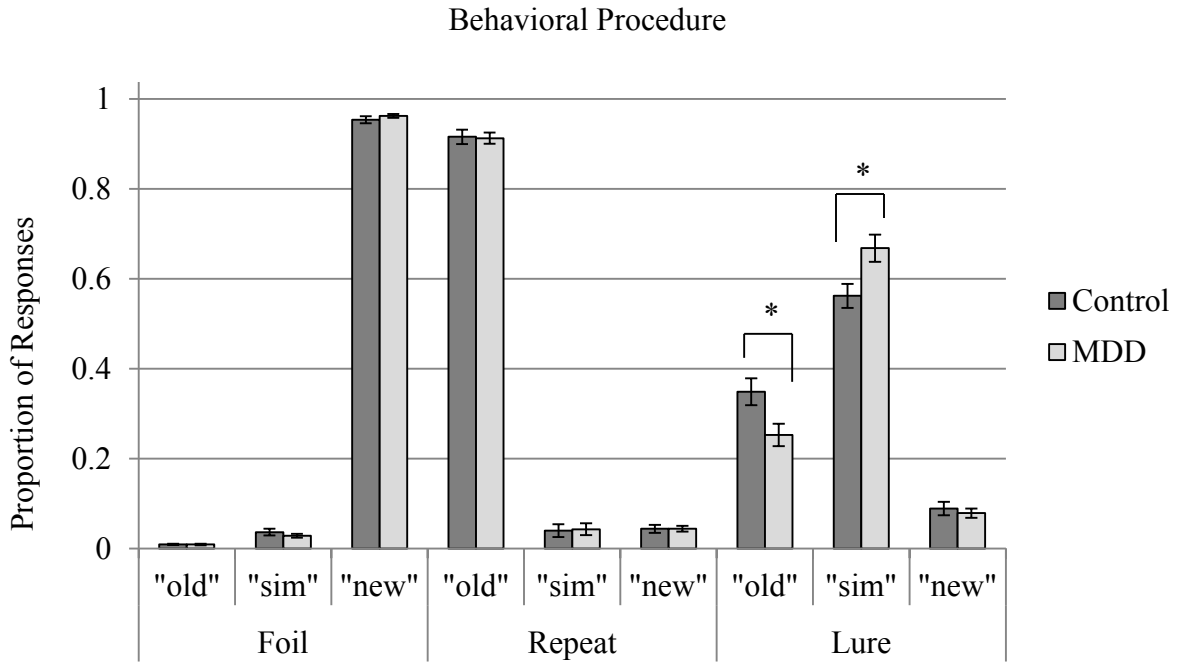


Figure 3. Plot of proportion of responses to the behavioral procedures task for control and MDD participants in Experiment 1. Stimuli consisted of photographs of everyday objects: foils were only shown once; repeats were shown twice (repeats); and lures consisted of paired images that are visually and conceptually similar. Participants were asked to identify stimuli as "new" (if they did not remember seeing the image before), "similar" (if they remembered seeing an image that was similar to, but not exactly the same), or "old" (if they remembered seeing the exact same image before). Analysis of correct responses revealed significant differences between groups for "similar" responses to lure stimuli; ($F(1, 34) = 6.800$; $p = .013$; partial $\eta 2 = .167$). Analysis of errors revealed significant differences between groups for "old" responses to lure stimuli; $F(1, 34) = .322$; $p = .574$; partial $\eta^2 = .009$. Error bars depict *SEM*.

Shelton and Kirwan (2013) had previously found a correlation between pattern separation scores and depression indicator scores. Thus, a post-hoc correlation analysis was conducted between the pattern separation scores and BDI scores among the MDD and control participants;

there was no correlation found between these variables (r = 0.136, n = 36, p = .428). An independent samples t-test revealed significant differences for BDI scores between the groups (MDD M=19.84, SD=7.93; Control M=11.29, SD=9.90; t(31)=-2.84, p = .008).

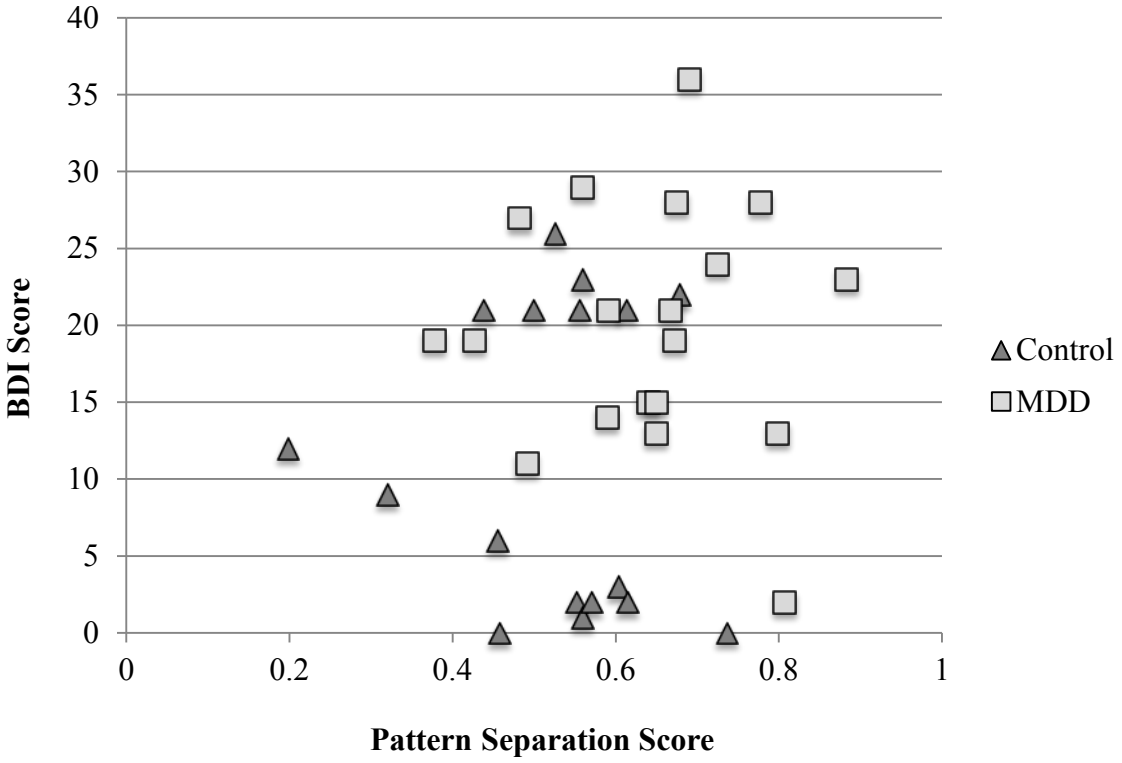


Figure 4. Scatterplot of pattern separation scores and Beck Depression Inventory-II (BDI-II) scores for control and MDD participants in Experiment 1. Analysis revealed no correlation; (r = 0.136, n = 36, p = .428).

Finally, a series of independent samples t-tests were conducted to evaluate whether the groups (MDD and control) differed with regards to performance on the RAVLT or TOPF. These results revealed no significant difference between groups for RAVLT delayed recall (MDD M=13.84, SD=1.17, Control M=13.53, SD=1.66; t(34)=-.659, p = .515), RAVLT immediate recall (MDD M=8.42, SD=1.22, Control M=8.76, SD=2.01; t(31)=.620, p = .539), RAVLT total performance (MDD M=62.68, SD=4.68, Control M=62.47, SD=6.69; t(31)=-.112, p = .912), or TOPF (MDD M=120.84, SD=7.19, Control M=120.59, SD=6.25; t(31)=-.112, p = .911).

Performance on the RAVLT was not expected to differentiate between the MDD and control participants. Others have also found no significant differences between MDD and control participants on performance of the RAVLT (Baune, Czira, Smith, Mitchell, & Sinnamon, 2012) and other verbal learning and memory tasks (Dietsche et al., 2014). Since the TOPF is a measure of general cognitive functioning and has been used to determine premorbid IQ (for example, see Fallows & Hilsabeck, 2013) the lack of differences between the MDD and control groups suggests that these groups were equivalent in IQ.

Table 1.
Summary of demographic and variable information (mean, standard deviation) for major depressive disorder (MDD) and control participants in Experiment 1.

	MDD		Control	
N	19		17	
Age (years)	20	(1.63)	20.7	(1.27)
Education	12.47	(1.17)	12.47	(1.13)
BDI[a]	19.8	(7.93)	11.3	(9.90)
TOPF[b]	120.8	(7.19)	120.6	(6.25)
RAVLT[c] Delayed	13.8	(1.17)	13.5	(1.66)
RAVLT Immediate	8.4	(1.22)	8.8	(2.01)
RAVLT Total	62.7	(4.68)	62.5	(6.69)
PS[d] Score	0.6396	(0.13)*	0.5255	(0.13)*
PS - PC[e] Score	0.396	(0.23)*	0.1862	(0.24)*

Note. *Significant difference, $p < 0.05$. [a]Beck Depression Inventory-II (Beck, Steer, & Brown, 1996). [b]Test of Premorbid Functioning (Wechsler, 2001). [c]Rey Auditory Verbal Learning Test (Rey, 1964). [d]Pattern Separation. [e]Pattern Completion.

Discussion

It was hypothesized that clinically depressed participants (as diagnosed by the M.I.N.I.) would have lower overall pattern separation scores and would be more likely to engage in pattern completion compared to control participants. Contrary to this original prediction, clinically depressed participants did not have lower pattern separation scores. In fact, they performed

significantly better than the control participants. To determine whether participants would be more likely to engage in successful pattern separation verses pattern completion (determined as responding "old" to a lure stimulus), we calculated a generalization score (Shelton & Kirwan, 2013). Higher scores suggest that participants are successfully engaged in pattern separation, while lower scores indicate they are biased towards pattern completion (Shelton & Kirwan, 2013). Surprisingly, the controls were more likely to be biased towards pattern completion, rather than the depressed participants. When comparing how these groups performed to specific categories of stimuli, depressed participants were significantly more likely to correctly respond "similar" to lure stimuli; however there were no group differences to other correct responses (i.e., responding "new" to foil stimuli and "old" to repeat stimuli). When comparing errors to the lure stimuli for this task (i.e. responding to lure stimuli as either "new" or "old"), the control participants were significantly more likely to incorrectly respond to lure stimuli as "old" when making an error, compared to the depressed participants.

These surprising results may be due to a couple of factors. First, the majority of MDD participants were in their first episode of depression (n = 14) and in young adulthood, with a mean age of 20 years. A recent review of neuropsychological performance in adolescents and young adults (ages 12-25 years) found a wide variation of cognition performance, with most deficits occurring in working memory and psychomotor and processing speed tasks (Baune, Fuhr, Air, & Hering, 2014). They also found minor evidence for executive functioning, verbal fluency, and visual memory deficits and no evidence for attention or verbal memory. Thus, cognitive impairments seem to vary greatly in this younger age demographic. Fossati et al. (2004) found no differences on verbal memory performance between controls and participants in their first-episode of depression; however, greater cognitive impairments were found with

participants who had recurrent episodes of depression; specifically, these individuals had impaired free recall, normal-cued recall, and recognition. Several recent studies also found correlations between the number of depressed episodes and cognitive or structural measurements. One found a negative correlation between depression duration and hippocampal body volumes with lower visual memory scores for MDD participants compared to controls (Travis et al., 2014). Another study found significant reductions in DG and left medial prefrontal cortex volumes that were associated with an increased number of depressive episodes (Treadway et al., 2015). Perhaps individuals who have had MDD for greater lengths of time, with multiple episodes, or who are older in age would be more likely to perform on this task as originally hypothesized.

Shelton and Kirwan (2013) had previously found a negative correlation between depression scores and pattern separation scores. They found that healthy, non-clinically depressed individuals who had higher depression scores also had lower pattern separation scores. The current study did not find any correlation between depression scores and pattern separation scores. However, the previous study used a different depression inventory, the Depression Anxiety Stress Scales (DASS), than the current study, which used the BDI-II. Fujii, Saito, Yanaka, Kosaka, and Okazawa (2014) also failed to find a correlation between BDI scores and percent correct scores on a pattern separation task. Perhaps BDI scores are not a sensitive enough measure for these types of discrimination tasks when comparing clinically depressed and control individuals.

Examination of Figure 4 reveals a possible trend for some of the control participants, with higher BDI scores associated with lower pattern separation scores. Curiously, there is another cluster of control participants who had higher BDI scores, but not necessarily lower

pattern separation scores, much like the MDD participants. Upon further examination it was revealed that this group of control participants all participated in this study at the very end of the semester. It could be that an increase in stress associated with typical end-of-semester occurrences may have inflated their BDI scores. If they had participated in this study during another point in time, their BDI scores and performance on this task may have resembled those of the rest of the control participants. If this is the case, it raises another intriguing idea that depression scores may only correlate with pattern separation scores below a particular threshold; once this threshold is exceeded, such as would be the case for individuals with clinical depression, this relationship falls apart.

Finally, the MDD participants may have been more motivated to perform well and may have been more attentive during the task than the control participants. Several of the women who were clinically depressed verbalized their believed importance of studies addressing MDD at the end of their participation in this study. It may have been that those individuals with MDD, who chose to participate in this study, had a greater personal affiliation with this research and were more motivated to attend to the stimuli and perform as well as they could. In contrast, the control participants may not have been as driven to perform to their best level. This disparity may be due to the different recruitment methods used to obtain participants for Experiment 1, thus resulting in a sampling bias. Depressed participants were recruited directly through the BYU Counseling Center from among women who had sought counseling for their depression. However, the control participants were recruited from the BYU community at large. Perhaps if the participants with MDD had also been recruited through the community, their scores may not have differed as much from the control participants.

Chapter 3: The Impact of Physical Activity on Pattern Separation (Experiment 2)

The American Heart Association (2013) recommends adults engage in approximately 30 minutes of moderate-intensity aerobic activity at least five days per week and a moderate- to high-intensity muscle-strengthening activity at least two days per week. However, the Centers for Disease Control and Prevention (2010) reported that only 43.5% of adults in the United States meet the minimum physical activity recommendations and 25.4% do not engage in any leisure-time physical activity. Adults who regularly engage in physical activity have lower rates of mortality and morbidity (US Department of Health and Human Services, 2008).

Physical activity is linked with improved cognitive functioning. For example, variability in cognitive performance decreases as physical activity increases in older adults (Kimura, Yasunaga, & Wang, 2013) and highly athletic older adults perform better in letter fluency, category fluency and reading skills compared to sedentary individuals (Thomas et al., 2013). Interestingly, low-level physical activity levels of daily life, but not aerobic fitness (as measured by a step test and ergometry), is associated with enhanced episodic memory encoding in older adults (Flöel et al., 2010). Thus, physical activity acquired through embedded routines in day-to-day life is beneficial for memory functionality.

Two meta-analyses (Colcombe & Kramer, 2003; Smith et al., 2010), evaluating physical activity in older adults, found that a combination of strength training and aerobic exercise produced the greater cognitive benefits than aerobic exercise alone; with greatest improvements occurring in executive-control processes (Colcombe & Kramer, 2003) and attention, processing speed, and working memory (Smith et al., 2010). A more recent study found increased physical activity was associated with increased conflict resolution (i.e., smaller response time costs) in a flanker task, which measures functioning of attentional control processes (Winneke, Godde,

Reuter, Vieluf, & Voelcker-Rehage, 2012). Physical activity levels seemed to be particularly important in younger middle-aged adults (aged 35 to 48 years), with highly active younger middle-aged adults showing smaller response time costs compared to low active younger middle-aged adults and no differences between activity groups in the older middle-aged adults (aged 55 to 65 years). Having an active lifestyle in middle adulthood may contribute to stabilizing cognitive function processes (Winneke et al., 2012). Richards, Hardy, and Wadsworth (2003) found higher levels of physical exercise at 36 years was associated with higher memory scores at 43 years and increased physical exercise between 43 and 53 years was associated with a slower rate of memory score decline. Individuals may experience some degree of memory protection if they begin exercising after 36 years, while those who are active during their younger adult years, but stop after 36 years, receive little protection in memory.

After a single bout of intense aerobic exercise male young adults acquired lexical learning 20% faster than those who engaged in a single bout of moderate aerobic exercise or who were sedentary (Winter et al., 2007). In an event related potential (ERP) study, regular physical activity was shown to improve executive functioning in young adults and was associated with lower P300 amplitudes (an ERP component associated with oddball paradigms), suggesting that active individuals (compared to sedentary individuals) may be better at allocating attentional resources (Kamijo & Takeda, 2010). Finally, adolescents who engage in regular exercise exhibit increased performance on neuropsychological assessments compared to matched sedentary adolescents (Lee et al., 2014). Specifically, these athletic adolescents had improved associative memory, inhibitory control, and cognitive flexibility and these favorable cognitive effects were only found in assessments measuring functions related with frontal and medial temporal lobe areas.

Physical activity is associated with improved neurological health, such as preserved cerebral blood flow in older adults (Thomas et al., 2013) and increased DG angiogenesis in adult mice (Creer, Romberg, Saksida, van Praag, & Bussey, 2010). Pereira and associates (2007) found that DG CBV, measured by MRI, correlated with exercise-induced neurogenesis in mice and noteworthy similarities between exercise-induced CBV changes within the hippocampus in mice and humans. Other animal studies find that exercise promotes neurogenesis in the DG (Marlatt, Potter, Lucassen, & van Praag, 2012; van Praag, Christie, Sejnowski, & Gage, 1999; van Praag, Kempermann, & Gage, 1999; van Praag, Shubert, Zhao, & Gage, 2005) and enhances learning in young (van Praag, Kempermann, et al., 1999) and aged (Marlatt et al., 2012; van Praag et al., 2005) mice. Furthermore, running results in greater neurogenesis in young, compared to aged, mice and old running mice have an equivalent amount of neurogenesis to young, nonrunning mice, which suggests that exercise may restore some neurogenesis in aged mice (van Praag et al., 2005). Increased hippocampal neurogenesis (Creer et al., 2010; Sahay, Scobie, et al., 2011) and exercise (Creer et al., 2010) are associated with enhanced pattern separation in mice, leading some to speculate that exercise may only be beneficial to pattern separation if it increases hippocampal neurogenesis (Yassa & Stark, 2011). Déry and associates (2013) found that, after a six-week exercise training intervention, human adults with the greatest increases in fitness (as measured by improvement in VO_2 peaks) had improved pattern separation performance which resulted in an enhanced ability to distinguish similar stimuli from targets which were previously studied.

In addition, exercise is linked with brain-derived neurotrophic factor (BDNF) induction in all subregions of the rat hippocampus (Soya et al., 2007) and with increased BDNF mRNA in the rat hippocampus and enhanced contextual learning (Greenwood, Strong, Foley, & Fleshner,

2009). Aerobic training also increases BDNF concentrations and improves hippocampal dependent learning in young human adult males (Griffin et al., 2011). Even a single bout of intense aerobic exercise is linked to elevated levels of BDNF and catecholamines and sustained levels of BDNF are related to better short-term learning, while absolute levels of dopamine and epinephrine are linked to better intermediate and long-term (respectively) retention of novel vocabulary (Winter et al., 2007). Furthermore, one-year of moderately intense aerobic exercise increases the size of the anterior hippocampus (by 2%), produces greater BDNF concentrations, and improves spatial memory in older human adults (Erickson et al., 2011). Whiteman et al. (2014) found that BDNF levels measured at resting were negatively correlated with recognition memory accuracy for individuals with low fitness levels, but positively correlated for individuals with high fitness levels in healthy young adults. Adolescent exercises have reduced levels of neurotrophic factors (BDNF and IGF-1) compared to matched sedentary controls, although this may be due to whether neurotrophic factors are measured immediately after engaging in exercise or at rest (Lee et al., 2014).,

Based on the vast literature surrounding physical activity and its association to cognition and neurogenesis, Kempermann et al. (Kempermann, 2008; Kempermann et al., 2010) have proposed the neurogenic reserve hypothesis. According to this hypothesis, physical activity maintains adult neurogenesis and conserves the potential for neuronal-based plasticity. This potential "[represents] an event-triggered investment for the future and [prepares] the hippocampal network for coming situations that are similar to the one that…induced the integration of [new neurons]" (p. 167). Because most physical activity for animals is associated with enhanced cognitive challenges (such as finding food), the authors speculate that physical activity engaged in over long periods of time may indicate an increased chance of encountering

complex and novel situations, which stimulates the brain to build up a reserve of neuronal resources to accommodate these future challenges. This model proposes that the brain uses previous experience combined with activity levels to predict future neuronal needs. Thus, it is not necessarily isolated physical activity that is "good for the brain", but physical activity accompanied with cognitive challenges that really matters. Physical activity may signal the likelihood of encountering a future cognitive challenge and this is why physical activity has been extensively correlated with enhances in both cognition and neurogenesis (Kempermann, 2008; Kempermann et al., 2010).

Experiment 2 used high-resolution fMRI to evaluate neuronal activity differences during the performance of a continuous recognition pattern separation task among individuals with assumed higher levels of neurogenesis; specifically, considering different levels of physical activity. High-resolution fMRI is particularly well-suited when evaluating the relative contributions of mnemonic processes in medial temporal lobe substructures (Carr et al., 2010). In a high-resolution fMRI study, Bakker et al. (2008) demonstrated that pattern separation is limited to CA3/DG subregions of the hippocampus. The present study sought to extend the pattern separation paradigm previously used by others (Bakker et al., 2008; Shelton & Kirwan, 2013; Toner et al., 2009) to examine the impact physical activity had on pattern separation. Given that physical activity has previously been linked with enhanced pattern separation in animals (Creer et al., 2010) it was hypothesized that adults who engaged in the recommended levels of physical activity ("American heart association recommendations for physical activity in adults," 2013) would have greater activation in the CA3/DG, indicative of greater pattern separation, compared to adults who did not meet recommended levels of physical activity.

Method

Participants. Sixty-one participants (30 men and 31 women) were recruited through BYU campus and the surrounding community. All participants were between the ages of 18 and 40 years and were screened to ensure they were right handed, native English-speakers who were in good overall health with no history of head injury or any physiological, psychological, or neurological disorders. Participants were also screened to ensure they were MRI-compatible. Participants were placed in one of three groups, depending on their responses to an online pre-qualification physical activity survey (Appendix A). Twenty-one individuals (ten men and eleven women) were recruited for the sedentary group (defined as engaging in no additional exercise outside of daily, routine physical activity), twenty individuals (ten men and ten women) were recruited for the low-physical activity group (defined as engaging in additional exercise outside of routine physical activity for at least 6 months, but not to the level that meets those recommended by the American Heart Association; "American heart association recommendations for physical activity in adults," 2013), and twenty individuals (ten men and ten women) were recruited for the high-physical activity group (defined as meeting or exceeding the recommended levels of at least 150 minutes per week of moderate-intensity aerobic activity – such as walking briskly – or 75 minutes a week of vigorous-intensity aerobic activity – such as jogging or running – and at least 2 days per week of muscle-strengthening activity for at least the previous 6 months). Participants were compensated $50 for their participation.

Two women from the sedentary group were excluded from MRI data collection, one due to equipment issues with the MRI scanner and one due to scanner-incompatibility. One male from the low-physical activity group self-terminated after initially entering the MRI scanner bore. Additionally, another woman from the sedentary group was excluded from data analysis

due to experimenter error and four men from the low-physical activity group and one man from the high-physical activity group was excluded from fMRI data analysis due to a high number of non-responses (defined as greater than two standard deviations above the mean) during the functional task. Finally, one man from the high-physical activity group was excluded from fMRI data analysis due to an equipment malfunction during his high-resolution scan.

Thus, fMRI data analysis was conducted on 51 participants (23 men and 28 women): 18 in the sedentary group (10 men and 8 women); 15 in the low-physical activity group (5 men and 10 women); and 18 in the high-physical activity group (8 men and 10 women). These groups did not differ by age (Sedentary M=23.44, SD=4.55; Low-PA M=22.80, SD=2.11; High-PA M=22.33, SD=3.53; $F(2,48)=.429$, $p = .654$), education (Sedentary M=14.42, SD=1.02; Low-PA M=14.27, SD=0.86; High-PA M=14.14, SD=1.23; $F(2,48)=.309$, $p = .735$), or body mass index (BMI; Sedentary M=22.58, SD=4.06; Low-PA M=22.75, SD=2.42; High-PA M=22.07, SD=2.23; $F(2,48)=.231$, $p = .795$). Demographic information is presented in Table 2 and although the groups did not differ by any demographic characteristic measured, it is interesting to note that the women in the sedentary group had the lowest BMI and the men in the low-PA group had the highest BMI. However, all of the groups were within normal BMI standards except for the low-PA men who had several members with a high level of strength activities.

Table 2.
Demographic information (mean, standard deviation) for sedentary, low-physical activity, and high-physical activity groups for Experiment 2.

	Sedentary				Low-PA				High-PA			
	Men		Women		Men		Women		Men		Women	
N	10		8		5		10		8		10	
Age (years)	25.10	(5.53)	21.38	(1.51)	24.60	(1.52)	21.90	(1.79)	25.13	(3.23)	20.10	(1.73)
Height (inches)	71.10	(2.47)	65.75	(1.83)	70.60	(1.95)	66.70	(2.75)	71.50	(3.07)	65.95	(1.61)
Weight (pounds)	172.60	(40.63)	129.00	(14.96)	178.40	(19.18)	136.60	(14.26)	169.25	(20.09)	130.80	(14.48)
BMI	23.90	(4.90)	20.94	(1.92)	25.13	(2.05)	21.56	(1.59)	23.19	(1.07)	21.17	(2.54)
Education	14.75	(0.98)	14.00	(0.96)	14.50	(0.00)	14.15	(1.06)	14.88	(1.06)	13.55	(1.07)

Note. Participants from the fMRI analyses (Experiment 2) consisted of the same group of individuals from the DTI analyses (Experiment 3); minus those whose fMRI data were either corrupted or had excessive behavioral errors. BMI calculated as: (weight / (height)^2) x 703.

Questionnaires. Participants met with the experimenter twice at the BYU MRI Research Facility, the first meeting lasted about 30 minutes and the second meeting lasted about 2.5 hours. During the first meeting, they fill out a demographic questionnaire and were given an Actigraph GT3X+ accelerometer (Pensacola, FL) to wear for one week; the Actigraph data were not analyzed as part of the current focus for this study. They were also given a meter log (Appendix B), and an exercise log (Appendix C) to keep track of accelerometer wear and any exercise they engaged in during the following 7 days. Participants also filled out a dietary questionnaire as part of a separate ongoing study. Participants were also asked to completed an online version of the Pittsburgh Sleep Quality Inventory (PSQI; Buysse, Reynolds III, Monk, Berman, & Kupfer, 1989) once before the second meeting as part of a separate study.

During the second meeting, participants had approximately 10 ml of their blood drawn by a certified phlebotomist. Blood samples were used to assess serum levels of BDNF, which were expected to vary among the three groups with increased BDNF levels associated with increased physical activity. Participants also filled out the State-Trait Anxiety Inventory (STAI; Spielberger & Gorsuch, 1983), the Recent Physical Activity Questionnaire (RPAQ; Besson, Brage, Jakes, Ekelund, & Wareham, 2010) and the BYU MRI Research Facility screening form ("BYU MRIRF Screening Form," 2014). The STAI measures both state anxiety and trait anxiety. The RPAQ is designed to evaluate an individual's overall physical activity level by asking questions regarding the amount and type of home, work, transport, and recreation physical activity engaged in during the past four weeks. RPAQ data were not analyzed as part of the current focus of this study.

BDNF assays. During the blood draw, blood was collected in sterile serum separator tubes (Becton Dickinson) and kept at room temperature for approximately 30 minutes to allow

for clotting. Blood was then kept at 4 C° until they were centrifuged at 1,000 x g for 15 minutes. Blood was centrifuged and processed by a trained molecular biologist. Serum was then separated, aliquoted, and stored at -80 °C until analyzed. Serum BDNF was analyzed using the Human BDNF Immunoassay Quantikine ELISA Kit (R&D Systems). All assays were performed according to the protocol provided by the manufacturer and all samples were run in duplicate. Tests failed on two samples, so these were rerun. BDNF levels were then obtained by reducing the data to a linear regression analysis. The biologist conducting the antibody assays was blind to gender and physical activity level and the same individual performed all of the assays in order to reduce the influence of pipetting error on the results.

Behavioral procedure. The behavioral task used in Experiment 2 was the same task used in Experiment 1, except it was performed inside of the MRI scanner. Participants were given instructions regarding the behavioral task prior to being positioned within the MRI scanner. Once participants were placed on the MRI scanning table they were given a 4-side button response cylinder (Current Designs Inc.; Philadelphia, PA) and instructed to press the first button with their pointer finger if the picture was exactly the same as one previously seen; press the second button with their middle finger if they had seen something similar, but not exactly the same; and press the third button with their ring finger if the picture was completely new. Stimuli were displayed on an MRI compatible LCD screen (BOLDscreen; Cambridge Research Systems; Rochester, UK) positioned at the head of the MRI scanner. Participants were able to view the stimuli by looking at a mirror placed on top of the head coil. Once participants were inside of the MRI scanner and just prior to the first functional scan, they were shown an example of what the stimuli would look like and an example of what two similar objects may look like. Instructions, regarding which button corresponded with which stimulus type, were also briefly restated.

Structural MRI parameters. All MR imaging was performed on a Siemens 3 Tesla Tim MAGNETOM® Trio scanner (Erlangen, Germany) using a 32-channel receive-only head coil at the BYU MRI Research Facility (Provo, UT). Structural images were acquired using a T1-weighted MPRAGE sequence with the following parameters: 192 interleaved slices; TA = 8:55 min; TR = 20 ms; TE = 4.92 ms; flip angle = 25°; field of view = 256 mm; slice thickness = 1 mm; voxel resolution = 1.0×1.0×1.0 mm; 1 average. In addition, high-resolution structural images were also obtained since these have been previously proposed to be particularly well-suited when evaluating medial temporal lobe subregions (Carr et al., 2010). Thus, a T2-weighted pulse sequence was acquired with the following parameters: 35 interleaved slices; TA = 9:44 min; TR = 6000 ms; TE = 64 ms; flip angle = 129°; field of view = 200 mm; slice thickness = 2 mm; voxel resolution = 0.4×0.4×2.0 mm; averages = 2. This scan was aligned with the longitudinal axis of the hippocampus for each participant prior to acquisition.

fMRI parameters. High-resolution functional images were acquired using gradient-echo echoplanar, T2*-weighted pulse sequence utilizing a multi-band (MB) technique (Xu et al., 2013). There were six functional scans conducted that coincided with six blocks of the behavioral memory discrimination task. These scans had the following parameters: 72 interleaved slices; TA = 6:25 min; TR = 875 ms; TE = 43.6 ms; flip angle 55°; field of view = 180 mm; slice thickness = 1.80 mm; voxel resolution = 1.8×1.8×1.8 mm; multi-band factor = 8; measurements = 428. These scans were also oriented along the longitudinal axis of the hippocampus for each participant. The first five TRs acquired were discarded to allow for T1 stabilization.

Results

BDNF comparisons. Serum levels of BDNF were expected to vary among the three groups with increased BDNF levels associated with increased physical activity. A one-way ANOVA was conducted on the BDNF levels for the 57 participants run in the DTI analysis (51 of which were included in the fMRI analysis). The difference between physical activity groups' BDNF levels was marginally significant (Sedentary M=31947.72, SD=8808.27, low-physical activity M=26548.32, SD=1966.71, high-physical activity M=25647.15, SD=7941.04; $F(2,54)=3.031$, $p = .057$). Surprisingly, BDNF levels were highest for sedentary participants, followed by low- and then high-physical activity groups. Post-hoc tests of Fisher's least significant difference (LSD) revealed a significant difference between sedentary at high-physical activity groups ($p = .025$), but not between sedentary and low-physical activity groups ($p = .057$) or between low- and high-physical activity groups ($p = .740$).

BDNF levels have been shown to vary with levels of anxiety, for example, when engaging in a short-term stressor, such as public speaking (Meng et al., 2011) or when experiencing long-term stress, such as a demanding job (Mitoma et al., 2008). To address any possible effects of anxiety, participants completed the STAI (Spielberger & Gorsuch, 1983) and one-way ANOVA results revealed no significant differences between physical activity groups (Sedentary M=63.17, SD=14.55, low-physical activity M=63.11, SD=12.33, high-physical activity M=57.35, SD=14.95; $F(2,54)=1.108$, $p = .337$). Nor did BDNF levels and STAI scores correlate with one another ($r = 0.154$, $n = 57$, $p = .252$).

fMRI processing. Data analysis was performed using the Analysis of Functional NeuroImages (AFNI) software (Cox, 1996). First, each participant's functional scans were time shifted to the same temporal origin; this is also known as slice-time correction and was used to

adjust for any shifting in the hemodynamic response in adjacent voxels due to acquisition time differences. Functional imaging data were then registered to the middle time point of each scan (i.e., measurement 214) to reduce the effect of any head motion. Large motion events, defined as TRs in which there was more than 0.3° of rotation or 0.6 mm of translation in any direction, were excluded in addition to TRs immediately before and after a motion-contaminated TR. The six functional scans were then aligned to one another and the structural scan was co-registered to the functional data in order to align the voxels between these scans for each individual.

Each participant's behavioral data were initially processed in Excel® (Redmond, WA) and response types were identified for each trial. Correct response (CR) trials were identified when the stimulus was categorized as a first presentation and the participant responded "new". Hit trials were classified when the stimulus was categorized as a repeat and the participant responded "old". Lure CR trials were identified when the stimulus was categorized as a lure and the participant responded "similar". Lure false alarm (FA) trials were classified when the stimulus was categorized as a lure and the participant responded "old". Foil trials were identified when the stimulus was categorized as a foil and the participant responded "new". Finally, other trials were classified when any other type of response was made to any of the stimulus types. These six categories were used as vectors, along with six motion vectors (coding for anterior-posterior, right-left, and inferior-superior translations as well as yaw, pitch, and roll rotations), to process the functional data. Specifically, these vectors were entered into a general linear model (GLM) to model each participant's functional data using a deconvolution approach treating the foil stimuli as the baseline condition. The resulting statistical maps of fit coefficients (β coefficients) represent the differences in activity between each of the trial types and the baseline condition.

Next, participants' structural scans were aligned via their anterior and posterior commissures (AC-PC) and cross-participant alignment was performed. First, all participants' structural and functional scans were normalized to the Talairach atlas (Talairach & Tournoux, 1988) and then resampled to $1.8mm^3$. Additional spatial normalization was carried out using Advanced Normalization Tools (ANTs, version 1.9, http://sourceforge.net/projects/advants; Avants et al., 2008; Klein et al., 2009; Lacy et al., 2011; Motley & Kirwan, 2012; Yassa et al., 2010), which uses diffeomorphic mapping to calculate a transformation from each participant to a template based on the structural scan.

After individual deconvolution analysis and spatial normalization, individual participant parameter estimate maps were entered into group-level analyses. First, regions of interest (ROIs) were hand segmented using the high-resolution structural images and these hand segmentations were used for functional localization. Based on the hypotheses for this study, the following bilateral ROIs were identified: CA1, CA3/DG, and subiculum subregions of the hippocampus.

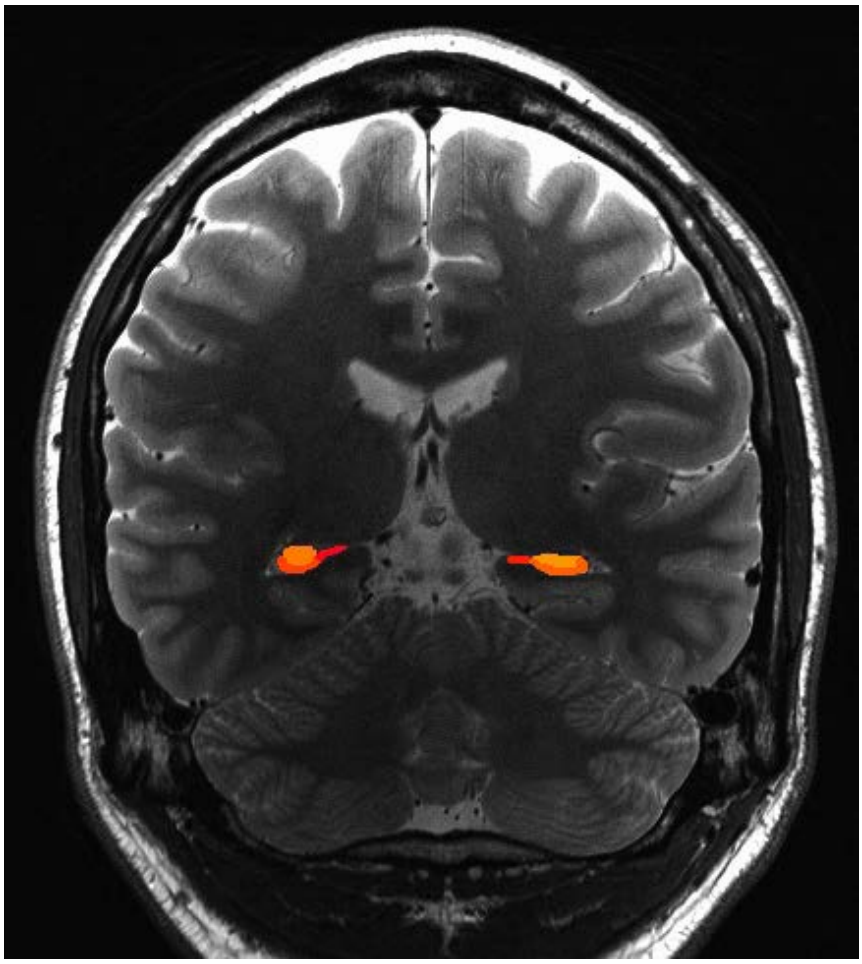


Figure 5. Hand-segmented bilateral ROIs in the hippocampus subregions: CA1 (orange), CA3/DG (yellow), and subiculum (red) for a male sedentary participant in Experiment 2.

These ROI hand-segmentations for each participant were then aligned and resampled to the functional scans. Next their values were thresholded at 50% to remove any partial voluming, which may have occurred during the alignment and resampling processes. Finally, each ROI was used as a structural mask and the mean functional data value for each participant was obtained from that region (left CA1, right CA1, left CA3/DG, right CA3/DG, left subiculum, and right subiculum).

fMRI data analysis. Processed functional data were then subjected to two 3 × 4 MANOVAs in SPSS (Version 21; Armonk, NY), one for each ROI of interest (left CA3/DG,

right CA3/DG) with physical activity level (sedentary, low, and high) as the between-subjects measure and trial-response type (CR, Hit, Lure CR, and Lure FA) as the within-subjects measure. As previously stated, it was hypothesized that participants in the high-physical activity group would have greater CA3/DG activation in response to CRs and Lure CRs than for Hits and Lure FAs, compared with sedentary and low-physical activity individuals.

Multivariate tests revealed no significant differences between groups for the left CA3/DG ($F(8, 90) = .496$, $p = .856$; Wilks' $\Lambda = 0.917$, partial $\eta^2 = .042$) or right CA3/DG ($F(8, 90) = .647$, $p = .736$; Wilks' $\Lambda = 0.894$, partial $\eta^2 = .054$).

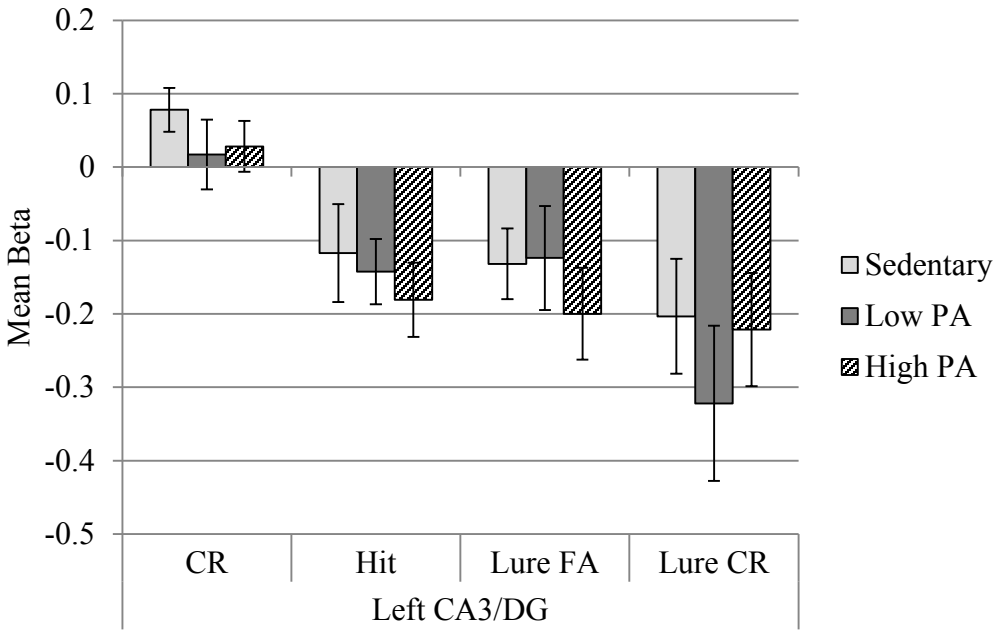


Figure 6. Plot of mean beta coefficients for each of the response types in the left CA3/DG subregion of the hippocampus for sedentary, low-physical activity, and high-physical activity participants in Experiment 2. Stimuli consisted of photographs of everyday objects. First presentation stimuli, responded to as "new" = correct response (CR); repeat stimuli, responded to as "old" = Hit; lure stimuli, responded to as "similar" = Lure CR; lure stimuli, responded to as "old" = Lure false alarm (FA). Foil stimuli (only shown once) were used as baseline. Analysis of response types revealed no significant differences between groups: $F(8, 90) = .496$, $p = .856$; Wilks' $\Lambda = 0.917$, partial $\eta^2 = .042$. Error bars depict *SEM*.

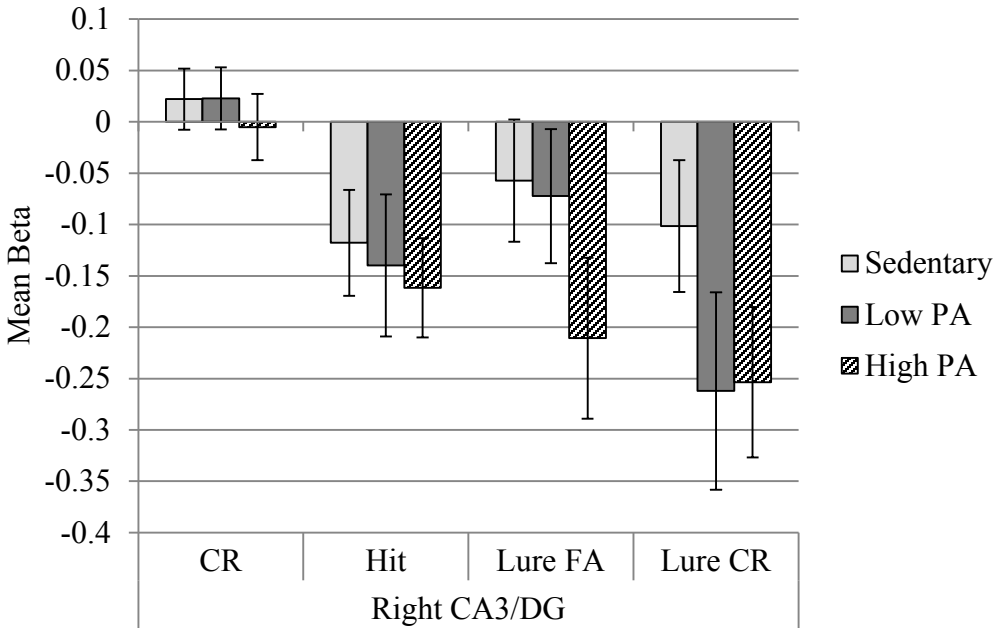


Figure 7. Plot of mean beta coefficients for each of the response types in the right CA3/DG subregion of the hippocampus for sedentary, low-physical activity, and high-physical activity participants in Experiment 2. Stimuli consisted of photographs of everyday objects. First presentation stimuli, responded to as "new" = correct response (CR); repeat stimuli, responded to as "old" = Hit; lure stimuli, responded to as "similar" = Lure CR; lure stimuli, responded to as "old" = Lure false alarm (FA). Foil stimuli (only shown once) were used as baseline. Analysis of response types revealed no significant differences between groups: $F(8, 90) = .647$, $p = .736$; Wilks' $\Lambda = 0.894$, partial $\eta^2 = .054$. Error bars depict *SEM*.

Additional post-hoc comparisons for the rest of the ROIs were also conducted. Four 3 × 4 MANOVAs revealed no significant differences between groups for the left CA1 ($F(8, 90) = .991$, $p = .449$; Wilks' $\Lambda = 0.845$, partial $\eta^2 = .081$), right CA1 ($F(8, 90) = .974$, $p = .461$; Wilks' $\Lambda = 0.847$, partial $\eta^2 = .080$), left subiculum ($F(8, 90) = 1.409$, $p = .203$; Wilks' $\Lambda = 0.790$, partial $\eta^2 = .111$), or right subiculum ($F(8, 90) = 1.419$, $p = .199$; Wilks' $\Lambda = 0.789$, partial $\eta^2 = .112$).

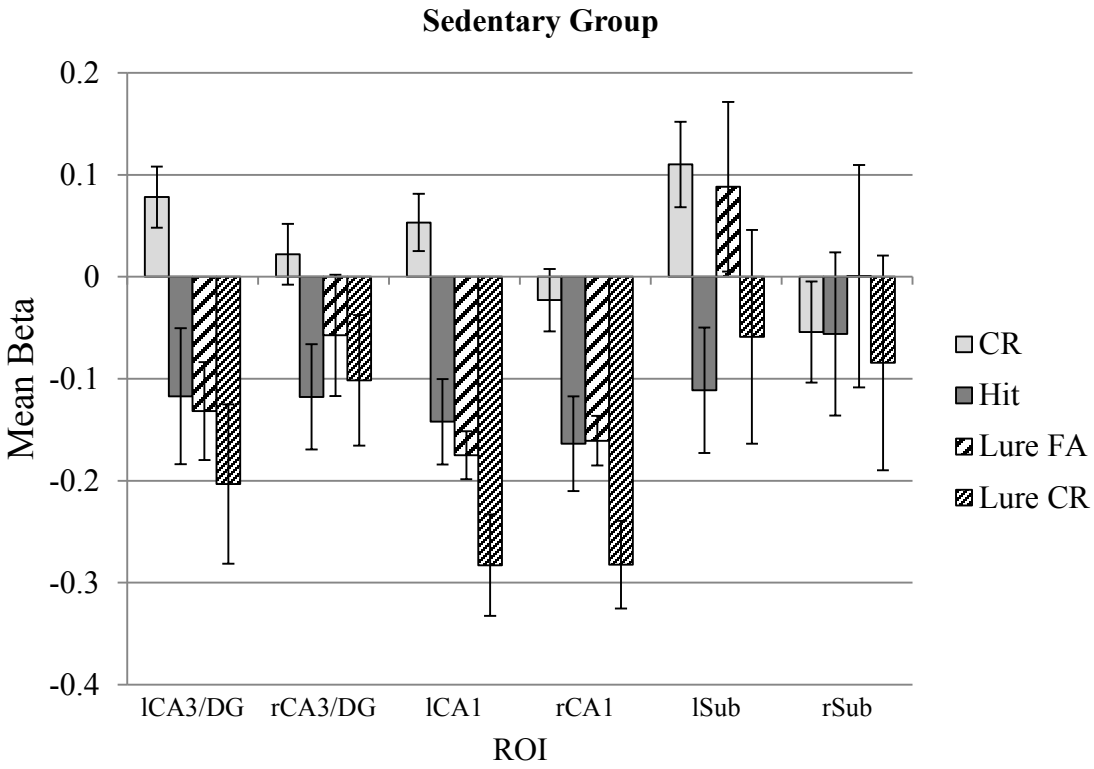


Figure 8. Plot of mean beta coefficients for each of the response types in each subregion of the hippocampus for sedentary participants in Experiment 2. Stimuli consisted of photographs of everyday objects. First presentation stimuli, responded to as "new" = correct response (CR); repeat stimuli, responded to as "old" = Hit; lure stimuli, responded to as "similar" = Lure CR; lure stimuli, responded to as "old" = Lure false alarm (FA). Foil stimuli (only shown once) were used as baseline. None of the analyses revealed significant differences. Error bars depict *SEM*.

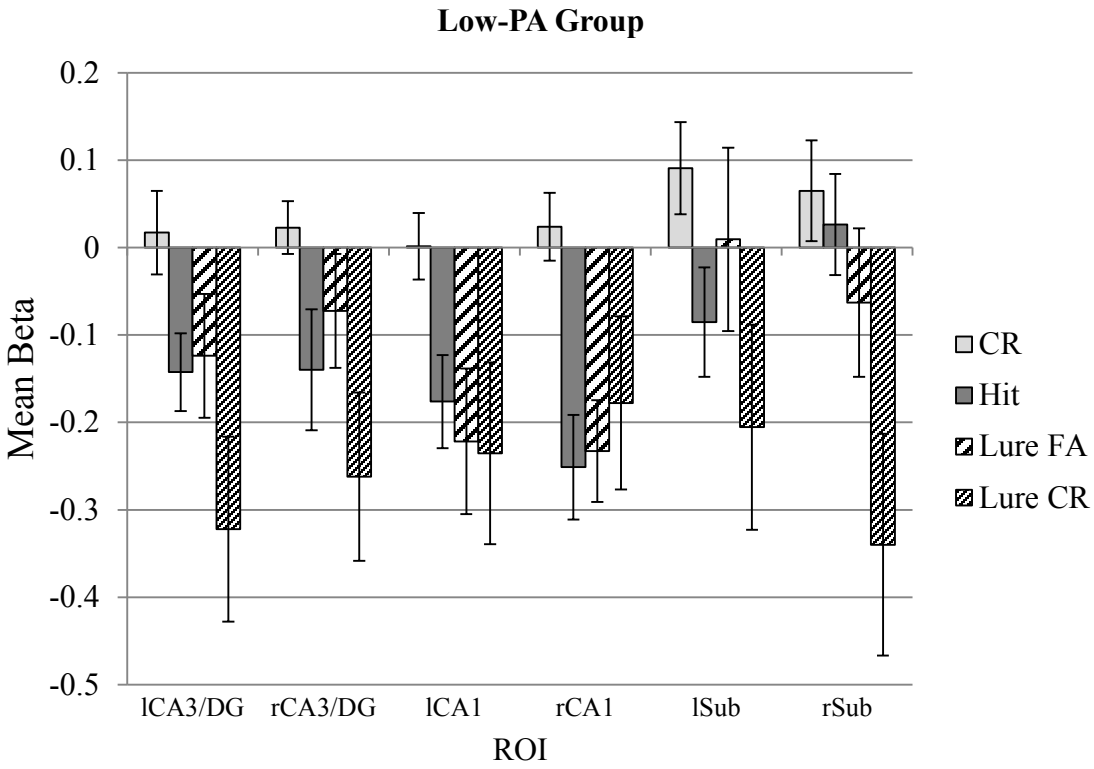


Figure 9. Plot of mean beta coefficients for each of the response types in each subregion of the hippocampus for low-physical activity participants in Experiment 2. Stimuli consisted of photographs of everyday objects. First presentation stimuli, responded to as "new" = correct response (CR); repeat stimuli, responded to as "old" = Hit; lure stimuli, responded to as "similar" = Lure CR; lure stimuli, responded to as "old" = Lure false alarm (FA). Foil stimuli (only shown once) were used as baseline. None of the analyses revealed significant differences. Error bars depict *SEM*.

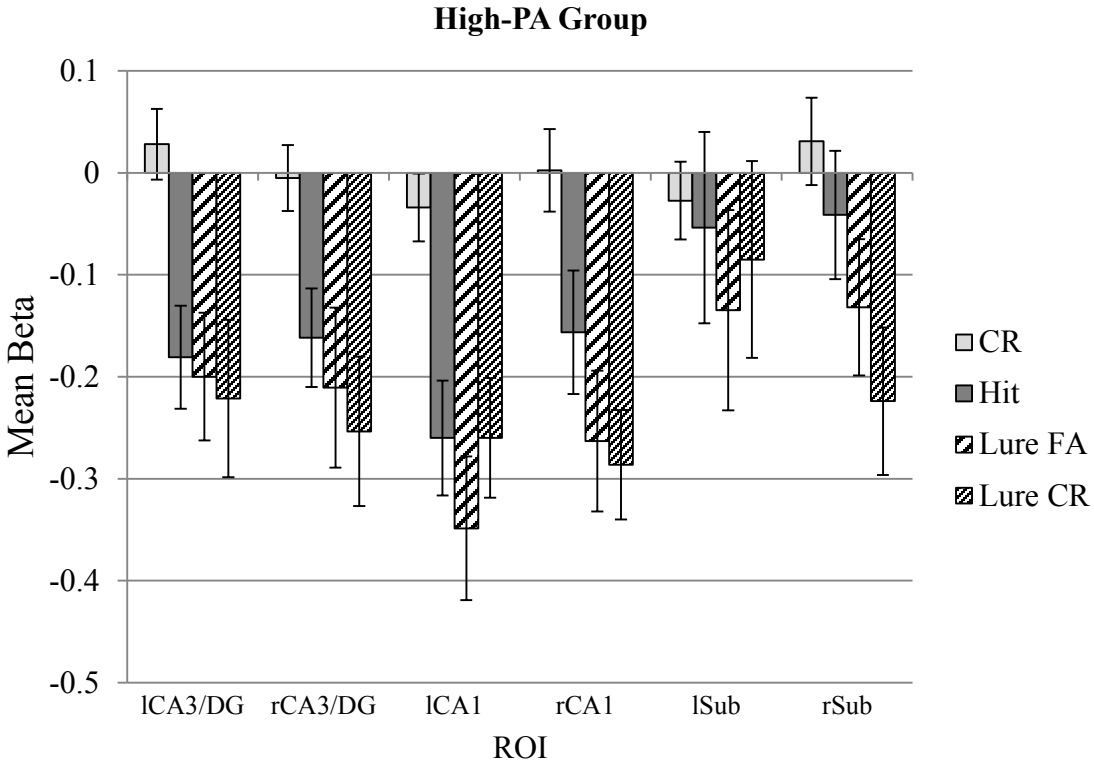


Figure 10. Plot of mean beta coefficients for each of the response types in each subregion of the hippocampus for high-physical activity participants in Experiment 2. Stimuli consisted of photographs of everyday objects. First presentation stimuli, responded to as "new" = correct response (CR); repeat stimuli, responded to as "old" = Hit; lure stimuli, responded to as "similar" = Lure CR; lure stimuli, responded to as "old" = Lure false alarm (FA). Foil stimuli (only shown once) were used as baseline. None of the analyses revealed significant differences. Error bars depict *SEM*.

Physical activity survey analysis. One-way ANOVA analysis of participants' self-reported physical activity revealed significant differences for current activity level ($F(2,48)=96.90$; $p < .0001$), frequency of aerobic activity ($F(2,48)=75.16$; $p < .0001$), length of aerobic activity ($F(2,48)=19.87$; $p < .0001$), level of aerobic activity ($F(2,48)=31.12$; $p < .0001$), frequency of strength activity ($F(2,48)=60.73$; $p < .0001$), length of strength activity ($F(2,48)=35.19$; $p < .0001$), and level of strength activity ($F(2,48)=61.42$; $p < .0001$). These results are consistent with groupings based on participants' responses to this physical activity measure. However, post-hoc comparisons using Fisher's LSD demonstrate that the high and low

physical activity groups did not differ by frequency of aerobic activity (p = .289) or length of aerobic activity (p = .559). They did marginally differ on level of aerobic activity (p = .048) and were significantly different on frequency of strength activity (p = .0003), length of strength activity (p = .025) and level of strength activity (p = .028). Thus, it appears that the two physical activity groups in Experiment 2 only differed with regards to strength activities and not aerobic activities. Comparisons between the sedentary and low-physical activity groups and sedentary and high-physical activity groups showed statistically significant differences with p <.0001 in each category of aerobic and strength activity.

Discussion

Contrary to the original hypothesis, activation in the CA3/DG did not distinguish the high-physical activity group from the sedentary or low-physical activity groups. Visual inspection of the data (reference Figures 6 and 7) reveals some differentiation between the groups; however, the variance within each group was large enough that no significant differences across groups were found. Of particular interest is the Lure FA comparison of the right CA3/DG (see Figure 7). It appears that there was greater activation in this region for the high-physical activity group in conjunction with lure stimuli called “old”. However, the current design lacked sufficient power to reveal any such difference. Post-hoc power analysis revealed a necessary sample size of 66 for global MANOVA effects using three groups with four response variables (effect size = 0.25; alpha = 0.01; power = 0.95).

Visual comparison of Figures 8, 9, and 10 show similarities in activation to response type within the other ROIs between the three groups. The one exception is the left subiculum where CRs look similar for sedentary and low-physical activity groups compared to the high-physical activity group and where Lure FAs look very dissimilar across all three groups. However, the

restricted size of the subiculum makes it difficult to draw strong conclusions regarding these data. Once again, increased power may be needed to draw strong conclusions regarding these data.

In addition, BDNF analysis revealed no differences between physical activity groups, although there was a difference found between sedentary and high-physical activity groups. Unfortunately, it was in the opposite direction of that predicted with sedentary participants having higher BDNF levels than participants in the high-physical activity group. Further indicating that the physical activity groups did not differ as much as originally anticipated. However, a recent study analyzing BDNF processing methods found that BDNF levels in an exercise sample were significantly different when blood was analyzed using whole blood and serum coagulated for 24 hours, but not when using plasma or serum coagulated for 10 minutes (Pareja-Galeano et al., 2015). They also found that serum samples must be kept at a consistent 4 C° or BDNF levels would degrade. Blood samples used in Experiment 2 were initially kept in a refrigerator shared with other laboratories and it is possible that the temperature varied from 4 C°. In addition, the amount of time that samples were kept at 4 C° before being centrifuged varied from several hours to several days. It is unknown how these longer initial storage times may have affected the BDNF levels.

Participant recruitment was focused mostly on the BYU campus and surrounding areas, with the majority of participants being BYU students or staff. Since BYU's campus design consists of a walking campus with parking lots on the perimeter and no roads connecting the inner buildings, it is likely that even the sedentary participants in Experiment 2 had more daily physical activity than desired for a "sedentary" group. In addition, as confirmed by the post-hoc analysis of physical activity levels, the physical activity differences between the low and high

groups did not differentiate. Future physical activity studies should ensure greater differences in physical activity between participant groups; ensuring "sedentary" participants have low levels of both exercise and daily physical activity and physical activity groups have wide differences in aerobic activity levels, perhaps by evaluating athletes with non-athletes.

A recent study of older adults evaluating hippocampal volumes and verbal memory also found no differences between individuals who engaged in an aerobic exercise intervention program and controls; although they did find a correlation between hippocampal perfusion and increased fitness levels (Maass et al., 2014). They attributed their null finding to the fact that their control group demonstrated increased baseline fitness levels as well as a more daily activity. However, others have found associations between low-levels of daily physical activity and enhanced episodic memory encoding in older adults, which did not hold for aerobic fitness (Flöel et al., 2010). As previously mentioned, other studies have found that a combination of strength and aerobic activities results in greatest cognitive improvements compared to aerobic activity alone (Colcombe & Kramer, 2003; Smith et al., 2010). Participants in Experiment 2 completed the RPAQ (Besson et al., 2010) and also wore accelerometers; perhaps re-grouping the participants based on their RPAQ scores or activity data would result in different fMRI findings in the current data set.

Participant age may also have played a factor in the fMRI results for Experiment 2. Many previous studies on physical activity and cognition have focused on older adults. For example, higher current physical activity is related to lower white matter lesion volumes in older adults (Wirth, Haase, Villeneuve, Vogel, & Jagust, 2014) and older adults who engaged in an exercise program for 2 years demonstrate improvements in attention, which correlates with bilateral prefrontal gray matter volumes (Tamura et al., 2014). Furthermore, older adults who engaged in

a 16-week exercise program demonstrate improved attention compared to control and cognitive training groups (Candela, 2015). Thus, cognitive benefits associated with physical activity may have greater measurability with age.

However, across three age groups (adults in their 20s, 40s, and 60s), more physically active adults demonstrated higher fluid cognition scores (consisting of perceptual speed and short-term, working, and episodic memory; Bielak, Cherbuin, Bunce, & Anstey, 2014). This effect was especially true for adults in their 20s who demonstrated that within-participant changes in physical activity over an 8-year span was associated with an increase in their cognitive score, with a weekly increase of 1 hour in exercise associated with a 0.3 increase in cognitive scores. Another recent study of young adults (18-34 years) found that aerobic fitness (as measured by VO_2 levels) was correlated with relational memory, but not item memory (Baym et al., 2014). Finally, Chang et al. (2014) found that, before and after participating in a 30 minute bout of aerobic cycling, young adults categorized as having moderate and low fitness showed shorter response times during Stroop incongruent trials, compared to those in the high fitness group; no differences were found between groups for the Stroop congruent trials. Future studies may wish to evaluate fitness levels (perhaps using VO_2 levels) and/or perform an exercise intervention to establish within-subjects comparisons on mnemonic specificity.

Previous fMRI studies using a similar version of the task used in Experiment 2 found increased comparable mean activation in bilateral CA3/DG for first presentation and lure stimuli (indicative of pattern separation), but not for repeat stimuli and comparable activation for repeat and lure stimuli (indicative of pattern completion) in CA1 and other regions (Bakker et al., 2008; Lacy et al., 2011; Yassa, Mattfeld, Stark, & Stark, 2011). The key difference between the task used in previous studies and the current study is that previous studies used an implicit version

whereas the current study used an explicit version of task. The implicit version of this task asks participants to rate each stimulus as being more likely to be found indoors or outdoors. However, the current study used the explicit version, where participants were told that some of the stimuli will be similar to others, but not exactly the same and to rate each stimulus as old, similar, or new. Thus, task demands in Experiment 2 may have biased hippocampal processing toward pattern completion, where mean activation to lure stimuli resembles that of repeat stimuli (aka "hits"), thus allowing participants to compare previously encoded object memory representations with incoming stimulus representations. This interpretation and pattern of results is consistent with previous studies that have used an explicit version of the task (e.g., Kirwan & Stark, 2007; Motley & Kirwan, 2012).

Chapter 4: The Impact of Physical Activity on White Matter Pathways (Experiment 3)

Several studies have utilized MRI and fMRI techniques to examine the role physical activity may play on neurogenesis and cognitive measures, with most finding that individuals who engage in regular exercise have enhanced plasticity and structural and functional integrity (for reviews see: Boecker, 2011; Hayes, Hayes, Cadden, & Verfaellie, 2013; Thomas, Dennis, Bandettini, & Johansen-Berg, 2012; Voelcker-Rehage & Niemann, 2013). However, only a few studies have utilized diffusion tensor imaging (DTI) to examine changes in white matter integrity due to physical activity. Higher fitness levels in young adults are associated with greater white matter integrity in the uncinate fasciculus and cingulum (Marks et al., 2007). Higher body mass index (BMI) scores in older individuals are related to less white matter integrity in the right posterior cingulum and greater physical fitness (as measured by higher VO_2 peaks) is associated with greater white matter integrity in the left anterior and middle cingulum areas (Marks, Katz, Styner, & Smith, 2011). Flöel et al. (2010) found that increased physical activity in daily life routines is associated with increased prefrontal and cingulate gray matter volume in older adults. In a population of older adults with small-vessel disease (SVD), lower physical activity levels are associated with lower microstructural white matter integrity of multiple tracks connecting cortical and subcortical regions throughout the brain (Gons et al., 2013).

When comparing aerobic fitness levels in male adolescents and white matter connectivity and microstructure, those with higher fitness levels have a greater number of streamlines in the corticospinal and forceps minor tracts, but lower FA values in the corticospinal tract (Herting, Colby, Sowell, & Nagel, 2014). These lower FA values may be due to increased numbers of glial cells and crossing fibers in those with increased aerobic fitness levels. Finally, greater gray matter volumes in the left superior frontal gyrus in martial artists (national and international

high-level competitive athletes) and endurance athletes (national long-distance competitive athletes), compared to controls, may be related to the acquisition and maintenance of motor skills frequently performed in high-performance athletes (Schlaffke et al., 2014). When comparing endurance-sport athletes with martial-art athletes, increased gray matter volumes are found bilaterally in the DG for the endurance-sport athletes, which may be related to an enhanced aerobic metabolism.

Experiment 3 used DTI to evaluate differences in white matter integrity among individuals with different levels of physical activity. While a few studies have utilized DTI to examine white matter and gray matter differences in physically active individuals, no studies found have examined such differences among various levels of physical activity. Therefore, it was predicted that there would be increasingly greater levels of white matter integrity (measured by fractional anisotropy (FA), radial diffusivity (RD), and axial diffusivity (AD) values) among adults who consider themselves to be active but do not meet the recommended exercise levels and those who do meet the recommended levels, compared with sedentary individuals. Specifically, it was hypothesized that adults who engaged in the AHA's recommended levels of physical activity would have greater white matter integrity in the uncinate fasciculus and cingulum networks, compared to adults who did not meet recommended levels and sedentary adults. These particular white matter pathways were selected based on findings from previous physical activity research. It was further hypothesized that group differences in white mater integrity would be found in the medial temporal lobe pathways as well since this region is involved with neurogenesis.

Method

Participants. The same participants used in Experiment 2 were used in Experiment 3. One woman in the high-physical activity group, who was excluded from the fMRI data analysis due to corrupted data, had intact DTI data and was included in Experiment 3. Additionally, one woman from the sedentary group, four men from the low-physical activity group, and one man from the high-physical activity group, who were excluded from fMRI data analysis, had intact DTI data and were also included in the current experiment.

Thus, DTI data analysis was conducted on 57 participants (29 men and 28 women): 18 in the sedentary group (10 men and 8 women); 19 in the low-physical activity group (9 men and 10 women); and 20 in the high-physical activity group (10 men and 10 women). These groups also did not differ by age (Sedentary M=23.44, SD=4.55; Low-PA M=22.89, SD=2.21; High-PA M=22.65, SD=3.48; $F(2,54)=.249$, $p = .780$), education (Sedentary M=14.42, SD=1.02; Low-PA M=14.45, SD=0.98; High-PA M=14.25, SD=1.24; $F(2,54)=.185$, $p = .832$), or BMI (Sedentary M=22.58, SD=4.06; Low-PA M=23.30, SD=2.67; High-PA M=22.61, SD=2.90; $F(2,54)=.294$, $p = .746$; see Table 3).

Table 3.
Demographic information (mean, standard deviation) for sedentary, low-physical activity, and high-physical activity groups for Experiment 3.

	Sedentary				Low-PA				High-PA			
	Men		Women		Men		Women		Men		Women	
N	10		8		9		10		10		10	
Age (years)	25.10	(5.53)	21.38	(1.51)	24.00	(2.18)	21.90	(1.79)	25.20	(2.86)	20.10	(1.73)
Height (inches)	71.10	(2.47)	65.75	(1.83)	71.11	(3.30)	66.70	(2.75)	71.50	(3.75)	65.95	(1.61)
Weight (pounds)	172.60	(40.63)	129.00	(14.96)	182.44	(29.33)	136.60	(14.26)	176.40	(34.83)	130.80	(14.48)
BMI	23.90	(4.90)	20.94	(1.92)	25.23	(2.30)	21.56	(1.59)	24.06	(2.58)	21.17	(2.54)
Education	14.75	(0.98)	14.00	(0.96)	14.78	(0.83)	14.15	(1.06)	14.95	(1.01)	13.55	(1.07)

Note. Participants from the fMRI analyses (Experiment 2) consisted of the same group of individuals from the DTI analyses (Experiment 3); minus those whose fMRI data were either corrupted or had excessive behavioral errors. BMI calculated as: (weight / (height)^2) x 703.

DTI parameters. Diffusion tensor imaging scans were acquired using a multi-shot spin echo sequence with the following parameters: 50 interleaved slices; TA = 3:55 min; TR = 7300 ms; TE = 96 ms; field of view = 230 mm; 2.5 mm slice thickness; voxel resolution = 2.5×2.5×2.5 mm; 30 diffusion directions; b1 = 0 s/mm^2; b2 = 1500 s/mm^2. Rather than conduct one scan with three averages, three identical scans with one average each and an anterior-to-posterior phase encoding direction were acquired. In a review of DTI advances, Tournier, Mori, and Leemans (2011) state "multiple repeat scans … may provide a better way to judge the quality of postprocessing" (p. 1535). In order to help minimized eddy-current distortions common in DTI scans, an additional scan with one average and a posterior-to-anterior phase encoding direction was acquired with the following parameters: 50 interleaved slices; TA = 0:16 min; TR = 7200 ms; TE = 96 ms; field of view = 230 mm; 2.5 mm slice thickness; voxel resolution = 2.5×2.5×2.5 mm; 30 diffusion directions; b = 0 s/mm^2. Images were combined and averaged during post-processing.

DTI processing. The Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB) software library (FSL; Smith et al., 2004), FMRIB's Diffusion Toolbox (FDT; (Behrens, Johansen-Berg, et al., 2003; Behrens, Woolrich, et al., 2003) was used to analyze the DTI data. First, each participant's DTI scans were converted from DICOM to Neuroimaging Informatics Technology Initiative (NIfTI) format using MRIcron© (Rorden, Karnath, & Bonilha, 2007). Next, an estimate of the susceptibility induced off-resonance field was obtained and the brain was extracted using the brain extraction tool (BET; Smith, 2002). Then the scans were corrected for eddy current effects, magnetic field inhomogeneities, and any head motion. Next, each participant's three anterior-to-posterior DTI scans were combined and averaged together.

Finally, DTIfit was used to calculate diffusion tensors and generate FA images as well as eigenvalue and eigenvector outputs (Rowley et al., 2013).

Voxelwise analysis of FA data was conducted using Tract-Based Spatial Statistics (TBSS; Smith et al., 2006). First, a tensor model was fit to the raw diffusion data using FDT to create FA maps. All of the participants' FA data were then aligned into a common space (i.e., normalized) using the nonlinear registration tool FNIRT (Andersson, Jenkinson, & Smith, 2007a, 2007b), which uses a b-spline representation of the registration warp field (Rueckert et al., 1999). Next, a mean FA image was created and thinned to create a mean FA skeleton, which represents the centers of all common tracts. Finally, each participant's aligned FA data were projected onto the FA skeleton.

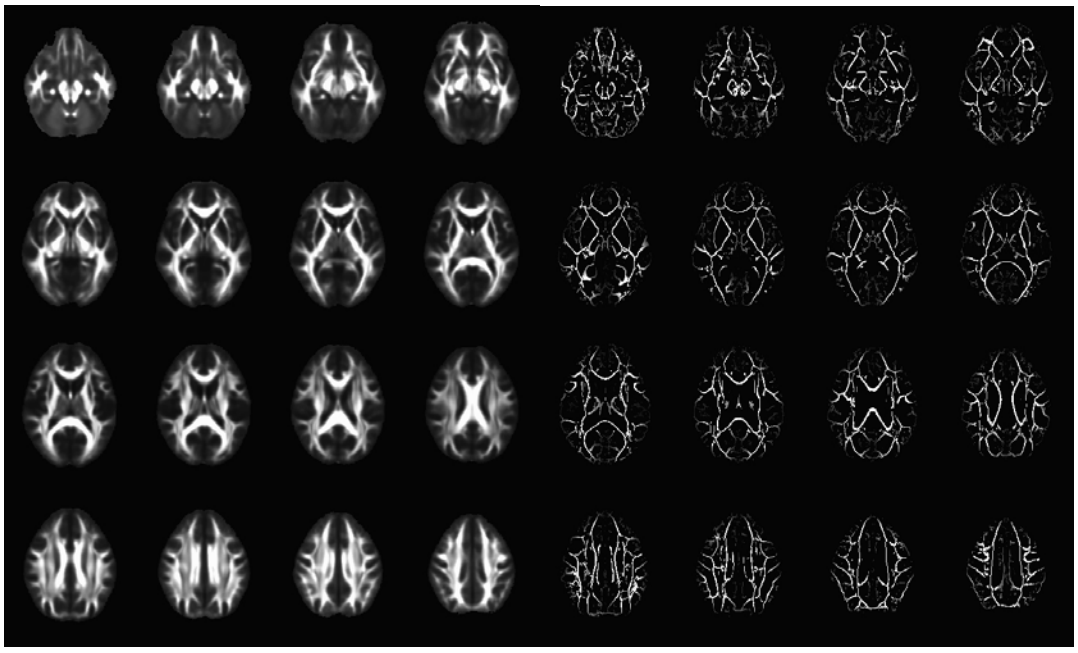
A  B

Figure 11. A: Axial montage of mean FA values across all participants. B: Axial montage of mean FA skeleton across all participants.

AD images came from the first, or principal, eigenvalues (L1 output from DTIfit) and RD images were procured for each participant by obtaining an average of the second and third, or non-prinicple, eigenvalues (L2 and L3 output from DTIfit; Yeh, Simpson, Durazzo, Gazdzinski, & Meyerhoff, 2009). Voxelwise analyses of AD and RD data were identical to that described above for the FA data.

White matter masks previously created using the MRI Atlas of Human White Matter (Oishi, Faria, van Zijl, & Mori, 2011) were used as ROIs (Doxey & Kirwan, 2015); specifically, bilateral cingulum, fornix, and white matter tracts of the superior, middle, and inferior temporal gyrus. An additional white matter mask for the uncinate fasciculus was created using the ANTS-averaged structural scan as a reference. TBSS skeletons (FA, AD, and RD separately) were then segmented into the white matter ROI masks. Areas outside of the TBSS skeletons were subtracted and FA, AD, and RD values were extracted for each white matter ROI within each FA, AD, and RD skeleton. Average FA, AD, and RD values within each ROI were then obtained for each participant and assessed via voxelwise group-level statistics.

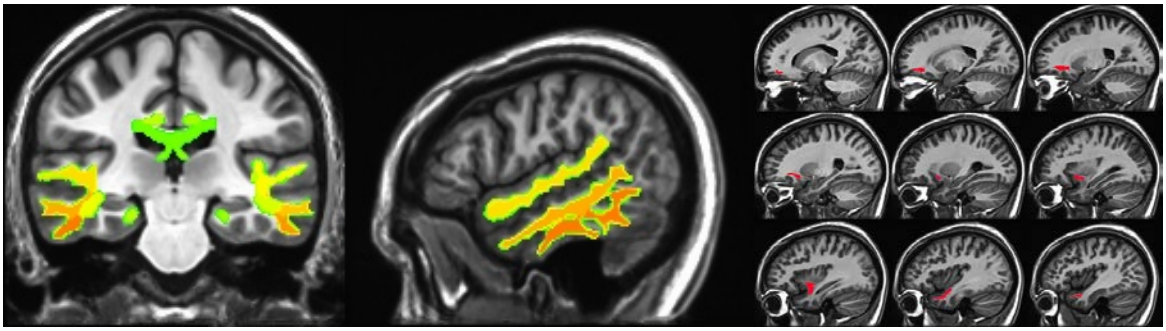


Figure 12. Example views of ROI masks used in Experiment 3. From left and middle panels, superior temporal gyrus (yellow), middle temporal gyrus (orange), and inferior temporal gyrus (red). Other tracts in green were not used in Experiment 3. From right panel, uncinate fasciculus mask (red) was created.

Results

It was hypothesized that the uncinate fasciculus and cingulum networks would differentiate among the three groups (sedentary, low-physical activity, and high-physical activity) and that white matter differences would also be found in the medial temporal lobe pathways. Thus, ROI analyses were conducted on the following white matter pathways: fornix, bilateral uncinate fasciculus, bilateral cingulum, and bilateral superior, middle, and inferior temporal gyri. The resulting DTI data were subjected to three MANOVAs (one each for FA, AD, and RD values) to examine group differences (sedentary, low physical activity, and high physical activity) within the various white matter pathway ROIs.

Multivariate tests revealed no significant differences in FA values between groups for the white matter ROIs ($F(22, 88) = 1.024$, $p = .445$; Wilks' $\Lambda = 0.634$, partial $\eta^2 = .204$). Analysis of RD values also found no significant differences between groups ($F(22, 88) = .508$, $p = .964$; Wilks' $\Lambda = 0.787$, partial $\eta^2 = .113$). However, multivariate analysis of AD values was significant ($F(22, 88) = 2.074$, $p = .009$; Wilks' $\Lambda = 0.434$, partial $\eta^2 = .341$). Univariate comparisons of the AD data revealed a significant effect for the left and right cingulum (left: $F(2, 54) = 4.270$; $p = .019$; partial $\eta^2 = .137$; right: $F(2, 54) = 4.214$; $p = .020$; partial $\eta^2 = .135$), the left middle temporal gyrus ($F(2, 54) = 3.363$; $p = .042$; partial $\eta^2 = .111$), and the right uncinate fasciculus ($F(2, 54) = 3.585$; $p = .035$; partial $\eta^2 = .117$).

Descriptive statistics show increased AD values for participants with greater reported physical activity for each of the white matter tracts. Left cingulum: sedentary M=.001333, SD=.00005; low physical activity M=.001378, SD=.00006; high physical activity M=.001379, SD=.00006. Right cingulum: sedentary M=.001316, SD=.00003; low physical activity M=.001350, SD=.00006; high physical activity M=.001354, SD=.00004. Left middle temporal

gyrus: sedentary M=.001209, SD=.00004; low physical activity M=.001231, SD=.00004; high physical activity M=.001241, SD=.00004. Right uncinate fasciculus: sedentary M=.001203, SD=.00002; low physical activity M=.001227, SD=.00004; high physical activity M=.001228, SD=.00003.

Post-hoc comparisons using Fisher's LSD revealed significant differences in the left cingulum between sedentary and low-physical activity groups (p = .016) and sedentary and high-physical activity groups (p = .012), but not between the two physical activity groups (p = .950). For the right cingulum, significant differences were also found between sedentary and low-physical activity (p = .021) and sedentary and high-physical activity (p = .010) groups, but not between low- and high-physical activity groups (p = .788). For the left middle temporal gyrus, significant differences were found between sedentary and high-physical activity groups (p = .014), but not between sedentary and low-physical activity (p = .084) or low- and high-physical activity (p = .445) groups. Finally, for the right uncinate fasciculus, significant differences were found between sedentary and low-physical activity (p = .026) and sedentary and high-physical activity (p = .021) groups, but not between low- and high-physical activity groups (p = .948).

Physical activity survey analysis. One-way ANOVA analysis of participants' self-reported physical activity revealed significant differences for current activity level ($F(2,54)=107.69$; $p < .0001$), frequency of aerobic activity ($F(2,54)=81.77$; $p < .0001$), length of aerobic activity ($F(2,54)=22.14$; $p < .0001$), level of aerobic activity ($F(2,54)=30.59$; $p < .0001$), frequency of strength activity ($F(2,54)=65.92$; $p < .0001$), length of strength activity ($F(2,54)=37.92$; $p < .0001$), and level of strength activity ($F(2,54)=63.88$; $p < .0001$). Once again, these results are not surprising and are essentially a repeat of the analysis conducted for the fMRI data. Post-hoc comparisons using Fisher's LSD demonstrate that the high and low

physical activity groups did not differ by frequency of aerobic activity (p = .329), length of aerobic activity (p = .420), level of aerobic activity (p = .139), length of strength activity (p = .120) or level of strength activity (p = .165). It would appear that these groups only differentiated meaningfully on the frequency of strength activity (p = .001). Once again, comparisons between the sedentary and low-physical activity groups and sedentary and high-physical activity groups showed statistically significant differences with p <.0001 in each category of aerobic and strength activity. Based on the post-hoc analysis for the AD data, it would appear that differences found in the left and right cingulum and right uncinate fasciculus were due to aerobic differences between the sedentary and physical activity groups. However, differences found in the left middle temporal gyrus between the sedentary and high-physical activity group may be due to the differences in strength activity.

Table 4.
RA, RD, and AD values (mean, standard deviation) for white matter regions of interest in sedentary, low-physical activity, and high-physical activity groups for Experiment 3.

	Sedentary		Low-PA		High-PA	
FA Fornix	0.5599	(0.05)	0.5758	(0.05)	0.5655	(0.06)
FA left cingulum	0.6351	(0.04)	0.6473	(0.04)	0.6510	(0.03)
FA right cingulum	0.6179	(0.03)	0.6309	(0.03)	0.6338	(0.03)
FA left superior temporal gyrus	0.3695	(0.02)	0.3713	(0.02)	0.3731	(0.02)
FA right superior temporal gyrus	0.4124	(0.03)	0.4100	(0.02)	0.4218	(0.02)
FA left middle temporal gyrus	0.4847	(0.01)	0.4916	(0.02)	0.5009	(0.02)
FA right middle temporal gyrus	0.5666	(0.02)	0.5737	(0.02)	0.5696	(0.03)
FA left inferior temporal gyrus	0.4777	(0.02)	0.4867	(0.02)	0.4876	(0.01)
FA right inferior temporal gyrus	0.4889	(0.02)	0.4906	(0.02)	0.4861	(0.02)
FA left uncinate fasciculus	0.5146	(0.02)	0.5251	(0.02)	0.5264	(0.03)
FA right uncinate fasciculus	0.5497	(0.02)	0.5579	(0.03)	0.5594	(0.03)
RD Fornix	0.6871	(0.13)	0.6572	(0.15)	0.6817	(0.18)
RD left cingulum	0.4032	(0.03)	0.3989	(0.03)	0.3992	(0.03)
RD right cingulum	0.4122	(0.03)	0.4075	(0.02)	0.4066	(0.02)
RD left superior temporal gyrus	0.5611	(0.02)	0.5593	(0.02)	0.5586	(0.02)
RD right superior temporal gyrus	0.5344	(0.03)	0.5385	(0.02)	0.5326	(0.02)
RD left middle temporal gyrus	0.5213	(0.02)	0.5223	(0.02)	0.5155	(0.02)
RD right middle temporal gyrus	0.4670	(0.02)	0.4695	(0.03)	0.4695	(0.04)
RD left inferior temporal gyrus	0.5133	(0.02)	0.5112	(0.03)	0.5097	(0.02)
RD right inferior temporal gyrus	0.5243	(0.02)	0.5260	(0.03)	0.5290	(0.03)
RD left uncinate fasciculus	0.4763	(0.02)	0.4756	(0.03)	0.4702	(0.03)
RD right uncinate fasciculus	0.4561	(0.02)	0.4568	(0.03)	0.4549	(0.03)
AD Fornix	1.8094	(0.13)	1.8117	(0.10)	1.7945	(0.12)
AD left cingulum	1.3327	(0.05)ŧ, ŧŧ	1.3785	(0.06)ŧ	1.3796	(0.06)ŧŧ
AD right cingulum	1.3164	(0.03)ŧ, ŧŧ	1.3504	(0.05)ŧ	1.3542	(0.04)ŧŧ
AD left superior temporal gyrus	0.9883	(0.03)	0.9987	(0.02)	0.9934	(0.04)
AD right superior temporal gyrus	1.0231	(0.03)	1.0231	(0.02)	1.0386	(0.03)
AD left middle temporal gyrus	1.2085	(0.04)ŧ	1.2315	(0.04)	1.2413	(0.04)ŧ
AD right middle temporal gyrus	1.2742	(0.03)	1.3047	(0.04)	1.2873	(0.04)
AD left inferior temporal gyrus	1.1167	(0.03)	1.1388	(0.03)	1.1326	(0.03)
AD right inferior temporal gyrus	1.1789	(0.04)	1.1842	(0.03)	1.1745	(0.03)
AD left uncinate fasciculus	1.1554	(0.03)	1.1745	(0.04)	1.1673	(0.04)
AD right uncinate fasciculus	1.2025	(0.02)ŧ, ŧŧ	1.2272	(0.04)	1.2279	(0.03)ŧŧ

Note. RD and AD values are reported as "value" x 10^{-3}. ŧ = significant difference for indicated groups; ŧŧ = significant difference for second set of indicated groups; $p < 0.05$.

Discussion

No significant differences between physical activity groups were found in the ROIs for FA or RD; however, significant differences were found some of the ROIs for AD. Originally, it was hypothesized that differences would be found in the cingulum and uncinate fasciculus with greatest values found for those in the high-physical activity group. For bilateral cingulum, AD values differentiated between sedentary and low-physical activity groups and sedentary and high-physical activity groups; however, AD values for the high-physical activity group were not distinguished from the low-physical activity group. This same pattern also held for the right uncinate fasciculus.

It was also hypothesized that highest AD values would be greatest in the high-physical activity group in the white matter tracts of the temporal lobe. However, significant differences were only found for the left middle temporal gyrus tract with differences found between sedentary and high-physical activity groups, but not between the physical activity groups or between the sedentary and low-physical activity group.

DTI analysis enables the inference of diffusion properties, such as the preference of diffusion direction (FA), the rate of diffusion along the main axis (AD), and the rate of transverse direction diffusion (RD; Soares, Marques, Alves, & Sousa, 2013). Thus, the participants in Experiment 3 did not appear to differentiate with regards to diffusion direction (either with preference or transverse direction); however, they did differ in their rate of axis diffusion. AD measures the direction of quickest diffusion and detects lengthwise axon diffusion (Soares et al., 2013). It has previously been associated with microstructural dimensions (Alexander et al., 2011) and structure alterations (Soares et al., 2013); however, others have stated that interpreting

changes in DTI eigenvalues as changes to underlying structures is inappropriate given the variability of alignment, which can occur across participants (Tournier et al., 2011).

It is advocated for studies to analyze multiple measures of diffusion and not just FA; for example, white matter abnormalities are associated with a decrease in anisotropy, which may be caused by either increased perpendicular diffusion (RD) or decreased parallel diffusion (AD; (Alexander, Lee, Lazar, & Field, 2007). Mean diffusivity (MD), which is the inverse measure of membrane density, has been recommended to be included, along with FA, in DTI studies (Alexander et al., 2011). However, since this value is an average of the eigenvalues (Alexander et al., 2007), and given that RD is an average of two of the eigenvalues and was not significant for Experiment 3, it is not likely to add any value to the current data set.

Others have recently found that increased physical activity (both increased steps and increased duration) is associated with higher FA values in the superior longitudinal fasciculus, inferior occipito-frontal fasciculus, and posterior cingulum and increased steps are associated with lower RD values (Tian et al., 2015). Furthermore, faster 400-meter walk times are associated with higher FA values in the cingulum and lower MD values in the entorhinal cortex; (Tian, Simonsick, et al., 2014). Exercise is also associated with decreased MD values in the medial temporal lobe and cingulate cortex (Tian, Erickson, et al., 2014). However, these participants ranged in age from 83 to 92 years in the first study, 79 to 90 years in the second study, and 70 to 79 years in the last study. It may be that FA and RD values do not differentiate among physical activity levels in young adults, such as those in Experiment 3, whose mean age was 23 years. Indeed, no differences in FA values were found between high and low physically active male adolescents (Herting et al., 2014). However, this group of adolescents did differentiate among tractography streamline counts in the bilateral corticospinal tracts and right

anterior corpus callosum, with significantly few streamlines among the low physically active group.

Tractography analysis would be an interesting follow-up in the Experiment 3 data set; however, it is unknown if significant results would be obtained as the adolescents from the previous study had a weekly average of at least 10 hours of organized highly aerobic activity (for the high physical activity group) or at most 1.5 hours of highly aerobic activity (for the low physical activity group; Herting et al., 2014). Whereas the physical activity groups in the current experiment were likely closer in physical activity rates since the inclusion criteria was a weekly average of at least 150 minutes of moderate or 75 minutes of vigorous activity and at least two episodes of strength training for the high physical activity group and anything less than this criteria for the low physical activity group. A recent review of DTI studies of obesity found that most studies showed a negative correlation between FA values and BMI in various regions of the corpus callosum and cingulum and a positive correlation between BMI and RD and MD values in the fornix (Kullmann, Schweizer, Veit, Fritsche, & Preissl, 2015). The groups in Experiment 3 did not differentiate by BMI, so this result is not likely to be found in the current data set; however, future DTI studies examining physical activity may want to include the corpus callosum as an ROI and include BMI in their analyses.

FA, AD, and RD are greatly affected by crossing or differentially oriented nearby fibers; thus, results should be interpreted with caution (Soares et al., 2013; Tournier et al., 2011). Furthermore, Wheeler-Kingshott and Cercignani (2009) point out that the DT eigenvectors should be statistically compared to their associated anatomical structures with each participant to ensure sameness of physical location across groups. They report that DT eigenvalues across groups are particularly sensitive to regions with crossing fibers. Alexander et al. (2011)

recommend using tensor shape (linear, planar, and spherical) to identify crossing fibers and provide useful formulas based on the eigenvalues (see p. 426). A necessary follow-up step to the DTI analysis conducted in Experiment 3 would be to conduct an eigenvector-structural comparison to ensure each participant's AD information is actually located within the same white-matter structure.

Once again, it is recommended that follow-up studies ensure greater differences in physical activity between low and high groups for both aerobic and strength activities. For example, future projects could consist of five groups: sedentary; low aerobic activity, no strength; low aerobic activity, strength activity; high aerobic activity, no strength; and high aerobic activity, strength activity. Additionally, since the majority of participants from the sedentary group were BYU students who likely engage in regular amounts of walking around campus, it is recommended that future sedentary groups consist of purer sedentary samples (i.e., lower levels of daily physical activity), which may be more likely to occur in samples recruited outside of a college population. A recent DTI study of children (9-10 years) separated groups based on VO_2 max scores (Chaddock-Heyman et al., 2014). Children in the "higher fit" category had significantly greater FA values in the body of the corpus callosum (but no differences in RD or AD), bilateral superior corona radiate (with significant differences in RD), and bilateral superior longitudinal fasciculus (with significant differences in RD). Future studies may also find more success with measuring VO_2 levels instead of relying on self-report.

Chapter 5: Conclusions

Data from the current project show surprising results with regards to pattern separation and neural variables. Contrary to the original hypotheses in Experiment 1, participants with MDD had significantly higher pattern separation scores and were more likely to successfully engage in pattern separation than control participants. Furthermore, participants with depression were more likely to correctly respond to lure stimuli and less likely to incorrectly respond "old" to lure stimuli, unlike the control participants who were significantly more likely to commit in this error. These unexpected outcomes may be the result of several confounding issues. First, the majority of depressed participants were in their first episode of depression and all were in young adulthood. It may be the case that a longer history of depression (i.e., experiencing multiple episodes) and/or greater age is necessary before individuals with MDD would perform poorly on this task.

However, previous studies (Déry et al., 2013; Shelton & Kirwan, 2013) showed differentiation of pattern separation scores on this and a similar task with non-depressed participants. Individuals with higher depression scores had significantly lower pattern separation scores than those with lower depression scores. The unanticipated results from Experiment 1 may be the result of the particular individuals who participated as controls. There was a sub-set of control participants who had BDI scores within the same range as the clinically depressed participants. In addition, the MDD participants may have been more motivated to perform well on the task and could have been more attentive than the control group. Indeed, in comparison to a large group of participants who have completed this task as part of other ongoing studies (n=110), the MDD participants had higher pattern separation scores and higher recognition memory scores compared to the group as a whole. It seems unlikely that these results were due to

better pattern separation processing in the MDD group. Rather, a more parsimonious explanation may be that this group was more motivated to perform well on the task, given the sampling parameters for the current study.

Participants from Experiment 1 also have structural and functional MRI data as well as DTI data. Planned follow-up analyses will compare pattern separation scores with structural volumes and diffusion tensor data of participants' medial temporal lobes. It may be the case that subtle neurologic changes exist where behavioral changes do not in the current group of participants.

Again, contrary to the Experiment 2 hypothesis, participants with higher levels of physical activity did not have greater activation in either CA3/DG in response to CRs (first presentation stimuli called "new") and Lure CRs (lure stimuli called "similar") compared to Hits (repeat stimuli called "old") and Lure FAs (lure stimuli called "old). Post-hoc analyses revealed no differences between physical activity groups for any of the other ROIs (bilateral CA1 and subiculum subregions of the hippocampus). It is possible that this particular explicit memory discrimination task was ill suited for the given fMRI hypothesis. It is likely that the implicit version of this task, where participants view foil, lure, and repeat objects, but do not explicitly look for objects to differentiate and instead judge each stimulus as either more likely to be found indoors or outdoors, would be more likely to distinguish CRs and Lure CRs from Hits and Lure FAs. It is also recommended that future studies wishing to examine pattern separation within physical activity groups use the implicit version of this task.

Additionally, there were no differences in FA or RD values between physical activity groups. However, significant differences were found in AD values for bilateral cingulum tracts, left middle temporal gyrus, and right uncinate fasciculus. Post-hoc tests revealed that these

differences existed between the sedentary and low-physical activity and sedentary and high-physical activity groups, but not between the low- and high-physical activity groups for the bilateral cingulum tracts and right uncinate fasciculus. For the left middle temporal gyrus tract, differences were found between the sedentary and high-physical activity group only. In each case participants with higher levels of physical activity had greater AD values; however, these values did not distinguish well between groups, particularly between the low- and high-physical activity groups.

Based on analyses of participants' self-reported physical activity and BDNF values, it appears that the groups did not differ as much in their levels of physical activity as originally anticipated. However, additional physical activity data were collected on the participants in Experiments 2 and 3 and follow-up data analyses will analyze the RPAQ and accelerometer data to determine if this information is a more accurate way to group the participants than the self-report method originally used. It is also recommended that future physical activity studies ensure that sedentary participants have low levels of both exercise and daily physical activity since it can be assumed that the sedentary participants likely had higher levels of daily physical activity.

Given the vast literature linking physical activity with increased cognitive performance it is expected that group differences from the current dataset may emerge through non-ROI methods. Planned follow-up analyses will conduct whole-brain fMRI comparisons of CRs, Lure CRs, Hits, and Lure FAs to determine if any other regions, outside of the hippocampus, vary in response to this task. Whole-brain high-resolution fMRI analysis has not previously been possible. However, the use of MB data acquisition during the fMRI task in Experiment 2 makes this a reality. Preliminary analyses have revealed novel findings across groups in the current data set in 18 neural regions, with most areas demonstrating similar levels of activation for Hits and

Lure CRs and increased levels of activation for Lure FAs. In addition to task-specific explorations, comparisons will also be conducted to determine if the physical activity groups varied in activation in other regions in the brain.

In addition to whole-brain analysis, multivariate fMRI data analysis may also tease out subtle differences between physical activity groups not found using univariate methods. Yassa and Stark (2011) have encouraged researchers to utilize multi-voxel pattern analysis (MVPA) in pattern separation and pattern completion fMRI studies, which may be more sensitive in depicting patterns of activation that may be missed through conventional univariate analyses. Thus, another planned follow-up of the data from Experiment 2 is an MVPA analysis using the Princeton MVPA toolbox for Matlab (http://code.google.com/p/princeton-mvpa-toolbox). For each participant, a simple neural network classifier will be trained based on the fMRI data for task trials (repeat, lure, foil). Classifer training will be performed on the data for CRs and Hits and the classifer will then be tested on the remaining Lure data. This process will be conducted three times: first, on the fMRI data for the whole brain; then, on data restricted to the medial temporal lobe (including the hippocampus and the perirhinal, entorhinal, and parahippocampal cortices); and finally, on data including the hippocampal subregions (CA1, CA3/DG, and subiculum). This multivariate approach may be a more sensitive measure than the standard methods used in Experiment 2.

A final planned follow-up will explore more of the DTI dataset from Experiment 3 by conducting a tractography analysis. Inclusion of additional white matter tracts and conducting an eigenvector-structural comparison (Alexander et al., 2011) of the FA, RD, and AD data to ensure sound structural alignment across participants would also be valuable. Once again, subtle

structural changes may exist, outside of the a priori ROIs, where functional changes do not in the current group of participants.

This project sought to explore pattern separation performance variations in depressed and physically active populations. Assumed changes in levels of neurogenesis across these groups was expected to drive behavioral changes in participants with MDD and neural changes in participants with varying levels of physical activity. However, Experiments 1 and 2 found results contrary to what was expected given the previous literature in these areas. Experiment 3 provided some support that individuals with varying levels of physical activity have white matter variations. Future depression studies should explore how multiple depression episodes impact pattern separation performance and also address motivation issues potentially found in the current project. In addition, future studies exploring physical activity should ensure greater differentiation of activity between sedentary and active groups.

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Appendix A

Physical Activity Survey

1. How would you rate your current activity level?

☐ Not active ☐ Somewhat active ☐ Moderately active ☐ Very active

2. How active do you think you are compared with other people your age?

☐ Less ☐ Same ☐ More

3. How important is it for you to be physically active?

☐ Not important ☐ Somewhat important ☐ Very important

4. How often do you engage in aerobic activity?

☐ Never ☐ 1-2 times a month ☐ 3-4 times a month ☐ 1-2 times a week

☐ 3-4 times a week ☐ Other (please describe):_____

5. How would you rate your level of aerobic activity?

☐ N/A ☐ Mild activity ☐ Moderate activity ☐ Intense activity

6. How often do you engage in muscle-strengthening activity?

☐ Never ☐ 1-2 times a month ☐ 3-4 times a month ☐ 1-2 times a week

☐ 3-4 times a week ☐ Other (please describe):_____

7. How would you rate your level of muscle-strengthening activity?

☐ N/A ☐ Mild activity ☐ Moderate activity ☐ Intense activity

8. How often do you engage in stretching activity?

☐ Never ☐ 1-2 times a month ☐ 3-4 times a month ☐ 1-2 times a week

☐ 3-4 times a week ☐ Other (please describe):_____

9. How would you rate your level of stretching activity?

☐ N/A ☐ Mild activity ☐ Moderate activity ☐ Intense activity

10. Please provide an example of your weekly aerobic and/or muscle-strengthening routine:

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday

11. How long have you had this routine?

☐ N/A ☐ 1-3 weeks ☐ 1-2 months ☐ 3-5 months

☐ 6-9 months ☐ 10 months or longer

Appendix B

Meter Log

The movement meter records your activity and sleep patterns; however, we will not be able to tell what kind of specific activity is happening. It is extremely important for our study that you wear the meter properly. If it is not worn properly, we may have to send it back for you to wear again.

Please wear the movement meter day and night for seven (7) consecutive days. In the table below, write down the dates and days on which you wear the meter. Note the times, including "a.m." or "p.m.", that you take it off and put it back on during each day. As a reminder, please only remove the movement meter when you will be getting wet (bathing, showering, swimming, etc.). Also note the reason you took the meter off. Below is an example entry.

Example:

Date	Tues, Aug 26, 2014	
	Off	On
	7:30am	8:00am
Reason	Shower	
	1:00pm	2:00pm
Reason	Swimming	
Reason		

- Wear the meter attached to the belt around your waist, just above your **right** hipbone
- Wear the meter either underneath or on top of your clothing
- Wear the meter so the nob is facing up
- Wear the meter **snug** against your body. Wear the belt tight enough so the meter doesn't move when you are active
- Do NOT submerge the meter in water
- Wear the meter all day and night, unless swimming, bathing, or showering
- Do NOT let anyone else wear the meter

Date														
	Off	On	Off	On	Off	On	Off	On	Off	On	Off	On	Off	On
Reason														
Reason														
Reason														

Appendix C

Exercise Log

Directions: Please fill out a line for each type of exercise you engage in each day; for example, if you walk and stretch, fill out a line with details regarding your walk and a separate line with details regarding your stretch. Please be as detailed as possible. If a category doesn't apply to your particular activity, please leave it blank. Examples are provided below.

Date	Time	Type of Exercise/Activity	Muscle Groups Targeted	Duration or Number of Sets	Intensity Level or Number of Reps
15-Mar-13	8:30 AM	Jogging		20 min (2 miles)	
16-Mar-13	5:00 PM	Weights	Arms/shoulders	3 sets	